BIG VS POWERFUL: MOLECULAR SIGNALLING RESPONSES TO HYPERTROPHIC AND POWER RESISTANCE EXERCISE MODALITIES

Roland Loh Fook Yuen

Master's Thesis
Exercise Physiology
Spring 2015
Department of Biology of Physical Activity
University of Jyvskylä
Supervisor: Juha Ahtiainen

ABSTRACT

Roland Loh Fook Yuen (2015). Big vs. Powerful: Molecular and recovery responses to hypertrophic and power resistance exercise modalities. Department of Biology of Physical Activity, University of Jyväskylä, xx pp.

Introduction: The effects of resistance exercise (RE) loading on molecular signalling proteins, including those involved in protein translation and thus skeletal muscle hypertrophy have been extensively studied. However, there is little research on high power RE loading and molecular signalling proteins, and also on possible relationships between signalling proteins and recovery from RE loading.

Methods: 7 young men (31±6 years, 178.9±4cms, 84.6±5 kgs) performed 1 hypertrophy loading session (HYP) (5x10 80% 1RM leg presses (LP)) and 1 power loading session (POW) (10x5 70% 1RM LP), with each session separated by 7 days, in a crossover design, prior and subsequent to 12 weeks of resistance training. Phosphorylated p70S6K1 at Thr389, p70S6K1 at Ser424, p38, ERK, rpS6, 4EBP1 assessed with western blotting of vastus lateralis (VL) tissue microbiopsied immediately post-exercise, but only for the post-training acute loading sessions. Mechanical work performed calculated using video recordings, and the relationship between mechanical work, kinetic energy and potential energy. Recovery from HYP was assessed everyday after exercise for 4 days, and from POW, for 2 days, via maximal isometric leg press force, static jump height, VL muscle thickness.

Results: No significant differences in protein signalling within or between HYP and POW conditions. No correlations between mechanical work performed and changes in signalling proteins. Recovery from HYP: changes in static jumps immediately post-exercise correlated with changes in p-p70S6K1 at Ser424 ($r=0.793$, $p= 0.033$), p-rpS6 ($r=0.821$, $p=0.023$) and p-ERK ($r=0.821$, $p=0.023$), changes in muscle thickness inversely correlated with changes in p-p38 ($r=-0.786$, $p=0.036$)) and p-ERK ($r=-0.786$, $p=0.023$) at 72h. Recovery from POW: changes in isometric LP immediately post-exercise correlated with changes in p-rpS6 ($r=0.786$, $p=0.014$), but changes in p-p70S6K at Thr389 ($r=-0.929$, $p=0.003$) inversely correlated with static jump height at 48h.

Discussion: Lack of any significant differences within and between HYP and POW conditions for phosphorylated proteins might be because of the biopsy time-point, small sample size, or participants' trained status. Correlations between some phosphorylated proteins and early recovery suggests that quicker recovery from resistance loading is associated with increased phosphorylation of signalling proteins after hypertrophy type loading.

Conclusion: No differences in molecular signalling proteins involved in protein translation as a result of HYP versus POW. There were divergent intra and inter-individual signalling responses to HYP versus POW. No relationships between mechanical work performed and changes in signalling proteins. In conclusion, in trained young men, leg pressing 5x10 at 80% of 1RM results in similar acute molecular signalling changes as 10x5at 70% of 1RM.

CONTENTS

1 INTRODUCTION

There has been much research on the molecular signalling responses to resistance exercise, primarily involving the proteins responsible for protein translation. For example, Hulmi et al. (2012) looked at phosphorylation of the mTOR and MAPK mechanisms in response to hypertrophy (5x10RM) vs heavy (15x1RM) resistance exercise. However, there is little research on the molecular signalling responses to "power type" resistance exercise, even though this type of resistance training is often used by athletes for the development of muscular power (Cormie et al. 2011). Galpin et al. (2012) assessed the time-course of MAPK signalling as a result of acute power training in trained male weightlifters, but did not compare power training with any other type of training, nor assess changes downstream mTORC1 target proteins such as p70S6K1 or 4EBP1. Ahtiainen et al. (2015) compared signalling responses to lower volume (5x10RM) vs higher volume (10x10RM) hypertrophic loading but did not compare hypertrophic loading versus power loading. Mitchell et al. (2012) assessed the effect of RT intensity on SkM hypertrophy and signalling, but the effects of movement velocity, and thus actual mechanical work performed was not explored.

Additionally, although many studies have been conducted on the acute molecular responses to various different resistance loading protocols, to the author's knowledge, little work has been done in humans on assessing whether there is any relationship between various acute physiological responses, that is molecular proteins, blood lactate, neuromuscular responses, that is isometric strength, static jump, and morphological responses, that is muscle thickness, to hypertrophic versus power type resistance loading. Using a mouse model, Rahnert & Burkholder (2013) discovered that high frequency electrical stimulation resulted in phosphorylation of ERK, p38, p70S6K1 at Thr389 and that p38 phosphorylation was correlated with force time integral even with a stimulus designed to result in minimal metabolic load but high mechanical load. Moreover, only Galpin et al (2012) have attempted to explore whether mechanical work performed is related to changes in signalling proteins. Participants in Galpin et al. (2012) were trained weightlifters who performed clean pulls, a resistance exercise that might require specific coaching / practice for some participants, and thus, might not be suitable outside of specific

athletic settings. Therefore, there is scope for research into the effects of traditional hypertrophy type training versus high power type training on molecular signalling mechanisms involved in SkM protein synthesis, using exercise loading that does not require specific coaching.

1.1 What is resistance training?

The movement of the whole body and its individual segments that is fundamental to human life is the responsibility of skeletal muscle (SkM). The plasticity of SkM in response to stimuli or lack thereof, whether mechanical (ACSM, 2009a) or nutritional (ACSM, 2009b; Breen & Phillips, 2012; Churchward-Venne et al., 2012), is well known. The increase in SkM mass, and strength: the ability to exert force against external resistance (Zatsiorksy, 1995), in response to chronic external mechanical work, that is, resistance training (RT), is widely recognised, both in the scientific literature (ACSM 2009a), and in popular culture amongst men (Fussell, 1992; Schwarzenegger, 1993) and women (Chapman & Vertinsky, 2011; Felkar, 2012; Heywood, 1998; Shilling & Bunsell, 2009). In ancient Greek history / mythology, Milo of Croton(a) reputedly engaged in progressive resistance training from childhood, by carrying a calf daily, increasing the mass carried, and thus, increasing his SkM mass, as both the calf, and he, grew older (Crowther, 1977). In ancient Persia also, there existed a tradition of weight training. Indeed, the Persian tradition of the Zoorkhaneh (home of strength), Varzesh-e-Bastani (ancient strength sport) and the role of the Pahlevan (champion athlete who demonstrated physical prowess and moral virtue) in society (Amirtash, 2008, Chehabi et al., 1995) might offer a partial explanation as to why modern Iran excels in weightlifting. Similarly, during the Warring States period, ~475 to 221 Before Christian Era (BCE), in ancient China, the lifting of tripods, of which the heaviest known weighed approximately 800 kilograms (kgs), was the main test of strength. The Qin king Wu (310-306 BCE) reputedly dropped a tripod on his leg during a contest against the strongman Meng Shuo, resulting in blood loss and death (Lorge 2011).

RT is based on the principle of progressive overload and specificity (Kraemer & Ratamess, 2004). Progressive overload is the systematic gradual increase in the stress placed on the body during RT, whether by increasing: the absolute or relative resistance or intensity of a given movement, the repetitions within a set, the total repetitions for a movement, the repetition speed,

the range of motion of that movement, the total volume within a particular time period, and by decreasing the rest periods between sets. Specificity refers to the training adaptions specific to the stimulus, whether that is variation in movement and thus muscles (Dudley et al. 1991) involved, speed of movement (Coburn et al. 2006), load or intensity (Rhea et al. 2003), volume (Rhea et al. 2003), range of motion (Knapik et al. 1983), muscle action, energy systems involved (Tesch et al. 1989).

1.2 Resistance Training for Hypertrophy

SkM which is the most abundant tissue in humans, comprising approximately 40% of body mass in healthy adults (Lecker et al. 2006), and 50-75% of total body protein, is important for locomotion and posture, but also, as an amino acid reserve against disease, starvation, malnutrition, injury, burns (Matthews, 1999). SkM hypertrophy is the chronic accretion of proteins, whether contractile such as actin and myosin, or structural such as titin, via protein synthesis, resulting in the enlargement of muscle fibres (ACSM, 2009a). Chronic resistance training (RT) results in hypertrophy of skeletal muscle (SkM) (Kraemer & Ratamess, 2004). Even 1 bout of acute resistance exercise (RE) can increase protein synthesis in SkM (Phillips et al. 1997). RT programs with the goal of SkM hypertrophy utilise moderate to high loading, relatively high volume: both repetitions per set and total repetitions, short rest intervals (Kraemer & Ratamess, 2004; Zatsiorsky 1995), and slow to moderate velocity of movement (Munn et al. 2005). Hypertrophy might result from total mechanical work performed (Moss et al., 1997). For example, Goto et al. (2004) showed that in resistance trained participants, performing an extra set of knee extensions to momentary exhaustion at 50% of 1RM, 30 seconds after 5 sets of knee extensions to momentary exhaustion at 90% of 1RM resulted in a tendency ($p=0.08$) for greater increases (~3%) in SkM cross-sectional area compared to just 5 sets alone. The group who performed the extra set also increased their 1RM more. Several studies have found that performing multiple sets of RE to momentary muscular failure results in similar increases in myofibrillar protein synthesis (Burd et al. 2010a), molecular signalling (Burd et al. 2010b; Burd et al. 2011; Léger et al., 2007), muscle fibre area and volume (Léger et al., 2007; Mitchell et al. 2012), regardless of intensity of load (80-90% of 1RM vs 30%, or 3-5RM vs 20-28RM) in recreationally active young men, contrary to conventional understanding (ACSM, 2009a; Campos et al. 2002). However, it should be noted that dynamic knee extensions at 70% of peak

torque to voluntary fatigue elicits greater EMG amplitude versus knee extensions at 20% peak torque, whether with or without blood flow occlusion in recreationally active, but untrained young men (Cook et al. 2013). Recently, Schoenfeld et al.(2014) found that 10 young resistance trained men had greater peak EMG activity when performing high load (75% of 1RM) leg presses to failure compared to when performing low load (30% of 1RM) leg presses to failure. It thus appears that acute loading with high loads appears to greater activate the motor unit pool, in quadriceps femoris (Cook et al. 2013; Schoenfeld et al. 2014) and hamstrings (Schoenfeld et al. 2014). Additionally, rest periods between sets, 2 minutes versus 5, did not appear to modulate hypertrophy in trained men (Ahtiainen et al. 2003) who underwent a 6 months training program using traditional hypertrophy protocols: 8-12 reps per set, multiple sets and exercise, 4 sessions per week.

1.3 Resistance training for power development

According to Newton's second law of motion, the law of acceleration, the acceleration of an object is directly proportional to the magnitude and direction of the net force and inversely proportional to its mass. Mechanical power is the product of an object's velocity and the force acting on it, or the time derivative of mechanical work done, and is measured in watts (Feynman, 1970). In untrained individuals, the fundamental determinant of an individual's ability to generate external power is probably strength, where strength is defined as the ability to generate force against an external resistance (Zatsiorsky, 1994) as strong individuals can produce more power (Cormie et al., 2011), and heavy strength training increases both strength and power output (Cormie et al., 2010; Häkkinen et al. 1985; Moss et al., 1997). Whereas peak power attained in a movement is dependent on the individual (Kilduff et al., 2007), and the type of exercise (Bevan et al., 2010), in general, submaximal moderate loads maximally accelerated, that is power training, are used to optimise power development (Behm & Sale, 1999; Cormie et al., 2011). Elite weightlifters are "real world" examples of some of the adaptations that can occur as a result of chronic "power" training. As weightlifters are required to achieve peak force and peak power in less than 260 milliseconds (Garhammer et al. 1991; Gourgoulis et al. 2000), rate of force development is of paramount importance in weightlifting. Isometric peak force and peak rate of force development in weightlifters has been reported to be 15-20% and 13-16% greater when

compared with other strength and power athletes, specifically, sprinters, throwers and jumpers (McGuigan & Winchester, 2008; Stone et al. 2008). This has been suggested to be due to the selective recruitment of motor units (Aagaard et al. 2002; Häkkinen & Kallinen, 1994; Hartman et al. 2007), and enhanced voluntary activation of motor units (Ewing et al. 1990; Nardone et al. 1989). During the second pull, male weightlifters have been reported to generate absolute peak power values of 5442W in the snatch and 6981W in the clean. In comparison, elite male powerlifters might produce 1300W of peak power in a maximal deadlift (Garhammer et al. 1991, 1993). Furthermore, whereas weightlifters demonstrate greater (13-36%) peak power in various lower body exercises such as jumping and clean pulling compared to other power athletes such as sprinters, powerlifters (McBride et al. 1999; Stone et al. 2003, 2008), they show no such advantage in upper body absolute or relative peak power (Izquierdo et al. 2002), thus demonstrating the specific effects that chronic training can have on neuromuscular function, as weightlifting training emphasises training of the lower body (Bai et al. 2008; Izquierdo et al. 2002).

1.4 Protein balance, synthesis

Deoxyribonucleic acid (DNA) is comprised of four nucleotide bases: adenine (A), thymine (T), guanine (G), cytosine (C), which consist of a nitrogen containing base, a 5-carbon sugar and one or more phosphate groups. A is bound to T, and G to C, via two and three hydrogen bonds respectively. Only approximately 5% of DNA encodes genes. DNA is transcribed to messenger ribonucleic acid (mRNA), which occurs in the nucleus, and translated into amino acids in the cytosol, a process known as the Central Dogma (Crick, 1958; Watson & Crick, 1953). A detailed explanation of the process of DNA transcription to mRNA and then translation to amino acids is inappropriate here, for a systematic explanation of the transcription of DNA to mRNA, by the RNA polymerases, most notably by RNA polymerase II which is primarily responsible for the transcription of genes encoding proteins, see for example, Alberts et al. (2008).

mRNA is then translated into proteins. It is estimated that as many as 100000 proteins are expressed in humans as a result of splicing. Proteins are formed from 20 amino acids. The basic structure of an amino acid is a molecule with an amino (NH_2) group at one end and a carboxyl

(COOH) group at the other. Amino acids are bound together by peptide bonds, resulting in a peptide. Peptides are then folded, modified post-translationally to become functional proteins. A protein is a polypeptide, that is many peptides, and thus amino acids, bound together. Proteins are present in and are the workhorse of, cells, tissues, and are the most abundant nitrogen-containing biomolecule in the body and the diet (Brosnan et al., 2011; Fukugawa & Yu, 2009). There might be hundreds of thousands of proteins in the body, compared to approximately 25000-30000 genes (Brosnan et al., 2011; Fukugawa & Yu, 2009). Proteins play key physiological roles as enzymes, regulators of gene expression, components of the cell membrane, endoplasmic reticulum, the proteasome which together with the autophagy lysosome system is responsible for the removal of proteins (Schiaffino et al., 2013), the contractile proteins (such as myosin) in muscle, whether skeletal, cardiac, or smooth (Brosnan et al., 2011).

Net protein balance, protein turnover, whether of specific proteins or of total protein, is the balance between protein synthesis and protein degradation / breakdown, the balance between anabolism and catabolism. Proteins are continually synthesized and degraded. More specifically, the maintenance of body protein is a balance between protein synthesis, protein breakdown, amino acid interconversion, transformation, oxidation, and amino acid excretion (Brosnan et al., 2011; Fukugawa & Yu, 2009). The balance between protein intake and excretion and the balance between protein synthesis and breakdown are the two nitrogen cycles determining the status of body protein. Whereas these 2 cycles are in balance in healthy adults, nonetheless their intensity is dissimilar, as amino acid flow rate for protein synthesis and breakdown is approximately triple that of intake and excretion (Brosnan et al., 2011; Fukugawa & Yu, 2009). In adults, as there is generally no growth, protein turnover is generally associated with cell, tissue, organ maintenance, remodeling, repair, and the removal of abnormal / misfolded proteins (Fukugawa & Yu, 2009; Schiaffino et al, 2013). Approximately 300 grams (g) of protein is synthesised and degraded daily in a healthy adult human in proteostasis, that is when protein synthesis and breakdown are balanced (Proud et al., 2009), and thus there is neither gain nor loss in SkM mass.

The precise regulation of protein synthesis and breakdown can vary in both a tissue and time specific manner, even though the basic mechanisms of protein synthesis and breakdown are common in all tissues. For example, whereas there is a net loss of protein from skeletal muscle

during catabolic illnesses, hepatic protein synthesis will be increased for the synthesis of positive acute-phase proteins (Fukugawa & Yu, 2009). Furthermore, the proteins within a single tissue, for example skeletal muscle, can turnover at different rates, with for example the cytoplasmic proteins in cells having differential rates of turnover compared to mitochondrial proteins. There can also be variations in response to physiological stimuli depending on muscle fibre type, and in different muscles (Schiaffino et al., 2013). Denervation results in atrophy of type 2X and 2B fibres in the rat diaphragm, and slight hypertrophy in type 1 fibres (Aravamudan et al., 2006); conversely type 1 fibres in the rat soleus atrophy after denervation. Additionally, different subunits, or isoforms of a protein, can also have different rates of turnover, for example, in skeletal muscle myosin light chain (MLC) turns over 3 times as rapidly as myosin heavy chain (MHC) (Brosnan et al., 2011); moreover, the turnover rate of myosin isoforms can vary as a result of contractile activity, for example long duration swimming (6 hours) in rats results in MHC and actin turnover rates decreasing post exercise, whereas turnover rates of MLC increased. But 48 hours later, this pattern was reversed (Seene et al, 1986). Also, endurance and sprint trained rats have high turnover rates for actin than non-trained rats. After 12 hours of exercise, trained rats exhibit higher rates of turnover in in myosin light chains and actin compared to controls (Seene & Alev, 1991)

As stated above, protein is translated from mRNA. A systematic overview of protein translation will not be provided here, see Hinnebusch and Lorsch (2012), Sonenberg & Hinnebusch (2009) for comprehensive treatments of the topic, and Gordon et al. (2013) for a discussion of translation in relation to SkM; instead, the mechanisms of translation will be summarized first, then, they will be discussed in relation to resistance exercise. Briefly, the major stages of translation are initiation, elongation, termination and ribosome recycling.The ribosome, comprised of 2/3 RNA and 1/3 protein, is the primary cellular component that is responsible for protein synthesis, by scanning along mRNA and assembling amino acids into polypeptide chains. 2 amino acids can be added to a polypeptide chain per second by the ribosome (Alberts et al. 2008). Thus, small proteins consisting of 100-200 amino acids can be synthesised in approximately a minute. Conversely, the giant protein titin, which is responsible in skeletal muscle for the regulation of actin filaments and force transmission, contains 30,000 amino acid residues and requires 2-3 hours to be synthesised (Lodish et al., 2013). Translation of mRNA into proteins is based on the

genetic code, with the start codon of AUG being for methionine. Translation regulation appears to be mostly regulated at the initiation stage (Gordon et al., 2013), and initiation might be the rate limiting step in protein synthesis in skeletal muscle (Augert et al. 1986). The mTOR pathway appears to play a key role in translation initiation via its downstream targets, 4E-BP1 and p70S6K1 especially, therefore, the explanation of initiation provided here will be in relation to mTOR.

1.5 Rapamycin and mTOR

Rapamycin was first discovered in 1965 as a compound produced by the microorganism Streptomyces hygroscopicus from a soil sample from Rapa Nui (Easter Island) (Li et al. 2014; Vezina et al., 1975). Rapamycin has been shown to be a specific allosteric inhibitor of the mechanistic / mammalian of target of rapamycin (mTOR) (Li, Kim & Blenis, 2014), said to be the master regulator of organismal growth (Laplante & Sabatini, 2012), which is considered a key nexus in the regulation of protein translation, and thus, SkM hypertrophy in response to resistance exercise (Pasiakos, 2012), as the highest levels of expression of mTOR, and regulator associated protein of mTOR (raptor), in tissue is in SkM, brain, kidney and placenta (Kim et al.,2002). Global profiling studies (Hsieh et al., 2012; Thoreen et al., 2012) have demonstrated that mTOR complex 1 (mTORC1) stimulates proteins involved in translation, cell proliferation, invasion, metabolism, and thus protein synthesis. mTOR, a member of the PI3K kinase related superfamily (PI3KK) (Keith & Schreiber, 1995), is a large, molecular mass ~289 kDA, evolutionarily conserved serine/threonine protein kinase (Brown et al., 1994; Sabatini et al., 1994) that forms two distinct complexes, mTOR complex 1(mTORC1) and mTOR complex 2 (mTORC2) (Kim et al. 2002). mTORC1 consists of 6 components, whereas mTORC2 consists of 7. Both contain the mTOR catalytic subunit and mammalian lethal with sec-13 protein 8 (mLST8, also known as G protein beta subunit like / GBL), DEP domain containing mTOR interacting protein (DEPTOR) and Tti1/TEL2 complex. mTORC1 additionally contains regulatory associated protein of mTOR (raptor) and proline rich Akt substrate 40 kDa (PRAS40), whereas rapamycin insensitive companion of mTOR (rictor), protein observed with rictor 1 and rictor 2 (protor1/2) and mammalian stress-activated map kinase-interacting protein 1(mSin1) are also components of mTORC2. Raptor functions as a scaffolding protein for mTORC1 (Hara et al.

2002; Kim et al. 2002), whereas rictor does so for mTORC2 (Jacinto et al. 2004, Sarbassov et al. 2004), controlling complex assembly and substrate binding. PRAS40 inhibits mTORC1 signalling. For a comprehensive characterisation of the two mTOR complexes, see Zhou and Huang (2010) or Weber and Gutmann (2012).

Rapamycin inhibits muscle growth, whether during postnatal development, muscle regeneration (Pallafachina et al., 2002) or as a result of synergist ablation (Bodine et al. 2001) in rats. In humans, 12 mg of rapamycin completely blocks increases in mixed muscle fractional synthesis rates during the two hours after 11 sets of 10 repetitions of bilateral knee extensions at 70% of 1RM, concurrently delays mTOR, S6K1, rpS6 signalling, and completely blocks S6K1 and ERK1/2 phosphorylation (Drummond et al. 2009). For safety reasons, the dosage of rapamycin used in Drummond et al. (2009), 0.15mg/kgbw, was lower than that used in animal studies, 0.75mg/kgbw. The same group showed subsequently that 16mg of rapamycin, ~0.195mg/kgbw, abrogated increases in mixed muscle FSR, and concurrent increases in mTOR signalling, as a result of four sets of blood flow restriction knee extensions at 20% 1RM (Gundermann et al. 2014). In mice, muscle specific knock out of mTOR causes reduced size of fast but not slow fibres, reduced postnatal growth, and myopathies that result in premature death, specifically, there are reduced levels of the entire dystrophin glycoprotein complex (Risson et al., 2009). Similarly, ablation of raptor, but not rictor, results in muscle dystrophy and metabolic changes in mice (Betnzinger et al., 2008), along with inhibition of mechanical load induced hypertrophy (Bentzinger et al. 2013). Also, in mouse skeletal muscle, eccentric contractions resulted in increased phosphorylation of raptor at several sites (Ser696, Thr706, Ser863) that was not inhibited by rapamycin. Furthermore, mTOR activation as a result of eccentric contractions was blunted in a phosphor-defective mutant of raptor at those 3 sites, suggesting that raptor plays an important role in molecular signal transduction as a result of mechanical loading (Frey et al., 2014).

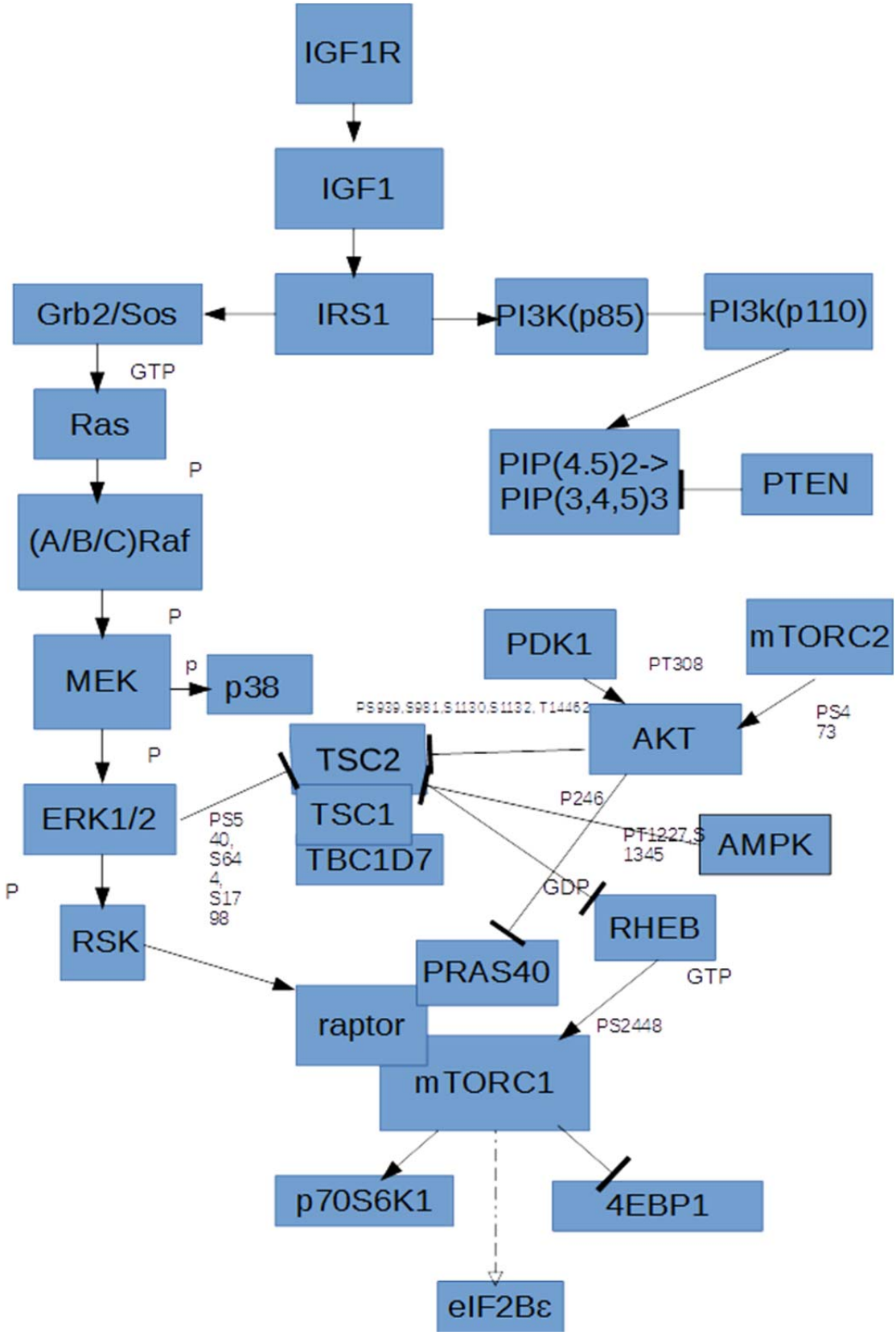
IGF1R
IGF1
IRS1
Grb2/Sos
PI3K(p85)
PI3k(p110)
GTP
Ras
P
(A/B/C)Raf
PIP(4.5)2->
PIP(3,4,5)3
PTEN
P
MEK
p
p38
PDK1
PT308
mTORC2
PS939,S981,S1130,S1132, T1462
AKT
PS4
73
P
TSC2
TSC1
TBC1D7
ERK1/2
PS5
40,
S64
4,
S17
98
P246
PT1227,S
1345
AMPK
P
RSK
GDP
RHEB
PRAS40
GTP
raptor
PS2448
mTORC1
p70S6K1
4EBP1
eIF2Bε

Figure 1: Summary of PI3K and MAPK signalling to p70S6K1 and 4EBP1, modified from LaPlante & Sabatini (2012) and Dibbe & Manning (2013)

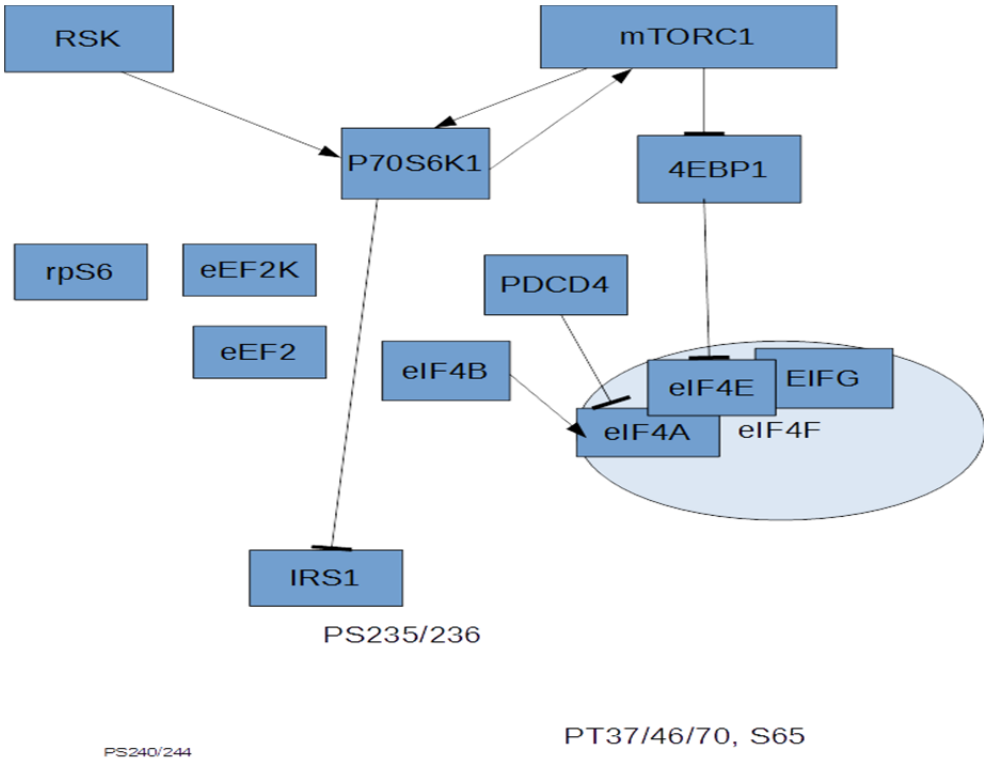

Figure 2: signalling downstream of p70S6K1 and 4EBP1, modified from LaPlante & Sabatini (2012) and Dibbe & Manning (2013)

mTOR integrates diverse inputs such as mechanical strain (You et al., 2012; Jacobs et al., 2014), amino acids (Bar-Peled & Sabatini, 2014), growth factors, nutritional and energy status (Kim et al., 2013; Jewell & Guan, 2013; Laplante & Sabatini, 2012), and appears to regulate numerous cellular processes such as transcription, translation, ribosome biogenesis, autophagy, apoptosis (Laplante & Sabtini, 2012). The signalling of mTOR via growth factors is in general better characterised than that of signalling via direct mechanical loading, not to mention that exercise can also affect secretion of growth factors, thus, an overview of growth factor signalling will first be provided here (Figures 1, 2). Growth factors such as insulin and insulin like growth factor can signal mTOR via two pathways, the so called canonical PI3K and Ras / Raf-ERK pathways. Tyrosine phosphorylation of IRS by IR / IGF1R results in the creation of binding sites for Src homology 2 (SH2) domain proteins, such as the p85 regulatory subunit of PI3K and Ras guanine

nucleotide exchange factor complex growth factor receptor bound protein 2 / son of sevenless (Gbr2/Sos) (Copps & White, 2012). The guanosine triphosphate hydrolase (GTPase) Ras is recruited to IRS1 by the recruitment and activation of growth factor receptor bound protein 2 / son of sevenless (Gbr2/Sos) or Src homology 2 domain containing (Shc) (Atzori et al, 2009). Sos is a guanosine nucleotide exchange factor (GEF) for Ras at the cytoplasmic side of the plasma membrane, activating Ras by causing the exchange of GDP bound to Ras with GTP. GTP bound Ras then functioning as a MAP kinase kinase kinase kinase (MAPKKKK) activates isoforms (A-, B-, C-Raf) of the serine / threonine kinase Raf which then functions as a MAP kinase kinase kinase (MAPKKK) to phosphorylate and activate MEK1 and MEK2, which in turn acts as a MAP kinase kinase (MAPKK) to phosphorylate and activate ERK1/2 in their activation loop, causing their translocation into the nucleus (Romeo, Zhang & Roux, 2012; Santarpia, Lippman & El-Naggar, 2012). Moreover, Ras can also interact directly with the p110 catalytic subunit of PI3K (Rodriguez-Viciana et al., 1994; Suire et al., 2002). Activated ERK can phosphorylate and inhibit TSC2 at Ser540, Ser644, Ser1798 (see below), and also phosphorylate 90kDA ribosomal S6 kinase (RSK1). Via RSK1, ERK1/2 can also activate eEF2, and thus modulate translation elongation (Wang et al. 2001; Wang & Proud, 2002). rpS6 can be phophorylated at Ser235/236 by ERK1/2 via RSK1, thus promoting the assembly of the cap binding complex and thus increased cap dependent translation (Roux et al. 2007). RSK can increase mTOR signalling by phosphorylating TSC2 at Ser1798 (Rolfe et al. 2005) (see below), inhibiting the inhibition of RHEB by Tsc2. Addtionally, RSK can also phosphorylate Raptor, which is part of the mTORC1 complex (Carriere et al. 2008). For a comprehensive discussion of RSK1 signalling and its effects on transcriptional and translation regulation, and also cell cycle progression and prolifereation, see Romeo, Zhang and Roux (2012). In rats, inhibiting MEK did not affect protein synthesis at rest, but lowered rates of synthesis in resistance exercised rats, an effect that was not rescued by insulin (Fluckey et al. 2006). Similarly, MAPK signalling was activated 1 day after synergist ablation, prior to mechanically induced enhanced protein synthesis in rat muscle hypertrophy (Miyazaki et al. 2011). MAPKK phosphorylates p38 on Thr and Tyr residues on the activation loop (Alonso et al. 2000; Brancho et al. 2003). In mice, p38gamma appears to inhibit the premature differentiation of satellite cells (Cuadrado et al. 2010), by promoting the association of MyoD and the histone methyltransferage KMT1A which together repress premature expression of myogenin (Gillespie et al. 2009). Conversely, p38alpha promotes SkM differentiation (Lluis et

al. 2006). In HeLA cells (Casas-Terradellas et al. 2008) and drosophila (Cully et al. 2010), p38 might regulate growth via mTORC1. Mechanical stress appears to activate p38, via focal adhesion kinase, resulting in hypertrophy in cardiac myocytes (Aikawa et al. 2002; Lal et al. 2007). p38 might also affect protein synthesis via eEF2 (Knebel et al. 2002).

Phosphatidylinositol 3 kinase (PI3K) consists of a p85 regulatory and a p110 catalytic subunit. The insulin like growth factor 1 receptor (IGF1R) transphosphorylates on tyrosine residues, and is activated in response to ligand binding of growth factors such as IGF1, which cause conformational changes and then tyrosine autophosphorylation on the beta-subunit of the receptor (Menting et al. 2013), creating a docking site for the scaffolding adaptor insulin receptor substrate 1 (IRS1) (Böhni et al., 1999). IRS1 binds to IGF1R, is phosphorylated on tyrosine residues, recruiting the p85 regulatory subunit of PI3K to bind to IRS1 (Backer et al. 1997; Valverde, Lorenzo, Pons, White, & Benito, 1998), resulting in p110 no longer being inhibited by p85 (Valentinis & Baserga, 2001). PI3K, which is thus activated, then phosphorylates and catalyses the conversion of phosphatidylinositol (4,5)-biphosphate (PIP2) to phosphatidylinositol (3,4,5)-triphosphate (PIP3) (Engelman et al., 2006; Glass, 2010; White, 2002), a process that can be antagonised by PTEN (Stambolic et al., 1998). PIP3 recruits AKT and PDK1, to the plasma membrane, where PIP3 binds to the pleckstrin homology (PH) domain of AKT, inducing a conformational change, allowing phosphorylation at Thr308 and thus activation by PDK1 (Alessi et al., 1997; Alessi & Downes, 1998; Stokoe et al., 1997) in the activation loop of the catalytic domain (Stephens et al., 1998), and by phosphorylation at Ser473 in the hydrophobic motif by mTORC2 (Sarbassov et al., 2005). Full activation of AKT might require phosphorylation at both Thr308 and Ser473 (Manning & Cantley, 2007). However, the role of Ser473 phosphorylation in the regulation of AKT signalling is not fully understood, and Ser473 phosphorylation could be cell or tissue specific (Moore et al., 2011; Riaz et al., 2012). Akt signalling is deactivated by dephosphorylation at Ser473 by PH domain specific leucine rich repeat phosphatase (PHLPP) (Brognard et al., 2007) and at Thr308 by protein phosphatase 2 (Andjelkovic et al., 1996). mTORC2 is far less well characterised than mTORC1, therefore the mechanism of activation of Akt Ser473 by mTORC2 is unclear. In addition, insulin can also activate the Akt1 isoform at Thr308 and Ser473 via PI3K, independent of PDK1, whereas Ak2 activation appears to require PDK1 in conjunction with PI3K (Tsuchiya et al., 2013).

