Building muscle

A translation of training adaptation

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Responsible publisher under Swedish law: the Dean of the Medical Faculty

ISBN: 978-91-7601-398-4

ISSN: 0346-6612; 1738

Cover: front ”Matthew 7: 1-6” back ”Ecclesiastes 1: 2-11” by Niklas Boman

Elektronisk version tillgänglig på http://umu.diva-portal.org/

Printed by: Print & Media

Umeå, Sweden 2016

Science is unchangeable, impersonal, general, abstract, insensible, like the laws of which it is but the ideal reproduction, reflected or mental – that is cerebral. Life is wholly fugitive and temporary, but also wholly palpitating with reality and individuality, sensibility, suffering, joys, aspirations, needs, and passions. Science creates nothing; it establishes and recognizes only the creations of life. And every time that scientific men, emerging from their abstract world, mingle with living creation of the real world, all that they propose or create is poor, ridiculously abstract, bloodless and lifeless…

- Mikhail Bakunin

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Acknowledgments

My family (Eva, Peter, Ida, Mikael, Mona, Jimmy, Martin, Ragnvi, Mats, Maria, Emma, Therese, Karl, Josefine) have with their hearts and homes been a source of rest and recovery.

I have learned much from my supervisor, Michael Svensson.

When it was needed, Jonas Burén shouldered responsibility beyond what was asked of him.

Henrik Antti, with his optimism and seemingly effortless way of finding solutions has saved the day on more than one occasion.

Malin Alvehus was perhaps the right person at the right time when I was in the wrong place.

Anna-Karin Olofsson, apart from her professional skills, also brought happiness to work.

Anyone who knows Lennart Burlin and Erkki Jakobsson will know why they have been included in this section.

Gunnar Andersson for reading and criticizing the draft of this thesis.

For the souls who, at one time or other, have shared the workplace with me (Andreas Hult, Andreas Isaksson, Margareta Danielson, Lars Stigell, Carl-Johan Olsson, Susanne Gidlund, Emma Wichardt).

Björn Wiström and Fredrik Nilsson, whose separate contributions and tolerance for caffeine have aided development of method and thinking.

The people at Idrottsmedicin, SMU, Department of Anatomy and the 6M building, for all the small things that makes us human.

The time, effort and pain donated in the doctoral project will not be forgotten any time soon.

Dedication

One person has paid a higher price than anyone else, one person has contributed more than all others put together.

This is for her.

To Emelie

Abstract

Training is preparation for what is expected to come through utilization of the plastic and resistive features of nature, known as adaptation. As such, training in humans may have a number of desired goals. These are typically related to sports performance or education. Whatever the goal, a plan needs to be made for reaching it. One needs to identify or select which activities and environments constitute the event or events to which adaptation is sought. Adaptations occurs by imposing something similar to said environment and practicing the selected activities in preparation for the events that can ultimately lead to goal fulfillment.

One quite common goal of physical training is to achieve a more lean and muscular physique, be it for reasons of performance or esthetics. A leaner and more muscular physique can have many advantages for health and quality of life. If we are to prepare the body's physical capabilities and properties, they should be utilized in the preparation. By proper design and execution of a program for physical preparation, we set out on the path to achieve the goal.

A factor that is often highlighted as an important key to building muscle in the human body is the steroid hormone testosterone. According to the hormone hypothesis, increases in muscle mass are achieved through transient elevations in anabolic hormones, such as testosterone and IGF1, induced by physical training. To achieve hypertrophy of the muscles through physical training, one must ensure sure that the muscles get the correct signal, the growth signal, as a result of the training.

The work presented in this thesis is, in part, an examination of the hormone hypothesis, with both empirical and theoretical elements. The empirical foundations are results of an experiment in which a group of young men were subjected to a program of physical training, designed for all intents and purposes in accordance with contemporary knowledge, to result in muscular hypertrophy in the subjects. The goal was achieved, with an average 4.6% increase in lean body mass in the subjects after the training program. However, there was no evidence that anabolic hormones were elevated at any time during the measurement period.