Akt itself, separate from its signalling to mTOR, appears to regulate different cellular processes, most notably glucose metabolism, proliferation, growth, angiogenesis (Jiang & Liu, 2008) and proteolysis (Manning & Cantley, 2007). There are known to be 3 different isoforms of Akt: Akt1, widely distributed in tissue, regulates cell growth and survival, whereas Akt2, which appears to mediate insulin signalling and thus glucose homeostasis is highly expressed in muscle and adipocytes. Akt3 is present mostly in the brain, and is involved in the development and organisation of the nervous system (Easton et al., 2005, Tschopp et al. 2005). Skeletal muscle expresses all 3 Akt isoforms, but only deletion of Akt2 results in insulin resistance and thus reduced insulin-stimulated glucose uptake (Garafalo et al., 2003), whereas Akt1 appears to be responsible for SkM hypertrophy (Lai et al. 2004). Constitutively active Akt expression in SkM leads rapidly to hypertrophy (Bodine et al. 200; Pallafacchina et al. 2002). See Schultze, Jensen, Hemmings, Tschopp & Niessen (2011) for a detailed review of the roles of Akt isoforms in metabolism. Subsequent to phosphorylation and activation at the plasma membrane, AKT translocates to the cytosol and nucleus, where it phosphorylates, amongst other downstream targets, AS160 / TBC1D4, GSK3b, Tuberous sclerosis complex 2 (TSC2, also known as tuberin), Forkhead Box O (FOXO) (Manning & Cantley, 2007). The roles of Akt in glucose transport, via TBC1D4, and then GLUT4, and glucose synthesis via GSK3b, is beyond the scope of this work, and thus, will not be covered here. For comprehensive reviews of the role of Akt in health and disease, see Manning & Cantley (2007), Hers, Vincent & Tavare (2011). With regards to protein synthesis, AKT phosphorylates, and inhibits, negative regulators of mTORC1, TSC2 at Ser939, Ser981, Ser1130, Ser1132, Thr1462, and PRAS40 at Ser246 (Ma & Blennis, 2009). Akt phosphorylation of PRAS40 disrupts its inhibitory interaction with raptor and mTORC1, whether as an inhibitor or as a competitive substrate, by causing its binding to 14-3-3 proteins (Sancak et al 2007). Akt phosphorylation of TSC2 inhibits the TSC1(hamartin)-TSC2-TBC1D7 ((TRE2/BUB2/CDC16 1 domain family member 7)) complex that functions as the GTPase activating protein (GAP) for the GTPase Ras homolog enriched in brain (Rheb). The inhibition of TSC2's GAP function inhibits its inhibition Rheb, 1 of the 2 known direct activators of mTORC1 (Jacobs, et al., 2014). When loaded with GTP by an as yet unknown guanine nucleotide exchange factor (GEF), Rheb binds to the catalytic domain of mTORC1 (Inoki et al., 2002) activating mTORC1 (Long et al., 2005; Shimobayashi & Hall, 2014); whereas it is unable to do so when

GDP loaded by TSC2. In cells, GDP dissociation and GTP binding is mediated by GEFs (Bos et al. 2007). The precise mechanism by which Rheb signals to mTORC1 has yet to be elucidated (Shimobayashi & Hall, 2014) and until recently, the exact mechanism by which Akt inhibits TSC1-TSC2 function was unknown (Magnuson et al., 2012). Menon et al. (2014) discovered that Akt phosphorylation of TSC2 in response to insulin causes TSC2 dissociation from the lysosome, such that it can no longer inactivate Rheb. Upon activation, mTOR appears to autophosphorylate at Ser2481 (Soliman et al. 2010), and there appears to be feedback loop phosphorylation at Ser2448 by S6K1 (Chiang & Abraham, 2005; Holz & Blenis, 2005), a downstream target of mTORC1. As already briefly mentioned above, Ras-Raf-ERK1/2 also appears to signal mTORC1 via TSC2. ERK1/2 and RSK1 can phosphorylate and inhibit TSC2 at Ser540, Ser644, Ser1798. Also, ERK phosphorylates Raptor Ser8/Ser696/Ser863 (Carriere et al. 2011), whereas RSK phosphorylates Raptor Ser719/Ser721/Ser722 (Carriere et al. 2008). Therefore, Ras-Raf-ERK and PI3K-Akt appear to signal to signal to mTOR in parallel, by converging on TSC2 and raptor. It should be noted here that phosphorylation of TSC2 at Thr1227 and Ser1345 by 5'-AMP-activatd protein kinase (AMPK) activates TSC1-TSC2, thus inhibiting mTORC1. As can be seen here, the TSC complex itself serves as a "hub" for numerous inputs. AMPK might also phosphorylate raptor directly at Ser722/792 in response to energy stress (Gwinn et al. 2008). Because AMPK is activated by energy stress, that is an increase in the cellular AMP/ATP ratio, mTORC1 is thus sensitive to energy stress.

Even though exercise, including resistance training, and also electrically stimulated muscle contraction (Derave et al. 2000), can lead to large increases in AMP concentration dependent on intensity and duration (Sriwijitkamol et al., 2007), and thus activate AMPK (Apro et al. 2015), characterisation of AMPK signalling is beyond the scope of this work. See the reviews by Friedrichsen et al. (2013), Hardie (2011), Richter and Ruderman (2009) for further details of the role of AMPK in exercise.

It has been demonstrated that mechanical loading, such as from RE, activates mTOR signalling, and increased protein synthesis and SkM hypertrophy from mechanical loading requires mTOR signalling (Bodine et al., 2001; Drummond et al. 2009; Gundermann et al. 2014; Hornberger et al. 2004; Kubica et al. 2005). Downstream of mTORC1, the 2 main targets of mTORC1 involved

in mRNA translation initiation and progression, and thus protein synthesis are p70S6K1 and 4EBP1 (Ma & Blennis, 2009).

1.6 Regulation of translation

In eukaryotes the 40S ribosomal subunit is loaded with methionyl tRNA (transfer RNA) specialised for initiation (Met-tRNAi) in a pre initiation complex (PIC), which then binds and scans the 5 untranslated region (5'UTR) for an AUG start codon. Therefore, translation initiation is regulated by the ability of ribosomes to interact with and scan the 5'UTR (Sonenberg & Hinnebusch, 2009). Eukaryotic initiation factors (eIFs) recognise the cap structure of the mRNA's 5' end and thus activate it for PIC binding. Furthermore, eIFs also recruit Met-tRNAi to the 40s ribosomal subunit. This means that translation initiation is regulated by the activity of eIFs.

There are two main steps in translation initiation. Firstly, a ternary complex (TC) consisting of eIF2, GTP and Met-tRNAi is formed. The formation of the TC appears to be most dependent on the catalytic ε (eIF2Bε) subunit of eIF2B, which is the only eIF2B subunit that is sufficient for guanine nucleotide exchange factor (GEF) function, to exchange the GDP that is initially bound to eIF2, without which TC assembly is decreased (Gordon et al., 2013; Sonenberg & Hinnebusch, 2009). Also, when eIF2α Ser51 is phosphorylated, eIF2-GDP becomes a competitive inhibitor of the GEF eIF2B resulting in accumulation of eIF2-GDP and decreased TC assembly. Mayhew et al., (2011) demonstrated that after 16 weeks of resistance training in humans, eIF2Bε abundance , and p70S6K Ser421/424 phosphorylation, was associated with myofibre hypertrophy, whereas neither the phosphorylation, nor the total abundance of eIF4E nor eIF4G was. Furthermore, overexpression of eIF2Bε increased global protein synthesis (Kubica et al. 2008), invitro cap dependent translation in myoblasts and myofibre size (Mayhew et al., 2011) in mice. Moreover, phosphorylation of eIF2Bε at various residues (Ser540 by GSK-3, Ser525) can inhibit eIF2B GEF activity independent of eIF2α (Gordon, Kelleher & Kimball, 2013; Wang & Proud, 2008; Welsh et al. 1998) and activation of mTORC1 is both necessary and sufficient to increase eIF2Bε mRNA levels (Kubica et al. 2008). In young men, knee extensions (Burd, Holwerda et al., 2010; Coffey et al., 2006; Glover et al.,2008) or leg press (Deldicque et al.,2010) at various intensities,

and also in fed and fasted states, reduced eIF2Bε Ser540 phosphorylation. However, Moore et al. (2009), Burd et al. (2012) found no changes.

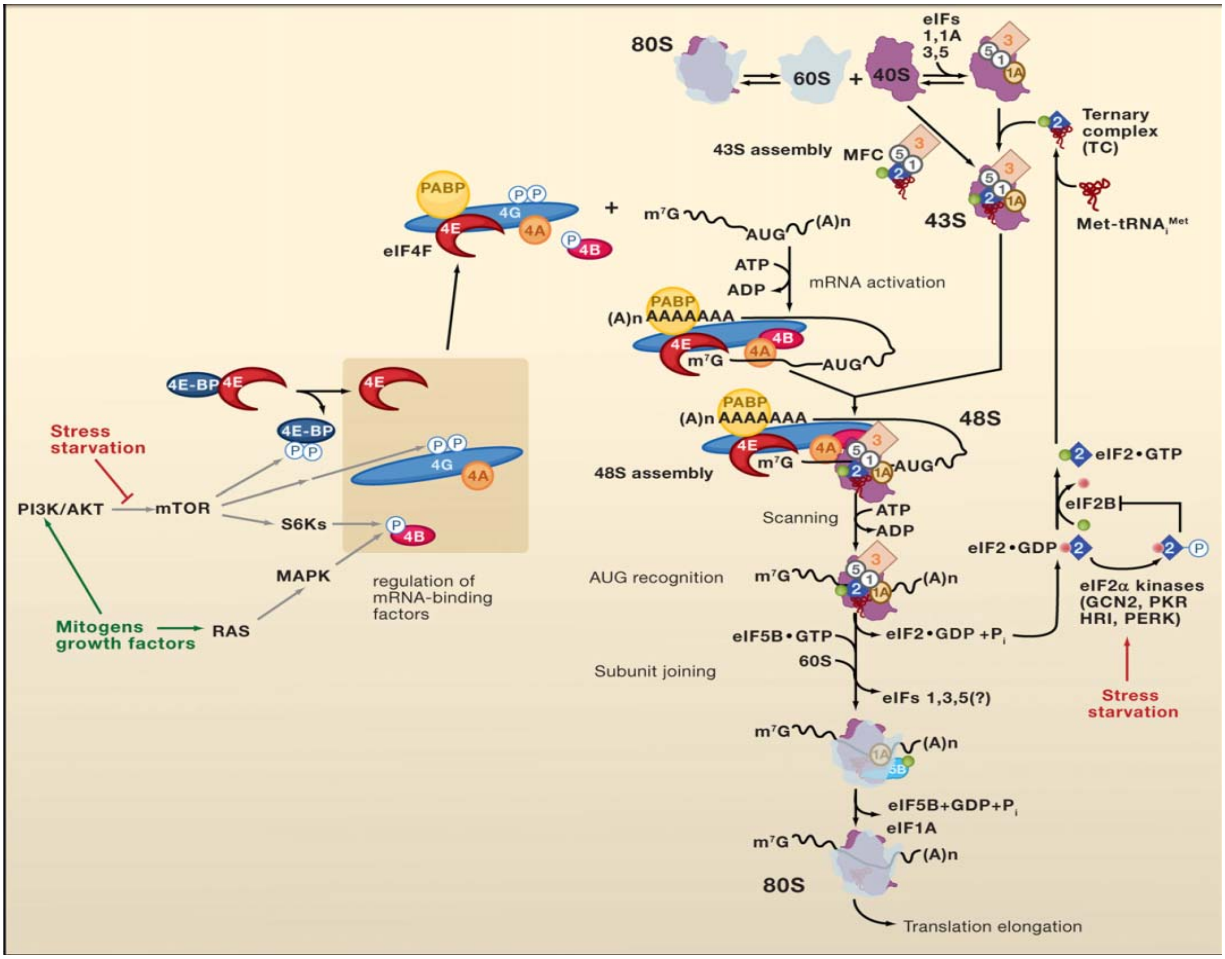

Figure 3: Overview of protein translation, from Hinnebush & Lorsch (2012)

Subsequent to TC formation, the TC and eIFs1, 1a, 3, 5 bind to the 40s ribosomal subunit to form the 43s PIC. The TC and eIFs 1, 3, 5 are linked in a multifactor complex (Sokabe et al. 2012). The 43s PIC binds near the 5'-7-methylguanosine cap of activated mRNA. This process of cap dependent translation is mediated by the eIF4F complex. eIF4E binding proteins (4EBP) compete exclusively with the modular scaffold eIF4G for a shared binding site on eIF4E, inhibiting eIF4E, and thus preventing the eIF4E and eIF4G forming the eIF4F complex (Vary & Lynch, 2006). Therefore, cap-dependent translation is inhibited by 4EBPs. When mTORC1 is activated by for example by mechanical loading, or protein feeding, it phosphorylates 4EBP1 on several sites, Thr37, Thr46, Thr70, Ser65, causing 4EBP1 to dissociate from eIF4E. eIF4G then binds to

eIF4E, and recruits the helicase eIF4A which is necessary for the unwinding of inhibitory structure in the 5' UTR of mRNA, to form the eIF4F (eIF4E-eIF4G-eIF4A) complex on the 5' cap. This eIF4F complex then recruits the 43s PIC (consisting of the TC and the 40S ribosomal subunit), and the 48s PIC is formed. Therefore, translation initiation can be regulated by regulation of TC formation, via eIF2B, and also cap binding, via eIF4E (Magnusson et al. 2012).

Once the PIC binds to the capped 5' end of mRNA, it scans downstream. When there is a perfect match with an AUG start codon, scanning is stopped, and the GTP in the eIF2-GTP-MetRNAi TC is partially hydrolysed to eIF2-GDP-Pi. eIF1 dissociates from the 40s platform and eIF2-GDP is released. The 60s ribosomal subunit then joins, catalyzed by eIF5b-GTP, and the subsequent hydrolysis and release of eIF5B-GDP and eIF1A, resulting in the final 80s initiation complex containing Met-TRNAi base paired to AUG in the P site (Sonenberg & Hinnebusch 2009).

Translation elongation, mediated by eukaryotic elongation factors (eEF), then commences. Elongation involves the binding of activated tRNA, the formation of peptide bonds and the release of inactive tRNA. Once translation has been initiated, elongation in general consists of a cycle of several steps: firstly, transfer RNAs (tRNA), which are small (80 nucleotides in length) adaptor RNAs, bond with a particular amino acid as aminoacyl-tRNA. Then, the aminoacyl-tRNA binds to the A-site of the ribosome, and the anticodon in tRNA base pairs with a codon in mRNA, resulting in activation and addition of the amino acid to the growing polypeptide chain, which is catalysed by peptidyl transferase. For example, the methionine AUG start codon on mRNA will be recognised by the first tRNA with methionine with the anti-codon UAC. tRNAs function as adaptors to ensure that that each amino acid is added in the correct sequence to the growing polypeptide chain during elongation. The large (60S) and small ribosomal (40S) subunit then translocate relative to the mRNA. The translocation of subunits results in the ribosome moving three nucleotides along mRNA, thus repositioning to start the next cycle. This cycle is repeated for each amino acid added to the polypeptide chain (Alberts et al. 2008; Brosnan et al., 2011; Roche et al. 2011). The ribosome proceeds along the mRNA until a stop codon, UAA, UAG or UGA is reached, at which point eukaryotic release factors terminate the process.

Regulation of translation by mTOR phosphorylation of 4EBP1 is well characterized, but the modulation of translation via mTOR-S6K is less well understood. S6K can be activated via several sites, most notably the hydrophobic motif site (Thr389) and the TM site (Ser371) in the linker domain, and also the T-loop site on the activation loop (Thr229), and proline directed sites in the C-terminal autoinhibitory pseudosubstrate domain (Ser421, Ser424). For S6K1 to be activated, phosphorylation at the hydrophobic motif, T-loop, TM, sites appears to be absolutely required, whereas phosphorylation of the C-terminal sites contributes to S6K1 activation but does not appear to be essential (Alessi et al. 1998; Weng et al. 1998). Maximal activation of S6K1 appears to especially require phosphorylation of Thr389 (Weng et al. 1998), by mTORC1, and Thr229, by PDK1 (Alessi et al. 1998). Apparently, whereas Akt activation by PDK1 at the membrane requires PtdIns(3,4,5)P3, S6K1 phosphorylation by PDK1 in the cytosol is PtdIns(3,4,5)P3 independent. Phosphorylation at the Ser371 TM site appears necessary, but the reason is still not understood. mTORC1 phosphorylation of Thr389 occurs before PDK1 phosphorylation of Thr229 (Alessi et al. 1998). Alternatively, phosphorylation of Thr229 could occur prior to that of Thr389 (Weng et al. 1998). Besides its role in the formation of the 43s PIC eIF3 also appears to be a scaffold that connects mTORC1 and p70S6K1. eIF3 is initially bound to inactive p70S6K; in response to physiological stimuli, such as nutrients and growth factors, mTORC1 binds to eIF3-p70S6K1 resulting in the phosphorylation, activation, and release of p70S6K1 from eIF3, and its consequent phosphorylation of several downstream targets (Holz et al. 2005). Overexpression of eIF3 induces an increase in phosphorylation of mTORC1 downstream substrates such as p70S6K, rpS6, 4EBP1, and a corresponding increase in protein synthesis (Csibi et al. 2009), and more pertinently, SkM hypertrophy both invitro and invivo (in mice) (Lagirand-Cantalouobe et al. 2008). It should be noted that in young women, eIF3a levels in VL do not appear to change as a result of acute resistance loading (Moberg et al. 2014).

Upon dissociation from eIF3, activated S6K1 phosphorylates substrates, such as rpS6, eIF4B, eEF2K, SKAR, that can drive protein synthesis whether via translation initiation or other mechanisms. Most notably, S6K1 phosphorylates (at Ser235, Ser236, Ser240, Ser244) and activates rpS6, a component of the 40S subunit, thus possibly modulating cap binding and hence cap dependent translation initiation; rpS6 can also be phosphorylated by RSK at Ser235, Ser236. Nonetheless, the functional significance of rpS6 remains to be elucidated (Meyuhas & Dreazen,

2009). In response to growth factors and amino acids, rapamycin sensitive S6K1 activation and rpS6 phosphorylation was correlated with increased translational efficiency of 5' terminal oligopyrimidine (TOP) mRNAs (Jefferies et al., 1994). 5'TOP mRNAs encode ribosomal proteins and elongation factors (Shimobayashi & Hall, 2014). Most mTOR translated mRNAs contain a 5' TOP (Hsieh et al. 2012; Thoreen et al. 2012), and mTORC1 inhibition of 4E-BP1 increased translation of eEF2 mRNA (Thoreen et al. 2012). Conversely, knock out of rpS6 phosphorylation in mice did not inhibit TOP translation, and there was unexpectedly 2.5 fold higher protein synthesis (Ruvinsky et al. 2005). Recently, it was shown that 78% of ribosome biogenesis mRNAs in S6K1 knock out mice are downregulated (Chauvin et al. 2014), suggesting a role for S6K1 in ribosome biogenesis. Additionally, the phosphorylation of eIF4B Ser422, whether by S6K1 or RSK, recruits eIF4B to eIF4A and eIF3, enhancing eIF4A's activity in unwinding the inhibitory structure in the 5' UTR (Holz et al., 2005; Raught et al. 2004; Shahbazian et al. 2006). Also, programmed cell death 4 (PDCD4), an inhibitor of eIF4A, is phosphorylated (at Ser67) and inhibited by S6K1, thus further enhancing eIF4A activity (Dorrello et al. 2006). S6K1 can also modulate translation elongation (see below) by phosphorylating (at Ser366) and inhibiting eukaryotic elongation factor 2 kinase (eEF2K), an inhibitor of eEF2. eEF2 catalyses codon shifting during elongation (Wang et al. 2001). S6K1 might also modulate the translational efficiency of newly spliced mRNAs via phosphorylation of SKAR Ser383.385 (Richardson et al., 2004) and folding of translated proteins via phosphorylation of chaperonin containing TCP-1 Ser260 (CCTB)(Abe et al. 2009).

With regards to the role of S6K1 in SkM, especially SkM hypertrophy modulated by RE, Baar and Esser (1999) famously found that in rats trained twice a week, increases in hypertrophy of 13.9% in the extensor digitorum longus and 14.4% in the soleus at 6 weeks correlated (r=0.998) with phosphorylation of p70S6k 6h after acute exercise. However, several recent human studies have been more equivocal with some (Terzis et al. 2008) supporting this association, but others either less so (Mitchell et al. 2013), or not at all (Fernandez-Gonzalo et al. 2013; Li et al. 2013; Mitchell et al. 2012, 2014). Furthermore, the S6Ks phosphorylate eIF4B Ser422, enhancing the interaction with eIF3 and eEF2K.

Resistance training can modulate translation initiation, and thus protein translation, via signal transduction pathways upstream of eIF4E, eIF4G, eIF4A, eIF2b, p70S6, specifically the mTOR pathway. It must be emphasised here that extensive research on signal transduction pathways involved in growth and metabolism over the last decade has revealed a complexity of integrated cellular networks dictating that no single pathway operates in isolation. In certain settings, Akt can inhibit the Erk pathway by directly phosphorylating c-Raf on Thr259 (Zimmermann & Moelling, 1999), and also can inhibit the other MAPKs, JNK and p38 (Manning & Cantley, 2007). More pertinently, even though the characterisation of mTORC1 signalling provided here so far is that of the canonical growth factor signalling pathway, mechanical loading might signal mTORC1 independently of PI3K. Hornberger et al. (2004) discovered that ex vivo stretching of rat extensor digitorum longus resulted in the activation of S6K1, even in the presence of the PI3K inhibitor wortmannin, and that this activation of S6K1 was rapamycin sensitive. In the absence of IGF signalling, that is in mouse SkM where the IGF receptor was inactivated (MKR) and thus could not be activated by insulin and IGF1, developmental (ie, progression into adulthood) muscle growth was 30% less (Spangenburg et al. 2008). However, muscle mass in the mice with inactive IGFR increased by 90% in response to mechanical overload, compared to 50% for wild type mice. Mechanistically, phosphorylation of Akt and S6K1 was similar in both groups of mice. The same group subsequently found however that there was delayed activation of S6K1 in the MKR mice (Witkowski et al. 2010). Miyazaki et al. (2011) elegantly demonstrated in a synergist ablation rat model that S6K1 activation precedes Akt activation; furthermore, inhibition of PI3K by wortmannin did not inhibit the mechanical overload induced activation of mTORC. Purified Rheb can directly activate mTORC invitro (Sato et al. 2009). Overexpression of Rheb activates mTORC1 in SkM independent of PI3K, increases cap dependent translation; is sufficient to increase protein synthesis, cross-sectional SkM fibre area, and thus hypertrophy (Goodman et al. 2011) in a rapamycin sensitive manner (Goodman et al. 2010). Moreover, there was no difference in synergist ablation induced hypertrophy of the plantaris, soleus, or EDL between muscle specific PTEN (which inhibits PIP3 and thus Akt) knockout and wild type mice, and also, RE did not alter the activity of the IGF1R nor recruit the regulatory p85 subunit of PI3K to IRS1/2, even though Akt and S6K1 Thr389 activity was elevated (Hamilton et al. 2010). It should be noted that PTEN KO in muscle did lead to increase in mass of cardiac muscle and tibialis anterior during development (Hamilton et al. 2010). Additionally, mechanical overload

induced hypertrophy following synergist ablation occurred in the absence of growth factor signalling, the complete loss of IRS-1/2 protein (Hamilton et al. 2014). Therefore, mTOR signalling as a result of mechanical loading, such as exercise, might occur via PI3K and ERK1/2 independent mechanisms (Hamilton et al. 2014) such as the second messenger phospatidic acid (You et al., 2012). Mechanical stimulation of SkM, via intermittent passive stretch (Hornberger et al., 2006) or eccentric contractions (O'Neil, Duffy, Frey & Hornberger, 2009), can increase the concentration of phospatidic acid (PA), a glycerophospholipid. PA can bind directly to the FKBP12 (12 kDA FK506 binding protein) binding domain of mTORC1 (You et al., 2012) and directly induce mTORC1 signalling (You et al., 2012). Conversely, phospatidic acid might also be able to signal mTOR via ERK1/2 (Miyazaki et al. 2011). Also, injection of PLD1 (phospholipase D1), which transforms phosphatidylcholine into PA, significantly increased myofibre CSA in mice (Jafar et al., 2013). Besides PLD regulated synthesis from phosphatidylcholine, PA is also synthesized by lysophosphatidic acid acyltransferases from lysophosphatidic acid (LPA) and from diacylglycerol by diacylglycerol kinases. Soy PA stimulated mTOR signalling to a greater extent than egg PA (Joy et al. 2014), and resistance trained men consuming 750mg daily of PA in combination with 8 weeks of RT had greater increased in lean body mass, VL CSA, and leg press strength compared to placebo participants (Joy et al. 2014).

1.7 Research Questions and Hypothesis

The primary aim of this work is to explore possible divergent response in molecular signalling proteins involved in protein translation to "hypertrophic loading"(HYP) versus "power loading" (POW). HYP imposes high metabolic stress whereas POW imposes high mechanical stress. A secondary aim is to explore possible relationships between post-exercise recovery from HYP and POW and changes in signalling proteins involved in protein translation.

1. Are there differential responses in phosphorylation of the canonical signalling proteins in protein translation, p70S6K1, 4EBP1, and the MAPKs, in response to hypertrophic (HYP) type vs power (POW) type loading?

i) Hypothesis: HYP and POW would result in differential responses in phosphorylation of signalling proteins as different types of resistance loading, that is hypertrophy vs maximal, results in differing molecular signalling responses (Hulmi et al. 2012).

2. Are changes in molecular signalling related to recovery from exercise loading, as represented by performance in measures of force, power, muscle swelling?
   ii) Hypothesis: There are relationships between recovery from exercise loading, as represented by performance in measures of force, power, muscle swelling, and changes in signalling proteins involved in protein translation, as these proteins are crucial for protein translation (Laplante & Sabatini, 2012).

3. Are there differences in the relationships between recovery from exercise and signalling proteins after HYP versus POW?
   iii) Hypothesis: Relationships between recovery from exercise and signalling proteins in HYP and POW diverge, as differing exercise loading regimes result in differing molecular signalling responses (Hulmi et al., 2012).

4. Is there a relationship between mechanical work performed and changes in phosphorylation of signalling proteins?
   iv) There is no relationship between mechanical work performed and changes in phosphorylation of signalling proteins (Galpin et al. 2012).

2 METHODS

2.1 Ethical Approval

All procedures were approved by the ethics committee of the University of Jyväskylä, in conformance with the Declaration of Helsinki and conducted after informed consent was obtained from participants.

2.2 Participants and study design

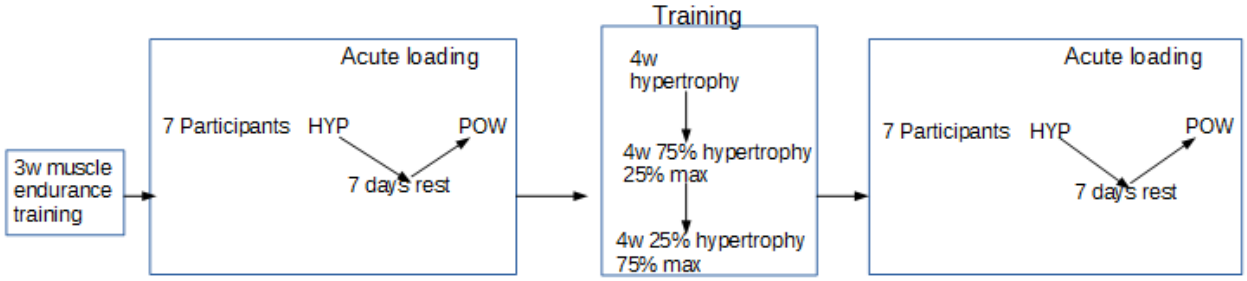

Figure 5: schematic of the study design, w(weeks), HYP (hypertrophic: 5x10 at 80% of 1RM), POW power: 10x5 at 70% of 1RM)

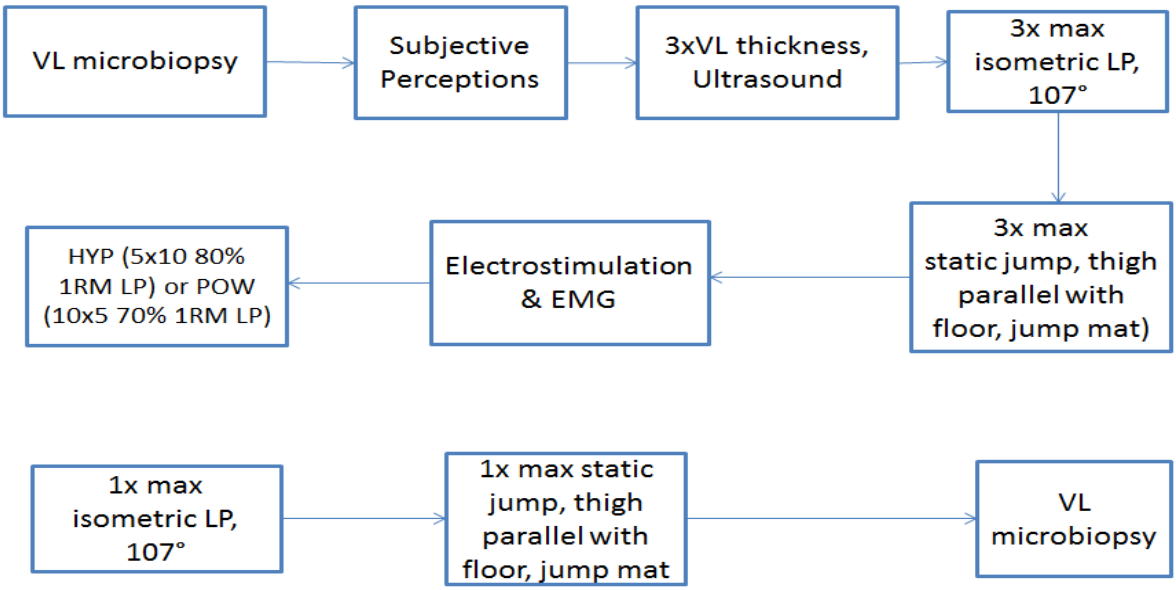

Figure 6: schematic of the acute loading sessions, VL: vastus lateralis, LP: leg press

Participants were recreationally active young men under the age of 40 (31±6 years, 178.9±4cms 84.6±5 kgs) without any sustained experience in resistance training prior to enrollment, who were part of a larger 16 week training study and who volunteered for this subgroup study (Table 4 for participant characteristics). All 7 participants performed 1 hypertrophic loading session (HYP): 5 sets of 10 repetitions at 80% of 1 repetition maximum (5x10 80%1RM) of leg presses, and 1 power loading session (POW): 10x5 70% 1RM of leg presses, with an interval of 1 week between sessions (figures 5, 6). These acute loading sessions were performed prior and subsequent to a 12 week long training period. The details and findings of the larger study will not be reported here,

but a concise description of the 16 week training will be provided; briefly, participants performed 3 weeks of "muscle endurance" training to familiarize them with resistance exercise prior to the "pre-training" acute loading sessions. This was followed by the "pre-training" acute loading sessions. They then performed 4weeks of hypertrophic training, followed by another 4 weeks of wherein total loading was 75% hypertrophic and 25% maximal. During the first two weeks of these blocks, there were 2 training sessions per week, whereas there were 3 sessions per week during the other 2 weeks of each block. Finally, participants executed another 4 weeks of 75% maximal 25% hypertrophic loading twice per week. Subsequently, they performed "post-training" acute loading sessions. Leg exercises, that is leg presses, knee extensions, knee curls were trained every training session, whereas other muscle groups were trained on alternate sessions.

Table 5: Participant anthropometric characteristics

	Age (years)	Height (cm)	bodymass pre-training (kgs)	bodymass post-training (kgs)	bodyfat% pre-training	bodyfat% post-training
Participant 1	32	181.4	77.2	80.1	12.8	13.9
Participant 2	33	186.5	86.5	87.1	22.8	20.6
Participant 3	23	178.6	88.2	86.9	27.1	20.8
Participant 4	22	178.5	88.6	84.6	32.3	27.4
Participant 5	38	176	84.9	83.9	31.3	27.1
Participant 6	35	174.5	77.7	81.2	23.7	24.2
Participant 7	35	177	89.1	89	35.7	36.4

2.3 Acute loading sessions

2.3.1 Muscle Biopsy

Muscle samples were collected before and immediately after exercise loading from the medial VL with a microbiopsy needle midway between the patella and the greater trochanter at the same depth via the markings on the needle. The surrounding area was first cleaned with antiseptics, and local anaethetics (the superficial injection of 2 mL lidocaine–adrenaline, 1 %) were then delivered subcutaneously prior to incision of the skin. The immediate post-exercise time=point was chosen so as to attempt to assess any possible responses to mechanical stress separate from

metabolic stress. The muscle sample was cleaned of any visible connective and adipose tissue as well as blood and frozen immediately in liquid nitrogen (−180 °C) and stored at −80 °C.

2.3.2 Subjective Perceptions

Participants then assessed their subjective perceptions of muscle soreness in their vastus lateralis on a visual analog scale of 0 (no soreness) to 100 (maximum soreness). Feelings of "power", or readiness to perform exercise were also assessed on a visual analog scale, of 100(maximum readiness) to 0.

Subsequently, muscle thickness on the leg contralateral to the biopsied leg was measured by ultrasonography. See the appendix for a sample of the questionnaires used for one participant.

2.3.3 Ultrasonography

VL muscle thickness was measured using B-mode ultrasound (model SSD-α10, Aloka Co Ltd, Tokyo, Japan). Ultrasonography has been validated against magnetic resonance imaging for the measurement of SkM hypertrophy (Miyatani et al. 2004), and has been widely used in different populations, ranging from young men to elderly women, using a variety of resistance loading protocols, such as low load or high load training, for the measurement of muscle adaptations to resistance exercise, whether muscle thickness or cross-sectional area in the vastus lateralis (Abe et al. 2000; Ahtiainen et al. 2009; Fahs et al. 2015; Li et al. 2013; Schoenfeld et al. 2015; Sipilä & Suominen 1996)

A point on the lateral surface, along the mid-sagittal axis of the left thigh, 50% between greater trochanter and the lateral epicondyle of the femur was measured with a tape measure and marked with a marker pen. This mark was "renewed" each day of measurement. The head of the 5MHZ convex scanning probe was coated with water-soluble gel (Aquasonic 100 Ultrasound) providing contact and placed on the marked site, with care taken to avoid depression of the skin. The subcutaneous adipose tissue-muscle interface (the superficial aponeurosis) and muscle bone interface (the deep aponeurosis) was identified in the image, and the perpendicular distance

between the two was defined as muscle thickness and measured on screen by marking of landmarks on the interfaces. 3 measurements were conducted each time for each individual and averaged. All measurements were made with the participant seated, with the VL relaxed, and the knee and hip angles at 90°.

2.3.4 Isometric Leg Press

Participants subsequently performed 2-3 "warm-up" repetitions on the bilateral isometric leg press device at what they were instructed to be 50% of self-perceived maximal effort. Then, participants performed 3 maximal isometric bilateral leg presses on a custom-built electromechanical dynamometer (Department of Biology of Physical Activity, University of Jyväskylä, Finland), with knee angle at 107° as measured by a goniometer, with 1 minute rest periods between each attempt. Participants were requested to push as hard as possible. The highest force value of the 3 attempts of each participant was defined as that participant's maximal peak force and used for the statistical analysis.

2.3.5 Static jumps

Immediately after, participants performed 3 maximal static jumps on jump mat (Department of Biology of Physical Activity, University of Jyväskylä, Finland), with the best attempt again being used for statistical analysis. Participants were instructed to begin from a standing position and perform a squat, until their gluteus maximus contacted a string, which height was used to mark the point at which the participant's hip joint was approximately parallel with their knee joint. After holding the position statically briefly, they maximally jumped using their typical jumping mechanics, with their hands on their hips at all times to eliminate any influence of arm swing. Verbal instructions were provided during all attempts, with participants only jumping on the researcher's cue. Following that, participants did maximal isometric knee extensions combined with electrostimulation, the details and results of which will not be reported here. Verbal encouragement was provided during all measurements.

2.3.6 Exercise loading

Finally, exercise loading, whether HYP or POW, commenced, with verbal encouragement provided to participants throughout. The acute loading sessions consisted of leg pressing on a David 210 machine (David Fitness and Medical, Finland). Range of movement was controlled, such that the concentric phase of each repetition began with the knee flexed at 60° and finished with the knee fully extended. Foot position was maintained to be identical between all repetitions. Knee joint angle was assessed with an electric goniometer. All sets were performed with the maximum target load. For HYP, loads on subsequent sets were either increased or decreased depending on the participant's fatigue levels; if the participant performed the set easily, the load was increased, conversely, if the participant failed to perform the targeted amount of repetitions, the weight was decreased. Slight assistance was provided for the completion of the concentric phase of a rep of set if necessary, with force of the assistance provided measured with electric dynamometers.

During HYP sessions, participants leg pressed 5x10RM at 80% of 1RM with 2 minutes of rest between sets. Muscle activity during each repetition was assessed with electromyography (Häkkinen & Komi 1983), but the specific details and results are beyond the scope of this work and will not be reported here. Changes in muscle architecture and muscle blood flow during each repetition was assessed with ultrasonography and near infrared spectroscopy respectively, but the specific details and results are beyond the scope of this work and will not be reported here. Immediately post-loading, participants performed again 1 maximal bilateral isometric leg press, and 1 static jump. Participants then walked to the biopsy room for VL biopsy. The time between completion of exercise loading, and successful collection of muscle samples, was approximately 5-10 minutes, including the time for the recovery measurements. Although the intention was to collect muscle samples as soon as possible post-exercise, inter-individual variation in biopsy times was unfortunately unavoidable as some participants bled more freely. Due to some logistical problems, muscle biopsy samples from the pre-training loading sessions unfortunately were not available for laboratory analysis.

During the POW sessions, participants performed the concentric portion of the first 2 reps each of the 1st, 5th and 10th set, paused for approximately 1 second, lowered the weight, paused for another second, lifted the weight, paused for another second, lowered the weight and paused again for another second. This was to allow for ultrasonographic assessment of muscle structure changes. All other reps were performed without pause. All reps were performed with maximal acceleration. Capillary blood was collected into capillary tubes for measurement of circulating blood lactate, from participants' fingertips after the 1st, 3rd set, and 5 minutes after the conclusion of the HYP session, and after the 1st, 3rd, 5th, 8th set, and 5 minutes after the conclusion of the POW session. The tubes were placed in a 1mL haemolysing solution and analysed automatically (EKF diagnostic, Biosen, Barleben, Germany).

2.4 Recovery measurements

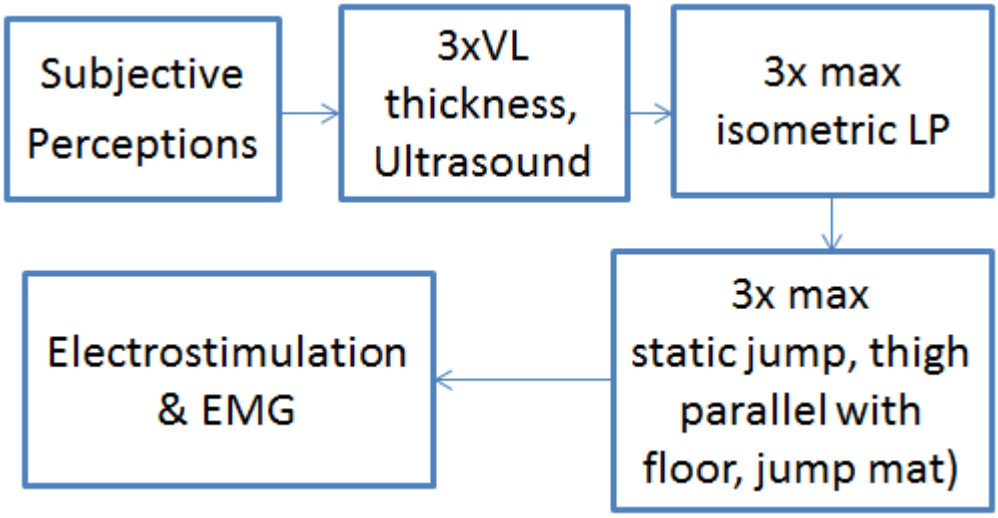

Figure 7: schematic of recovery measurements, VL: vastus lateralis, LP: leg press

On the weeks on which HYP sessions were performed, participants returned to the laboratory 24, 48, 72 and 96 hours subsequent to the exercise loading for recovery measurements of isometric bilateral leg press force, static jump height, and muscle thickness, whereas on the POW session weeks, participants returned to the laboratory 24 hours and 48 hours post-exercise for those recovery measurements. The times each day for each participant on the loading sessions and the subsequent recovery measurement sessions were kept the same, the schedules of the participants

permitting. One participant had to reschedule his pre-training POW session such that it was 14 days after his HYP session. Due to influenza that was unrelated to the exercise loading, one of the participants had to reschedule his post-training power loading session such that it was performed 22 days after the hypertrophy loading session, and not 1 week after as planned. Participants were instructed to refrain from exercise and to maintain their normal diet during the recovery days after the exercise loading sessions. However, one of the participants informed the researcher on a day during his post-training post-hypertrophic loading recovery week that he had spent much of the prior day walking, as that was required by his job. As these were free living volunteers, and not lab rats, such issues were unavoidable. Such details should be kept in mind when considering the findings.

On each recovery measurement day, after reporting to the laboratory, resting blood samples, both venous and capillary, were first collected from participants. Then, participants' VL muscle thickness was measured, with the average of 3 measurements used for statistical analysis (figure 7). After that, maximal bilateral isometric leg press force was measured exactly as pre-exercise loading, with 3 maximal attempts separated by a minute each. Following that, static jumps were also assessed exactly as pre-exercise loading, with 3 maximal attemtps separated by a minute each. All measurements were conducted by the same researcher.

2.5 Muscle tissue processing

Muscle biopsy samples were hand-homogenized, by vortexing Eppendorf tubes containing the tissue along with metal ball bearings, in ice-cold buffer [20 mM HEPES (pH 7.4), 1 mM EDTA 5 mM EGTA, 10 mM MgCl2, 100 mM b-glycerophosphate, 1 mM Na3VO4, 2 mM DTT, 1 % Triton X-100, 0.2 % sodium deoxycholate, 30 mg/mL leupeptin, 30 mg/mL aprotinin, 60 mg/mL PMSF, and 1 % phosphatase inhibitor cocktail (P 2850; Sigma, St Louis, Missouri, USA)] at a dilution of 15 mL/mg of wet weight muscle. To avoid excessive foaming during mechanical hand homogenization, samples were homogenized in short bursts, with the sample cooled in ice in-between (Peach et al., 2012). Total protein content was determined using the bicinchoninic acid protein assay (Pierce Biotechnology, Rockford, Illinois, USA). Homogenates were stored at −80 °C for subsequent analysis.

2.6 Western blot

14ml aliquots of muscle lysate containing 30µg of total protein were solubilized in 14ml Laemmli buffer (250 mM Tris·HCl, pH 6.8, 40% (v/v) glycerol, 8% (w/v) SDS, 20% (v/v) β-mercaptoethanol, and 0.01% (w/v)) (Bio-Rad Laboratories, Richmond, CA) (Laemmli, 1970), and then heated at 95 °C for 10 minutes to denature proteins. Subsequently, proteins were left on ice for 5 minutes, before brief centrifugation. Proteins were then were loaded onto 4–20 % acrylamide gradient gels and separated by SDS-PAGE, in running buffer (25 mM Tris base 190 mM glycine 0.1% SDS), for 60 min at 300V on ice at 4 °C using a Criterion electrophoresis cell (Bio-Rad Laboratories, Richmond, CA). All samples from each participant, along with a pooled sample and a molecular weight marker, were run on the same 18-sample gel. After electrophoresis, gels were equilibrated in ice cold transfer buffer (50 mM Trisbase, 383 mM glycine, 20% v/v methanol), for 15 minutes. Prior to protein transfer, PVDF membranes were activated by immersion in ice cold transfer buffer for 15 minutes. Proteins were transferred to PVDF membranes (Amersham Hybond LFP, GE Healthcare) in transfer buffer at 300 mA constant current for 2h on ice at 4 °C. Membranes were blocked in TBS containing 5% Odyssey fluorescent blocking buffer for 2 hours and then incubated overnight at 4 °C with rabbit polyclonal primary antibodies. Antibodies recognized phosphorylated Erk1/2(p44/p42)$^{Thr202/Tyr204}$ p38 MAPK$^{Thr180/Tyr182}$, p70S6K$^{Thr421/Ser424}$, p70S6K^{Thr389}, rpS6$^{Ser235/236\ and\ Ser240/244}$, 4EBP1$^{Thr37/46}$,. All antibodies were purchased from Cell Signalling Technology (Beverly, MA). All the primary antibodies were diluted 1:1000 in TBS containing 2.5 % Odyssey blocking buffer. Membranes were then washed 4 × 5 min in TBS-T (0.1%) before incubation with IRDye® fluorophore secondary antibody (LI-COR Biosciences, Cambridge, United Kingdom) and blocking buffer in TBS for 60 min in room temperature in 1:20,000 concentration. For visualization of proteins, membranes were scanned using a Odyssey® Sa Infrared Imaging System (LI-COR Biosciences) and blots quantified using ImageStudio.

Uniformity of protein loading onto gels was confirmed by staining the membranes with Ponceau S. Furthermore, alpha tubulin was used a loading control. Due to unclear images, only p70S6K1 at Thr389 could be normalized against Ponceau S and alpha tubulin. The other proteins were

normalized against the pooled sample. Quantification of p38 was based on the average of two bands at 42 and 44 kDa.

2.7 Calculation of mechanical work

Mechanical work performed during post-training exercise loadings was calculated as in Garhammer (1980), Chiu et al. (2008). Power loading sessions of 6 participants were recorded by video camera post-training, whereas that of 1 participant was recorded pre-training. The maximum height reached by the leg press weight stack during the 1st and 2nd repetition of the 1st, 5th and 10th sets of the POW sessions, that is the repetitions during which the participant held the weight statically at the end of the concentric phase for ultrasonographic assessment of muscle architecture, was obtained. This height was used along with the angle signal which was obtained from the electrical goniometer via Signal software version 2.16 (Cambridge Electronic Design Ltd, Cambridge, UK) to plot a regression line (R^2=0.4698). The angle signal value used was the highest point of the angle signal graph in the Signal software analysis. This regression line was used to estimate the height reached by the weight stack during HYP loadings, as it was assumed that the height reached by the weight stack during HYP would be the same as that reached by the weight stack during the reps in POW on the reps where there was a pause at the end of the concentric phase. This was because HYP sessions were not video-recorded. Then, kinetic energy (KE) and potential energy (PE) was calculated for every rep of the 2nd set of HYP, with time obtained from Signal, and it was assumed that KE and PE for every rep in every other set in HYP was similar to that of the average of that of the reps in 2nd set.

Maximum height reached by the weight stack during the POW loadings, when the weight stack was not held statically at the highest point, and during which there was no contact between the leg press foot platform and participants' feet because the foot platform was thrust explosively away at the end of the concentric phase was obtained for every repetition of every participant from the 4th set from video. This height for each rep was matched to the corresponding time of that rep, obtained via Signal. This height and time was then used to calculate KE and PE for each rep of that 4th set. The averages of these reps were then used as an estimate for every other repetition of the other sets. This was done because of time constraints; moreover, unfortunately,

not all repetitions of every set of the POW loadings were successfully recorded on video, there was also no Signal data for some repetitions.

Mechanical work (W) was calculated as the sum of the change in gravitational potential (ΔE_P) and kinetic (ΔE_K) energy:

$$W = \Delta E_P + \Delta E_K + \Delta E_E + Q$$

Gravitational potential energy was determined from mass of the weight stack of the leg press machine (m), gravitational acceleration (g), and weight stack height (h):

$$\Delta E_P = m \cdot g \cdot (h_{final} - h_{initial})$$

Kinetic energy was determined from weight stack mass (m) and velocity (v):

$$\Delta E_K = 1/2m(v_{final}^2 - v_{initial}^2)$$

Strain energy (ΔE_E) was not calculated due to methodological limitations. Non-conservative energy (Q) loss was ignored, although some energy may be lost as a result of friction in the leg press machine.

2.8 Statistical methods

The jump mat malfunctioned during one participant's measurements pre-training post hypertrophic loading, therefore, he was excluded from statistical analysis of static jumps. Fingertip blood failed to be collected for one participant 5 minutes after power loading post-training, he was thus excluded from statistical analysis involving blood lactates.

All data was tested for normality of distribution and homogeneity of variances using the Shapiro-Wilks and Levene's tests respectively. Data for p-rpS6, p-p70S6K at Thr389 and p-ERK were not normally distributed, thus, when conducting statistical analysis they were transformed. Data for p-rpS6 was transformed with the Box-Cox (Box & Cox, 1964) transformation, using lambda of

1.05. Data for p-p70S6K1 at Thr389 was transformed using a log10 transformation, whereas that for p-ERK was transformed with a square root transformation. Differences in protein phosphorylation between and within conditions were assessed with a 2(loading condition) x 2(time) repeated measures ANOVA. Data for post-training post-POW maximal isometric leg force was not normally distributed, therefore, comparisons for isometric force were performed with the data log10 transformed. A 2(pre, post-training) x 6 (time) repeated measures ANOVA was used to compare differences in isometric force in both HYP and POW. A 2 (loading condition) x 4 (time) repeated measures ANOVA was used to compare differences in isometric force both pre and post-training, A 2(pre, post-training) x 6 (time) repeated measures ANOVA was used to compare differences in static jump height in both HYP and POW. A 2 (loading condition) x 4(time) repeated measures ANOVA was used to compare differences in static jump height both pre and post-training. Post hoc pair-wise analysis using paired sample t-tests (with Bonferroni correction) to test at which time points a significant effect occurred. Where appropriate, significant differences between loading or training conditions were identified using paired-samples t-test, whereas significant differences within conditions were also identified using one way repeated measures ANOVA. Data for muscle thickness was not normally distributed at some time points, and could not be successfully transformed. Therefore, differences in VL thickness within loading conditions were compared non-parametrically using Friedman's ANOVA. Differences in VL between loading conditions at each time point compared using Wilcoxon sign rank test. Assumption of sphericity assessed, and if necessary, corrected using Greenhouse-Geiser epsilon. Subjective perceptions of muscle soreness, and readiness to perform assessed non-parametrically, using Friedman's ANOVA for within conditions comparisons and Wilcoxon sign rank test for between conditions comparisons at each time point

Correlations between recovery measures and protein phosphorylation were assessed non-parametrically using Spearman's rho, because of the non-normally distributed data for phosphorylated proteins, muscle thickness, maximal isometric force. Absolute differences between post-exercise timepoints and the pre-exercise timepoint for recovery measures were assessed against the absolute differences between pre and post-exercise phosphorylated proteins. Relative differences, post-exercise values divided by pre-exercise values, for phosphorylated proteins were assessed against the relative differences for recovery measures. Correlations

between mechanical work performed in the post-training acute loading sessions, both absolute and relative to bodymass, and changes in absolute phosphorylated proteins were assessed using Person's correlations.

Descriptive statistics presented as means and standard deviations, and also 95% confidence intervals. Effect sizes (Hedges g) (Fritz et al. 2012; Lakens 2013) between pre and post-exercise phosphorylated proteins also presented. All statistical analysis performed using SPSS version 21 (IBM Inc., Armonk, NY), except effect sizes which were calculated in Microsoft Excel, with statistical significance at $p < 0.05$.

3 RESULTS

There were no significant differences between and within conditions for both HYP and POW. See Table 2 for effect sizes for pre and post-exercise differences in HYP and POW, Figure 7 for the average mean differences (absolute differences) between pre and post-exercise in HYP and POW, Figure 8 for the fold changes (post-exercise divided by pre-exercise) between pre and post-exercise in HYP and POW.

Table 2: effect sizes for proteins

Proteins	Hypertrophy effect size, 95%CI of effect size	Power effect size, 95%CI of effect size
P-p70S6K1 at Thr389	0.60 (-0.48-1.67)	0.43 (-0.63-1.49)
P-p70S6K1 at Ser424	0.53 (-0.53-1.60)	0.56 (-0.51-1.63)
p-4EBP1	-0.52 (-1.58-0.55)	-0.21 (-1.26-0.84)
P-S6	0.31 (-0.74-1.36)	0.38 (-0.67-1.44)
P-ERK	-0.03 (-1.08-1.01)	0.26 (-0.79-1.31)
P-p38	1.06 (-0.06-2.18)	0.67 (-0.41-1.74)

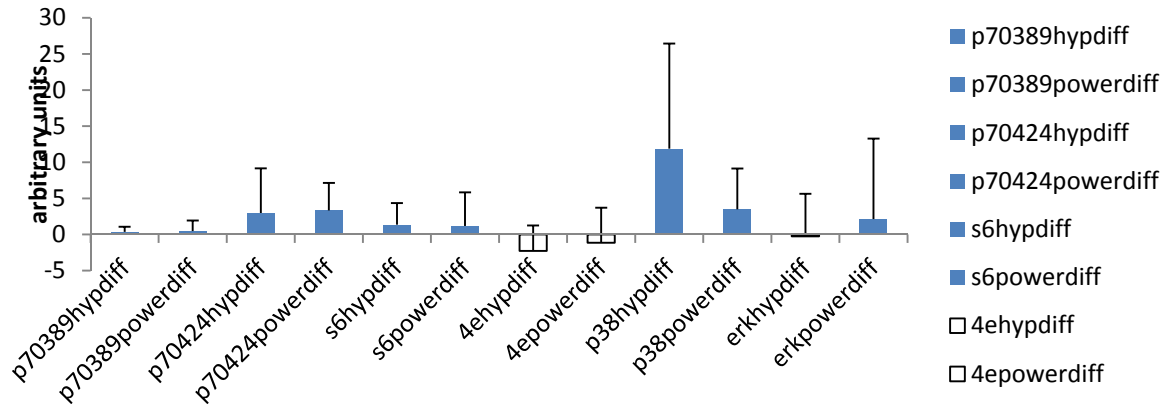

Figure 8: mean differences (post-exercise absolute values minus pre-exercise absolute values), hyp (hypertrophy) pow (power), p70389hypdiff= p-p70S6K1 post-hypertrophy - p-70S6K1 pre-hypertrophy, p70389powerdiff= p-p70S6K1 post-power - p-70S6K1 pre-power; similarly for other phosphorylated proteins

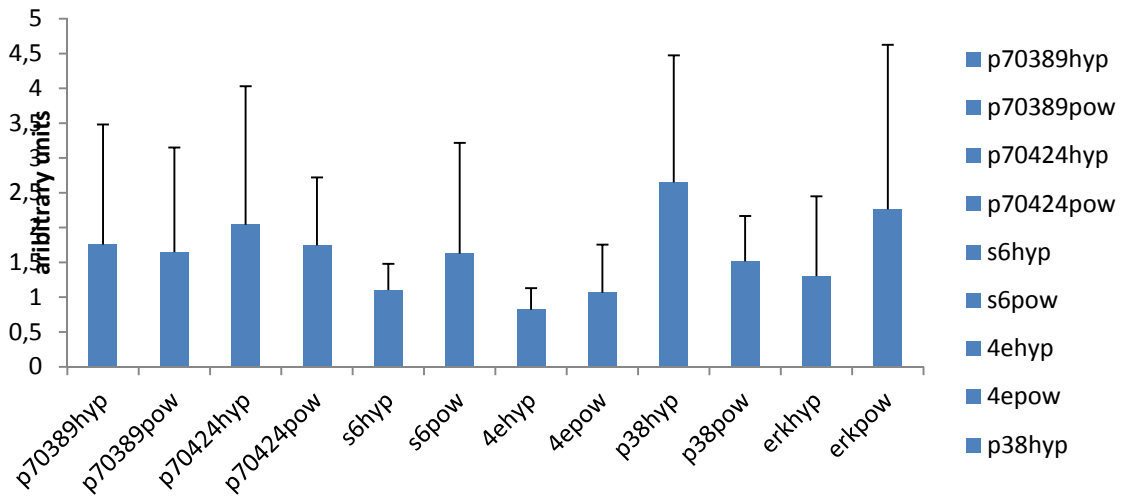

Figure 9: mean fold changes (post-exercise divided by pre-exercise), hyp (hypertrophy) pow (power);), p70389hyp: p-p70S6K1 post-hypertrophy / p-70S6K1 pre-hypertrophy; p70389pow: p-p70S6K1 post-power / p-70S6K1 pre-power; similarly for other phosphorylated proteins

3.1 p-p38

There were no main effects for loading condition (p=0.441) or time (p=0.061), the ~2.6 fold and ~1.5 fold relative change after HYP and POW respectively was not significant (figure 9); nor was there an interaction for time and loading (p=0.141). P-p38 levels increased in 5 out of 7 participants after HYP (figure 10), and in 6 out of 7 participants after POW (figure 11).

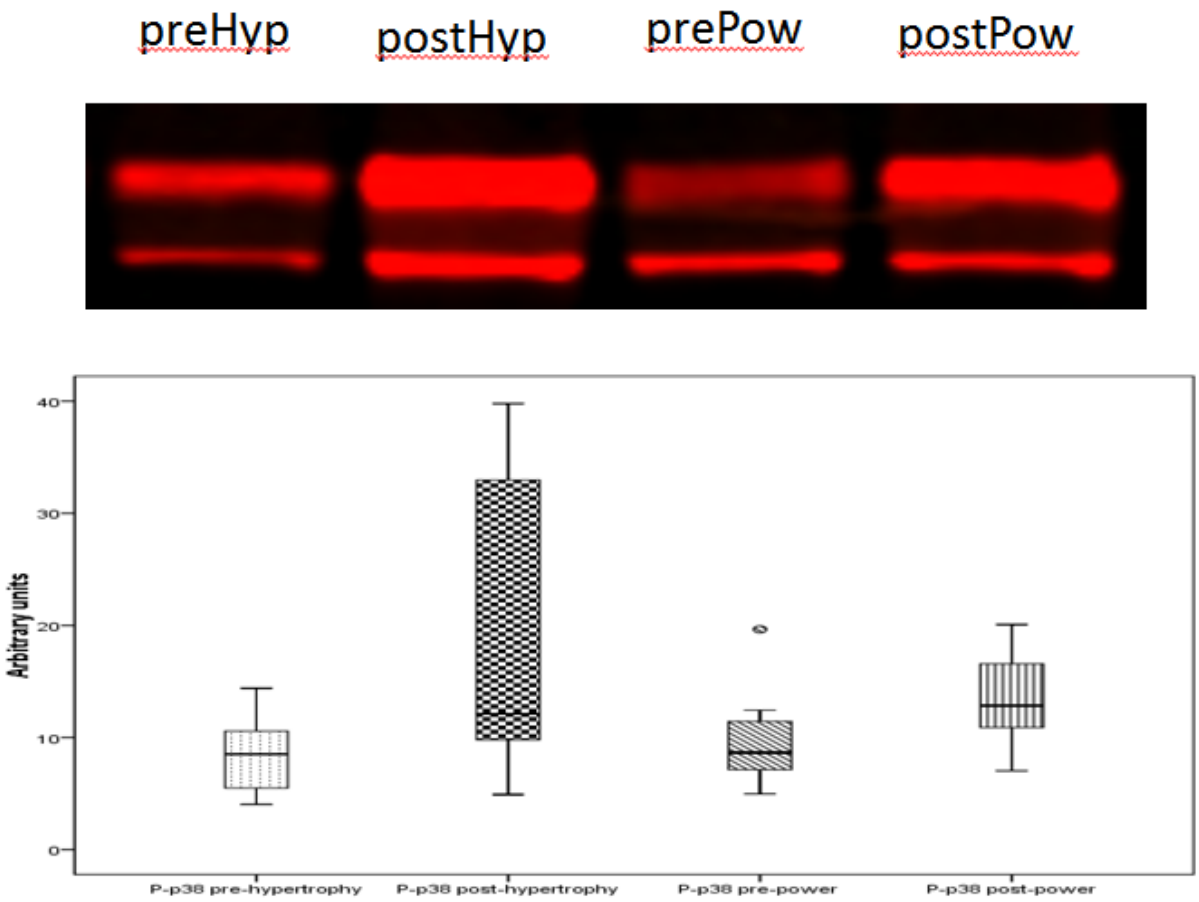

Figure 10: Representative blot and box plot for phosphorylated p38, points outside of boxes represent outliers

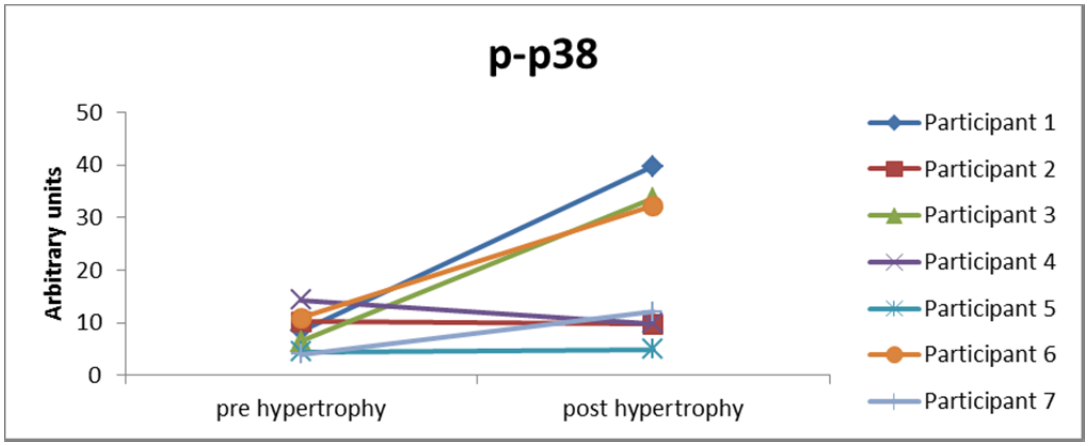

Figure 11: Scatterplot for phosphorylated p38 pre and post HYP loading

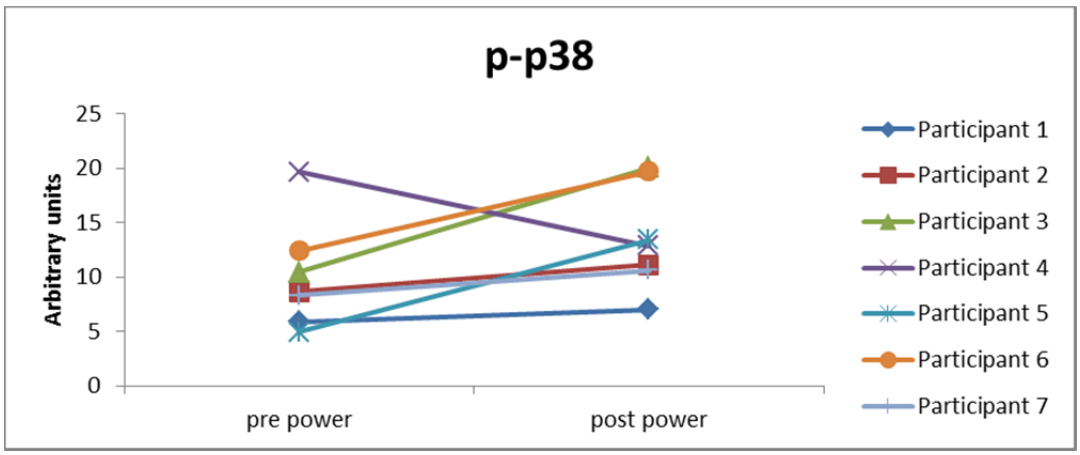

Figure 12: Scatter plot for phosphorylated p38 pre and post POW loading

3.2 p-ERK

There were no main effects for loading condition (p=0.707) nor time (p=0.718), the ~1.3 fold and ~2.26 fold relative change after HYP and POW respectively was not significant (figure 12); nor was there an interaction for time and loading (p=0.471). Of note was that even though there was an average 1.3 fold relative change in ERK signalling after HYP, signalling after HYP decreased absolutely, whereas that after POW increased absolutely. P-ERK in 4 out of 7 participants in both conditions increased, nonetheless, this increase was not in the same 4 participants for both conditions (figures 13, 14).

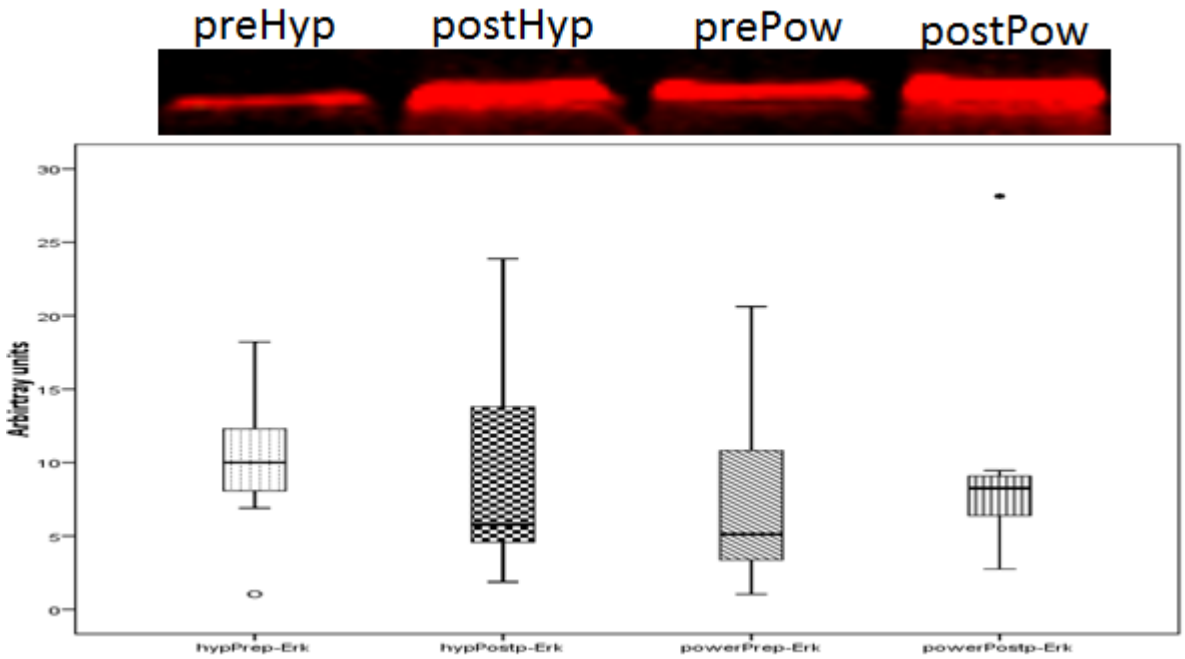

Figure 12: Representative blot and box plot for phosphorylated ERK, points outside of boxes represent outliers

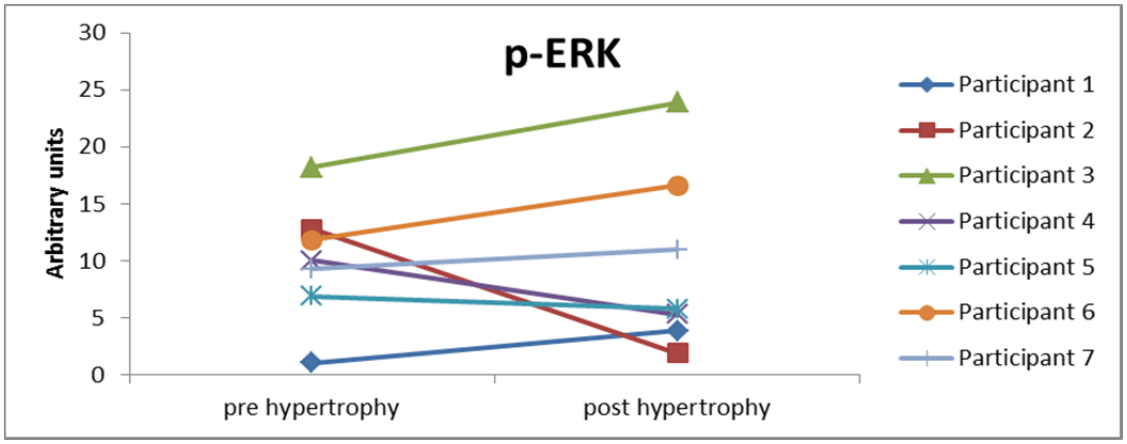

Figure 13: Scatterplot for phosphorylated ERK pre and post HYP loading

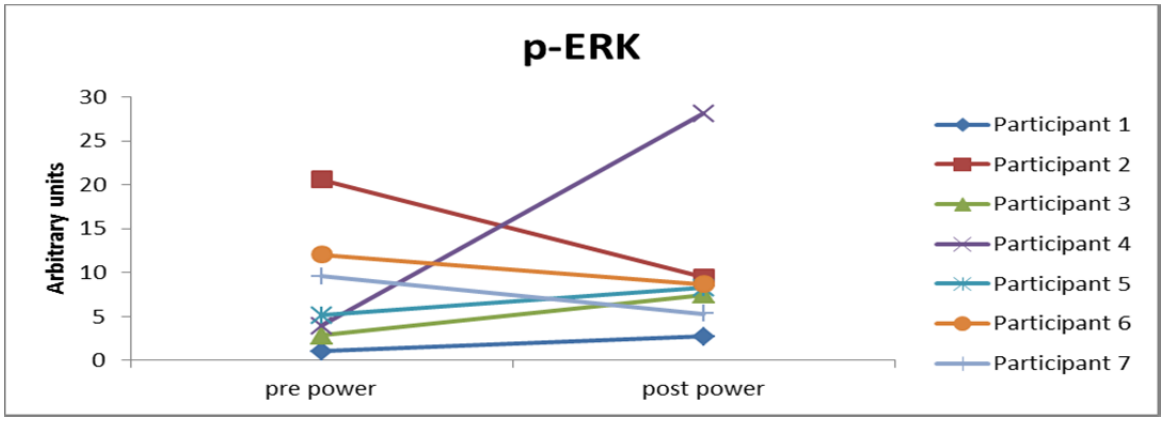

Figure 14: Scatterplot for phosphorylated ERK pre and post POW loading

3.3 p-p70S6K1 at Ser424

There were no main effects for loading condition (p=0.088) or time (p=0.1), the ~2 fold and ~1.74 fold relative change after HYP and POW respectively was not significant (figure 15); nor was there an interaction for time and loading (p=0.873). p-p70S6K1 at Ser424 increased in all 7 participants after POW, but only 4 out of 7 participants after HYP (figures 16, 17).

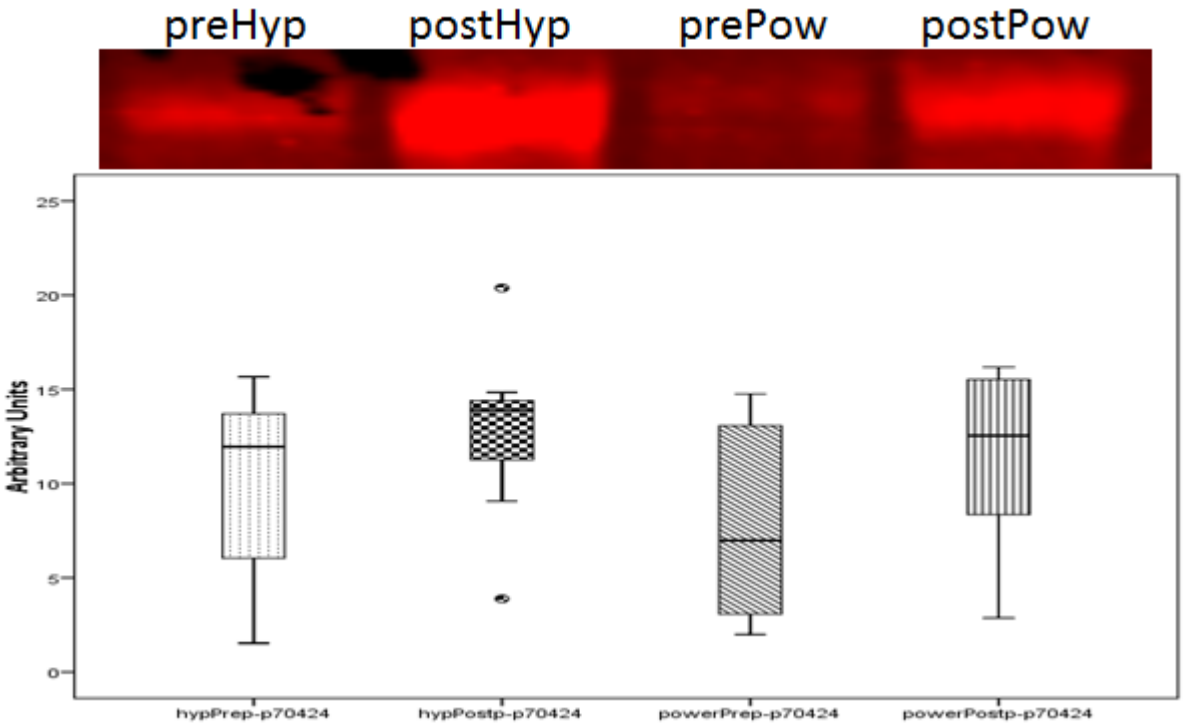

Figure 15: Representative blot and box plot for phosphorylated p70S6K1 at Ser424, points outside of boxes represent outliers

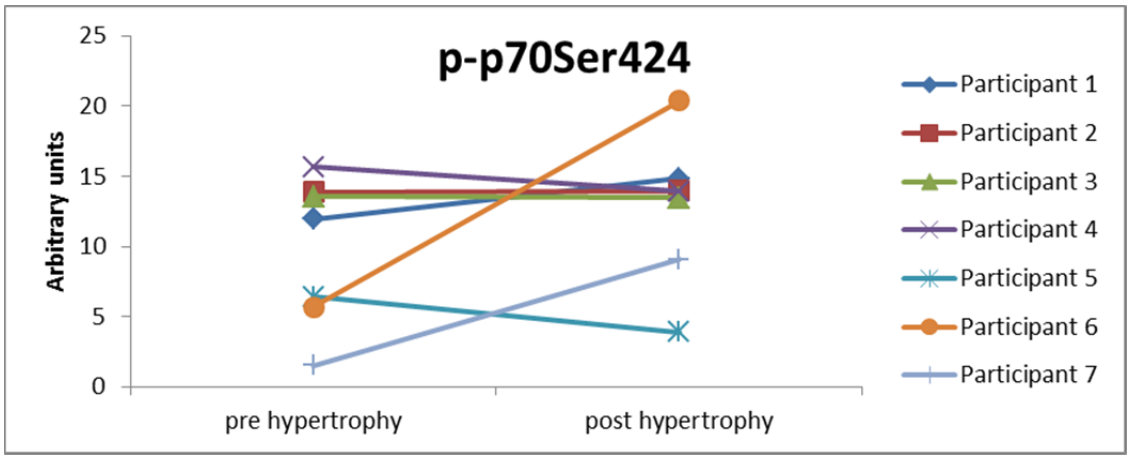

Figure 16: scatterplot of phosphorylated p70S6K1 at Ser424 pre and post HYP

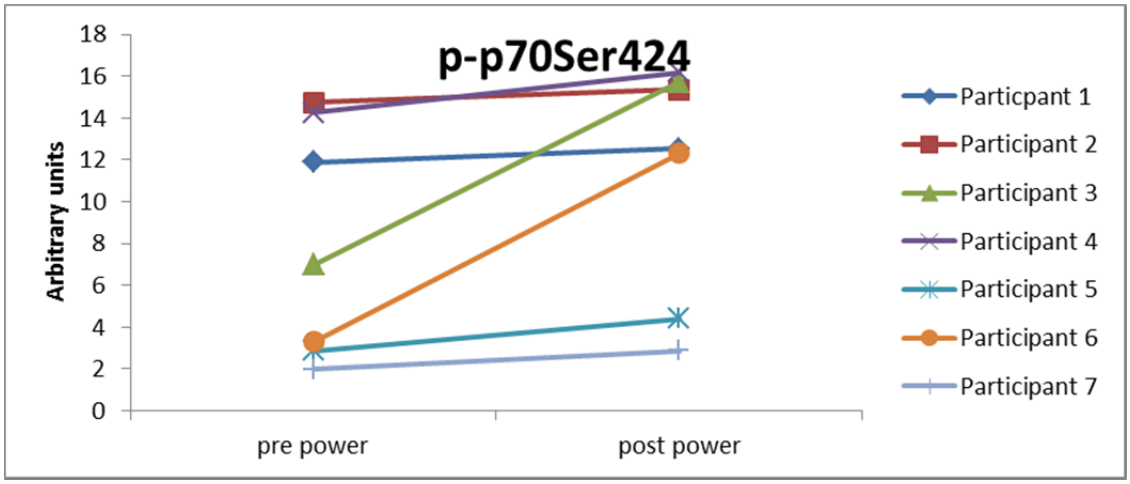

Figure 17: scatterplot of phosphorylated p70S6K1 at Ser424 pre and post POW

3.4 p-p70S6K1 at Thr389

There were no main effects for loading condition (p=0.186) or time (p=0.369), the ~1.7 fold and ~1.6 fold increase after HYP and POW respectively was not significant; nor was there an interaction for time and loading (p=0.823) (figure 18). p-p70S6K1 at Thr389 increased in 5 out of 7 participants after HYP, whereas this increase occurred only in 4 of those 5 participants after POW (figures 19, 20).