The major part of this thesis details a model for explaining the collected observations. It is not intended to merely provide a guide for achieving a leaner more muscular physique but rather is aimed at formulating the problem of inducing the desired adaptations and difficulties involved in approaching the problem. For reasons discussed in this thesis, I do not claim that this is the full and final word on the matter. However, it goes some way toward explaining why, and perhaps how, desired goals should be formulated so that the muscles may understand them.

List of appended papers

A. Boman, N., Burén, J., Antti, H., & Svensson, M. B. (2015). Gene expression and fiber type variations in repeated vastus lateralis biopsies. *Muscle & Nerve, 52*(5):812-7. doi:10.1002/mus.24616

B. Alvehus, M., Boman, N., Söderlund, K., Svensson, M. B., & Burén, J. (2014). Metabolic adaptations in skeletal muscle, adipose tissue, and whole-body oxidative capacity in response to resistance training. *European Journal of Applied Physiology*, *114*(7), 1463–71. doi:10.1007/s00421-014-2879-9

C. Boman, N., Burén, J., Åkerfeldt, T., & Svensson, M. B. Effects of protein ingestion on the hormonal response to resistance exercise and increases in lean body mass after eight weeks of training. (Manuscript)

Introduction

About the author

"No one asked me, so I asked myself"

-Ken Robinson

As I set out on the journey undertaken to reach the point where I wrote this thesis, I thought that I was on a quest to find the truth, at least I thought that it was the truth I was looking for. As the process evolved, I came to see that it was certainty that I was looking for. I really hoped that there was an ultimate truth or irrefutable certainty to find, or at least an answer that unravels reality. At this stage, I have not found the certainty that I set out to achieve. I have in fact abandoned my initial quest on the basis that I did not fully understand the problem. The problem did not lead to a solution, it led to another problem.

When faced with a situation such as this, I found inspiration from my favorite author, Terry Pratchett. On numerous points in his books he describes the strategy of academics faced with difficult situations or problems; go to the library and find a book about the subject! The best outcome is that someone else has faced the same problem before and written a book on how to deal with it, the worst outcome is that you will be performing indoor work that involves a lot of sitting down.

Luckily, others have intensively addressed the question of whether we can perceive the world in its true form, to find the final truth. Sadly, the answer seems to be no. According to Kant (2004), we only experience the world as it appears to us, not as it is. What appears to me is the world, but also my knowledge about the world that I am observing.

On a cold and dark winter evening, I came into contact with Critical Rationalism[1], presented as a system of thought to avoid the pitfalls of infinite regression, circular arguments and dogmatism, which occur when one tries to prove the truth of a theory. This led me to Karl Popper and his writings.

[1] Presented by Gunnar Andersson at "Filosofiska Föreningen"121211. Briefly, critical realism centers on the idea that all (scientific) statements are fallible. Hence, an inquiry into any subject is aimed at falsifying the investigated statement or hypothesis. As there is no possibility of proving a statement to be true, the rational option is to hold statements that have survived severe testing as true. However, this does not make them true - one should keep in mind that a statement will at best be "well tested". As the possibility of testing is ever present, no statement is ever final.

After reading and pondering on some of Popper's work, my problem of finding the truth[2] seemed to dissolve, many of my views were changed by the ideas Popper suggested. For example, Popper considers three worlds: world one consists of physical states, world two consists of mental states, and world three contains the products of mind. Among other things, the third world contains products of language. All statements of science are made in language. Thus, all the statements of science can be found in world three (Popper, 1979)[3]. This converts all statements or knowledge into objects. Thus, our so-called knowledge becomes objects open to examination and testing.

The notion that knowledge can be viewed as objects turned so many things around for me, all of a sudden there was a possibility of examining knowledge in a different way. Knowledge was no longer mystical or divine in any way, it was now open to be tested and changed. The objective of science is to produce conjectures in the form of statements about reality, statements with great content of explanation about the observed reality (Popper, 1979)[4]. It is when a theory is unable to explain an observation that a new theory must be constructed. This means that we must sometimes adapt our theories if we encounter situations that are not logically consistent with the said theory.