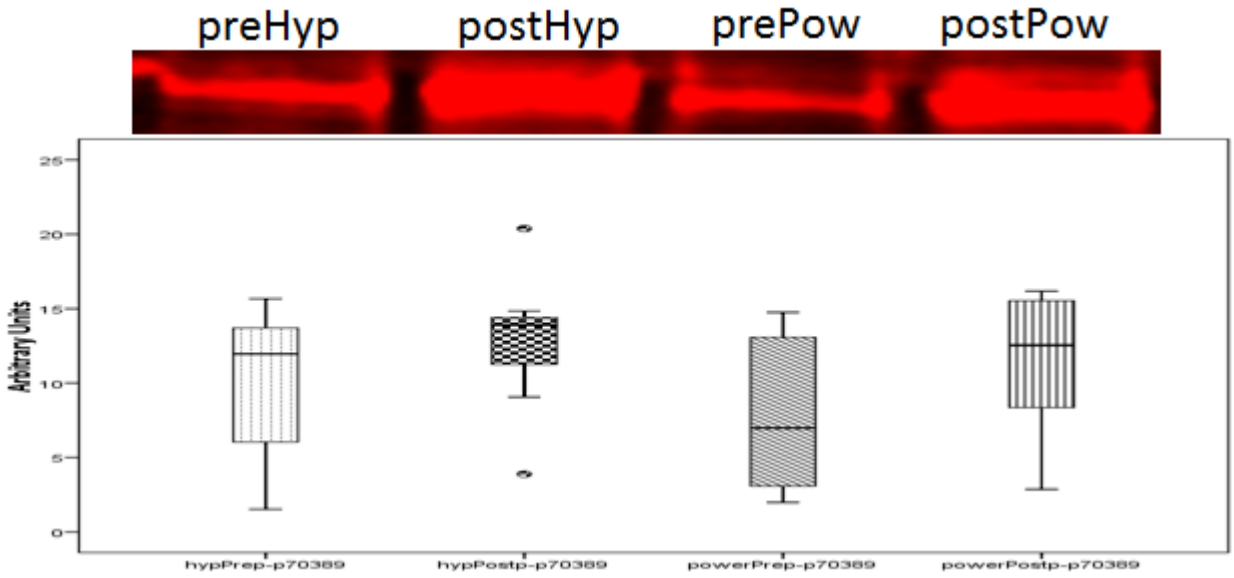

Figure 18: Representative blot and box plot for phosphorylated p70S6K1 at Thr389, points outside of boxes represent outliers

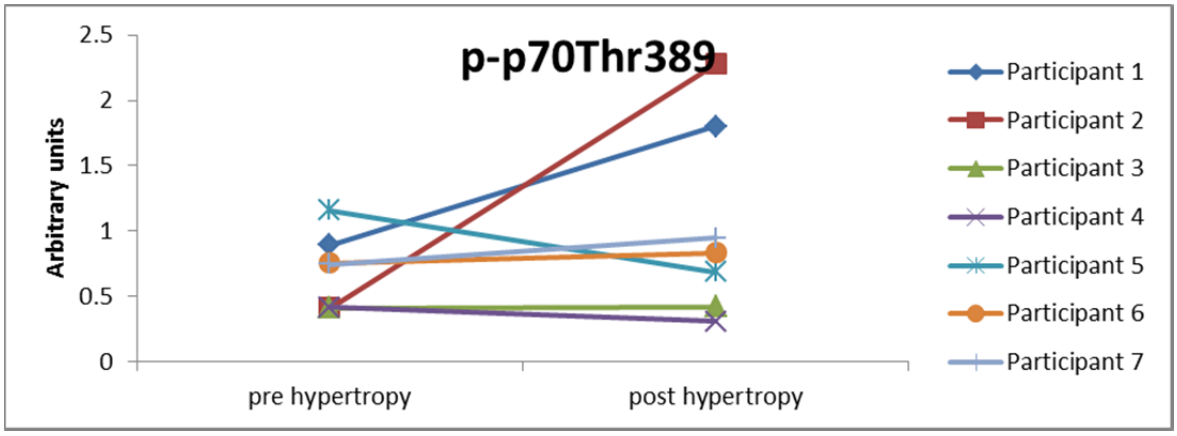

Figure 19: scatterplot of phosphorylated p70S6K1Thr389 pre and post HYP

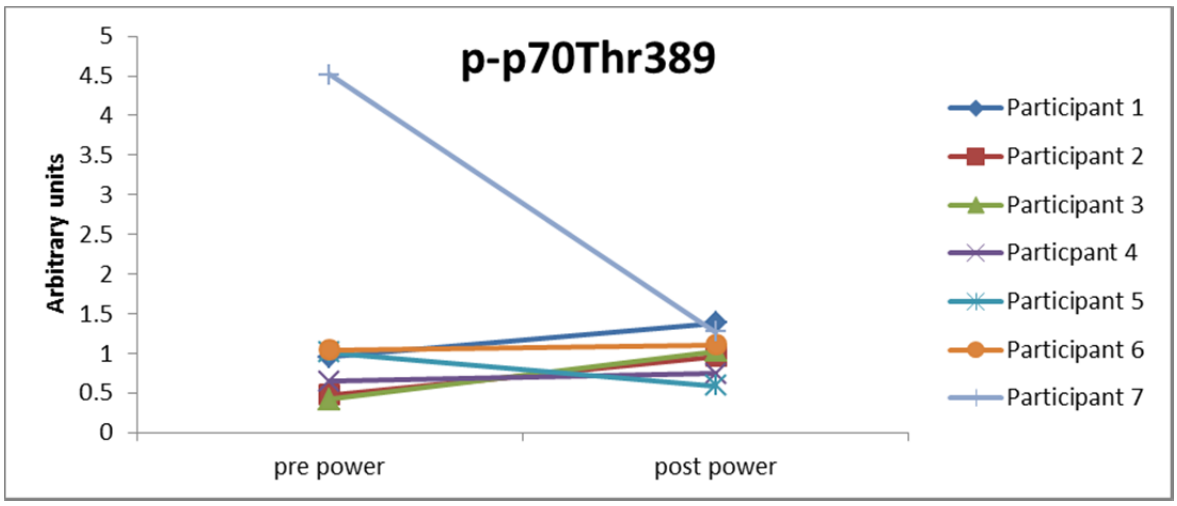

Figure 20: scatterplot of phosphorylated p70S6K1 Th389 pre and post POW

3.5 p-4EBP1

There were no main effects for loading condition (p=0.069) or time (p=0.267), the ~0.8 fold and ~1.06 relative change after HYP and POW respectively was not significant; nor was there an interaction for time and loading (p=0.496) (figure 21). Of note was that even though there was an average 1.06 fold relative change in ERK signalling after POW, signalling after POW decreased absolutely, just as it did after HYP. P-4EBP1 decreased in 5 out of 7 participants after HYP and POW, but this decrease was not in the same 5 participants for both conditions (figures 22, 23).

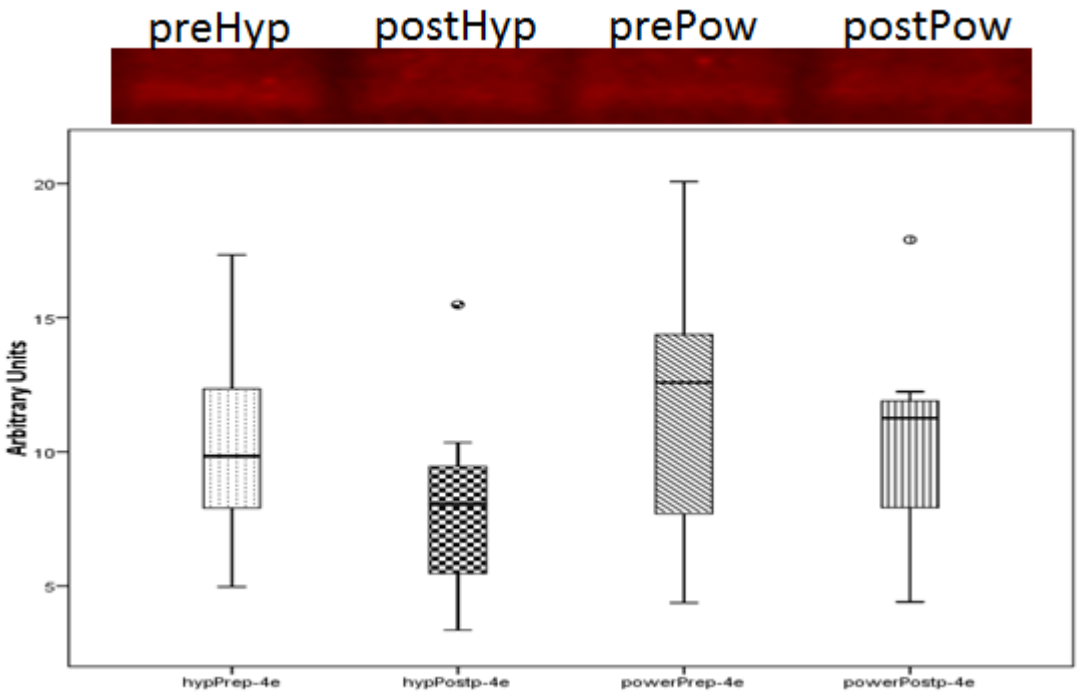

Figure 21: Box plot for phosphorylated 4EBP1, points outside of boxes represent outliers

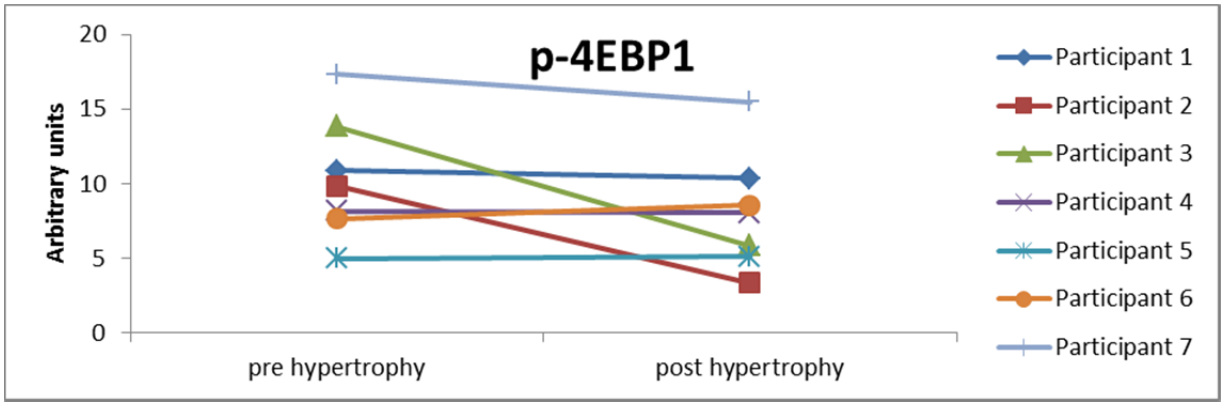

Figure 22: scatterplot of phosphorylated4EBP1 pre and post HYP

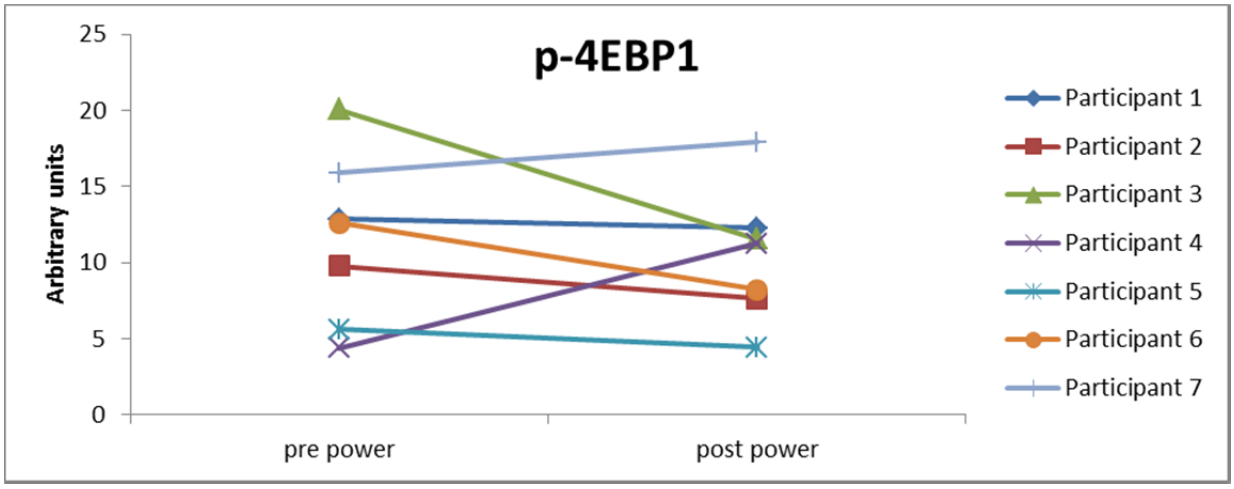

Figure 23: scatterplot of phosphorylated4EBP1 pre and post HYP

3.6 p-rpS6

There were no main effects for loading condition (p=0.526) or time (p=0.13), the ~1.1 fold and ~1.62 fold relative after HYP and POW respectively was not significant; nor was there an interaction for time and loading (p=0.937) (figure 24). p-rpS6 increased in 4 out of 7 participants after HYP, compared to 5 out of 7 after POW (figures 25, 26).

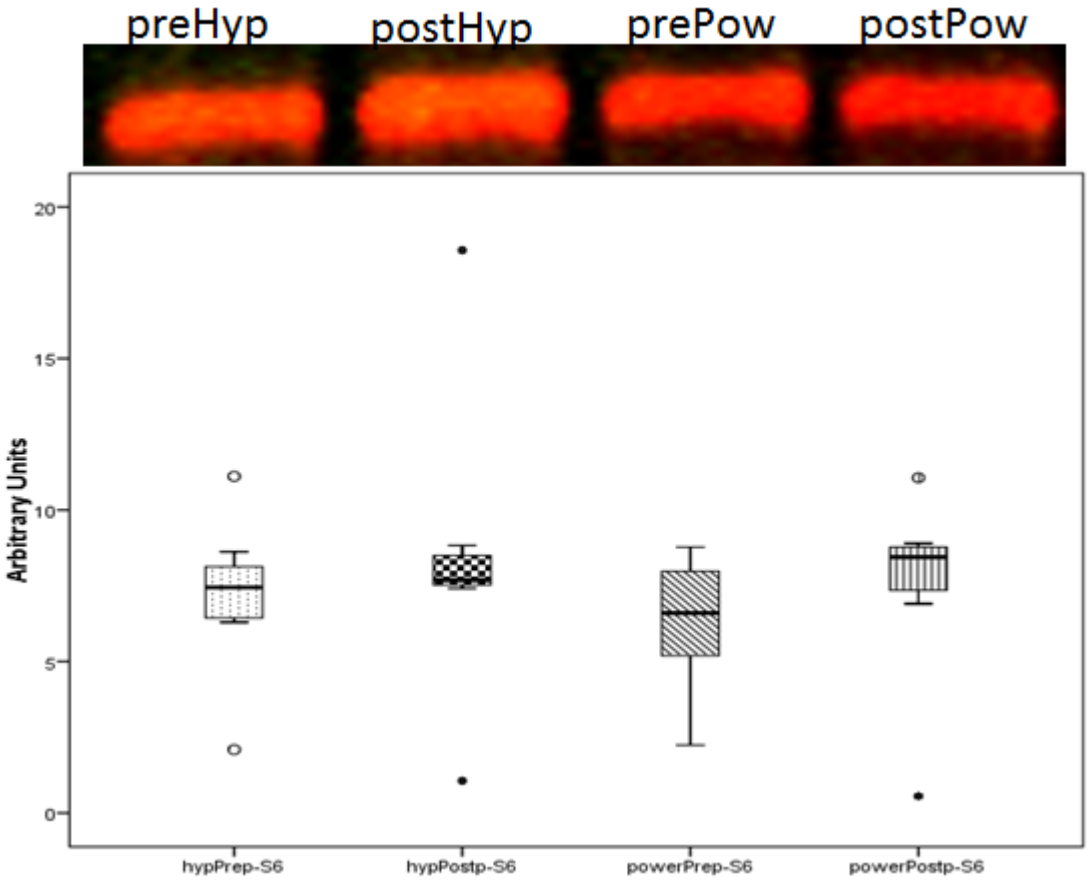

Figure 24: Representative blot and box plot for phosphorylated rpS6, points outside of boxes represent outliers

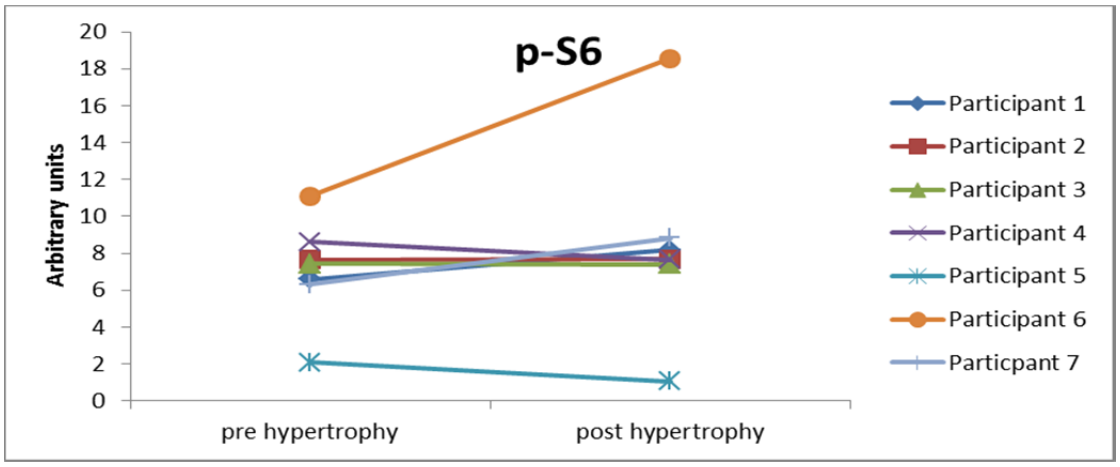

Figure: 25: scatterplot of phosphorylated rpS6 pre and post HYP

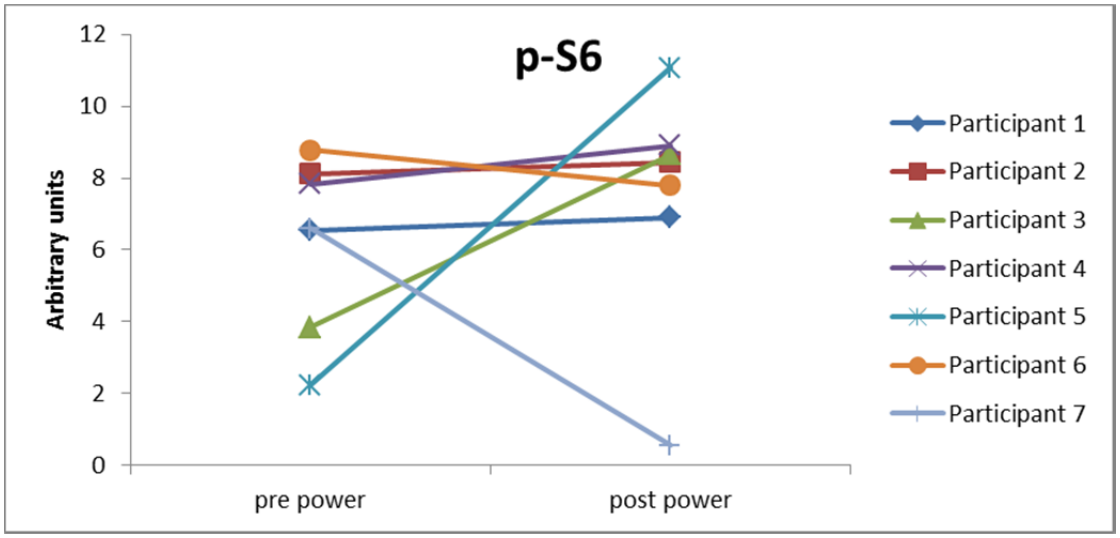

Figure 26: scatterplot of phosphorylated rpS6 pre and post POW

3.7 Isometric LP, Static jumps, VL thickness

3.7.1 Isometric LP

In the hypertrophic loading condition, there was a main effect for time (p=0.001, Greenhouse-Geisser) and training (pre,post) x time interaction, but no main effect for training between pre and post-training. In the power loading condition, there were no main effects for training (p=0.392), and no interaction effects (p=0.17), although the main time effect approached significance (p=0.056, Greenhouse-Geisser; p=0.047, Huynh-Feldt). Pre-training, there was a main time effect for the hypertrophic loading condition (p=0.001, Greenhouse-Geisser), and significant differences between some time points, especially immediately after loading (p=0.046) (Figure 27) (Table 3, 4). Maximal isometric leg extension strength at the 24 (p=0.027), 72 (p=0.045), 96 (p=0.046) hour time-points was also higher than at the post-exercise time-point. Post-training, there was a main time effect (p<0.001) for the hypertrophic loading condition, and significant differences between some time points: there was greater isometric leg press strength at the 48 (p=0.049), 72 (p=0.009), 96 (p=0.043) hour time-points compared to immediately post-exercise. Pre-training, there was a main time effect (p=0.034) for the power loading condition, but no significant differences between any time points, although the difference immediately after loading approached statistical significance (p=0.055). Post-training, there was a main time effect for the power loading condition (p=0.022), but no significant differences between any time

points. Pre-training, there was a main effect for time ($p<0.001$), and a loading x time interaction effect ($p=0.001$), but no difference between HYP and POW ($p=0.999$). Within subjects contrasts revealed that this interaction effect was at the post-loading and 24 hour time points. However, paired samples t-tests at these time-points found that the differences between the hypertrophic and power loading conditions at these time-points was not statistically significant (post-loading: $p=0.070$, 24h: $p=0.128$). The data for maximal isometric leg extension strength for the POW condition after training was not normally distributed, therefore, any statistical tests involving that condition was conducted with all data log transformed. Post-training, there was a main effect for time ($p<0.001$), but no loading ($p=0.864$) or loading x time interaction effects ($p=0.206$).

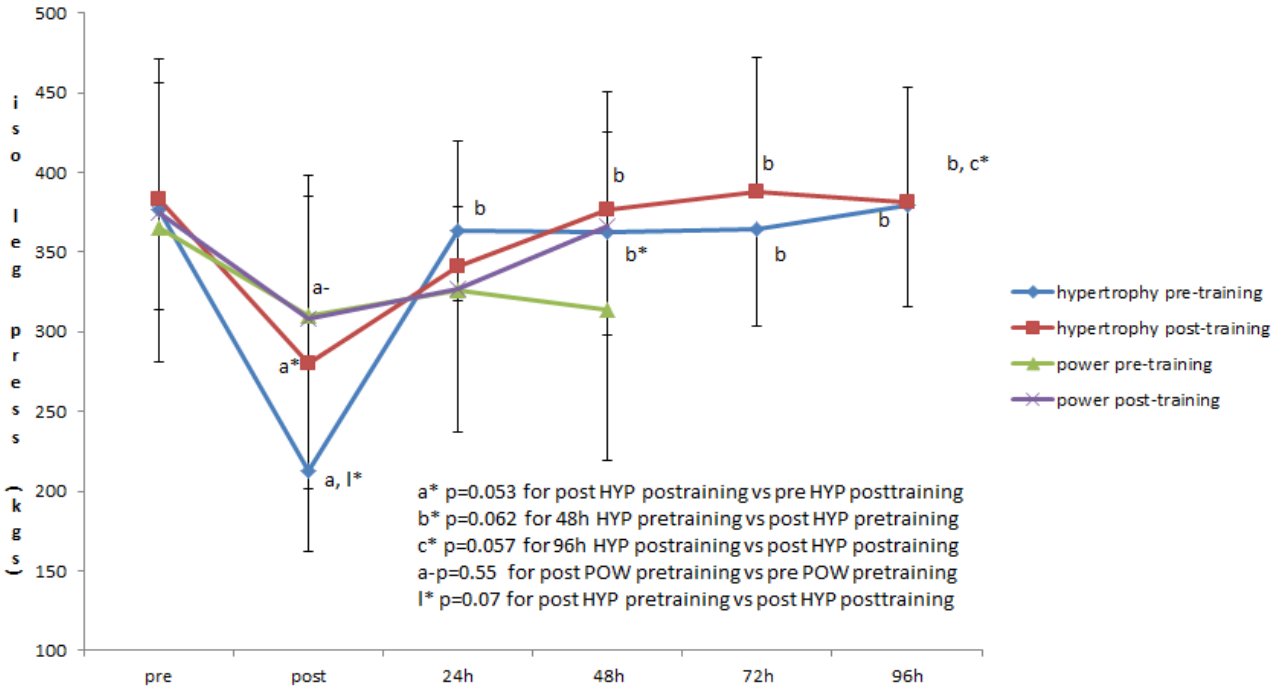

Figure 27: time course results for maximal isometric leg press, letters represent differences from preceding timepoints or loading conditions; a represents $p<0.05$ from pre-exercise in that loading or training condition, b represents $p<0.05$ from immediately post-exercise, c represents difference from 24hours after exercise, l: difference between loading conditions

Table 3: Recovery results for isometric leg press, a represents $p<0.05$ from pre-exercise in that loading or training condition, b represents $p<0.05$ from immediately post-exercise

	Pre(means±SD, 95% CI for mean)	Post 0h	24h	48h	72h	96h
Isometric LP pre-training, hypertrophy (N)	376.29±62.26 318.70-433.87	213±50.85[a] 165.98-260.02	363.14±43.97[b] 322.48-403.81	362.43±64.90 302.40-422.45	364.14±61.06[b] 307.67-420.62	379.71±64.32[b] 320.23-439.20
Isometric LP post-training, hypertrophy (N)	383.29±87.82 302.07-464.50	279.86±105.01 182.74-376.97	340.71±79.22[b] 267.45-413.98	376.43±74.58[b] 307.45-445.40	388.14±83.58[b] 310.84-465.44	381.29±72.53[b] 314.21-448.36
Isometric LP pre-training, power (N)	365.14±83.67 287.76-442.52	310.14±108.33 209.95-410.33	326.00±89.12 243.58-408.42	313.43±94.47 226.06-400.80		
Isometric LP post-training, power (N)	374.86±81.40 299.57-450.14	308.14±89.66 225.22-391.07	326.86±51.41 279.31-374.40	366.57±58.54 312.43-420.71		

Table 4: changes for isometric leg press from pre-exercise time-point

		Post 0h	24h	48h	72h	96h
Pretraining hypertrophy, isometric LP	% change from pre-exercise	-41.65	-2.91	-3.74	-3.10	1.11
	SD of % change	17.27	4.55	5.08	4.68	7.20
	95% CI of absolute difference (kgs)	-229.49 to -97.09	-75.92 to 49.62	-87.92 to 60.20	-85.67 to 57.95	-70.30 to 77.14
Post-training hypertrophy, isometric LP	% change from pre-exercise	-27.8	-10.76	-0.78	2.16	0.63
	SD of % change	14	9	9	10	9
	95% CI of absolute difference (kgs)	-216.16 to 9.30	-139.98 to 54.82	-101.74 to 88.02	-94.99 to 104.69	-95.80 to 91.80
Pre-training, Power, isometric LP	% change from pre-exercise	-15.64	-11.28	-14.88		
	SD of % change	12.33	13.76	13.33		
	95% CI of absolute difference (kgs)	-167.72 to 57.72	-139.81 to 61.53	-155.63 to 52.21		
Post-training power isometric LP	% change from pre-exercise	-18.20	-10.90	-0.32		
	SD of % change	12.33	13.23	13.74		
	95% CI of absolute difference (kgs)	-166.45 To 33.01	-127.28 To 31.28	-90.86 to 74.28		

3.7.2 Static jumps

In the hypertrophic loading condition, there was main effect for time (p=0.005, Greenhouse-Geisser) but no training (p=0.21) or interaction effect (p=0.26) (figure 28) (Table 5,6). In the power loading condition, there were no training (p=0.809), time (p=0.174, Greenhouse-Geisser), interaction effects (p=0.673).

Pre-training, 1 way repeated measures ANOVA found a significant main time effect (p=0.015, Greenhouse Geiser) for the hypertrophic loading condition, but none of the differences between timepoints, even immediately post-loading, were significant. Post-training, there was a significant main time effect (p=0.003, Greenhouse-Geisser) for the hypertrophic loading condition, but post-hoc pairwise analysis found no significant differences between any specific time points: the difference between the immediate post-loading and 72 hour time point was p=0.072. Pre-training, 1 way repeated measures ANOVA found no significant main time effect (p=0.236) for the power loading condition, and thus, none of the differences between timepoints, even immediately post-loading, were significant. Post-training, there was also no significant main time effect (p=0.2. Greenhouse-Geisser) for the power loading condition. Pre-training, there were main effects for time (p=0.012, Greenhouse-Geisser), loading (p<0.001), and a loading (hyp,pow) x time interaction effect (p=0.044), Greenhouse-Geisser). Pre-training, paired t-tests between the loading conditions at each time point revealed that the decrease in static jump height immediately after hypertrophic loading was significantly greater than the decrease immediately subsequent to power loading (p=0.008). Also, the difference between the two loading conditions at the 48h timepoint was also significant (p=0.049). Post-training, there was a main effect for time (p=0.014, Greenhouse-Geisser), and a loading x time interaction effect. (p=0.049, Greenhouse-Geisser) Within subjects contrast revealed that this interaction effect was at the post-loading time point (p=0.037). Therefore, paired t-tests between the loading conditions at that time point revealed that the decrease in static jump height immediately after hypertrophic loading was significantly greater than the decrease immediately subsequent to power loading (p=0.032).

There were no significant differences between loading conditions at any other time point.

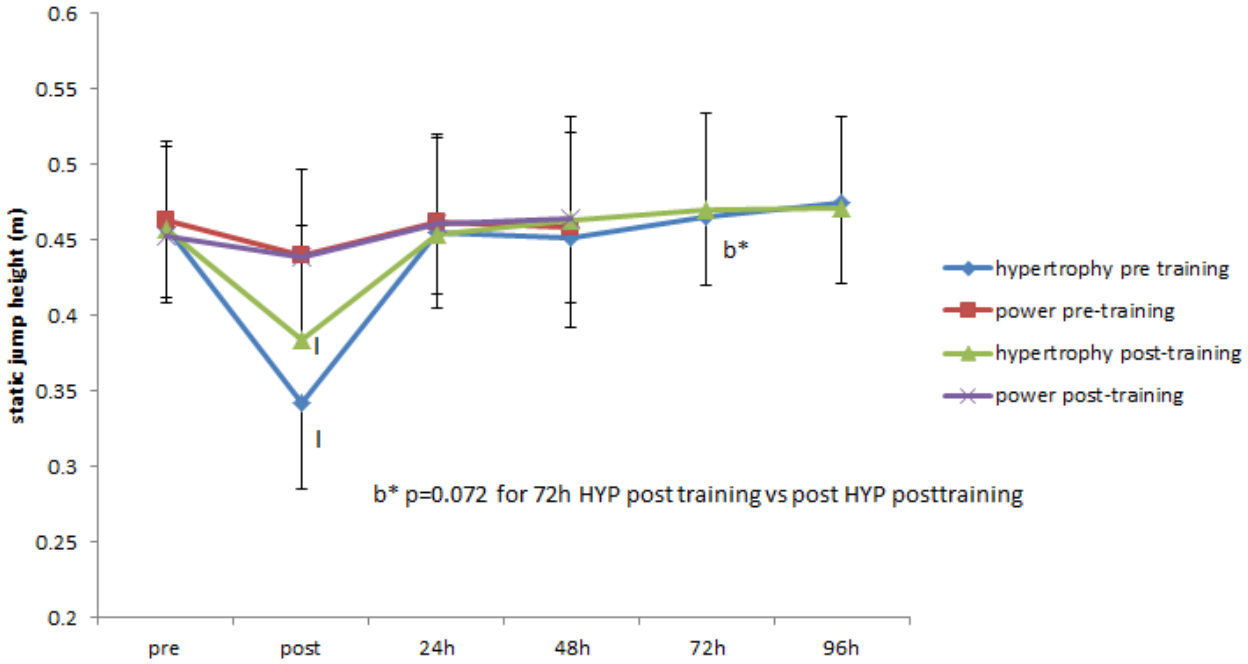

Figure 28: time course results for maximal static jump height, a represents $p<0.05$ from pre-exercise in that loading or training condition, b represents $p<0.05$ from immediately post-exercise, c represents difference from 24hours after exercise, l: difference between loading conditions

Table 5: Recovery results for static jumps, l: difference between loading conditions

	Pre(means±SD, 95% CI for mean)	Post 0h	24h	48h	72h	96h
Static jump pre-training hypertrophy (m)	0.46±0.05 0.41-0.51	0.34±0.14[l] 0.16-0.42	0.45±0.04 0.42-0.49	0.45±0.04 0.41-0.49	0.46±0.04 0.42-0.51	0.47±0.05 0.43-0.52
Static jump post-training hypertrophy (m)	0.46±0.06 0.40-0.51	0.38±0.08[l] 0.31-0.45	0.45±0.06 0.39-0.51	0.46±0.07 0.40-0.53	0.47±0.06 0.41-0.53	0.47±0.06 0.42-0.53
Static jump pre-training power (m)	0.46±0.05 0.42-0.51	0.44±0.05 0.39-0.49	0.46±0.06 0.41-0.52	0.46±0.07 0.40-0.52		
Static jump post-training power (m)	0.45±0.06 0.40-0.51	0.44±0.06 0.38-0.49	0.46±0.06 0.41-0.52	0.46±0.06 0.41-0.52		

Table 6: changes for static jumps from pre-exercise time-point

		Post 0h	24h	48h	72h	96h
Pre-training hypertrophy, static jumps	% change from pre-exercise	-25.96	-0.63	-1.32	1.45	3.32
	SD of % change	14.88	5.30	4.37	2.20	2.32
	95% CI of absolute difference (m)	-0.24 to 0.00	-0.06 to 0.04	-0.06 to 0.04	-0.05 to 0.04	-0.05 to 0.07
Post-training hypertrophy, static jumps	% change from pre-exercise	-16.14	-0.98	1.08	2.56	3.06
	SD of % change	11.04	2.66	3.18	2.67	4.88
	95% CI of absolute difference (m)	-0.16 to 0.00	-0.08 To 0.06	-0.08 To 0.08	-0.06 To 0.08	-0.06 To 0.08
Pre-training power, static jumps	% change from pre-exercise	-4.92	-0.20	3.71		
	SD of % change	8.18	4.93	9.64		
	95% CI of absolute difference (m)	-0.08 To 0.04	-0.06 To 0.06	-0.07 To 0.07		
Post-training power, static jumps	% change from pre-exercise	-2.90	2.02	2.60		
	SD of % change	7.82	2.87	2.15		
	95% CI of absolute difference (m)	-0.08 To 0.06	-0.06 To 0.08	-0.06 To 0.08		

3.7.3 Muscle thickness

For the hypertrophy condition, there was an overall main effect for time both pre ($p=0.003$) and post-training ($p<0.001$) (figure 29) (Table 7,8). Pre-training, muscle thickness at 48h ($p=0.011$) and 96h ($p=0.047$) was greater than prior to exercise. Post-training, muscle thickness at 24h ($p<0.001$) and 48h ($p=0.002$) was greater than prior to exercise, and muscle thickness at 72h was greater than at 24h ($p=0.008$). In the HYP condition, there were significant increases post-training compared to pre-training at 24h ($p=0.001$), 48h ($p=0.007$), 72h ($p=0.032$), 96h ($p=0.007$), but not prior to exercise loading ($p=0.454$)

For the power condition, there was no overall main effect for time pre ($p=0.14$) and post-training ($p=0.141$).). In the POW condition, there were significant differences between pre and post training prior to exercise loading ($p=0.026$), at 24h, ($p=0.037$), but not at 48h ($p=0.164$). Pre-training, muscle thickness in the HYP and POW conditions, were not different at the pre-loading (0.230), 24h (0.130), 48h (0.192) timepoints. Post-training, muscle thickness was not different between HYP and POW pre-exercise ($p=0.457$) but HYP was greater than power at 24h ($p<0.001$) and 48h ($p=0.002$). VL thickness was greater post-training compared to pre-training, at every time-point in the power condition and greater 24, 48, 72, 96 hours after acute hypertrophy loading post-training. Overall, in the hypertrophy loading condition, VL thickness significantly increased by 1.7mm after training; similarly in the power loading condition VL thickness overall significantly increased by 0.91 mm after training.

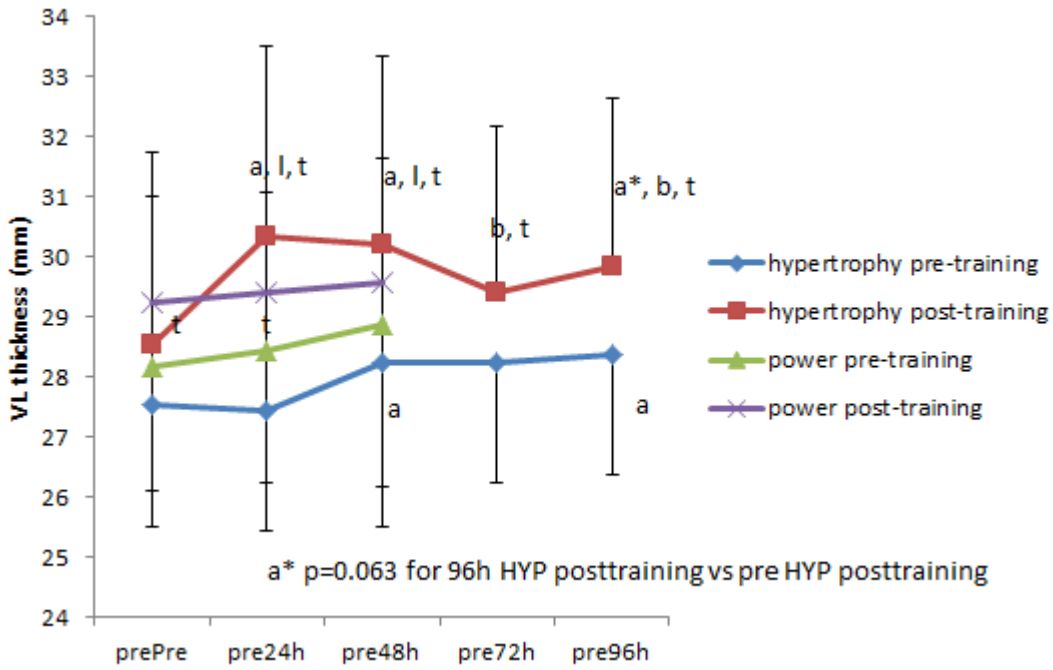

Figure 29: VL thickness measured by ultrasound. a: $p < 0.05$ from preloading time-point; b: $p<0.05$ from the 24h time point; l: $p<0.05$ from corresponding time-point in the alternate loading condition at that time-point; t: $p<0.05$ between pre and post-training at that time-point

Table 7: Recovery results for vastus lateralis thickness. a: $p < 0.05$ from preloading time-point; b: $p<0.05$ from the 24h time point; l: $p<0.05$ from corresponding time-point in the alternate loading condition at that time-point; t: $p<0.05$ between pre and post-training at that time-point

	Pre(means±SD, 95% CI for mean)	24h	48h	72h	96h
VL thickness (mm) pre-training (hypertrophy)	27.55±2.04 26.62-28.48	27.44±2.01 26.52-28.35	28.24±2.72[a] 27.00-29.48	28.23±1.99 27.32-29.13	28.37±1.99[a] 27.46-29.28
VL thickness (mm) post-training (hypertrophy)	28.55±3.20 27.09-30.01	30.33±3.19 28.88-31.78[a,l,t]	30.20±3.13 28.77-31.63[a,l,t]	29.40±2.76 28.14-30.66[b,t]	29.85±2.79 28.58-31.12[b,t]
VL thickness (mm) pre-training (power)	28.18±2.81 26.90-29.46[t]	28.42±2.64 27.22-29.63[t]	28.88±2.78 27.61-30.14		
VL thickness (mm) post-training (power)	29.25±3.15 27.82-30.68	29.40±3.17 27.96-30.84	29.56±3.39 28.01-31.10		

Table 8: changes for vastus lateralis thickness from pre-exercise time-point;

		Post 0h	24h	48h	72h	96h
Pre-training hypertrophy, muscle thickness	% change from pre-exercise		-0.07	2.56	2.56	3.18
	SD of % change		8.69	2.91	3.88	6.21
	95% CI of absolute difference (mm)		-2.47 To 2.25	-2.11 To 3.49	-1.67 To 3.03	-1.53 To 3.17
Post-training hypertrophy, muscle thickness	% change from pre-exercise		6.38	5.99	3.22	4.85
	SD of % change		4.56	5.61	4.31	5.22
	95% CI of absolute difference (mm)		-1.94 To 5.50	2.04 5.34	-2.63 4.33	-2.20 4.80
Pre-training power, muscle thickness	% change from pre		0.96	2.53		
	SD of % change		2.71	2.36		
	95% CI of absolute difference(mm)		-2.94 to 3.42	-2.56 to 3.96		
Post-training power, muscle thickness	% change from pre-exercise		0.56	1.07		
	SD of % change		2.98	4.22		
	95% CI of absolute difference (mm)		-3.53 to 3.83	-3.50to 4.12		

3.7.4 Blood lactates

Pre-training, in the HYP condition, there was a main time effect ($p<0.001$) (figure 31). Pairwise comparison revealed that blood lactate after the third ($p<0.001$) set, and 5 minutes post-exercise ($p=0.001$), was higher than pre-exercise. Post-training, in the HYP condition, there was a main time effect ($p<0.001$). Pairwise comparison revealed that blood lactate after the third ($p=0.003$) set, and 5 minutes post-exercise ($p=0.003$), was higher than pre-exercise.For the power condition, there was an overall main effect for time ($p<0.001$), but none for training ($p=0.478$), nor was there a time x training interaction effect ($p=0.082$).For the hypertrophy condition, there was an overall main effect for time ($p<0.001$), but none for training ($p=0.193$), nor was there a time x training interaction effect ($p=0.140$).Pre-training, there were main effects for time ($p<0.001$), loading condition ($p=0.003$) and an interaction effect between time and loading condition ($p=0.002$). Post-training, there were main effects for time ($p=0.003$), loading condition ($p=0.001$) and an interaction effect between time and loading condition ($p=0.006$). Paired t-tests found that blood lactate was higher in HYP than in POW, both pre-training ($p=0.002$) and post-training ($p=0.003$). Pre-training, in the POW condition, there was a main time effect ($p<0.001$) (figure 30). Pairwise comparison revealed that blood lactate after the third ($p=0.017$) and eight ($p=0.017$) set was higher than pre-exercise. Blood lactate after the third set ($p=0.017$) and eighth ($p=0.025$) was higher than 5 minutes post-exercise. Post-training, in the POW condition, there was a main time effect ($p=0.019$, Greenhouse-Geisser). Pairwise comparison showed that blood lactate after the fifth ($p=0.022$) and eight ($p=0.005$) set was higher than pre-exercise.

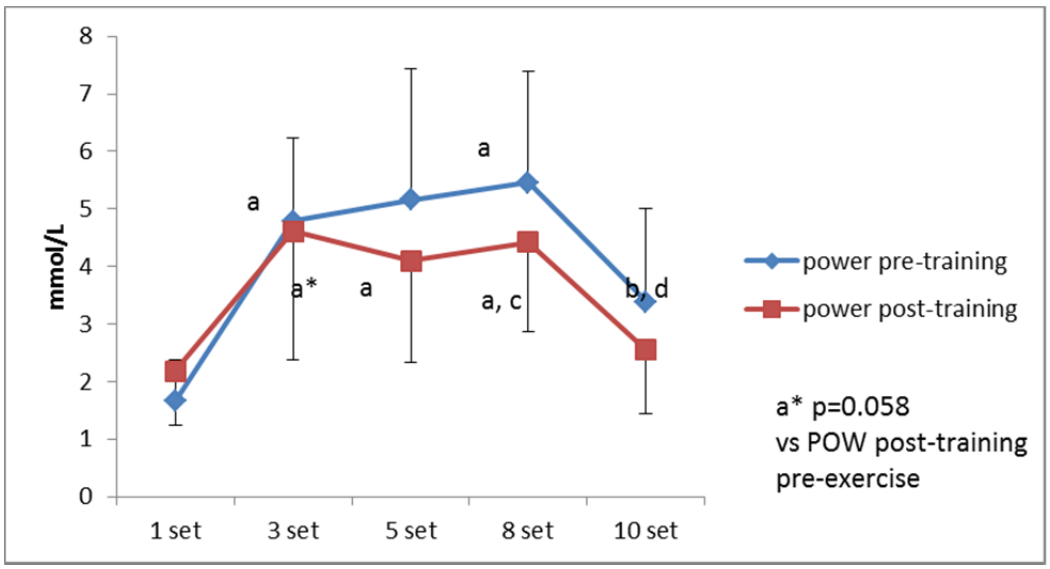

Figure 30: blood lactates in POW, a: $p<0.05$ from preloading time-point; b: $p<0.05$ from the 3rd set time point; c: $p<0.05$ from the 5th set, d: $p<0.05$ from the 8th set

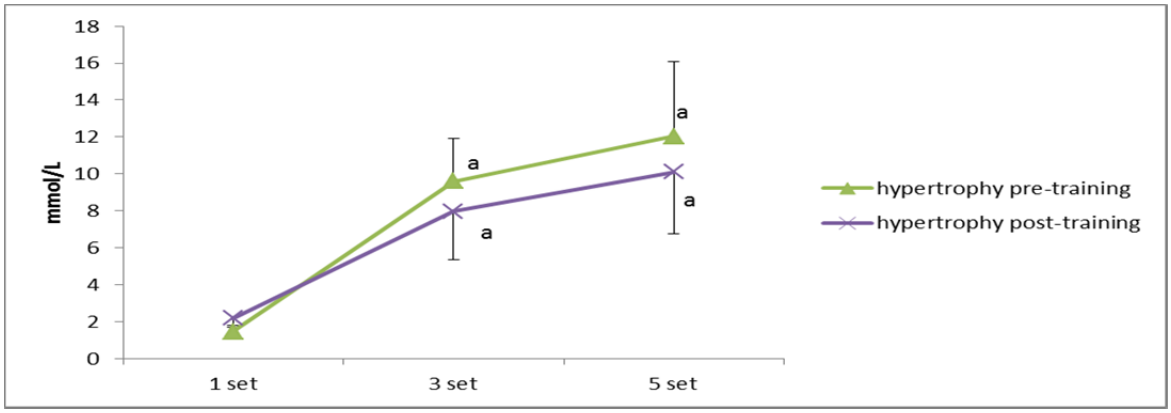

Figure 31: blood lactates in HYP, a: $p< 0.05$ from preloading time-point

3.8 Mechanical work

Mean mechanical work performed, post-training, in POW was greater than that in HYP (Table 9), whether absolute mechanical work ($p<0.001$) or relative to bodyweight ($p<0.001$). Conversely, total tonnage, that is mean total weight lifted, was greater in the HYP condition ($p=0.035$)

Table 9: mechanical work performed in HYP and POW, total weight lifted (reps * sets * weight), mechworkHYP: mechanical work in HYP, mechworkPOW: mechanical work in POW, relatveMWHYP: mechanical work in HYP relative to bodymass, relativeMWPOW: mechanical work in POW relative to bodymass

	mech workHYP (J)	mechworkPow (J)	relativeMWHyp (J/kg)	relativeMWPow (J/kg)	WeightliftedHYP (kg)	WeightliftedPOW (kg)
Participant 1	16740.68	29852.59	217.98	388.71	9250	7750
Participant 2	18927.13	35991.36	218.56	415.60	8750	9000
Participant 3	19581.76	30474.22	221.76	345.12	10710	9125
Participant 4	14322.75	23357.27	161.11	262.74	7735	6625
Participant 5	16246.19	26088.97	190.91	306.57	9280	7125
Participant 6	16400.86	26154.42	210.54	335.74	10295	6250
Participant 7	12373.69	28234.39	138.41	315.82	7825	7750

3.9 Subjective Perceptions

There were main time effects for muscle soreness pre and post-training after HYP ($p<0.001$, $p=0.001$) and POW ($p=0.006$, $p=0.016$). Pre-training, the increase in muscle soreness after HYP was greater than after POW at 24 ($p=0.018$) and 48 hours (p-0.028). Post-training, the increase in muscle after HYP was greater than after POW at 48 hours ($p=0.027$), but not 24 hours ($p=0.173$). There were main time effects for power to perform pre ($p<0.001$) and post-training ($p<0.001$) after HYP, but only pre-training ($p=0.002$) and not post-training ($p=0.108$) for POW. Pre-training, differences in readiness to perform between HYP and POW were significant at the 48h time-point ($p=0.016$), but not at the 24h time-point ($p=0.453$). Post-training there were no significant differences between HYP and POW in readiness to perform whether at the 24h ($p=0.375$) or 48h ($p=0.453$) time-points.

3.10 Correlations

3.11 Hypertrophic Loading

After HYP, relative changes in both p-rpS6 ($r=0.821$, $p=0.023$) (figure 32) and p-ERK ($r=0.821$, $p=0.023$) were correlated with relative changes in static jump height immediately post-exercise. There was also a significant correlation ($r=0.793$, $p= 0.033$) between the absolute change in p-p70S6K1 at Ser424 and the absolute change in static jump height immediately after HYP.

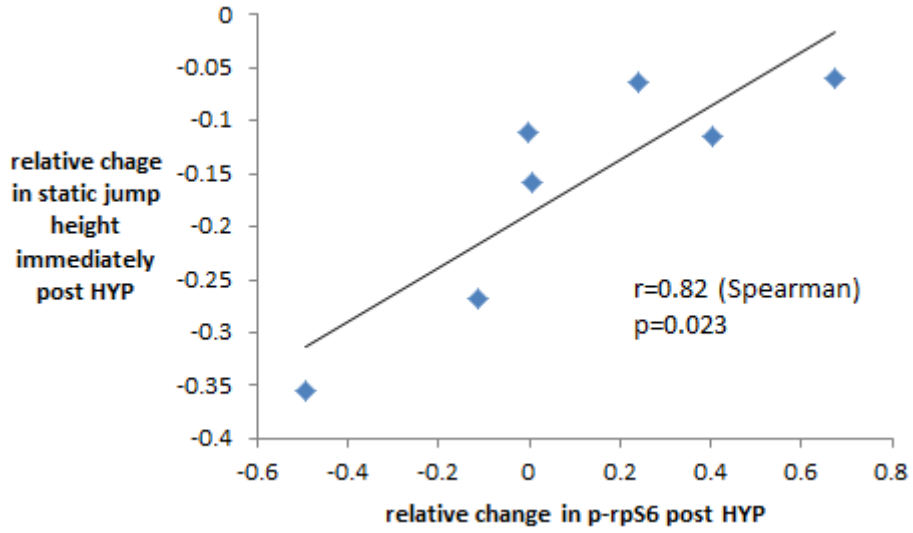

Figure 32: correlation of relative changes (post divided by pre) in p-rpS6 and relative changes in static jump height immediately after HYP

Relative changes in p-38 post-HYP were inversely correlated with relative changes in VL muscle thickness at 72 hours (r=-0.786, p=0.036) (figure 33) and 96 hours (r=-0.786, p=0.036). Relative change in p-ERK was also inversely correlated with VL thickness at 72 hours (r=-0.821, p=0.023).

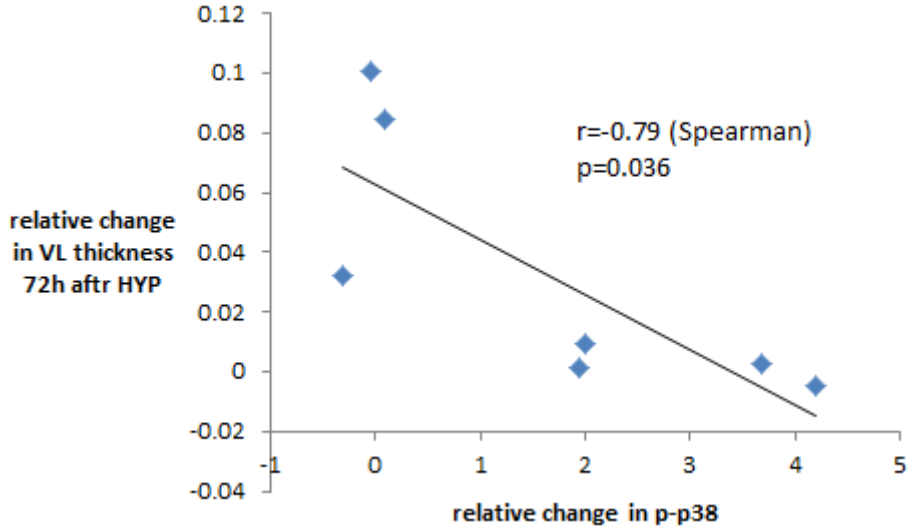

Figure 33: correlation of relative changes in p-p38 (post divided by pre) and relative changes in VL thickness at 72h after HYP

3.12 Power Loading

The relative change in p-p70S6K1 at Thr389 was inversely correlated (r=-0.929, p=0.003) (figure 34) the relative change in static jump height at 48 hours after POW. But, the relative changes in p-rpS6 (r=0.857, p=0.014) (figure 35) and p-ERK (r=0.821, p=0.023) were correlated with the relative change maximal isometric leg force at 24 hours after POW.

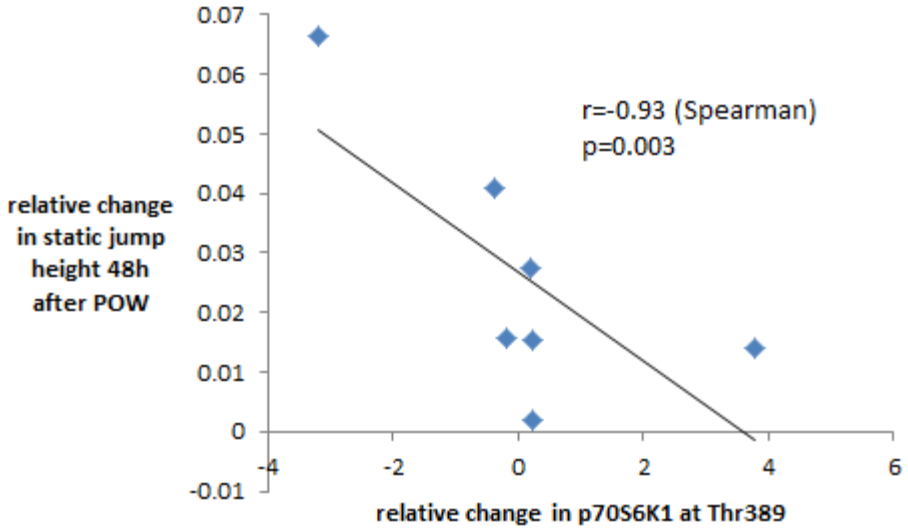

Figure 34: Correlation between relative changes in p-p70S6K1 at Thr389 and relative changes in static jump height 48h after POW

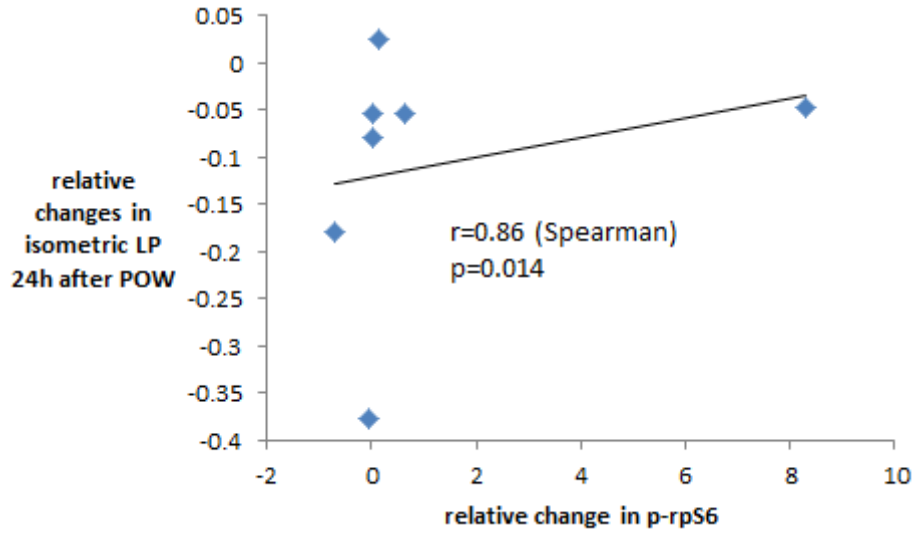

Figure 35: Correlation between relative changes in p-rpS6 at and relative changes in maximal isometric LP 24h after POW

3.13 Mechanical Work

No correlations between mechanical work performed, whether absolute or relative to body mass, and any changes in phosphorylated proteins post-exercise.

4 DISCUSSION

4.1 Phosphorylated proteins

The main finding of the current work was that there were no significant changes in any of the signalling proteins involved in protein translation assessed, after either hypertrophy or power loading post-training. This was surprising, as many previous studies in the literature have found significant changes in at least some of these signalling proteins after resistance training, whether in untrained (Hulmi et al. 2012; Walker et al. 2013) or trained (Apró et al. 2015; Galpin et al. 2012; Walker et al. 2013) participants, using maximal (Hulmi et al. 2012), hypertrophic high load (Hulmi et al. 2012), hypertrophic low load (Burd et al. 2010; Burd et al. 2011; Léger et al., 2007), hypertrophic high volume (Ahtiainen et al. 2015), power loading stimulus (Galpin et al. 2012), or varying resistance load (Walker et al. 2013), in fasted (Apró et al. 2013; Apró et al. 2015; Dreyer et al. 2010; Harber et al. 2008;) or fed states (Areta et al. 2014; Moberg et al. 2014; West et al. 2012), in a low glycogen state (Creer et al. 2005; Camera et al. 2012), in young men (Apró et al. 2015; Hulmi et al. 2012;) or young women (Dreyer et al. 2010; Harber et al. 2008; West et al. 2012).

Previously, Hulmi et al. (2012) demonstrated that in young men, a hypertrophic loading protocol that was exactly the same as in the current work significantly increased p-p70S6K1 at Ser424 and Thr389., p-rps6 at Ser235/236 and Ser240/244, p-ERK1/2, p-p38 alpha at Thr180/Tyr182and p-p38 γ at Thr180/Tyr182. Hulmi et al. (2012) used untrained participants, whereas in the current work vastus lateralis was biopsied after 3 months of training. Using the same 5x10 at 80% of 1RM protocol, Walker et al. (2013), found significant increases in p-p70S6K1 at Thr389, p-rpS6 at Ser235/236, p-rpS6 at Ser240/244 and p-p38 Thr180/Tyr182 both pre and post-training. p-ERK ½ at Thr202/Tyr204 significantly increased pre-training, but not post-training. Although there was some attenuation in phosphorylation of proteins after training, there were still significant changes after acute exercise loading (Walker et al. 2013). Unfortunately in the current work, even though pre-training biopsies were collected, they were unavailable for western blot analysis due to a logistical accident. Similar to Walker et al. (2013), various different loading

protocols have elicited significant increases in hypertrophic signalling in trained men whether in p70S6K (Apró et al. 2015) or the MAPKs (Galpin et al. 2012). ERK ½ phosphorylation at after 8 sets and 90 minutes after 16 sets of clean pulling in trained competitive young male weightlifters was not significant, but there was a main time effect. Conversely, increases in p38 Thr180/Tyr182 and JNK phosphorylation at both midpoint and post-exercise were significant (Galpin et al. 2012). Additionally, Vissing et al. (2011) found no differences in signalling proteins after acute resistance exercise pre and post-training.

However, there were no statistically significant increases in p-p70S6K1 and p-rpS6 either immediately after 8x5 maximal isokinetic unilateral knee extensions or 3 hours after, in trained overnight fasted male powerlifters (Coffey et al. 2006). There were also no significant increases in p-ERK1/2 and p-p38. In the same study, there was a significant increase in p70S6K1, S6 and p38 phosphorylation in endurance trained cyclists who had been undergoing regular endurance training for 8 years without any resistance training. Therefore, Coffey et al. (2006) postulated that the lack of significant increases in the resistance trained participants might be due to negative feedback. Similarly, 12 weeks of training of the arm muscles of young men and women attenuated acute exercise induced increases in phosphorylated rpS6 in the biceps brachii, such that post-training increases were not statistically significant, unlike pre-training increases (Nader et al. 2014). There were no significant changes in p-ERK½ whether immediately post-exercise, 2.5, 5, or 22 hours after in trained men after 4x12 of leg presses, knee extensions and knee curls (Møller et al., 2013). In support of this, Hamilton et al. (2014) demonstrated that significant increases in p70S6K1 at Thr389 phosphorylation at days 3, 6, 9, 12 in the plantaris of female Wistar rats that had their gastrocs and soleus ablated, concurrent with significant increases in plantaris muscle hypertrophy, were attenuated by day 21. Taken together, this suggests that the lack of significant changes post-exercise loading in the current work might be because participants were trained.

The lack of any significant changes might also be explained by the time point at which muscle was biopsied in the current work, that is as soon as the exercise loading were complete. Muscle samples were collected approximately 5-10 minutes after the conclusion of the post exercise loading static jump measurement in the current work. p70S6K Thr389 phosphorylation increased significantly only 60 minutes after resistance exercise consisting of 8x5 knee extensions at 80%

of 1RM, in young men, whereas the increases at 0, 15, and 30 minutes post-exercise were not significant (Camera et al., 2010). 4EBP1 phosphorylation at Thr37/46 and Thr70 did not change significantly from rest at any time-point. Similarly, there were significant increases in p70S6K Thr389 phosphorylation after 24 hours, but not immediately after exercise in recreationally active young men who performed 10x10 knee extensions at 80% of 1RM with 150 seconds of rest between sets, (Deldicque et al. 2008). However, both p70S6K at Thr421/Ser424 and 4EBP1 Thr 37/46 phosphorylation increased significantly immediately after. Additionally, in active but untrained young men and women who performed 10x10 knee extensions at 70 of 1RM, increases in p70S6K1 phosphorylation were only significant after 2 hours, but not immediately or 1 hour subsequent to exercise (Dreyer et al. 2006).

In a systematic review of 77 resistance exercise studies that the author conducted, 20 performed biopsies within 10 minutes post-exercise and assessed phosphorylation of p70S6K1 and / or the MAPKs. 15 found no significant increases in p70S6K1 at Thr389 phosphorylation immediately post-exercise, whereas 2 (Apró et al. 2010; Koopman et al. 2007) did. In 9 of the 15 studies that found no significant changes immediately post-exercise, participants were overnight fasted, whereas 2 of the 2 studies in which a significant increase occurred were with participants provided with protein supplements. Koopman et al. (2007) reported no significant changes if only carbohydrate was supplemented, but there were significant changes if protein and carbohydrate was consumed. In the current work, participants were provided with instructions to consume breakfast prior to arriving at the laboratory. It appears that statistically significant increases in p70S6K phosphorylation occur only at least 15 minutes post-exercise (Coffey, Jemiolo et al. 2009; Lundberg et al. 2012; Mascher et al. 2008), whereas most authors (Deldicque et al. 2008; Galpin et al., 2012; Harber et al. 2008), but not all (Møller et al., 2013), have found significant increases in ERK1/2 phosphorylation immediately post-exercise. Decreases in 4EBP1 occurred within 10 minutes of resistance loading in some whether fasted (Deldicque et al. 2008; Dreyer et al. 2006; Spiering et al. 2008), or fed (Witard et al. 2009), but not in others: fed (Borgenvik et al. 2012), fasted (Camera et al. 2010; Creer et al. 2005). There were no significant changes in rpS6 phoshorylation right after exercise in fasted (Koopman et al. 2006) or fed conditions (Karlsson et al. 2004), conversely, there were in some other fed conditions (Witard et al. 2009).

Taken together, significant changes in p-p70S6K Thr389 occurs least 30 minutes post-exercise, whereas MAPK signalling is rapid. In support of this, post exercise biopsies in many studies are conducted at least 30 minutes subsequent (Ahtiainen et al., 2015; Hulmi et al., 2012; Terzis et al. 2008, 2010; Walker et al., 2013).

The lack a detectable change in phosphorylated p70S6K1 at Thr389 might also be due to the use of too small a sample size, resulting in low statistical power to detect a significant change, as only a very large effect size would be statistically significant with such small number of participants McGlory et al. (2014) reported that whereas western blotting detected no significant changes in p70S6K1 phosphorylation in 6 young men provided with protein supplements, with biopsies at 1 and 3 hours after 4x10 leg presses at 70% 1RM and 4x10 knee extensions at 70% 1RM, there was a significant increase when p70S6K1 was quantified by kinase assays (KA), which is considered the gold standard for assessing protein kinase activity (Hastie et al., 2006). In their work, McGlory et al. (2014) estimated that a sample size of 12 would have been necessary for statistical significance. In the current work, post-hoc calculation of statistical power found that a sample size of 24 participants would have been necessary for the post hypertrophy loading increases in p70S6K1 at Thr389 phosphorylation to reach significance, similarly, a sample size of 13 would have been necessary for the power loading increases. Nonetheless, it must be noted that many other studies have found much larger fold changes than the current work, and have found significant changes in protein signalling with for example 8 participants, following resistance exercise and / or protein feeding stimulus (Cuthbertson et al. 2006).

4.1.1 Molecular response to hypertrophy versus power loading

There were no significant differences in phosphorylation of proteins in response to the hypertrophic versus the power loading conditions. Therefore, hypothesis (i), that hypertrophic and power loadings would elicit different responses in protein signalling mechanisms involved in skeletal muscle hypothesis was rejected.

There was a divergent response to HYP and POW in p-ERK levels which decreased after HYP, but increased after POW, although these changes were not significant. Similarly, although p-ERK increased in 4 individuals post-exercise in both loading conditions, these increases were not in the

same individuals in both conditions. There were also divergent responses in individual signalling proteins amongst individuals, in that phosphorylation in some individuals increased, while it decreased in others. Furthermore, these responses diverged based on the loading condition, in that whereas HYP resulted in increased phosphorylation in some individuals and decreased in others, for example in p-70S6K1 at Ser424, p-4EBP1, p-rpS6, p-ERK, this was reversed in POW. There can be considerable inter-individual variation in the effects of both aerobic and resistance exercise on health outcomes (Bouchard et al., 2012) and muscle fibre cross-sectional area (Bamman et al. 2007). The variation in intra and inter-individual signalling responses to HYP and POW in the current work might suggest that just as there is individual variation in training outcomes, there should likewise be, and is, individual variation in the mechanisms responsible for those outcomes. Mayhew et al. (2011) postulates that increased p70S6K phosphorylation, and thus translation initiation, myofibre size, and muscle mass only occurs in some animals prone to muscle hypertrophy, "extreme responders". However, these individual differences in the current work were not reflected in statistically significantly mean differences at the group level.

The lack of individualization of the load used might be responsible for the lack of difference between the HYP and POW sessions, in that participants were not generating their potential maximum peak power in POW, and thus, the stimuli from both sessions were too similar, as while the loading sessions resulted in differences in static jump height immediately post exercise, and in muscle thickness at 24 and 48 hours,, there were no other differences in other recovery measures. On the other hand this also suggests perhaps that loading schemes might not be a key factor in hypertrophy, a possibility supported by some recent research in untrained (Léger et al., 2007; Mitchell et al. 2012) and trained participants (Schoenfeld et al. 2015), except in extreme conditions, that is elite bodybuilders versus elite weightlifters. Even in such cases, whereas there are differences in limb girths between weightlifters and bodybuilders, such group differences are present only for the shoulders, chest, biceps relaxed and flexed, forearm (Katch et al. 1980), that is, muscles that are generally not trained in any systematic manner by weightlifters. Indeed, weightlifters generally avoid direct biceps training, as excessive biceps hypertrophy can interfere with fixation of the barbell on the clavicles and frontal deltoids during the clean (Drechsler, 1998; Vorobyev 1978). However, Huygens et al. (2002) found that bodybuilders have larger limb circumferences than powerlifters and weightlifters, even in the thigh. In an acute intervention study, Holm et al. (2010) found that when loads were work matched, heavy load , that is 10x8 at

70% of 1RM, elicited greater increases in phoshorylated ERK1/2 and AKT Ser473, than light load, that is 10x36 at 16% of 1RM, and also greater increases in myofibrillar FSR. Nonetheless, Schoenfeld et al. (2015) recently found that when workload was not matched, light load (20-35 reps) to momentary failure resulted in similar increases in the thickness of the elbow flexors, elbow extensors and quadriceps femoris of trained young men as high load (8-12 reps) to momentary failure resistance training

4.1.2 Relationship between phoshorylated proteins and recovery measures

HYP and POW elicited some differing responses with regards to both immediate post-exercise measures of power (static jumps), and muscle thickness in the days post-exercise, which were correlated with some changes in signalling proteins, in support of the hypothesis (ii), that there would be relationships between recovery from exercise loading, as assessed by static jumps, maximal isometric leg press force, muscle thickness, and changes in signalling proteins post-exercise.

In the HYP condition changes in static jump height immediately after exercise were correlated with changes in p-ERK, p-38, p-70S6K1 at Ser424 and p-rpS6, but there was no such correlation for p-p70S6K1 at Thr389, as would be expected, as phosphorylation of p70S6K1 at Thr389, the hydrophobic motif, is necessary for full activation of p70S6K1 (Alessi et al. 1998; Weng et al. 1998) and thus downstream activation of S6. These correlations suggest perhaps a relationship between recovery from hypertrophic type loading and molecular signalling proteins involved in SkM hypertrophy. There were inverse correlations between muscle thickness at 72 and 96 hours after HYP and p-p38 and p-ERK levels. These too might posit that there is a relationship between recovery from exercise and signalling proteins, in that muscle swelling diminishing to pre-exercise levels more quickly is associated with increased phosphorylation of MAPK proteins.

However, after POW, although changes in maximal isometric leg press force immediately post-exercise was correlated with changes in rpS6 and ERK phosphorylation, there was confoundingly an inverse correlation between p70S6K1 phosphorylation at Thr389 and changes in static jump height after 48 hours.

Therefore, hypothesis (iii), that relationships between recovery from exercise and signalling proteins in HYP and POW diverge was accepted.

4.1.3 Relationships between mechanical work and phosphorylated proteins

There were no correlations between mechanical work performed, whether absolute mechanical work or mechanical work relative to bodyweight, and any changes in molecular signalling proteins, thus resulting in the rejection of hypothesis (iv), that there would be a relationship between mechanical work and changes in molecular signalling proteins. These findings are in agreement with Galpin et al. (2012) who reported no distinct correlation patterns between MAPK signalling and mechanical work or power output after clean pulling in trained male weightlifters.

4.2 Recovery measures

The decrease in static jump height immediately after HYP, pre and post-training, was greater than that after POW. Similarly, HYP resulted in significantly increased muscle swelling whereas POW did not, and this increased swelling in HYP was greater than that of POW post-training. There were significant differences in VL thickness before and after training, suggesting that some tissue hypertrophy occurred after training. Notably, after training, hypertrophy loading caused a greater post-exercise VL swelling compared to power loading. In young and middle-aged men and women undergoing progressive heavy hypertrophic type resistance training over 12 weeks, there was a (non-significant) mean 7% increase in quadriceps muscle thickness (Abe et al. 2000). In the current work, the differences in muscle thickness prior and subsequent to 12 weeks of training were 4.9%. Cellular swelling might promote anabolism whereas catabolism might be the result of cell shrinkage (Häussinger et al., 1993; Häussinger, 1996). Swelling can increase amino acid transport in cultured muscle fibres, which is prevented by inhibition of PI3K (Low et al., 1997) and increased protein synthesis can occur as a result of hydration mediated cell swelling (Lang et al. 1998). It has been suggested that the effects of cell swelling on SkM hypertrophy are mediated via integrin signalling (Carson & Wei, 2001) as phosphorylation of focal adhesion kinase (FAK), a signaling protein linked to integrins, increases as a result of mechanical loading (Gordon et al. 2001). Alternatively, MAPK signalling might be the main mediator of swelling

induced hypetrophy (Schliess et al. 1995). Lactate accumulation, for example as seen after hypertrophic type loading versus power loading in the current work, might be the primary cause of osmotic changes in SkM (Sjogaard et al. 1985, 1986), and lactate might play a role in modulating myogenesis in myoblasts (Willkomm et al. 2014), thus providing a link for increased cell swelling as a result of anaerobic glycolytic exercise

Li et al. (2013) found an increase in FAK at Tyr397 phosphorylation in 6 young men who underwent 9 weeks of leg extension training. There were also concurrent increases in VL thickness as measured by ultrasonography, VL anatomical cross-sectional area, and type 1 muscle fibre CSA, from pre to post-training. The increases in FAK Tyr397 phosphorylation and type 1 muscle fibre CSA were correlated ($r>0.65$). Surprisingly, p70S6K1 at Thr389 phosphorylation decreased, and was inversely associated with type 2 muscle fibre CSA. It must be cautioned however that the current work assessed neither FAK phosphorylation nor muscle (fibre) CSA, therefore, it is merely speculation as to the role of exercise induced swelling in SkM hypertrophy.

4.3 Limitations and future research

The limitations of the current work must be mentioned. As already stated above, the number of participants, 7 in total, was small. Furthermore, only p70S6K1 at Thr389 could be normalised against either total proteins as assessed via Ponceau S staining, or alpha tubulin as a control. The other proteins were only normalised against the pooled sample on each gel run. Also, only phosphorylated, but not total amounts of each protein was assessed; previous work in this laboratory by other researchers (Hulmi et al. 2012), and elsewhere (Dreyer et al. 2008), have found no changes in total amounts of each protein after resistance exercise. This study did not include any non-exercising controls. Previous work, including by other researchers in this laboratory (Hulmi et al. 2009), and elsewhere (Galpin et al. 2012) have found that muscle biopsy does not cause any changes in protein phosphorylation in non-exercising controls. More importantly, only 1 post-exercise biopsy was conducted, and although this biopsy was conducted immediately post-exercise, the exact timing of collection was not the same for all participants, with the collection time-point ranging from 5-10 minutes post-exercise, as some participants bled

more freely. Thus, the molecular protein results are only 1 "snapshot" of acute intramuscular responses at that particular moment in time. To study whether, and how, recovery from resistance exercise loading interacts with changes in molecular signalling, there would ideally be multiple biopsies, on each day recovery testing was conducted. However, this was not done in the current work due to logistical issues. Future research should attempt to remedy this, to properly assess any interactions between molecular signalling, and performance in recovery measures, such as jump height, maximal strength.