This suggests that the growth of knowledge is an evolutionary process, much like the evolution of life from a biological perspective (Popper, 1979)[5]. This means that knowledge, which is now considered "well tested", may be falsified in the future by new conditions arising from the changing environment. Thus, statements will never be final, as our measures of finality are also fallible. How then can knowledge grow, or how can science work to make knowledge grow, if there is no way of knowing how close to the truth we are? Popper suggests that the goal of science is to produce statements with great truth content. There may be a great truth content to the statement, in the sense that the truth consists of correspondence to facts[6], if the statement is

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[2] It dissolved some conceptual problems I had that prevented me from progressing, it was not in any way a fixed point in the universe from which the truth about all could be measured. Mostly, there was now a way of determining the truth of a statement, a measure that was also human, like our theories. However fallible a human-made truth may be, at least we have the hope of improving it and our understanding in the process.

[3] "Epistemology without a knowing subject", section 3-4.

[4] PP 191 "The aim of science". The book referenced is a collection of essays by Popper. Although it makes for a shorter list of references, the book is a great collection of essays.

[5] "Evolution and the tree of knowledge", section 1. "… the growth of knowledge proceeds from old problem to new problems, by means of conjectures and refutation.".

[6] The truth of statements will be uncertain. Popper (and myself, thanks to reading Popper) makes use of Alfred Tarski's semantic truth definition (Tarski, 1944) to make it possible to talk about the correspondence to facts. The uncertainty of axioms and the changing of conditions may for some seem unsound, it is contrary to the meta-context of most western philosophies, which are

capable of explaining many particulars of a phenomenon (Popper, 1979)[7]. Popper holds that statements with large content are good for the practice of science as they provide a lot of grounds for testing and falsification. Surviving many attempts of falsification means that it is rational to hold a statement as a true description of the phenomena concerned.

By studying these two processes, i.e., growth of knowledge and biological evolution, one can learn much about both, and possibly even things that could not have been learnt from either field alone. The idea is that the growth of knowledge, like life, is free of guided direction, i.e., there is no ultimate goal and there is no justification that can be made. Current knowledge remains because it has survived testing by all known and unknown factors capable of destroying it, up to that point. There are no guarantees for the survival of life or ideas; existence is an uncertain state as it is constantly changing. The only defense is to remain flexible, by trial and error-elimination, to adapt strategies to the situations capable of falsifying or hindering solutions to maintain stability in an existence were everything else is changing due to the same process of testing.

But how do we accept knowledge that isn't certain? What kind of proof of certainty would be acceptable? We can have logically coherent discussion as long as we are aware of what goes into the definitions and the logic used. Any statement that is consistent with the definitions may be considered a true statement in the discussion. However, the truth is not any more certain than the definitions we assign. We can of course alter our definitions to make more refined statements about our observations. Accurate definitions, and thereby certainty, will however only be achievable by convention or agreement. To get rid of all uncertainty about our knowledge, we need proof that does not rely on our logic/language. You may of course feel certain, I will not argue against that, but a proof that does not rely on logic and some basic statement is something else.

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concerned with the justification of true belief (Bartley, 1982). Taking a critical approach enables us to actually evaluate the content of our theories without making it personal, hopefully strengthening our theories. The recognition that all our knowledge represents lines in the sand is to me very humbling - if one can entertain this proposition then perhaps one can start using knowledge in a different manner than before. We may be able to reach different results than previously because of this. But it also offers a degree of hope, to me anyway, as it may be possible to change perspective on the lines in the sand and perhaps even move the lines. It also includes a measure of responsibility, as theories are created rather than discovered. No amount of searching will lead to the discovery of a new theory, only by creating theories which are true can our understanding of the world be improved.

[7] "Two faces of common sense" sections 6-11.

This approach to the world and science can be described metaphorically as being like moving around on a frozen body of water, with treacherous ice, where there is no way of knowing whether the ice will hold at a precise spot without stepping on it. Only in the spots where the ice does not break when stood upon can one be sure that the ice holds. If the ice breaks, your best choice is to swim back to stronger ice and try another path forward. The essence of science is that it is an attempt to map out where the ice is strong enough. However, science can still not tell us where on the ice we are, if there is a shore to reach, or if it is right to try to find land. It seems that the water under the ice is indifferent to us, but it will kill us if we are reckless. Above the ice, there is only each other and the cold air that will eventually kill us. The testing will not stop, the only way out is to escape the playing field, which in our metaphor would be to either go down into the water or wait for the cold air to take us.