Mechanical work was not calculated for every repetition, on every set, but rather, it was calculated for one set for each participant for each loading, and the mechanical work performed during that set was assumed to be the same for all other sets for that participant in that loading condition. Previously, other researchers (Walker et al. 2013) from this laboratory have attached a force plate to the leg press to assess mechanical work performed during resistance loading. Similarly, Galpin et al. (2012) calculated mechanical work using video recordings of every repetition performed. Neither of these was done in the current work because of time and logistical constraints.

The load used in the power loading condition was 70% of 1 repetition maximum. It has been shown that peak power achieved during resistance exercise varies according to the individual (Bevan et al. 2010) and movement (Kilduff et al. 2007). Ideally, participants would have been tested prior to exercise loading, on a force plate, to determine at what percentage of 1RM each individual achieves peak power output.

Muscle thickness was only measured at the 50% point of the VL between the lateral epicondyle and the greater trochanter. Whereas this region might be considered to be best indicative of muscle swelling and growth, there might be site dependent differences responses, both in terms of acute swelling and chronic growth in response to resistance loading, mediated by the type of exercise performed (Fahs et al. 2014; Wakahara et al. 2012, 2013).

It must be remembered that acute changes in protein phosphorylation do not necessarily correlate well with measured muscle protein synthesis (Burd, Holwerda et al. 2010; Burd, West et al. 2010), or even correlate at all with chronic training outcomes such as muscle strength, total cross-sectional area; muscle fibre cross-sectional area, fibre size, muscle volume, or muscle size

(Fernandez-Gonzalo et al. 2013; Hulmi et al. 2009; Mitchell et al. 2012). It might be that attempting to assess statistically the relationship between results from a semi-quantitative measurement method such as western blotting with results from quantitative methods is inappropriate (McGlory & Phillips, 2014).Western blotting (WB) is the most commonly used method to assess changes in phosphorylation of protein kinases, with the activity of the kinase inferred from the magnitude of the phosphorylation. However, WB is not fully quantitative, and can lead to type 2 errors (Jensen et al. 2007), and also show inflated responses that are not representative of physiological change in activity (MacKenzie et al. 2009; Philp et al. 2011). Furthermore, WB might not be sensitive enough to detect significant changes, especially if the number of participants is small and statistical power is low. As mentioned above, WB failed to detect significant increases, whereas KA did, after resistance loading (McGlory et al. 2014). But, whereas KA might be more sensitive than western blotting, they are unable to assess site specific phosphorylation, and can only assess phosphorylation of the whole protein. At the same time, site specific phosphorylation might not offer the most accurate readout of a specific protein kinase's activity (McGlory et al. 2014).

Additionally, "traditional" measures of muscle protein synthesis, using intravenous infusion of amino acids such as leucine or phenylalanine labelled with stable isotope tracers such as heavy carbon (13C), deuterium (2H) or nitrogen (15N) motifs, which allow the fractional synthetic rate of MPS via the rate at which the labelled amino acids are incorporated into the muscle proteins (Rennie et al. 1982, 1994), just like assessment of protein phosphorylation, provide only a "snapshot" of what is occurring intramuscularly, at the point at which the muscle sample is biopsied. Several research groups have begun to use a bolus of orally ingested deuterium oxide (D2O), ie, "heavy water", as a tracer, allowing for the measurement of MPS for several days whether in rats (Gasier et al. 2009a, 2011), other animals (Gasier et al. 2009b) or humans (Gasier et al. 2012; Wilkinson et al. 2014). Wilkinson et al. (2014) was able to measure synthesis rates of different fractions, myofibrillar (MyoPS), collagen (CPS), and sarcoplasmic protein synthesis (SPS), in response to resistance exercise, versus no exercise, from 48 hours until 8 days after. That there are discrepancies in results from the various methodologies used to study acute hypertrophic responses to resistance exercise in exercised muscle, and how such acute responses relate to chronic adaptations, suggests that in future, studies should use a combination of methods, as suggested by McGlory et al. (2014): western blotting to assess site-specific protein

phosphorylation, kinase assays to assess protein phosphorylation, and protein synthesis measured preferably using orally ingested D2O.

It should be noted that the biopsy method used in the current work was microbiopsy. Most previous studies on molecular response to exercise have used the Bergström biopsy method. To the author's knowledge, only Popov et al. (2015) also used microbiopsy. Hayot et al. (2005) reported excellent agreement between microbiopsy and Bergström biopsy for myosin heavy chain (MHC) and citrate synthase (CS), but only moderate agreement for phosphofructokinase (PFK). To the author's knowledge, criterion validity of microbiopsy against Bergström biopsy has yet to be tested for the "canonical" proteins involved in protein translation and thus, SkM hypertrophy, that is p70S6, 4EBP1.

Strength of the current work is that recovery measures of maximal leg force, power, muscle swelling were collected up to 4 days post-exercise. Additionally, other than Galpin et al. (2012), to the author's knowledge, no other work has attempted to evaluate molecular responses to "power" type training. More research should be done on power training, with total mechanical work performed properly calculated fully, including the molecular responses to, as this is a form of resistance training that is not as metabolically demanding, and does not result in as much increases in blood lactate, as "traditional" hypertrophic type resistance training to momentary failure, as demonstrated in the current work. Furthermore, in the current work, hypertrophic type resistance loading resulted in greater increases in subjective perception of soreness, and lower perceptions of readiness to perform exercise. Therefore, power type training might result in decreased perceptions of fatigue and intensity, and thus less perceptions of negative affect in beginners who are unused to exercise training. In beginners at least, exercise that results in greater blood lactate accumulation and increased muscle soreness might result in negative affective responses, decreases in pleasure from exercise (Ekkekakis et al. 2014), and thus, decreased exercise adherence.

4.4 Conclusion

In this group of trained young men, there were no differences in molecular signalling proteins involved in protein translation as a result of hypertrophic versus high power resistance exercise.

Nor were there any relationships between mechanical work performed and changes in signalling proteins. There were correlations between changes in static jump heights post-exercise and phosphorylated p70S6K1 at Ser424 and rpS6. There were also inverse correlations between changes in muscle thickness and phosphorylated p38 and ERK, after hypertrophic loading. This suggests that changes in phosphorylation of key proteins responsible for protein translation mediate acute post-exercise recovery responses to hypertrophic resistance loading. Correlations between POW and phosphorylated proteins were unclear. In trained young men, acute molecular signalling responses to hypertrophic 5x10 at 80% 1RM leg pressing and power type 10x5 at 70% 1RM leg pressing are similar. Therefore, both of these resistance loading protocols might be similar as training stimuli.

4.5 Acknowledgements

The author expresses profound gratitude to Juha Ahtiainen, Phd, for his guidance, advice, and patience in the course of the completion of this work, especially in the face of stupid questions by the author. Similarly, the author also profusely thanks Heikki Peltonen for his advice and patience. Thanks are also extended to all the biochemical lab staff who kindly tolerated the author. Lastly, this work obviously would not have been possible without the participants who so kindly volunteered their time, effort, blood, and muscle tissue: thank you very much.

APPENDIX

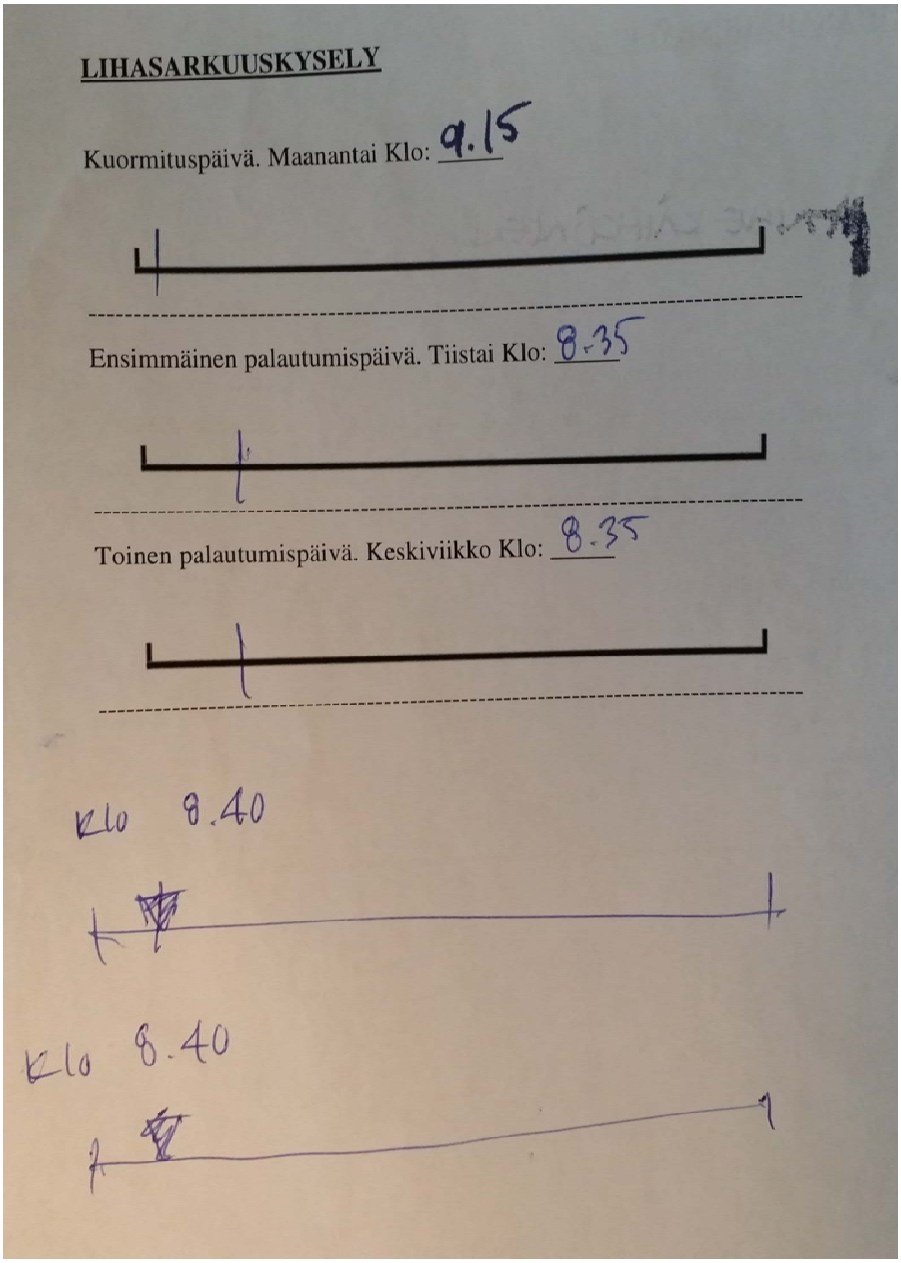

Figure 36: Visual analog scale for subjective perceptions in muscle soreness, 0 (left side of scale) represents no soreness, 100 (right side of scale) represents maximum soreness, each scale represents a different day; this was the perceptions for 1 participant before and after (24h, 48h, 72h, 96h) hypertrophic loading

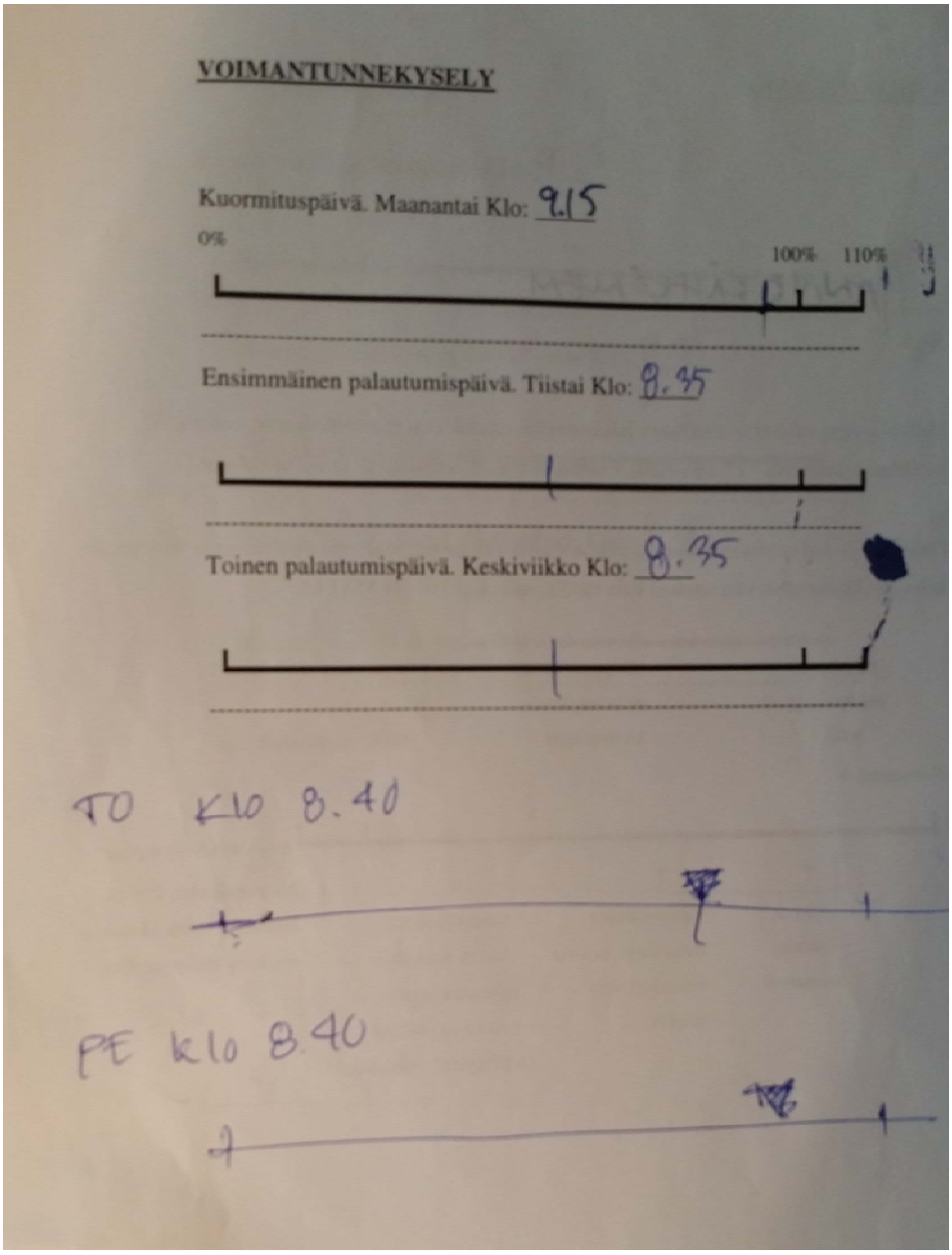

Figure 37: Visual analog scale for subjective perceptions of feelings of power (to exercise), 0 (left side of scale) represents minimum power, 100 (right side of scale) represents maximum power, each scale represents a different day; this was the perceptions for 1 participant before and after (24h, 48h, 72h, 96h) hypertrophic loading

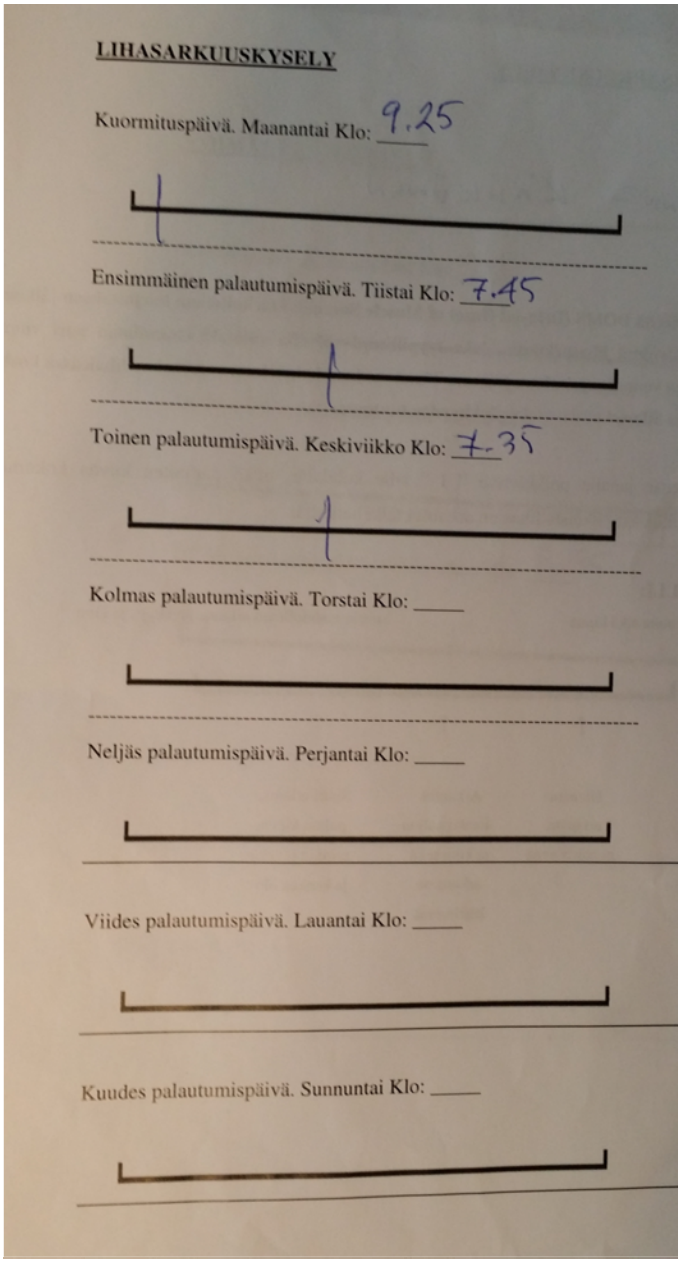

Figure 38: Visual analog scale for subjective perceptions in muscle soreness, 0 (left side of scale) represents no soreness, 100 (right side of scale) represents maximum soreness, each scale represents a different day; this was the perceptions for 1 participant before and after (24h, 48h) power loading

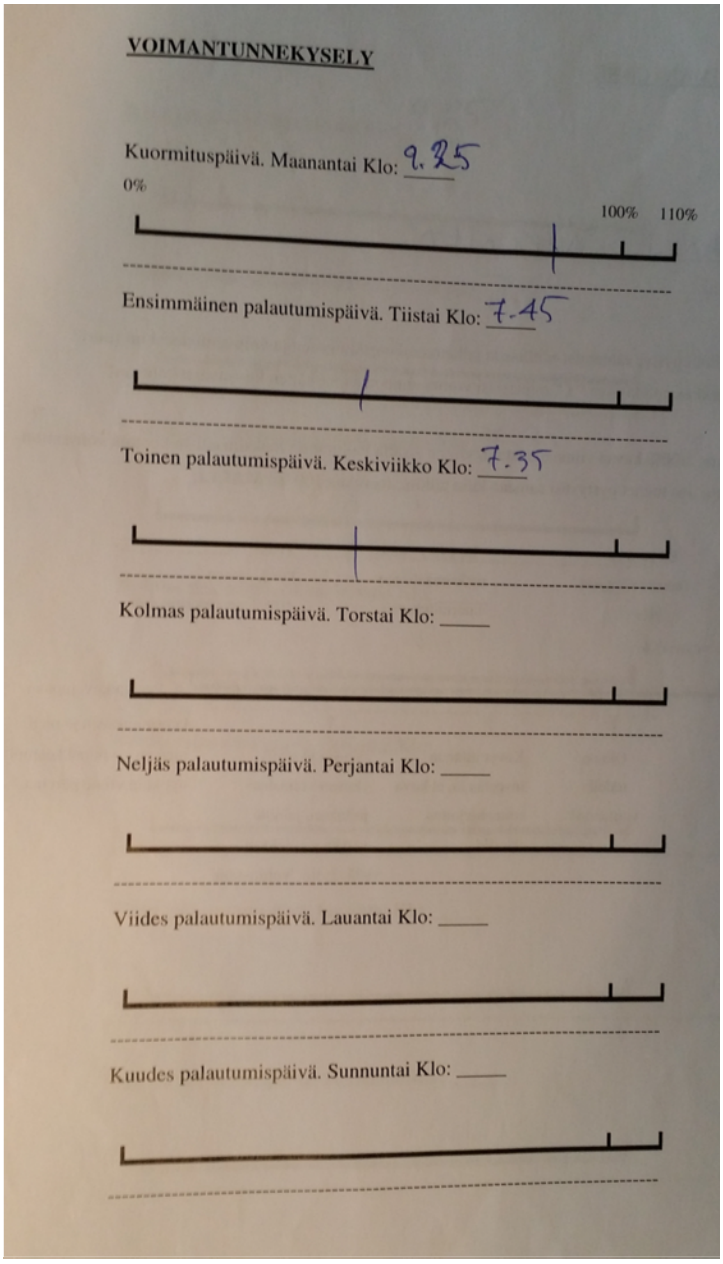

Figure 39: Visual analog scale for subjective perceptions of feelings of power (to exercise), 0 (left side of scale) represents minimum power, 100 (right side of scale) represents maximum power, each scale represents a different day; this was the perceptions for 1 participant before and after (24h, 48h) power loading

REFERENCES

Aagaard, P., Simonsen, E. B., Andersen, J. L., Magnusson, P., & Dyhre-Poulsen, P. (2002). Neural adaptation to resistance training: changes in evoked V-wave and H-reflex responses. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *92*(6), 2309–2318. http://doi.org/10.1152/japplphysiol.01185.2001

Abe, Y., Yoon, S.-O., Kubota, K., Mendoza, M. C., Gygi, S. P., & Blenis, J. (2009). p90 ribosomal S6 kinase and p70 ribosomal S6 kinase link phosphorylation of the eukaryotic chaperonin containing TCP-1 to growth factor, insulin, and nutrient signaling. *The Journal of Biological Chemistry*, *284*(22), 14939–14948. http://doi.org/10.1074/jbc.M900097200

Ahtiainen, J. P., Hoffren, M., Hulmi, J. J., Pietikäinen, M., Mero, A. A., Avela, J., & Häkkinen, K. (2010). Panoramic ultrasonography is a valid method to measure changes in skeletal muscle cross-sectional area. *European Journal of Applied Physiology*, *108*(2), 273–279. http://doi.org/10.1007/s00421-009-1211-6

Ahtiainen, J. P., Lehti, M., Hulmi, J. J., Kraemer, W. J., Alen, M., Nyman, K., … Häkkinen, K. (2011). Recovery after heavy resistance exercise and skeletal muscle androgen receptor and insulin-like growth factor-I isoform expression in strength trained men. *Journal of Strength and Conditioning Research / National Strength & Conditioning Association*, *25*(3), 767–777. http://doi.org/10.1519/JSC.0b013e318202e449

Aikawa, R., Nagai, T., Kudoh, S., Zou, Y., Tanaka, M., Tamura, M., … Komuro, I. (2002). Integrins play a critical role in mechanical stress-induced p38 MAPK activation. *Hypertension*, *39*(2), 233–238.

Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., Walter, P. (2008). Molecular Biology of the Cell, 5th Edition. New York, NY, USA: Garland Science.

Alessi, D. R., Deak, M., Casamayor, A., Caudwell, F. B., Morrice, N., Norman, D. G., … Bownes, M. (1997). 3-Phosphoinositide-dependent protein kinase-1 (PDK1): structural and functional homology with the Drosophila DSTPK61 kinase. *Current Biology: CB*, *7*(10), 776–789.

Alessi, D. R., & Downes, C. P. (1998). The role of PI 3-kinase in insulin action. *Biochimica Et Biophysica Acta*, *1436*(1-2), 151–164.

Alessi, D. R., Kozlowski, M. T., Weng, Q. P., Morrice, N., & Avruch, J. (1998). 3-Phosphoinositide-dependent protein kinase 1 (PDK1) phosphorylates and activates the p70 S6 kinase in vivo and in vitro. *Current Biology: CB*, *8*(2), 69–81.

Alonso, G., Ambrosino, C., Jones, M., & Nebreda, A. R. (2000). Differential activation of p38 mitogen-activated protein kinase isoforms depending on signal strength. *The Journal of Biological Chemistry*, *275*(51), 40641–40648. http://doi.org/10.1074/jbc.M007835200

American College of Sports Medicine. (2009a). American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Medicine and Science in Sports and Exercise*, *41*(3), 687–708. http://doi.org/10.1249/MSS.0b013e3181915670

American Dietetic Association, Dietitians of Canada, American College of Sports Medicine, Rodriguez, N. R., Di Marco, N. M., & Langley, S. (2009b). American College of Sports Medicine position stand. Nutrition and athletic performance. *Medicine and Science in Sports and Exercise*, *41*(3), 709–731. http://doi.org/10.1249/MSS.0b013e31890eb86

Amirtash, A.M. (2008). Zoorkhaneh and Varzesh-E-Bastani. *Journal of Movement Sciences and Sports, Special Issue(1), 59-73.*

Andjelković, M., Jakubowicz, T., Cron, P., Ming, X. F., Han, J. W., & Hemmings, B. A. (1996). Activation and phosphorylation of a pleckstrin homology domain containing protein kinase (RAC-PK/PKB) promoted by serum and protein phosphatase inhibitors. *Proceedings of the National Academy of Sciences of the United States of America*, *93*(12), 5699–5704.

Apró, W., & Blomstrand, E. (2010). Influence of supplementation with branched-chain amino acids in combination with resistance exercise on p70S6 kinase phosphorylation in resting and exercising human skeletal muscle. *Acta Physiologica (Oxford, England)*, *200*(3), 237–248. http://doi.org/10.1111/j.1748-1708.2010.02151.x

Apró, W., Wang, L., Pontén, M., Blomstrand, E., & Sahlin, K. (2013). Resistance exercise induced mTORC1 signaling is not impaired by subsequent endurance exercise in human skeletal muscle. *American Journal of Physiology. Endocrinology and Metabolism*, *305*(1), E22–32. http://doi.org/10.1152/ajpendo.00091.2013

Aravamudan, B., Mantilla, C. B., Zhan, W.-Z., & Sieck, G. C. (2006). Denervation effects on myonuclear domain size of rat diaphragm fibers. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *100*(5), 1617–1622. http://doi.org/10.1152/japplphysiol.01277.2005

Areta, J. L., Burke, L. M., Camera, D. M., West, D. W. D., Crawshay, S., Moore, D. R., … Coffey, V. G. (2014). Reduced resting skeletal muscle protein synthesis is rescued by resistance exercise and protein ingestion following short-term energy deficit. *American Journal of Physiology. Endocrinology and Metabolism*, *306*(8), E989–997. http://doi.org/10.1152/ajpendo.00590.2013

Areta, J. L., Burke, L. M., Ross, M. L., Camera, D. M., West, D. W. D., Broad, E. M., … Coffey, V. G. (2013). Timing and distribution of protein ingestion during prolonged recovery from resistance

exercise alters myofibrillar protein synthesis. *The Journal of Physiology*, *591*(Pt 9), 2319–2331. http://doi.org/10.1113/jphysiol.2012.244897

Atzori, F., Traina, T. A., Ionta, M. T., & Massidda, B. (2009). Targeting insulin-like growth factor type 1 receptor in cancer therapy. *Targeted Oncology*, *4*(4), 255–266. http://doi.org/10.1007/s11523-009-0123-z

Augert, G., Monier, S., & Le Marchand-Brustel, Y. (1986). Effect of exercise on protein turnover in muscles of lean and obese mice. *Diabetologia*, *29*(4), 248–253.

Averous, J., Lambert-Langlais, S., Carraro, V., Gourbeyre, O., Parry, L., B'Chir, W., … Fafournoux, P. (2014). Requirement for lysosomal localization of mTOR for its activation differs between leucine and other amino acids. *Cellular Signalling*, *26*(9), 1918–1927. http://doi.org/10.1016/j.cellsig.2014.04.019

Backer, J. M., Wjasow, C., & Zhang, Y. (1997). In vitro binding and phosphorylation of insulin receptor substrate 1 by the insulin receptor. Role of interactions mediated by the phosphotyrosine-binding domain and the pleckstrin-homology domain. *European Journal of Biochemistry / FEBS*, *245*(1), 91–96.

Baar, K., & Esser, K. (1999). Phosphorylation of p70(S6k) correlates with increased skeletal muscle mass following resistance exercise. *The American Journal of Physiology*, *276*(1 Pt 1), C120–127.

Bamman, M. M., Petrella, J. K., Kim, J., Mayhew, D. L., & Cross, J. M. (2007). Cluster analysis tests the importance of myogenic gene expression during myofiber hypertrophy in humans. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *102*(6), 2232–2239. http://doi.org/10.1152/japplphysiol.00024.2007

Bar-Peled, L., Chantranupong, L., Cherniack, A. D., Chen, W. W., Ottina, K. A., Grabiner, B. C., … Sabatini, D. M. (2013). A Tumor suppressor complex with GAP activity for the Rag GTPases that signal amino acid sufficiency to mTORC1. *Science (New York, N.Y.)*, *340*(6136), 1100–1106. http://doi.org/10.1126/science.1232044

Bar-Peled, L., & Sabatini, D. M. (2014). Regulation of mTORC1 by amino acids. *Trends in Cell Biology*, *24*(7), 400–406. http://doi.org/10.1016/j.tcb.2014.03.003

Benjamin, D., & Hall, M. N. (2014). mTORC1: turning off is just as important as turning on. *Cell*, *156*(4), 627–628. http://doi.org/10.1016/j.cell.2014.01.057

Bentzinger, C. F., Lin, S., Romanino, K., Castets, P., Guridi, M., Summermatter, S., … Rüegg, M. A. (2013). Differential response of skeletal muscles to mTORC1 signaling during atrophy and hypertrophy. *Skeletal Muscle*, *3*(1), 6. http://doi.org/10.1186/2044-5040-3-6

Bentzinger, C. F., Romanino, K., Cloëtta, D., Lin, S., Mascarenhas, J. B., Oliveri, F., … Rüegg, M. A. (2008). Skeletal muscle-specific ablation of raptor, but not of rictor, causes metabolic changes and

results in muscle dystrophy. *Cell Metabolism*, *8*(5), 411–424. http://doi.org/10.1016/j.cmet.2008.10.002

Betz, C., & Hall, M. N. (2013). Where is mTOR and what is it doing there? *The Journal of Cell Biology*, *203*(4), 563–574. http://doi.org/10.1083/jcb.201306041

Bevan, H. R., Bunce, P. J., Owen, N. J., Bennett, M. A., Cook, C. J., Cunningham, D. J., … Kilduff, L. P. (2010). Optimal loading for the development of peak power output in professional rugby players. *Journal of Strength and Conditioning Research / National Strength & Conditioning Association*, *24*(1), 43–47. http://doi.org/10.1519/JSC.0b013e3181c63c64

Bodine, S. C., Latres, E., Baumhueter, S., Lai, V. K., Nunez, L., Clarke, B. A., … Glass, D. J. (2001). Identification of ubiquitin ligases required for skeletal muscle atrophy. *Science (New York, N.Y.)*, *294*(5547), 1704–1708. http://doi.org/10.1126/science.1065874

Bodine, S. C., Stitt, T. N., Gonzalez, M., Kline, W. O., Stover, G. L., Bauerlein, R., … Yancopoulos, G. D. (2001). Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. *Nature Cell Biology*, *3*(11), 1014–1019. http://doi.org/10.1038/ncb1101-1014

Böhni, R., Riesgo-Escovar, J., Oldham, S., Brogiolo, W., Stocker, H., Andruss, B. F., … Hafen, E. (1999). Autonomous control of cell and organ size by CHICO, a Drosophila homolog of vertebrate IRS1-4. *Cell*, *97*(7), 865–875.

Bonaldo, P., & Sandri, M. (2013). Cellular and molecular mechanisms of muscle atrophy. *Disease Models & Mechanisms*, *6*(1), 25–39. http://doi.org/10.1242/dmm.010389

Booth, F. W., & Thomason, D. B. (1991). Molecular and cellular adaptation of muscle in response to exercise: perspectives of various models. *Physiological Reviews*, *71*(2), 541–585.

Bos, J. L., Rehmann, H., & Wittinghofer, A. (2007). GEFs and GAPs: critical elements in the control of small G proteins. *Cell*, *129*(5), 865–877. http://doi.org/10.1016/j.cell.2007.05.018

Bouchard, C., Blair, S. N., Church, T. S., Earnest, C. P., Hagberg, J. M., Häkkinen, K., … Rankinen, T. (2012). Adverse metabolic response to regular exercise: is it a rare or common occurrence? *PloS One*, *7*(5), e37887. http://doi.org/10.1371/journal.pone.0037887

Box, G,.E.,P. & Cox, D.R. (1964). An analysis of transformations (with discussion). *Journal of the Royal Statistical Society - Statistical Methodology 26*: 211 - 252

Breen, L., & Phillips, S. M. (2012). Nutrient interaction for optimal protein anabolism in resistance exercise. *Current Opinion in Clinical Nutrition and Metabolic Care*, *15*(3), 226–232. http://doi.org/10.1097/MCO.0b013e3283516850

Brognard, J., Sierecki, E., Gao, T., & Newton, A. C. (2007). PHLPP and a second isoform, PHLPP2, differentially attenuate the amplitude of Akt signaling by regulating distinct Akt isoforms. *Molecular Cell*, *25*(6), 917–931. http://doi.org/10.1016/j.molcel.2007.02.017

Brosnan, M.E., Brosnan, J.T., & Young, V.,R. (2011). Integration of metabolism 3: Protein and amino acids. In Lanham-New, S.,A., Macdonald, I.,A., & Roche, H.,M. (Eds.), Sport and Exercise Nutrition (pp. 72-101). Chichester, UK: John Wiley & Sons

Brown, E. J., Albers, M. W., Shin, T. B., Ichikawa, K., Keith, C. T., Lane, W. S., & Schreiber, S. L. (1994). A mammalian protein targeted by G1-arresting rapamycin-receptor complex. *Nature*, *369*(6483), 756–758. http://doi.org/10.1038/369756a0

Burd, N. A., Andrews, R. J., West, D. W. D., Little, J. P., Cochran, A. J. R., Hector, A. J., … Phillips, S. M. (2012). Muscle time under tension during resistance exercise stimulates differential muscle protein sub-fractional synthetic responses in men. *The Journal of Physiology*, *590*(Pt 2), 351–362. http://doi.org/10.1113/jphysiol.2011.221200

Burd, N. A., Holwerda, A. M., Selby, K. C., West, D. W. D., Staples, A. W., Cain, N. E., … Phillips, S. M. (2010a). Resistance exercise volume affects myofibrillar protein synthesis and anabolic signalling molecule phosphorylation in young men. *The Journal of Physiology*, *588*(Pt 16), 3119–3130. http://doi.org/10.1113/jphysiol.2010.192856

Burd, N. A., West, D. W. D., Moore, D. R., Atherton, P. J., Staples, A. W., Prior, T., … Phillips, S. M. (2011). Enhanced amino acid sensitivity of myofibrillar protein synthesis persists for up to 24 h after resistance exercise in young men. *The Journal of Nutrition*, *141*(4), 568–573. http://doi.org/10.3945/jn.110.135038

Burd, N. A., West, D. W. D., Staples, A. W., Atherton, P. J., Baker, J. M., Moore, D. R., … Phillips, S. M. (2010b). Low-load high volume resistance exercise stimulates muscle protein synthesis more than high-load low volume resistance exercise in young men. *PloS One*, *5*(8), e12033. http://doi.org/10.1371/journal.pone.0012033

Burke, L. M., Hawley, J. A., Ross, M. L., Moore, D. R., Phillips, S. M., Slater, G. R., … Coffey, V. G. (2012). Preexercise aminoacidemia and muscle protein synthesis after resistance exercise. *Medicine and Science in Sports and Exercise*, *44*(10), 1968–1977. http://doi.org/10.1249/MSS.0b013e31825d28fa

Camera, D. M., West, D. W. D., Burd, N. A., Phillips, S. M., Garnham, A. P., Hawley, J. A., & Coffey, V. G. (2012). Low muscle glycogen concentration does not suppress the anabolic response to resistance exercise. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *113*(2), 206–214. http://doi.org/10.1152/japplphysiol.00395.2012

Camera, D. M., West, D. W. D., Phillips, S. M., Rerecich, T., Stellingwerff, T., Hawley, J. A., & Coffey, V. G. (2015). Protein ingestion increases myofibrillar protein synthesis after concurrent exercise. *Medicine and Science in Sports and Exercise*, *47*(1), 82–91. http://doi.org/10.1249/MSS.0000000000000390

Campos, G. E. R., Luecke, T. J., Wendeln, H. K., Toma, K., Hagerman, F. C., Murray, T. F., … Staron, R. S. (2002). Muscular adaptations in response to three different resistance-training regimens: specificity of repetition maximum training zones. *European Journal of Applied Physiology*, *88*(1-2), 50–60. http://doi.org/10.1007/s00421-002-0681-6

Carrière, A., Cargnello, M., Julien, L.-A., Gao, H., Bonneil, E., Thibault, P., & Roux, P. P. (2008). Oncogenic MAPK signaling stimulates mTORC1 activity by promoting RSK-mediated raptor phosphorylation. *Current Biology: CB*, *18*(17), 1269–1277. http://doi.org/10.1016/j.cub.2008.07.078

Carriere, A., Ray, H., Blenis, J., & Roux, P. P. (2008). The RSK factors of activating the Ras/MAPK signaling cascade. *Frontiers in Bioscience: A Journal and Virtual Library*, *13*, 4258–4275.

Carriere, A., Romeo, Y., Acosta-Jaquez, H. A., Moreau, J., Bonneil, E., Thibault, P., … Roux, P. P. (2011). ERK1/2 phosphorylate Raptor to promote Ras-dependent activation of mTOR complex 1 (mTORC1). *The Journal of Biological Chemistry*, *286*(1), 567–577. http://doi.org/10.1074/jbc.M110.159046

Carson, J. A., & Wei, L. (2000). Integrin signaling's potential for mediating gene expression in hypertrophying skeletal muscle. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *88*(1), 337–343.

Casas-Terradellas, E., Tato, I., Bartrons, R., Ventura, F., & Rosa, J. L. (2008). ERK and p38 pathways regulate amino acid signalling. *Biochimica Et Biophysica Acta*, *1783*(12), 2241–2254. http://doi.org/10.1016/j.bbamcr.2008.08.011

Chapman, D., L. & Vertinsky, P. (2010). *Venus with Biceps. A Pictorial History of Muscular Women.* Vancouver: Arsenal Pulp Press

Chauvin, C., Koka, V., Nouschi, A., Mieulet, V., Hoareau-Aveilla, C., Dreazen, A., … Pende, M. (2014). Ribosomal protein S6 kinase activity controls the ribosome biogenesis transcriptional program. *Oncogene*, *33*(4), 474–483. http://doi.org/10.1038/onc.2012.606

Chehabi, H.E. (1995). Sport and politics in Iran: the legend of Gholamreza Takhti. *The International Journal of the History of Sport, 12(3)*, 48-60. DOI: 10.1080/09523369508713909

Chiang, G. G., & Abraham, R. T. (2005). Phosphorylation of mammalian target of rapamycin (mTOR) at Ser-2448 is mediated by p70S6 kinase. *The Journal of Biological Chemistry*, *280*(27), 25485–25490. http://doi.org/10.1074/jbc.M501707200

Chiu, L. Z. F., Schilling, B. K., Fry, A. C., & Salem, G. J. (2008). The influence of deformation on barbell mechanics during the clean pull. *Sports Biomechanics / International Society of Biomechanics in Sports*, *7*(2), 260–273. http://doi.org/10.1080/14763140701841795

Churchward-Venne, T. A., Burd, N. A., Mitchell, C. J., West, D. W. D., Philp, A., Marcotte, G. R., … Phillips, S. M. (2012). Supplementation of a suboptimal protein dose with leucine or essential amino acids: effects on myofibrillar protein synthesis at rest and following resistance exercise in men. *The Journal of Physiology*, *590*(Pt 11), 2751–2765. http://doi.org/10.1113/jphysiol.2012.228833

Coburn, J. W., Housh, T. J., Malek, M. H., Weir, J. P., Cramer, J. T., Beck, T. W., & Johnson, G. O. (2006). Neuromuscular responses to three days of velocity-specific isokinetic training. *Journal of Strength and Conditioning Research / National Strength & Conditioning Association*, *20*(4), 892–898. http://doi.org/10.1519/R-18745.1

Coffey, V. G., Jemiolo, B., Edge, J., Garnham, A. P., Trappe, S. W., & Hawley, J. A. (2009). Effect of consecutive repeated sprint and resistance exercise bouts on acute adaptive responses in human skeletal muscle. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *297*(5), R1441–1451. http://doi.org/10.1152/ajpregu.00351.2009

Coffey, V. G., Pilegaard, H., Garnham, A. P., O'Brien, B. J., & Hawley, J. A. (2009). Consecutive bouts of diverse contractile activity alter acute responses in human skeletal muscle. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *106*(4), 1187–1197. http://doi.org/10.1152/japplphysiol.91221.2008

Coffey, V. G., Zhong, Z., Shield, A., Canny, B. J., Chibalin, A. V., Zierath, J. R., & Hawley, J. A. (2006). Early signaling responses to divergent exercise stimuli in skeletal muscle from well-trained humans. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, *20*(1), 190–192. http://doi.org/10.1096/fj.05-4809fje

Cook, S. B., Murphy, B. G., & Labarbera, K. E. (2013). Neuromuscular function after a bout of low-load blood flow-restricted exercise. *Medicine and Science in Sports and Exercise*, *45*(1), 67–74. http://doi.org/10.1249/MSS.0b013e31826c6fa8

Copps, K. D., & White, M. F. (2012). Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. *Diabetologia*, *55*(10), 2565–2582. http://doi.org/10.1007/s00125-012-2644-8

Cormie, P., McGuigan, M. R., & Newton, R. U. (2010). Influence of strength on magnitude and mechanisms of adaptation to power training. *Medicine and Science in Sports and Exercise*, *42*(8), 1566–1581. http://doi.org/10.1249/MSS.0b013e3181cf818d

Cormie, P., McGuigan, M. R., & Newton, R. U. (2011). Developing maximal neuromuscular power: part 2 - training considerations for improving maximal power production. *Sports Medicine (Auckland, N.Z.)*, *41*(2), 125–146. http://doi.org/10.2165/11538500-000000000-00000

Creer, A., Gallagher, P., Slivka, D., Jemiolo, B., Fink, W., & Trappe, S. (2005). Influence of muscle glycogen availability on ERK1/2 and Akt signaling after resistance exercise in human skeletal muscle. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *99*(3), 950–956. http://doi.org/10.1152/japplphysiol.00110.2005

Crick, F., H., C. (1958). On Protein Synthesis. *The Symposia of the Society for Experimental Biology 12,* 138-163

Crowther, N.B. (1977). Weightlifting in antiquity: achievement and training. In McAuslen I, Walcot, P., eds. Greece and Rome, vol XXIV, Oxford, UK: Oxford University, 1977; 111-120

Csibi, A., Leibovitch, M. P., Cornille, K., Tintignac, L. A., & Leibovitch, S. A. (2009). MAFbx/Atrogin-1 controls the activity of the initiation factor eIF3-f in skeletal muscle atrophy by targeting multiple C-terminal lysines. *The Journal of Biological Chemistry*, *284*(7), 4413–4421. http://doi.org/10.1074/jbc.M807641200

Cully, M., Genevet, A., Warne, P., Treins, C., Liu, T., Bastien, J., … Downward, J. (2010). A role for p38 stress-activated protein kinase in regulation of cell growth via TORC1. *Molecular and Cellular Biology*, *30*(2), 481–495. http://doi.org/10.1128/MCB.00688-09

Cuthbertson, D. J., Babraj, J., Smith, K., Wilkes, E., Fedele, M. J., Esser, K., & Rennie, M. (2006). Anabolic signaling and protein synthesis in human skeletal muscle after dynamic shortening or lengthening exercise. *American Journal of Physiology. Endocrinology and Metabolism*, *290*(4), E731–738. http://doi.org/10.1152/ajpendo.00415.2005

Deldicque, L., Atherton, P., Patel, R., Theisen, D., Nielens, H., Rennie, M. J., & Francaux, M. (2008). Decrease in Akt/PKB signalling in human skeletal muscle by resistance exercise. *European Journal of Applied Physiology*, *104*(1), 57–65. http://doi.org/10.1007/s00421-008-0786-7

Deldicque, L., De Bock, K., Maris, M., Ramaekers, M., Nielens, H., Francaux, M., & Hespel, P. (2010). Increased p70s6k phosphorylation during intake of a protein-carbohydrate drink following resistance exercise in the fasted state. *European Journal of Applied Physiology*, *108*(4), 791–800.

Demetriades, C., Doumpas, N., & Teleman, A. A. (2014). Regulation of TORC1 in response to amino acid starvation via lysosomal recruitment of TSC2. *Cell*, *156*(4), 786–799. http://doi.org/10.1016/j.cell.2014.01.024

Derave, W., Ai, H., Ihlemann, J., Witters, L. A., Kristiansen, S., Richter, E. A., & Ploug, T. (2000). Dissociation of AMP-activated protein kinase activation and glucose transport in contracting slow-twitch muscle. *Diabetes*, *49*(8), 1281–1287.

De Souza, E. O., Tricoli, V., Roschel, H., Brum, P. C., Bacurau, A. V. N., Ferreira, J. C. B., … Ugrinowitsch, C. (2013). Molecular adaptations to concurrent training. *International Journal of Sports Medicine*, *34*(3), 207–213. http://doi.org/10.1055/s-0032-1312627

Dorrello, N. V., Peschiaroli, A., Guardavaccaro, D., Colburn, N. H., Sherman, N. E., & Pagano, M. (2006). S6K1- and betaTRCP-mediated degradation of PDCD4 promotes protein translation and cell growth. *Science (New York, N.Y.)*, *314*(5798), 467–471. http://doi.org/10.1126/science.1130276

Drechsler, A. J. (1998). The Weightlifting Encyclopedia: A Guide to World Class Performance. New York, NY, USA: A is A Communications.

Dreyer, H. C., Drummond, M. J., Pennings, B., Fujita, S., Glynn, E. L., Chinkes, D. L., … Rasmussen, B. B. (2008). Leucine-enriched essential amino acid and carbohydrate ingestion following resistance exercise enhances mTOR signaling and protein synthesis in human muscle. *American Journal of Physiology. Endocrinology and Metabolism*, *294*(2), E392–400. http://doi.org/10.1152/ajpendo.00582.2007

Dreyer, H. C., Fujita, S., Cadenas, J. G., Chinkes, D. L., Volpi, E., & Rasmussen, B. B. (2006). Resistance exercise increases AMPK activity and reduces 4E-BP1 phosphorylation and protein synthesis in human skeletal muscle. *The Journal of Physiology*, *576*(Pt 2), 613–624. http://doi.org/10.1113/jphysiol.2006.113175

Dreyer, H. C., Fujita, S., Glynn, E. L., Drummond, M. J., Volpi, E., & Rasmussen, B. B. (2010). Resistance exercise increases leg muscle protein synthesis and mTOR signalling independent of sex. *Acta Physiologica (Oxford, England)*, *199*(1), 71–81. http://doi.org/10.1111/j.1748-1716.2010.02074.x

Drummond, M. J., Fry, C. S., Glynn, E. L., Dreyer, H. C., Dhanani, S., Timmerman, K. L., … Rasmussen, B. B. (2009). Rapamycin administration in humans blocks the contraction-induced increase in skeletal muscle protein synthesis. *The Journal of Physiology*, *587*(Pt 7), 1535–1546. http://doi.org/10.1113/jphysiol.2008.163816

Dudley, G. A., Tesch, P. A., Miller, B. J., & Buchanan, P. (1991). Importance of eccentric actions in performance adaptations to resistance training. *Aviation, Space, and Environmental Medicine*, *62*(6), 543–550.

Easton, R. M., Cho, H., Roovers, K., Shineman, D. W., Mizrahi, M., Forman, M. S., … Birnbaum, M. J. (2005). Role for Akt3/protein kinase Bgamma in attainment of normal brain size. *Molecular and Cellular Biology*, *25*(5), 1869–1878. http://doi.org/10.1128/MCB.25.5.1869-1878.2005

Efeyan, A., Zoncu, R., & Sabatini, D. M. (2012). Amino acids and mTORC1: from lysosomes to disease. *Trends in Molecular Medicine*, *18*(9), 524–533. http://doi.org/10.1016/j.molmed.2012.05.007

Ekkekakis, P., Parfitt, G., & Petruzzello, S. J. (2011). The pleasure and displeasure people feel when they exercise at different intensities: decennial update and progress towards a tripartite rationale for exercise intensity prescription. *Sports Medicine (Auckland, N.Z.)*, *41*(8), 641–671. http://doi.org/10.2165/11590680-000000000-00000

Engelman, J. A., Luo, J., & Cantley, L. C. (2006). The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nature Reviews. Genetics*, *7*(8), 606–619. http://doi.org/10.1038/nrg1879

Fahs, C. A., Loenneke, J. P., Thiebaud, R. S., Rossow, L. M., Kim, D., Abe, T., … Bemben, M. G. (2015). Muscular adaptations to fatiguing exercise with and without blood flow restriction. *Clinical Physiology and Functional Imaging*, *35*(3), 167–176. http://doi.org/10.1111/cpf.12141

Farnfield, M. M., Breen, L., Carey, K. A., Garnham, A., & Cameron-Smith, D. (2012). Activation of mTOR signalling in young and old human skeletal muscle in response to combined resistance exercise and whey protein ingestion. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquée, Nutrition Et Métabolisme*, *37*(1), 21–30. http://doi.org/10.1139/h11-132

Felkar, V. (2012). Marginalised Muscle: Transgression And The Female Bodybuilder. *Ignite: Undergraduate Journal for Gender, Race Sexuality & Social Justice, 4(1)*, 40-49

Fernandez-Gonzalo, R., Lundberg, T. R., & Tesch, P. A. (2013). Acute molecular responses in untrained and trained muscle subjected to aerobic and resistance exercise training versus resistance training alone. *Acta Physiologica (Oxford, England)*, *209*(4), 283–294. http://doi.org/10.1111/apha.12174

Feynman, R., P. (1970). The Feynman Lectures on Physics. New York, NY, USA: Addison Wesley Longman.

Fluckey, J. D., Knox, M., Smith, L., Dupont-Versteegden, E. E., Gaddy, D., Tesch, P. A., & Peterson, C. A. (2006a). Insulin-facilitated increase of muscle protein synthesis after resistance exercise involves a MAP kinase pathway. *American Journal of Physiology. Endocrinology and Metabolism*, *290*(6), E1205–1211. http://doi.org/10.1152/ajpendo.00593.2005

Fluckey, J. D., Knox, M., Smith, L., Dupont-Versteegden, E. E., Gaddy, D., Tesch, P. A., & Peterson, C. A. (2006b). Insulin-facilitated increase of muscle protein synthesis after resistance exercise involves a MAP kinase pathway. *American Journal of Physiology. Endocrinology and Metabolism*, *290*(6), E1205–1211. http://doi.org/10.1152/ajpendo.00593.2005

Frey, J. W., Jacobs, B. L., Goodman, C. A., & Hornberger, T. A. (2014). A role for Raptor phosphorylation in the mechanical activation of mTOR signaling. *Cellular Signalling*, *26*(2), 313–322. http://doi.org/10.1016/j.cellsig.2013.11.009

Friedrichsen, M., Mortensen, B., Pehmøller, C., Birk, J. B., & Wojtaszewski, J. F. P. (2013). Exercise-induced AMPK activity in skeletal muscle: role in glucose uptake and insulin sensitivity. *Molecular and Cellular Endocrinology*, *366*(2), 204–214. http://doi.org/10.1016/j.mce.2012.06.013

Fry, C. S., Drummond, M. J., Glynn, E. L., Dickinson, J. M., Gundermann, D. M., Timmerman, K. L., … Rasmussen, B. B. (2013a). Skeletal muscle autophagy and protein breakdown following resistance exercise are similar in younger and older adults. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *68*(5), 599–607. http://doi.org/10.1093/gerona/gls209

Fry, C. S., Drummond, M. J., Glynn, E. L., Dickinson, J. M., Gundermann, D. M., Timmerman, K. L., … Rasmussen, B. B. (2013b). Skeletal muscle autophagy and protein breakdown following resistance exercise are similar in younger and older adults. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *68*(5), 599–607. http://doi.org/10.1093/gerona/gls209

Fry, C. S., & Rasmussen, B. B. (2011). Skeletal muscle protein balance and metabolism in the elderly. *Current Aging Science*, *4*(3), 260–268.

Fukugawa, N & Yu. Y.,M. (2009). Nutrition and metabolism of proteins and amino acids. In Gibney, M.,J., Lanham-New, S.,A., Cassidy, A., Vorster, H.,H. (Eds.), Introduction to Human Nutrition (pp. 49-73). Chichester, UK: John Wiley & Sons.

Fussell, S. (1992). Confessions of an Unlikely Bodybuilder. London, UK:Abacus

Galpin, A. J., Fry, A. C., Chiu, L. Z. F., Thomason, D. B., & Schilling, B. K. (2012). High-power resistance exercise induces MAPK phosphorylation in weightlifting trained men. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquée, Nutrition Et Métabolisme*, *37*(1), 80–87. http://doi.org/10.1139/h11-131

Garhammer, J. (1980). Power production by Olympic weightlifters. *Medicine and Science in Sports and Exercise*, *12*(1), 54–60.

Garhammer, J. (1991). A comparison of maximal power outputs between elite male and female weightlifters in competition. *Int. J. Sport Biomechanics 7(1)*: 3-11.

Garhammer, J. (1993). A review of power output studies of Olympic and Power lifting: Methodology, performance prediction, and evaluation tests. *J. Strength & Conditioning Research 7(2)*: 76-89

Garofalo, R. S., Orena, S. J., Rafidi, K., Torchia, A. J., Stock, J. L., Hildebrandt, A. L., … Coleman, K. G. (2003). Severe diabetes, age-dependent loss of adipose tissue, and mild growth deficiency in mice lacking Akt2/PKB beta. *The Journal of Clinical Investigation*, *112*(2), 197–208. http://doi.org/10.1172/JCI16885

Gasier, H. G., Fluckey, J. D., Previs, S. F., Wiggs, M. P., & Riechman, S. E. (2012). Acute resistance exercise augments integrative myofibrillar protein synthesis. *Metabolism: Clinical and Experimental*, *61*(2), 153–156. http://doi.org/10.1016/j.metabol.2011.07.001

Gasier, H. G., Previs, S. F., Pohlenz, C., Fluckey, J. D., Gatlin, D. M., & Buentello, J. A. (2009). A novel approach for assessing protein synthesis in channel catfish, Ictalurus punctatus. *Comparative Biochemistry and Physiology. Part B, Biochemistry & Molecular Biology*, *154*(2), 235–238. http://doi.org/10.1016/j.cbpb.2009.06.012

Gasier, H. G., Riechman, S. E., Wiggs, M. P., Previs, S. F., & Fluckey, J. D. (2009). A comparison of 2H2O and phenylalanine flooding dose to investigate muscle protein synthesis with acute exercise in rats. *American Journal of Physiology. Endocrinology and Metabolism*, *297*(1), E252–259. http://doi.org/10.1152/ajpendo.90872.2008

Gillespie, M. A., Le Grand, F., Scimè, A., Kuang, S., von Maltzahn, J., Seale, V., … Rudnicki, M. A. (2009). p38-{gamma}-dependent gene silencing restricts entry into the myogenic differentiation program. *The Journal of Cell Biology*, *187*(7), 991–1005. http://doi.org/10.1083/jcb.200907037

Glover, E. I., Oates, B. R., Tang, J. E., Moore, D. R., Tarnopolsky, M. A., & Phillips, S. M. (2008). Resistance exercise decreases eIF2Bepsilon phosphorylation and potentiates the feeding-induced stimulation of p70S6K1 and rpS6 in young men. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *295*(2), R604–610. http://doi.org/10.1152/ajpregu.00097.2008

Goodman, C. A., Mayhew, D. L., & Hornberger, T. A. (2011). Recent progress toward understanding the molecular mechanisms that regulate skeletal muscle mass. *Cellular Signalling*, *23*(12), 1896–1906. http://doi.org/10.1016/j.cellsig.2011.07.013

Goodman, C. A., McNally, R. M., Hoffmann, F. M., & Hornberger, T. A. (2013). Smad3 induces atrogin-1, inhibits mTOR and protein synthesis, and promotes muscle atrophy in vivo. *Molecular Endocrinology (Baltimore, Md.)*, *27*(11), 1946–1957. http://doi.org/10.1210/me.2013-1194

Goodman, C. A., Miu, M. H., Frey, J. W., Mabrey, D. M., Lincoln, H. C., Ge, Y., … Hornberger, T. A. (2010). A phosphatidylinositol 3-kinase/protein kinase B-independent activation of mammalian target of rapamycin signaling is sufficient to induce skeletal muscle hypertrophy. *Molecular Biology of the Cell*, *21*(18), 3258–3268. http://doi.org/10.1091/mbc.E10-05-0454

Gordon, B. S., Kelleher, A. R., & Kimball, S. R. (2013a). Regulation of muscle protein synthesis and the effects of catabolic states. *The International Journal of Biochemistry & Cell Biology*, *45*(10), 2147–2157. http://doi.org/10.1016/j.biocel.2013.05.039

Gordon, B. S., Kelleher, A. R., & Kimball, S. R. (2013b). Regulation of muscle protein synthesis and the effects of catabolic states. *The International Journal of Biochemistry & Cell Biology*, *45*(10), 2147–2157. http://doi.org/10.1016/j.biocel.2013.05.039

Goto, K., Nagasawa, M., Yanagisawa, O., Kizuka, T., Ishii, N., & Takamatsu, K. (2004). Muscular adaptations to combinations of high- and low-intensity resistance exercises. *Journal of Strength and Conditioning Research / National Strength & Conditioning Association*, *18*(4), 730–737. http://doi.org/10.1519/R-13603.1

Gourgoulis, V., Aggelousis, N., Mavromatis, G., & Garas, A. (2000). Three-dimensional kinematic analysis of the snatch of elite Greek weightlifters. *Journal of Sports Sciences*, *18*(8), 643–652. http://doi.org/10.1080/02640410050082332

Greig, C. A., Gray, C., Rankin, D., Young, A., Mann, V., Noble, B., & Atherton, P. J. (2011). Blunting of adaptive responses to resistance exercise training in women over 75y. *Experimental Gerontology*, *46*(11), 884–890. http://doi.org/10.1016/j.exger.2011.07.010

Greenhalgh, T., & Peacock, R. (2005). Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. *BMJ (Clinical Research Ed.)*, *331*(7524), 1064–1065. http://doi.org/10.1136/bmj.38636.593461.68

Gundermann, D. M., Walker, D. K., Reidy, P. T., Borack, M. S., Dickinson, J. M., Volpi, E., & Rasmussen, B. B. (2014). Activation of mTORC1 signaling and protein synthesis in human muscle following blood flow restriction exercise is inhibited by rapamycin. *American Journal of Physiology. Endocrinology and Metabolism*, *306*(10), E1198–1204. http://doi.org/10.1152/ajpendo.00600.2013

Gwinn, D. M., Shackelford, D. B., Egan, D. F., Mihaylova, M. M., Mery, A., Vasquez, D. S., … Shaw, R. J. (2008). AMPK phosphorylation of raptor mediates a metabolic checkpoint. *Molecular Cell*, *30*(2), 214–226. http://doi.org/10.1016/j.molcel.2008.03.003

Häkkinen, K., & Kallinen, M. (1994). Distribution of strength training volume into one or two daily sessions and neuromuscular adaptations in female athletes. *Electromyography and Clinical Neurophysiology*, *34*(2), 117–124.

Häkkinen, K., Komi, P. V., & Alén, M. (1985). Effect of explosive type strength training on isometric force- and relaxation-time, electromyographic and muscle fibre characteristics of leg extensor muscles. *Acta Physiologica Scandinavica*, *125*(4), 587–600. http://doi.org/10.1111/j.1748-1716.1985.tb07759.x

Hamilton, D. L., Philp, A., MacKenzie, M. G., & Baar, K. (2010). A limited role for PI(3,4,5)P3 regulation in controlling skeletal muscle mass in response to resistance exercise. *PloS One*, *5*(7), e11624. http://doi.org/10.1371/journal.pone.0011624

Hamilton, D. L., Philp, A., MacKenzie, M. G., Patton, A., Towler, M. C., Gallagher, I. J., … Baar, K. (2014). Molecular brakes regulating mTORC1 activation in skeletal muscle following synergist ablation. *American Journal of Physiology. Endocrinology and Metabolism*, *307*(4), E365–373. http://doi.org/10.1152/ajpendo.00674.2013

Hara, K., Maruki, Y., Long, X., Yoshino, K., Oshiro, N., Hidayat, S., … Yonezawa, K. (2002). Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. *Cell*, *110*(2), 177–189.

Harber, M. P., Crane, J. D., Douglass, M. D., Weindel, K. D., Trappe, T. A., Trappe, S. W., & Fink, W. F. (2008). Resistance exercise reduces muscular substrates in women. *International Journal of Sports Medicine*, *29*(9), 719–725. http://doi.org/10.1055/s-2007-989442

Hardie, D. G. (2011). Energy sensing by the AMP-activated protein kinase and its effects on muscle metabolism. *The Proceedings of the Nutrition Society*, *70*(1), 92–99. http://doi.org/10.1017/S0029665110003915

Hastie, C. J., McLauchlan, H. J., & Cohen, P. (2006). Assay of protein kinases using radiolabeled ATP: a protocol. *Nature Protocols*, *1*(2), 968–971. http://doi.org/10.1038/nprot.2006.149

Hawley, S. A., Boudeau, J., Reid, J. L., Mustard, K. J., Udd, L., Mäkelä, T. P., … Hardie, D. G. (2003). Complexes between the LKB1 tumor suppressor, STRAD alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. *Journal of Biology*, *2*(4), 28. http://doi.org/10.1186/1475-4924-2-28

Hayot, M., Michaud, A., Koechlin, C., Caron, M.-A., Leblanc, P., Préfaut, C., & Maltais, F. (2005). Skeletal muscle microbiopsy: a validation study of a minimally invasive technique. *The European Respiratory Journal*, *25*(3), 431–440. http://doi.org/10.1183/09031936.05.00053404

Herrero-Martín, G., Høyer-Hansen, M., García-García, C., Fumarola, C., Farkas, T., López-Rivas, A., & Jäättelä, M. (2009). TAK1 activates AMPK-dependent cytoprotective autophagy in TRAIL-treated epithelial cells. *The EMBO Journal*, *28*(6), 677–685. http://doi.org/10.1038/emboj.2009.8

Heywood, L. (1998) Bodymakers. *Cultural Anatomy of Women's Bodybuilding*. New Brunswick, NJ: Rutgers University press.

Hinnebusch, A. G., & Lorsch, J. R. (2012a). The mechanism of eukaryotic translation initiation: new insights and challenges. *Cold Spring Harbor Perspectives in Biology*, *4*(10). http://doi.org/10.1101/cshperspect.a011544

Hinnebusch, A. G., & Lorsch, J. R. (2012b). The mechanism of eukaryotic translation initiation: new insights and challenges. *Cold Spring Harbor Perspectives in Biology*, *4*(10). http://doi.org/10.1101/cshperspect.a011544

Holm, L., van Hall, G., Rose, A. J., Miller, B. F., Doessing, S., Richter, E. A., & Kjaer, M. (2010). Contraction intensity and feeding affect collagen and myofibrillar protein synthesis rates differently in human skeletal muscle. *American Journal of Physiology. Endocrinology and Metabolism*, *298*(2), E257–269. http://doi.org/10.1152/ajpendo.00609.2009

Holz, M. K., & Blenis, J. (2005). Identification of S6 kinase 1 as a novel mammalian target of rapamycin (mTOR)-phosphorylating kinase. *The Journal of Biological Chemistry*, *280*(28), 26089–26093. http://doi.org/10.1074/jbc.M504045200

Hornberger, T. A., Chu, W. K., Mak, Y. W., Hsiung, J. W., Huang, S. A., & Chien, S. (2006). The role of phospholipase D and phosphatidic acid in the mechanical activation of mTOR signaling in skeletal muscle. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(12), 4741–4746. http://doi.org/10.1073/pnas.0600678103

Hornberger, T. A., Stuppard, R., Conley, K. E., Fedele, M. J., Fiorotto, M. L., Chin, E. R., & Esser, K. A. (2004). Mechanical stimuli regulate rapamycin-sensitive signalling by a phosphoinositide 3-kinase-, protein kinase B- and growth factor-independent mechanism. *The Biochemical Journal*, *380*(Pt 3), 795–804. http://doi.org/10.1042/BJ20040274

Hsieh, A. C., Liu, Y., Edlind, M. P., Ingolia, N. T., Janes, M. R., Sher, A., … Ruggero, D. (2012). The translational landscape of mTOR signalling steers cancer initiation and metastasis. *Nature*, *485*(7396), 55–61. http://doi.org/10.1038/nature10912

Hulmi, J. J., Tannerstedt, J., Selänne, H., Kainulainen, H., Kovanen, V., & Mero, A. A. (2009). Resistance exercise with whey protein ingestion affects mTOR signaling pathway and myostatin in men. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *106*(5), 1720–1729. http://doi.org/10.1152/japplphysiol.00087.2009

Hulmi, J. J., Walker, S., Ahtiainen, J. P., Nyman, K., Kraemer, W. J., & Häkkinen, K. (2012). Molecular signaling in muscle is affected by the specificity of resistance exercise protocol. *Scandinavian Journal of Medicine & Science in Sports*, *22*(2), 240–248. http://doi.org/10.1111/j.1600-0838.2010.01198.x

Huygens, W., Claessens, A. L., Thomis, M., Loos, R., Van Langendonck, L., Peeters, M., … Beunen, G. (2002). Body composition estimations by BIA versus anthropometric equations in body builders and other power athletes. *The Journal of Sports Medicine and Physical Fitness*, *42*(1), 45–55.

Inoki, K., Li, Y., Zhu, T., Wu, J., & Guan, K.-L. (2002). TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. *Nature Cell Biology*, *4*(9), 648–657. http://doi.org/10.1038/ncb839

Izquierdo, M., Häkkinen, K., Gonzalez-Badillo, J. J., Ibáñez, J., & Gorostiaga, E. M. (2002). Effects of long-term training specificity on maximal strength and power of the upper and lower extremities in athletes from different sports. *European Journal of Applied Physiology*, *87*(3), 264–271. http://doi.org/10.1007/s00421-002-0628-y

Jacinto, E., Loewith, R., Schmidt, A., Lin, S., Rüegg, M. A., Hall, A., & Hall, M. N. (2004). Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. *Nature Cell Biology*, *6*(11), 1122–1128. http://doi.org/10.1038/ncb1183

Jacobs, B. L., Goodman, C. A., & Hornberger, T. A. (2014). The mechanical activation of mTOR signaling: an emerging role for late endosome/lysosomal targeting. *Journal of Muscle Research and Cell Motility*, *35*(1), 11–21. http://doi.org/10.1007/s10974-013-9367-4

Jacobs, B. L., You, J.-S., Frey, J. W., Goodman, C. A., Gundermann, D. M., & Hornberger, T. A. (2013). Eccentric contractions increase the phosphorylation of tuberous sclerosis complex-2 (TSC2) and alter the targeting of TSC2 and the mechanistic target of rapamycin to the lysosome. *The Journal of Physiology*, *591*(Pt 18), 4611–4620. http://doi.org/10.1113/jphysiol.2013.256339

Jensen, T. E., Rose, A. J., Hellsten, Y., Wojtaszewski, J. F. P., & Richter, E. A. (2007). Caffeine-induced Ca(2+) release increases AMPK-dependent glucose uptake in rodent soleus muscle. *American Journal of Physiology. Endocrinology and Metabolism*, *293*(1), E286–292. http://doi.org/10.1152/ajpendo.00693.2006

Jewell, J. L., & Guan, K.-L. (2013). Nutrient signaling to mTOR and cell growth. *Trends in Biochemical Sciences*, *38*(5), 233–242. http://doi.org/10.1016/j.tibs.2013.01.004

Jiang, B.-H., & Liu, L.-Z. (2008). AKT signaling in regulating angiogenesis. *Current Cancer Drug Targets*, *8*(1), 19–26.

Joy, J. M., Gundermann, D. M., Lowery, R. P., Jäger, R., McCleary, S. A., Purpura, M., … Wilson, J. M. (2014a). Phosphatidic acid enhances mTOR signaling and resistance exercise induced hypertrophy. *Nutrition & Metabolism*, *11*, 29. http://doi.org/10.1186/1743-7075-11-29

Joy, J. M., Gundermann, D. M., Lowery, R. P., Jäger, R., McCleary, S. A., Purpura, M., … Wilson, J. M. (2014b). Phosphatidic acid enhances mTOR signaling and resistance exercise induced hypertrophy. *Nutrition & Metabolism*, *11*, 29. http://doi.org/10.1186/1743-7075-11-29

Karlsson, H. K. R., Nilsson, P.-A., Nilsson, J., Chibalin, A. V., Zierath, J. R., & Blomstrand, E. (2004). Branched-chain amino acids increase p70S6k phosphorylation in human skeletal muscle after resistance exercise. *American Journal of Physiology. Endocrinology and Metabolism*, *287*(1), E1–7. http://doi.org/10.1152/ajpendo.00430.2003

Katch, V. L., Katch, F. I., Moffatt, R., & Gittleson, M. (1980). Muscular development and lean body weight in body builders and weight lifters. *Medicine and Science in Sports and Exercise*, *12*(5), 340–344.

Kalista, S., Schakman, O., Gilson, H., Lause, P., Demeulder, B., Bertrand, L., … Thissen, J. P. (2012). The type 1 insulin-like growth factor receptor (IGF-IR) pathway is mandatory for the follistatin-induced skeletal muscle hypertrophy. *Endocrinology*, *153*(1), 241–253. http://doi.org/10.1210/en.2011-1687

Keith, C. T., & Schreiber, S. L. (1995). PIK-related kinases: DNA repair, recombination, and cell cycle checkpoints. *Science (New York, N.Y.)*, *270*(5233), 50–51.

Kendrick, N. (2014). A gene's mRNA level does not usually predict its protein levels. http://www.kendricklabs.com/WP1_mRNAvsProtein-New2014.pdf

Kilduff, L. P., Bevan, H., Owen, N., Kingsley, M. I. C., Bunce, P., Bennett, M., & Cunningham, D. (2007). Optimal loading for peak power output during the hang power clean in professional rugby players. *International Journal of Sports Physiology and Performance*, *2*(3), 260–269.

Kim, D.-H., Sarbassov, D. D., Ali, S. M., King, J. E., Latek, R. R., Erdjument-Bromage, H., … Sabatini, D. M. (2002). mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. *Cell*, *110*(2), 163–175.

Kim, S. G., Buel, G. R., & Blenis, J. (2013). Nutrient regulation of the mTOR complex 1 signaling pathway. *Molecules and Cells*, *35*(6), 463–473. http://doi.org/10.1007/s10059-013-0138-2

Knapik, J. J., Wright, J. E., Mawdsley, R. H., & Braun, J. (1983). Isometric, isotonic, and isokinetic torque variations in four muscle groups through a range of joint motion. *Physical Therapy*, *63*(6), 938–947.

Knebel, A., Haydon, C. E., Morrice, N., & Cohen, P. (2002). Stress-induced regulation of eukaryotic elongation factor 2 kinase by SB 203580-sensitive and -insensitive pathways. *The Biochemical Journal*, *367*(Pt 2), 525–532. http://doi.org/10.1042/BJ20020916

Koopman, R., Pennings, B., Zorenc, A. H. G., & van Loon, L. J. C. (2007). Protein ingestion further augments S6K1 phosphorylation in skeletal muscle following resistance type exercise in males. *The Journal of Nutrition*, *137*(8), 1880–1886.

Koopman, R., Zorenc, A. H. G., Gransier, R. J. J., Cameron-Smith, D., & van Loon, L. J. C. (2006). Increase in S6K1 phosphorylation in human skeletal muscle following resistance exercise occurs mainly in type II muscle fibers. *American Journal of Physiology. Endocrinology and Metabolism*, *290*(6), E1245–1252. http://doi.org/10.1152/ajpendo.00530.2005

Kraemer, W. J., & Ratamess, N. A. (2004). Fundamentals of resistance training: progression and exercise prescription. *Medicine and Science in Sports and Exercise*, *36*(4), 674–688.

Kubica, N., Bolster, D. R., Farrell, P. A., Kimball, S. R., & Jefferson, L. S. (2005). Resistance exercise increases muscle protein synthesis and translation of eukaryotic initiation factor 2Bepsilon mRNA in a mammalian target of rapamycin-dependent manner. *The Journal of Biological Chemistry*, *280*(9), 7570–7580. http://doi.org/10.1074/jbc.M413732200

Kubica, N., Crispino, J. L., Gallagher, J. W., Kimball, S. R., & Jefferson, L. S. (2008). Activation of the mammalian target of rapamycin complex 1 is both necessary and sufficient to stimulate eukaryotic initiation factor 2Bvarepsilon mRNA translation and protein synthesis. *The International Journal of Biochemistry & Cell Biology*, *40*(11), 2522–2533. http://doi.org/10.1016/j.biocel.2008.04.010

Kumar, V., Selby, A., Rankin, D., Patel, R., Atherton, P., Hildebrandt, W., … Rennie, M. J. (2009). Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. *The Journal of Physiology*, *587*(Pt 1), 211–217. http://doi.org/10.1113/jphysiol.2008.164483

Lagirand-Cantaloube, J., Offner, N., Csibi, A., Leibovitch, M. P., Batonnet-Pichon, S., Tintignac, L. A., … Leibovitch, S. A. (2008). The initiation factor eIF3-f is a major target for atrogin1/MAFbx function in skeletal muscle atrophy. *The EMBO Journal*, *27*(8), 1266–1276. http://doi.org/10.1038/emboj.2008.52

Lai, K.-M. V., Gonzalez, M., Poueymirou, W. T., Kline, W. O., Na, E., Zlotchenko, E., … Glass, D. J. (2004). Conditional activation of akt in adult skeletal muscle induces rapid hypertrophy. *Molecular and Cellular Biology*, *24*(21), 9295–9304. http://doi.org/10.1128/MCB.24.21.9295-9304.2004

Lal, H., Verma, S. K., Smith, M., Guleria, R. S., Lu, G., Foster, D. M., & Dostal, D. E. (2007). Stretch-induced MAP kinase activation in cardiac myocytes: differential regulation through beta1-integrin and focal adhesion kinase. *Journal of Molecular and Cellular Cardiology*, *43*(2), 137–147. http://doi.org/10.1016/j.yjmcc.2007.05.012

Laplante, M., & Sabatini, D. M. (2012). mTOR signaling in growth control and disease. *Cell*, *149*(2), 274–293. http://doi.org/10.1016/j.cell.2012.03.017

Matthews D. (1999). Proteins and Amino Acids. Baltimore, MD: Williams & Wilkins, p. 11–48.