In a sense, I found what I was looking for, not what I set out to find, but something that helped me evolve my problem. By treating everything, including myself and my thinking as objects[8], and critically testing my observations by comparing them to several explanations about the said objects I attempted to test my means of observing the world while trying to explain the world. This is how my ideas, my conjectures about observations, about the world have evolved.

Explanation of content

The layout of this thesis is as follows: first the background is presented and discussed to give a theoretical foundation. The second half of the thesis is a presentation of the empirical findings and a discussion of the said findings.

In this thesis, I attempt to present a model of a human by describing the integrative levels of physical training in humans and, at the same time, aim to present an alternate point of view between "looking up" and "looking down". By doing so, I endeavor to apply several perspectives and clarify their relations and interactions. I am in a way trying to see the process from the perspective of the world, not from the perspective of a human. I reach into the realm of philosophy with the intention of clarifying my process of

[8] (Popper, 1979), "A realist view of Logic, Physics, and History." Section 4. " [argument for strong logic]… for we want our criticism to be *severe*. In order that the criticism should be severe, we must use the full apparatus; we must use all the guns we have. Every shot is important. It doesn't matter if we are over-critical - if we are, we shall be answered by counter-criticism."

thinking (Wittgenstein, 2005)[9]. It is not my aim to explore comprehensively the philosophical theories mentioned in this thesis, at least not more than necessary for explaining my thoughts and processes of explaining training adaptation. The intention is to provide a discourse to help tackle consequences which arise when one tries to steer development toward what is believed to be needed in the future.

[9] 4.112 “Philosophy aims at the logical clarification of thoughts. Philosophy is not a body of doctrine but an activity. A philosophical work consists essentially of elucidations. Philosophy does not result in 'philosophical propositions', but rather in the clarification of propositions. Without philosophy thoughts are, as it were, cloudy and indistinct: its task is to make them clear and to give them sharp boundaries.”.

Physical training in humans

"We have this very mechanistic [view] in our Greco-roman, western, reductionist, linear, fragmented, compartmentalized, disconnected, democratized, individualized, parts-oriented thought process."

-Joel Salatin

Why train? What is this very human behavior? Ontologically, these are very interesting questions behind the deliberate behavior of training. The idea is something like this: performing particular behaviors will lead to improvements in the performance of those behaviors. The thought that present behavior will lead to different, desired, behaviors in the future has very strong components of plans, desires and even dreams. Hence it raises interesting and complex questions. Dissection of the ontological elements is not the main goal of this thesis, but they are important components of the topic. We cannot deny that it seems to work! Training works, sometimes dreams come true. I asked: how does it work? What are the components that contribute to the fulfillment of human dreams and desires?

In sports and athletics, training is supposed to enhance performance in the discipline of choice (Matveyev, 1981)[10]. Preparation for performance can be broken down into four categories: psychological, tactical, technical, and physical (Bompa & Haff, 2009; Matveyev, 1981)[11]. Psychological training refers mainly to motivation and concentration. Tactical and technical training is preparation for performance according to the specific rules and execution of the chosen sport or discipline. Physical training, on the other hand, is aimed at preparing the physical body to withstand and overcome the particular demands for force production of the chosen sport or performance discipline.

Performance will be optimal when the body's force production capabilities are maximal, the performing subject has the most efficient movement patterns, the strategy and equipment for performance are optimal, and the person is in a cognitive state that enables utilization of these components (Matveyev, 1981)[12]. In other words one must have the will to, know how and when to produce force. Depending on the sport and situation, the relative importance of these components varies. However, the physical capabilities of the body are the easiest to quantify and tend to show some

[10] PP 7.

[11] Matveyev, PP 22. Bompa and Haff PP 57 text and Figure 3, Chapter 3.

[12] PP 31-32.

degree of consistency, whereas strategy, for example, is highly situational. The four categories of training are often conducted in an overlapping and intertwined manner called periodization, where the goal is to prepare in all categories in such a way that performance in the chosen discipline can be maximal at the time of competition (Bompa & Haff, 2009; Matveyev, 1981)[13].