Léger, B., Cartoni, R., Praz, M., Lamon, S., Dériaz, O., Crettenand, A., … Russell, A. P. (2006). Akt signalling through GSK-3beta, mTOR and Foxo1 is involved in human skeletal muscle hypertrophy and atrophy. *The Journal of Physiology*, *576*(Pt 3), 923–933. http://doi.org/10.1113/jphysiol.2006.116715

Lee, S.-J., Huynh, T. V., Lee, Y.-S., Sebald, S. M., Wilcox-Adelman, S. A., Iwamori, N., … Fan, C.-M. (2012). Role of satellite cells versus myofibers in muscle hypertrophy induced by inhibition of the

myostatin/activin signaling pathway. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(35), E2353–2360. http://doi.org/10.1073/pnas.1206410109

Li, J., Kim, S. G., & Blenis, J. (2014). Rapamycin: one drug, many effects. *Cell Metabolism*, *19*(3), 373–379. http://doi.org/10.1016/j.cmet.2014.01.001

Li, R., Narici, M. V., Erskine, R. M., Seynnes, O. R., Rittweger, J., Pišot, R., … Flück, M. (2013). Costamere remodeling with muscle loading and unloading in healthy young men. *Journal of Anatomy*, *223*(5), 525–536. http://doi.org/10.1111/joa.12101

Li, M., Verdijk, L. B., Sakamoto, K., Ely, B., van Loon, L. J. C., & Musi, N. (2012). Reduced AMPK-ACC and mTOR signaling in muscle from older men, and effect of resistance exercise. *Mechanisms of Ageing and Development*, *133*(11-12), 655–664. http://doi.org/10.1016/j.mad.2012.09.001

Lindholm, M. E., Marabita, F., Gomez-Cabrero, D., Rundqvist, H., Ekström, T. J., Tegnér, J., & Sundberg, C. J. (2014). An integrative analysis reveals coordinated reprogramming of the epigenome and the transcriptome in human skeletal muscle after training. *Epigenetics*, *0*(ja), 00–00. http://doi.org/10.4161/15592294.2014.982445

Lluís, F., Perdiguero, E., Nebreda, A. R., & Muñoz-Cánoves, P. (2006). Regulation of skeletal muscle gene expression by p38 MAP kinases. *Trends in Cell Biology*, *16*(1), 36–44. http://doi.org/10.1016/j.tcb.2005.11.002

Long, X., Lin, Y., Ortiz-Vega, S., Yonezawa, K., & Avruch, J. (2005). Rheb binds and regulates the mTOR kinase. *Current Biology: CB*, *15*(8), 702–713. http://doi.org/10.1016/j.cub.2005.02.053

Lodish, H., Berk, A., Kaiser, C., H., Krieger, M., Bretscher, A., Ploegh, H., Amon, A., Scott, M., P. (2012). Molecular Cell Biology. New York, NY, USA: W.H. Freeman and Company.

Lorge, P. (2011). Chinese Martial Arts: From Antiquity to the Twenty-First Century. Cambridge, UK: Cambridge University Press.

Lundberg, T. R., Fernandez-Gonzalo, R., Gustafsson, T., & Tesch, P. A. (2012). Aerobic exercise alters skeletal muscle molecular responses to resistance exercise. *Medicine and Science in Sports and Exercise*, *44*(9), 1680–1688. http://doi.org/10.1249/MSS.0b013e318256fbe8

Lundberg, T. R., Fernandez-Gonzalo, R., & Tesch, P. A. (2014). Exercise-induced AMPK activation does not interfere with muscle hypertrophy in response to resistance training in men. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *116*(6), 611–620. http://doi.org/10.1152/japplphysiol.01082.2013

MacKenzie, M. G., Hamilton, D. L., Murray, J. T., Taylor, P. M., & Baar, K. (2009). mVps34 is activated following high-resistance contractions. *The Journal of Physiology*, *587*(Pt 1), 253–260. http://doi.org/10.1113/jphysiol.2008.159830

Magnuson, B., Ekim, B., & Fingar, D. C. (2012). Regulation and function of ribosomal protein S6 kinase (S6K) within mTOR signalling networks. *The Biochemical Journal*, *441*(1), 1–21. http://doi.org/10.1042/BJ20110892

Manning, B. D., & Cantley, L. C. (2007). AKT/PKB signaling: navigating downstream. *Cell*, *129*(7), 1261–1274. http://doi.org/10.1016/j.cell.2007.06.009

Mascher, H., Tannerstedt, J., Brink-Elfegoun, T., Ekblom, B., Gustafsson, T., & Blomstrand, E. (2008). Repeated resistance exercise training induces different changes in mRNA expression of MAFbx and MuRF-1 in human skeletal muscle. *American Journal of Physiology. Endocrinology and Metabolism*, *294*(1), E43–51. http://doi.org/10.1152/ajpendo.00504.2007

Ma, X. M., & Blenis, J. (2009a). Molecular mechanisms of mTOR-mediated translational control. *Nature Reviews. Molecular Cell Biology*, *10*(5), 307–318. http://doi.org/10.1038/nrm2672

Ma, X. M., & Blenis, J. (2009b). Molecular mechanisms of mTOR-mediated translational control. *Nature Reviews. Molecular Cell Biology*, *10*(5), 307–318. http://doi.org/10.1038/nrm2672

Mayhew, D. L., Hornberger, T. A., Lincoln, H. C., & Bamman, M. M. (2011). Eukaryotic initiation factor 2B epsilon induces cap-dependent translation and skeletal muscle hypertrophy. *The Journal of Physiology*, *589*(Pt 12), 3023–3037. http://doi.org/10.1113/jphysiol.2010.202432

McGlory, C., & Phillips, S. M. (2014). Assessing the regulation of skeletal muscle plasticity in response to protein ingestion and resistance exercise: recent developments. *Current Opinion in Clinical Nutrition and Metabolic Care*, *17*(5), 412–417. http://doi.org/10.1097/MCO.0000000000000083

McGlory, C., White, A., Treins, C., Drust, B., Close, G. L., Maclaren, D. P. M., … Hamilton, D. L. (2014). Application of the [γ-32P] ATP kinase assay to study anabolic signaling in human skeletal muscle. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *116*(5), 504–513. http://doi.org/10.1152/japplphysiol.01072.2013

McGuigan, M. R., & Winchester, J. B. (2008). The relationship between isometric and dynamic strength in college football players. *Journal of Sports Science & Medicine*, *7*(1), 101–105.

Menon, S., Dibble, C. C., Talbott, G., Hoxhaj, G., Valvezan, A. J., Takahashi, H., … Manning, B. D. (2014). Spatial control of the TSC complex integrates insulin and nutrient regulation of mTORC1 at the lysosome. *Cell*, *156*(4), 771–785. http://doi.org/10.1016/j.cell.2013.11.049

Menting, J. G., Whittaker, J., Margetts, M. B., Whittaker, L. J., Kong, G. K.-W., Smith, B. J., … Lawrence, M. C. (2013). How insulin engages its primary binding site on the insulin receptor. *Nature*, *493*(7431), 241–245. http://doi.org/10.1038/nature11781

Meyuhas, O., & Dreazen, A. (2009). Ribosomal protein S6 kinase from TOP mRNAs to cell size. *Progress in Molecular Biology and Translational Science*, *90*, 109–153. http://doi.org/10.1016/S1877-1173(09)90003-5

Mitchell, C. J., Churchward-Venne, T. A., Bellamy, L., Parise, G., Baker, S. K., & Phillips, S. M. (2013). Muscular and systemic correlates of resistance training-induced muscle hypertrophy. *PloS One*, *8*(10), e78636. http://doi.org/10.1371/journal.pone.0078636

Mitchell, C. J., Churchward-Venne, T. A., Parise, G., Bellamy, L., Baker, S. K., Smith, K., … Phillips, S. M. (2014). Acute post-exercise myofibrillar protein synthesis is not correlated with resistance training-induced muscle hypertrophy in young men. *PloS One*, *9*(2), e89431. http://doi.org/10.1371/journal.pone.0089431

Mitchell, C. J., Churchward-Venne, T. A., West, D. W. D., Burd, N. A., Breen, L., Baker, S. K., & Phillips, S. M. (2012). Resistance exercise load does not determine training-mediated hypertrophic gains in young men. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *113*(1), 71–77. http://doi.org/10.1152/japplphysiol.00307.2012

Miyatani, M., Kanehisa, H., Ito, M., Kawakami, Y., & Fukunaga, T. (2004). The accuracy of volume estimates using ultrasound muscle thickness measurements in different muscle groups. *European Journal of Applied Physiology*, *91*(2-3), 264–272. http://doi.org/10.1007/s00421-003-0974-4

Miyazaki, M., McCarthy, J. J., Fedele, M. J., & Esser, K. A. (2011). Early activation of mTORC1 signalling in response to mechanical overload is independent of phosphoinositide 3-kinase/Akt signalling. *The Journal of Physiology*, *589*(Pt 7), 1831–1846. http://doi.org/10.1113/jphysiol.2011.205658

Moberg, M., Apró, W., Ohlsson, I., Pontén, M., Villanueva, A., Ekblom, B., & Blomstrand, E. (2014). Absence of leucine in an essential amino acid supplement reduces activation of mTORC1 signalling following resistance exercise in young females. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquée, Nutrition Et Métabolisme*, *39*(2), 183–194. http://doi.org/10.1139/apnm-2013-0244

Møller, A. B., Vendelbo, M. H., Rahbek, S. K., Clasen, B. F., Schjerling, P., Vissing, K., & Jessen, N. (2013). Resistance exercise, but not endurance exercise, induces IKKβ phosphorylation in human skeletal muscle of training-accustomed individuals. *Pflügers Archiv: European Journal of Physiology*, *465*(12), 1785–1795. http://doi.org/10.1007/s00424-013-1318-9

Moore, D. R., Robinson, M. J., Fry, J. L., Tang, J. E., Glover, E. I., Wilkinson, S. B., … Phillips, S. M. (2009). Ingested protein dose response of muscle and albumin protein synthesis after resistance exercise in young men. *The American Journal of Clinical Nutrition*, *89*(1), 161–168. http://doi.org/10.3945/ajcn.2008.26401

Moore, S. F., Hunter, R. W., & Hers, I. (2011). mTORC2 protein complex-mediated Akt (Protein Kinase B) Serine 473 Phosphorylation is not required for Akt1 activity in human platelets [corrected].

The Journal of Biological Chemistry, *286*(28), 24553–24560. http://doi.org/10.1074/jbc.M110.202341

Moss, B. M., Refsnes, P. E., Abildgaard, A., Nicolaysen, K., & Jensen, J. (1997). Effects of maximal effort strength training with different loads on dynamic strength, cross-sectional area, load-power and load-velocity relationships. *European Journal of Applied Physiology and Occupational Physiology*, *75*(3), 193–199. http://doi.org/10.1007/s004210050147

Munn, J., Herbert, R. D., Hancock, M. J., & Gandevia, S. C. (2005). Resistance training for strength: effect of number of sets and contraction speed. *Medicine and Science in Sports and Exercise*, *37*(9), 1622–1626.

Nada, S., Hondo, A., Kasai, A., Koike, M., Saito, K., Uchiyama, Y., & Okada, M. (2009). The novel lipid raft adaptor p18 controls endosome dynamics by anchoring the MEK-ERK pathway to late endosomes. *The EMBO Journal*, *28*(5), 477–489. http://doi.org/10.1038/emboj.2008.308

Nader, G. A., von Walden, F., Liu, C., Lindvall, J., Gutmann, L., Pistilli, E. E., & Gordon, P. M. (2014). Resistance exercise training modulates acute gene expression during human skeletal muscle hypertrophy. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *116*(6), 693–702. http://doi.org/10.1152/japplphysiol.01366.2013

Nedergaard, A., Jespersen, J. G., Pingel, J., Christensen, B., Sroczynski, N., Langberg, H., … Schjerling, P. (2012). Effects of 2 weeks lower limb immobilization and two separate rehabilitation regimens on gastrocnemius muscle protein turnover signaling and normalization genes. *BMC Research Notes*, *5*, 166. http://doi.org/10.1186/1756-0500-5-166

O'Neil, T. K., Duffy, L. R., Frey, J. W., & Hornberger, T. A. (2009). The role of phosphoinositide 3-kinase and phosphatidic acid in the regulation of mammalian target of rapamycin following eccentric contractions. *The Journal of Physiology*, *587*(Pt 14), 3691–3701. http://doi.org/10.1113/jphysiol.2009.173609

Pallafacchina, G., Calabria, E., Serrano, A. L., Kalhovde, J. M., & Schiaffino, S. (2002). A protein kinase B-dependent and rapamycin-sensitive pathway controls skeletal muscle growth but not fiber type specification. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(14), 9213–9218. http://doi.org/10.1073/pnas.142166599

Pasiakos, S. M. (2012). Exercise and amino acid anabolic cell signaling and the regulation of skeletal muscle mass. *Nutrients*, *4*(7), 740–758. http://doi.org/10.3390/nu4070740

Phillips, S. M., Tipton, K. D., Aarsland, A., Wolf, S. E., & Wolfe, R. R. (1997). Mixed muscle protein synthesis and breakdown after resistance exercise in humans. *The American Journal of Physiology*, *273*(1 Pt 1), E99–107.

Philp, A., Hamilton, D. L., & Baar, K. (2011). Signals mediating skeletal muscle remodeling by resistance exercise: PI3-kinase independent activation of mTORC1. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *110*(2), 561–568. http://doi.org/10.1152/japplphysiol.00941.2010

Popov, D. V., Lysenko, E. A., Bachinin, A. V., Miller, T. F., Kurochkina, N. S., Kravchenko, I. V., … Vinogradova, O. L. (2015). Influence of resistance exercise intensity and metabolic stress on anabolic signaling and expression of myogenic genes in skeletal muscle. *Muscle & Nerve*, *51*(3), 434–442. http://doi.org/10.1002/mus.24314

Raught, B., Peiretti, F., Gingras, A.-C., Livingstone, M., Shahbazian, D., Mayeur, G. L., … Hershey, J. W. B. (2004). Phosphorylation of eucaryotic translation initiation factor 4B Ser422 is modulated by S6 kinases. *The EMBO Journal*, *23*(8), 1761–1769. http://doi.org/10.1038/sj.emboj.7600193

Rennie, M. J., Smith, K., & Watt, P. W. (1994). Measurement of human tissue protein synthesis: an optimal approach. *The American Journal of Physiology*, *266*(3 Pt 1), E298–307.

Rhea, M. R., Alvar, B. A., Burkett, L. N., & Ball, S. D. (2003). A meta-analysis to determine the dose response for strength development. *Medicine and Science in Sports and Exercise*, *35*(3), 456–464. http://doi.org/10.1249/01.MSS.0000053727.63505.D4

Riaz, A., Zeller, K. S., & Johansson, S. (2012). Receptor-specific mechanisms regulate phosphorylation of AKT at Ser473: role of RICTOR in β1 integrin-mediated cell survival. *PloS One*, *7*(2), e32081. http://doi.org/10.1371/journal.pone.0032081

Richardson, C. J., Bröenstrup, M., Fingar, D. C., Jülich, K., Ballif, B. A., Gygi, S., & Blenis, J. (2004). SKAR is a specific target of S6 kinase 1 in cell growth control. *Current Biology: CB*, *14*(17), 1540–1549. http://doi.org/10.1016/j.cub.2004.08.061

Richter, E. A., & Ruderman, N. B. (2009). AMPK and the biochemistry of exercise: implications for human health and disease. *The Biochemical Journal*, *418*(2), 261–275. http://doi.org/10.1042/BJ20082055

Risson, V., Mazelin, L., Roceri, M., Sanchez, H., Moncollin, V., Corneloup, C., … Gangloff, Y.-G. (2009). Muscle inactivation of mTOR causes metabolic and dystrophin defects leading to severe myopathy. *The Journal of Cell Biology*, *187*(6), 859–874. http://doi.org/10.1083/jcb.200903131

Rivas, D. A., Morris, E. P., Haran, P. H., Pasha, E. P., Morais, M. da S., Dolnikowski, G. G., … Fielding, R. A. (2012). Increased ceramide content and NFκB signaling may contribute to the attenuation of anabolic signaling after resistance exercise in aged males. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *113*(11), 1727–1736. http://doi.org/10.1152/japplphysiol.00412.2012

Roche, H.,M., Popeijus, H.,E., Mensink, R.,M. (2009). Molecular Aspects of Nutrition. In Lanham-New, S.,A., Macdonald, I.,A., Roche, H.,M. (Eds.), Nutrition & Metabolism (pp. 7-34). Chichester, UK: John Wiley & Sons.

Rodriguez, J., Vernus, B., Chelh, I., Cassar-Malek, I., Gabillard, J. C., Hadj Sassi, A., … Bonnieu, A. (2014). Myostatin and the skeletal muscle atrophy and hypertrophy signaling pathways. *Cellular and Molecular Life Sciences: CMLS*. http://doi.org/10.1007/s00018-014-1689-x

Rodriguez-Viciana, P., Warne, P. H., Dhand, R., Vanhaesebroeck, B., Gout, I., Fry, M. J., … Downward, J. (1994). Phosphatidylinositol-3-OH kinase as a direct target of Ras. *Nature*, *370*(6490), 527–532. http://doi.org/10.1038/370527a0

Romeo, Y., Zhang, X., & Roux, P. P. (2012). Regulation and function of the RSK family of protein kinases. *The Biochemical Journal*, *441*(2), 553–569. http://doi.org/10.1042/BJ20110289

Roux, P. P., Shahbazian, D., Vu, H., Holz, M. K., Cohen, M. S., Taunton, J., … Blenis, J. (2007). RAS/ERK signaling promotes site-specific ribosomal protein S6 phosphorylation via RSK and stimulates cap-dependent translation. *The Journal of Biological Chemistry*, *282*(19), 14056–14064. http://doi.org/10.1074/jbc.M700906200

Ruvinsky, I., Sharon, N., Lerer, T., Cohen, H., Stolovich-Rain, M., Nir, T., … Meyuhas, O. (2005). Ribosomal protein S6 phosphorylation is a determinant of cell size and glucose homeostasis. *Genes & Development*, *19*(18), 2199–2211. http://doi.org/10.1101/gad.351605

Sabatini, D. M., Erdjument-Bromage, H., Lui, M., Tempst, P., & Snyder, S. H. (1994). RAFT1: a mammalian protein that binds to FKBP12 in a rapamycin-dependent fashion and is homologous to yeast TORs. *Cell*, *78*(1), 35–43.

Sagné, C., Agulhon, C., Ravassard, P., Darmon, M., Hamon, M., El Mestikawy, S., … Giros, B. (2001). Identification and characterization of a lysosomal transporter for small neutral amino acids. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(13), 7206–7211. http://doi.org/10.1073/pnas.121183498

Sancak, Y., Bar-Peled, L., Zoncu, R., Markhard, A. L., Nada, S., & Sabatini, D. M. (2010). Ragulator-Rag complex targets mTORC1 to the lysosomal surface and is necessary for its activation by amino acids. *Cell*, *141*(2), 290–303. http://doi.org/10.1016/j.cell.2010.02.024

Sancak, Y., Peterson, T. R., Shaul, Y. D., Lindquist, R. A., Thoreen, C. C., Bar-Peled, L., & Sabatini, D. M. (2008). The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1. *Science (New York, N.Y.)*, *320*(5882), 1496–1501. http://doi.org/10.1126/science.1157535

Sancak, Y., Thoreen, C. C., Peterson, T. R., Lindquist, R. A., Kang, S. A., Spooner, E., … Sabatini, D. M. (2007). PRAS40 is an insulin-regulated inhibitor of the mTORC1 protein kinase. *Molecular Cell*, *25*(6), 903–915. http://doi.org/10.1016/j.molcel.2007.03.003

Sandri, M. (2013). Protein breakdown in muscle wasting: role of autophagy-lysosome and ubiquitin-proteasome. *The International Journal of Biochemistry & Cell Biology*, *45*(10), 2121–2129. http://doi.org/10.1016/j.biocel.2013.04.023

Santarpia, L., Lippman, S. M., & El-Naggar, A. K. (2012). Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. *Expert Opinion on Therapeutic Targets*, *16*(1), 103–119. http://doi.org/10.1517/14728222.2011.645805

Sarbassov, D. D., Ali, S. M., Kim, D.-H., Guertin, D. A., Latek, R. R., Erdjument-Bromage, H., … Sabatini, D. M. (2004). Rictor, a novel binding partner of mTOR, defines a rapamycin-insensitive and raptor-independent pathway that regulates the cytoskeleton. *Current Biology: CB*, *14*(14), 1296–1302. http://doi.org/10.1016/j.cub.2004.06.054

Sarbassov, D. D., Guertin, D. A., Ali, S. M., & Sabatini, D. M. (2005). Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. *Science (New York, N.Y.)*, *307*(5712), 1098–1101. http://doi.org/10.1126/science.1106148

Sartori, R., Milan, G., Patron, M., Mammucari, C., Blaauw, B., Abraham, R., & Sandri, M. (2009). Smad2 and 3 transcription factors control muscle mass in adulthood. *American Journal of Physiology. Cell Physiology*, *296*(6), C1248–1257. http://doi.org/10.1152/ajpcell.00104.2009

Schliess, F., Richter, L., vom Dahl, S., & Häussinger, D. (2006). Cell hydration and mTOR-dependent signalling. *Acta Physiologica (Oxford, England)*, *187*(1-2), 223–229. http://doi.org/10.1111/j.1748-1716.2006.01547.x

Schliess, F., Schreiber, R., & Häussinger, D. (1995). Activation of extracellular signal-regulated kinases Erk-1 and Erk-2 by cell swelling in H4IIE hepatoma cells. *The Biochemical Journal*, *309 (Pt 1)*, 13–17.

Schiaffino, S., Dyar, K. A., Ciciliot, S., Blaauw, B., & Sandri, M. (2013). Mechanisms regulating skeletal muscle growth and atrophy. *The FEBS Journal*, *280*(17), 4294–4314. http://doi.org/10.1111/febs.12253

Schoenfeld, B. J., Contreras, B., Willardson, J. M., Fontana, F., & Tiryaki-Sonmez, G. (2014). Muscle activation during low- versus high-load resistance training in well-trained men. *European Journal of Applied Physiology*, *114*(12), 2491–2497. http://doi.org/10.1007/s00421-014-2976-9

Schoenfeld, B. J., Peterson, M. D., Ogborn, D., Contreras, B., & Sonmez, G. T. (2015). Effects of Low- Versus High-Load Resistance Training on Muscle Strength and Hypertrophy in Well-Trained Men. *Journal of Strength and Conditioning Research / National Strength & Conditioning Association*. http://doi.org/10.1519/JSC.0000000000000958

Schultze, S. M., Jensen, J., Hemmings, B. A., Tschopp, O., & Niessen, M. (2011). Promiscuous affairs of PKB/AKT isoforms in metabolism. *Archives of Physiology and Biochemistry*, *117*(2), 70–77. http://doi.org/10.3109/13813455.2010.539236

Schwarzenegger, A. (1999). The New Encyclopedia of Modern Bodybuilding. New York, NY, USA: Simon & Schuster

Seene, T., & Alev, K. (1991). Effect of muscular activity on the turnover rate of actin and myosin heavy and light chains in different types of skeletal muscle. *International Journal of Sports Medicine*, *12*(2), 204–207. http://doi.org/10.1055/s-2007-1024668

Seene, T., Alev, K., & Pehme, A. (1986). Effect of muscular activity on the turnover rate of actin and myosin heavy and light chains in different types of skeletal muscle. I. Changes in the turnover rate of myosin and actin during and after single-bout physical activity. *International Journal of Sports Medicine*, *7*(5), 287–290. http://doi.org/10.1055/s-2008-1025776

Shahbazian, D., Roux, P. P., Mieulet, V., Cohen, M. S., Raught, B., Taunton, J., … Sonenberg, N. (2006). The mTOR/PI3K and MAPK pathways converge on eIF4B to control its phosphorylation and activity. *The EMBO Journal*, *25*(12), 2781–2791. http://doi.org/10.1038/sj.emboj.7601166

Shimobayashi, M., & Hall, M. N. (2014). Making new contacts: the mTOR network in metabolism and signalling crosstalk. *Nature Reviews. Molecular Cell Biology*, *15*(3), 155–162. http://doi.org/10.1038/nrm3757

Shilling, C., & Bunsell, T. (2009). The Female Bodybuilder as a Gender Outlaw. *Qualitative Research in Sport and Exercise 1.2* 141-59

Sjøgaard, G. (1986). Water and electrolyte fluxes during exercise and their relation to muscle fatigue. *Acta Physiologica Scandinavica. Supplementum*, *556*, 129–136.

Sjøgaard, G., Adams, R. P., & Saltin, B. (1985). Water and ion shifts in skeletal muscle of humans with intense dynamic knee extension. *The American Journal of Physiology*, *248*(2 Pt 2), R190–196.

Sipilä, S., & Suominen, H. (1996). Quantitative ultrasonography of muscle: detection of adaptations to training in elderly women. *Archives of Physical Medicine and Rehabilitation*, *77*(11), 1173–1178.

Sokabe, M., Fraser, C. S., & Hershey, J. W. B. (2012). The human translation initiation multi-factor complex promotes methionyl-tRNAi binding to the 40S ribosomal subunit. *Nucleic Acids Research*, *40*(2), 905–913. http://doi.org/10.1093/nar/gkr772

Soliman, G. A., Acosta-Jaquez, H. A., Dunlop, E. A., Ekim, B., Maj, N. E., Tee, A. R., & Fingar, D. C. (2010). mTOR Ser-2481 autophosphorylation monitors mTORC-specific catalytic activity and clarifies rapamycin mechanism of action. *The Journal of Biological Chemistry*, *285*(11), 7866–7879. http://doi.org/10.1074/jbc.M109.096222

Sonenberg, N., & Hinnebusch, A. G. (2009). Regulation of translation initiation in eukaryotes: mechanisms and biological targets. *Cell*, *136*(4), 731–745. http://doi.org/10.1016/j.cell.2009.01.042

Spangenburg, E. E., Le Roith, D., Ward, C. W., & Bodine, S. C. (2008). A functional insulin-like growth factor receptor is not necessary for load-induced skeletal muscle hypertrophy. *The Journal of Physiology*, *586*(1), 283–291. http://doi.org/10.1113/jphysiol.2007.141507

Spiering, B. A., Kraemer, W. J., Anderson, J. M., Armstrong, L. E., Nindl, B. C., Volek, J. S., … Maresh, C. M. (2008). Effects of elevated circulating hormones on resistance exercise-induced Akt signaling. *Medicine and Science in Sports and Exercise*, *40*(6), 1039–1048. http://doi.org/10.1249/MSS.0b013e31816722bd

Sriwijitkamol, A., Coletta, D. K., Wajcberg, E., Balbontin, G. B., Reyna, S. M., Barrientes, J., … Musi, N. (2007). Effect of acute exercise on AMPK signaling in skeletal muscle of subjects with type 2 diabetes: a time-course and dose-response study. *Diabetes*, *56*(3), 836–848. http://doi.org/10.2337/db06-1119

Stambolic, V., Suzuki, A., de la Pompa, J. L., Brothers, G. M., Mirtsos, C., Sasaki, T., … Mak, T. W. (1998). Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN. *Cell*, *95*(1), 29–39.

Stefanetti, R. J., Zacharewicz, E., Della Gatta, P., Garnham, A., Russell, A. P., & Lamon, S. (2014). Ageing has no effect on the regulation of the ubiquitin proteasome-related genes and proteins following resistance exercise. *Frontiers in Physiology*, *5*, 30. http://doi.org/10.3389/fphys.2014.00030

Stokoe, D., Stephens, L. R., Copeland, T., Gaffney, P. R., Reese, C. B., Painter, G. F., … Hawkins, P. T. (1997). Dual role of phosphatidylinositol-3,4,5-trisphosphate in the activation of protein kinase B. *Science (New York, N.Y.)*, *277*(5325), 567–570.

Stone, M. H., Sands, W. A., Pierce, K. C., Ramsey, M. W., & Haff, G. G. (2008). Power and power potentiation among strength-power athletes: preliminary study. *International Journal of Sports Physiology and Performance*, *3*(1), 55–67.

Suire, S., Hawkins, P., & Stephens, L. (2002). Activation of phosphoinositide 3-kinase gamma by Ras. *Current Biology: CB*, *12*(13), 1068–1075.

Suter, M., Riek, U., Tuerk, R., Schlattner, U., Wallimann, T., & Neumann, D. (2006). Dissecting the role of 5'-AMP for allosteric stimulation, activation, and deactivation of AMP-activated protein kinase. *The Journal of Biological Chemistry*, *281*(43), 32207–32216. http://doi.org/10.1074/jbc.M606357200

Terzis, G., Georgiadis, G., Stratakos, G., Vogiatzis, I., Kavouras, S., Manta, P., … Blomstrand, E. (2008). Resistance exercise-induced increase in muscle mass correlates with p70S6 kinase phosphorylation in human subjects. *European Journal of Applied Physiology*, *102*(2), 145–152. http://doi.org/10.1007/s00421-007-0564-y

Terzis, G., Spengos, K., Mascher, H., Georgiadis, G., Manta, P., & Blomstrand, E. (2010). The degree of p70 S6k and S6 phosphorylation in human skeletal muscle in response to resistance exercise

depends on the training volume. *European Journal of Applied Physiology*, *110*(4), 835–843. http://doi.org/10.1007/s00421-010-1527-2

Tesch, P. A., Thorsson, A., & Essén-Gustavsson, B. (1989). Enzyme activities of FT and ST muscle fibers in heavy-resistance trained athletes. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *67*(1), 83–87.

Thoreen, C. C., Chantranupong, L., Keys, H. R., Wang, T., Gray, N. S., & Sabatini, D. M. (2012). A unifying model for mTORC1-mediated regulation of mRNA translation. *Nature*, *485*(7396), 109–113. http://doi.org/10.1038/nature11083

Tintignac, L. A., Lagirand, J., Batonnet, S., Sirri, V., Leibovitch, M. P., & Leibovitch, S. A. (2005). Degradation of MyoD mediated by the SCF (MAFbx) ubiquitin ligase. *The Journal of Biological Chemistry*, *280*(4), 2847–2856. http://doi.org/10.1074/jbc.M411346200

Tschopp, O., Yang, Z.-Z., Brodbeck, D., Dummler, B. A., Hemmings-Mieszczak, M., Watanabe, T., … Hemmings, B. A. (2005). Essential role of protein kinase B gamma (PKB gamma/Akt3) in postnatal brain development but not in glucose homeostasis. *Development (Cambridge, England)*, *132*(13), 2943–2954. http://doi.org/10.1242/dev.01864

Tsuchiya, A., Kanno, T., & Nishizaki, T. (2014). PI3 kinase directly phosphorylates Akt1/2 at Ser473/474 in the insulin signal transduction pathway. *The Journal of Endocrinology*, *220*(1), 49–59. http://doi.org/10.1530/JOE-13-0172

Tsun, Z.-Y., Bar-Peled, L., Chantranupong, L., Zoncu, R., Wang, T., Kim, C., … Sabatini, D. M. (2013). The folliculin tumor suppressor is a GAP for the RagC/D GTPases that signal amino acid levels to mTORC1. *Molecular Cell*, *52*(4), 495–505. http://doi.org/10.1016/j.molcel.2013.09.016

Valentinis, B., & Baserga, R. (2001). IGF-I receptor signalling in transformation and differentiation. *Molecular Pathology: MP*, *54*(3), 133–137.

Valverde, A. M., Lorenzo, M., Pons, S., White, M. F., & Benito, M. (1998). Insulin receptor substrate (IRS) proteins IRS-1 and IRS-2 differential signaling in the insulin/insulin-like growth factor-I pathways in fetal brown adipocytes. *Molecular Endocrinology (Baltimore, Md.)*, *12*(5), 688–697. http://doi.org/10.1210/mend.12.5.0106

Vary, T. C., & Lynch, C. J. (2006). Meal feeding enhances formation of eIF4F in skeletal muscle: role of increased eIF4E availability and eIF4G phosphorylation. *American Journal of Physiology. Endocrinology and Metabolism*, *290*(4), E631–642. http://doi.org/10.1152/ajpendo.00460.2005

Vézina, C., Kudelski, A., & Sehgal, S. N. (1975). Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. *The Journal of Antibiotics*, *28*(10), 721–726.

Vissing, K., McGee, S. L., Farup, J., Kjølhede, T., Vendelbo, M. H., & Jessen, N. (2011). Differentiated mTOR but not AMPK signaling after strength vs endurance exercise in training-accustomed individuals. *Scandinavian Journal of Medicine & Science in Sports*. http://doi.org/10.1111/j.1600-0838.2011.01395.x

Vorobyev, AN. A Textbook on Weightlifting. In: Trans. W.J. Brice, ed. Budapest, Hungary: International Weightlifting Federation, 1978.

Watson, J.,D., & Crick, F.,H.,C. (1953). *Nature 171*, 737-73.

Walker, S., Hulmi, J. J., Wernbom, M., Nyman, K., Kraemer, W. J., Ahtiainen, J. P., & Häkkinen, K. (2013). Variable resistance training promotes greater fatigue resistance but not hypertrophy versus constant resistance training. *European Journal of Applied Physiology*, *113*(9), 2233–2244. http://doi.org/10.1007/s00421-013-2653-4

Wang, L., & Proud, C. G. (2002). Regulation of the phosphorylation of elongation factor 2 by MEK-dependent signalling in adult rat cardiomyocytes. *FEBS Letters*, *531*(2), 285–289.

Wang, Q., & McPherron, A. C. (2012). Myostatin inhibition induces muscle fibre hypertrophy prior to satellite cell activation. *The Journal of Physiology*, *590*(Pt 9), 2151–2165. http://doi.org/10.1113/jphysiol.2011.226001

Wang, X., Li, W., Williams, M., Terada, N., Alessi, D. R., & Proud, C. G. (2001). Regulation of elongation factor 2 kinase by p90(RSK1) and p70 S6 kinase. *The EMBO Journal*, *20*(16), 4370–4379. http://doi.org/10.1093/emboj/20.16.4370

Wang, X., & Proud, C. G. (2008). A novel mechanism for the control of translation initiation by amino acids, mediated by phosphorylation of eukaryotic initiation factor 2B. *Molecular and Cellular Biology*, *28*(5), 1429–1442. http://doi.org/10.1128/MCB.01512-07

Weber, J. D., & Gutmann, D. H. (2012). Deconvoluting mTOR biology. *Cell Cycle (Georgetown, Tex.)*, *11*(2), 236–248. http://doi.org/10.4161/cc.11.2.19022

Welsh, G. I., Miller, C. M., Loughlin, A. J., Price, N. T., & Proud, C. G. (1998). Regulation of eukaryotic initiation factor eIF2B: glycogen synthase kinase-3 phosphorylates a conserved serine which undergoes dephosphorylation in response to insulin. *FEBS Letters*, *421*(2), 125–130.

Weng, Q. P., Kozlowski, M., Belham, C., Zhang, A., Comb, M. J., & Avruch, J. (1998). Regulation of the p70 S6 kinase by phosphorylation in vivo. Analysis using site-specific anti-phosphopeptide antibodies. *The Journal of Biological Chemistry*, *273*(26), 16621–16629.

Wernbom, M., Apro, W., Paulsen, G., Nilsen, T. S., Blomstrand, E., & Raastad, T. (2013). Acute low-load resistance exercise with and without blood flow restriction increased protein signalling and

number of satellite cells in human skeletal muscle. *European Journal of Applied Physiology*, *113*(12), 2953–2965. http://doi.org/10.1007/s00421-013-2733-5

West, D. W. D., Burd, N. A., Churchward-Venne, T. A., Camera, D. M., Mitchell, C. J., Baker, S. K., … Phillips, S. M. (2012). Sex-based comparisons of myofibrillar protein synthesis after resistance exercise in the fed state. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *112*(11), 1805–1813. http://doi.org/10.1152/japplphysiol.00170.2012

White, M. K., & Strayer, D. S. (2002). Survival signaling in type II pneumocytes activated by surfactant protein-A. *Experimental Cell Research*, *280*(2), 270–279.

WHO. (2008). Ageing (online) http://www.who.int/topics/ageing/en

Winbanks, C. E., Weeks, K. L., Thomson, R. E., Sepulveda, P. V., Beyer, C., Qian, H., … Gregorevic, P. (2012). Follistatin-mediated skeletal muscle hypertrophy is regulated by Smad3 and mTOR independently of myostatin. *The Journal of Cell Biology*, *197*(7), 997–1008. http://doi.org/10.1083/jcb.201109091

Wilkinson, D. J., Franchi, M. V., Brook, M. S., Narici, M. V., Williams, J. P., Mitchell, W. K., … Smith, K. (2014). A validation of the application of D(2)O stable isotope tracer techniques for monitoring day-to-day changes in muscle protein subfraction synthesis in humans. *American Journal of Physiology. Endocrinology and Metabolism*, *306*(5), E571–579. http://doi.org/10.1152/ajpendo.00650.2013

Willkomm, L., Schubert, S., Jung, R., Elsen, M., Borde, J., Gehlert, S., … Bloch, W. (2014). Lactate regulates myogenesis in C2C12 myoblasts in vitro. *Stem Cell Research*, *12*(3), 742–753. http://doi.org/10.1016/j.scr.2014.03.004

Witard, O. C., Tieland, M., Beelen, M., Tipton, K. D., van Loon, L. J. C., & Koopman, R. (2009). Resistance exercise increases postprandial muscle protein synthesis in humans. *Medicine and Science in Sports and Exercise*, *41*(1), 144–154. http://doi.org/10.1249/MSS.0b013e3181844e79

Witkowski, S., Lovering, R. M., & Spangenburg, E. E. (2010). High-frequency electrically stimulated skeletal muscle contractions increase p70s6k phosphorylation independent of known IGF-I sensitive signaling pathways. *FEBS Letters*, *584*(13), 2891–2895. http://doi.org/10.1016/j.febslet.2010.05.003

You, J. S., Frey, J. W., & Hornberger, T. A. (2012). Mechanical stimulation induces mTOR signaling via an ERK-independent mechanism: implications for a direct activation of mTOR by phosphatidic acid. *PloS One*, *7*(10), e47258. http://doi.org/10.1371/journal.pone.0047258

Zatsiorsky, V. (1995). Science and Practice of Strength Training. Champaign, IL, USA: Human Kinetics

Zhou, H., & Huang, S. (2010). The complexes of mammalian target of rapamycin. *Current Protein & Peptide Science*, *11*(6), 409–424.

Zoncu, R., Bar-Peled, L., Efeyan, A., Wang, S., Sancak, Y., & Sabatini, D. M. (2011). mTORC1 senses lysosomal amino acids through an inside-out mechanism that requires the vacuolar H(+)-ATPase. *Science (New York, N.Y.)*, *334*(6056), 678–683. http://doi.org/10.1126/science.1207056

Zimmermann, S., & Moelling, K. (1999). Phosphorylation and regulation of Raf by Akt (protein kinase B). *Science (New York, N.Y.)*, *286*(5445), 1741–1744.