In training, one needs a goal - there is a need to describe what is being prepared for. In sports, usually the event in which achievements are to be measured. In the training context, this event constitutes the competitive exercise, the exercise in which the subject is supposed to attain expertise. The competitive exercise not only mimics the competitive event, but is exactly like the event would be in an actual competition. Exercises which have a general relationship with the competitive exercise are called specialized preparatory exercises. These exercises differ between athletes depending on the competitive event chosen - specialized exercises for a runner are not the same as those used by gymnasts. Specialized exercises have two major functions, training selected parameters of the corresponding competitive event and learning new actions of the competitive event. Exercises meant to improve physical qualities in the event are labeled as developing exercises, whereas the learning exercises are called preliminary exercises. This may seem redundant, as both developing and preliminary exercises are specialized, meaning that they do not have much leeway to diverge from the competitive event. The separation of these terms rests on the fact that the exercises serve different purposes, and thus are employed at different stages of training and will utilize different loading (Matveyev, 1981)[14]. The last major group of exercise comprises general preparatory exercises. These exercises are chosen based firstly on the performing subject and secondly on the particulars of the competitive event. The purpose of general preparatory training is to develop the abilities that the subject needs in order to perform the specialized training, to develop abilities that are insufficient for the chosen event, and sometimes, to break the monotony of the training regime.

Although the training in itself is interesting, the effects of training are perhaps of greater interest to the athlete and coach (Matveyev, 1981)[15]. The effects of training comprise any changes to the subject induced by an exercise session. These can be categorized as immediate, delayed or cumulative. The focus on immediate effects is usually limited to tiredness and a general decrease in performance, characterized by depletion of the subject's energy resources, leading to reductions in power/force development. However,

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[13] Matveyev, Chapter 3 Section 2, Bompa and Haff, PP 126.

[14] Chapter 2 section 3, Chapter 3 Section 2

[15] Chapter 2 section 4

at the same time, restoration of the subject's metabolic properties begins, to the extent that such a restoration is possible with the macromolecules available to the organism. This restoration leads to the delayed effects of training. During the delayed phase performance levels are restored back to and then enhanced beyond the initial levels. This phenomenon is called supercompensation (Zatsiorsky & Kraemer, 2006)[16], and is the main desired outcome of a training session. Cumulative effects are the sum of effects from multiple sessions, in which the goal is to accumulate post-exercise supercompensations to enhance performance substantially beyond initial levels.

There is also an unavoidable factor of planning and choice involved in training. This is preferably undertaken under the supervision of a coach (Matveyev, 1981)[17]. Coaches consider situations and plan the exercises, loads and timing of training. The methods used in coaching, training and teaching affect the performance of the subject. However, these topics are beyond the scope of this thesis.

Before further considering the specifics of training, we will first look closer into the requirements of the human body and what happens when they are challenged.

This is what life demands

"We will now discuss in a little more detail the struggle for existence."

- Charles Darwin

According to The New Oxford American Dictionary, adaptation is the process by which organisms become better at living in their habitats or environments, while an adaptive trait is a result of such adaptation. The dominant theory of evolution is that the most well adapted organisms will be most likely to survive and reproduce, thus allowing the successful adaptive traits to be passed on and enhanced. This process is called evolution by natural selection - the individuals that are best adapted for living and surviving in a habitat will have the highest probability of procreation. But in order to procreate, an organism first needs to be alive. So, a key question is, what does an organism need in order to remain alive?

[16] PP 10-11. In a one-factor model of training effects. In other models the effects will appear different. However, this is probably the most widespread model.

[17] Part 2 "the main aspects of coaching an athlete in the process of training"

Living organisms need to support a fairly stable internal environment to live, a state and process called homeostasis (Cannon, 1949)[18]. Organisms are subjected to a myriad of stimuli, internal and external, each of which affects the organism's homeostasis[19]. The organism itself has the ability to counteract the effects of the stimuli, within limits that vary strongly among and within species, and restore its internal environment to a state favorable for life. Theories on how organisms respond to external and internal stimuli have been around for a long time, but those mentioned here can to a large extent be accredited to Hans Selye and Walter Cannon for their work on stress and homeostasis of the body, respectively.

Cannon has pointed out that there is a need to describe the coordinated physiological processes that maintain the delicate structure of the organism. He states that homeostasis does not describe something fixed and rigid, but rather a state that can vary while at the same time remaining relatively constant. Consistency is needed because there are some requirements that are absolutely necessary to maintain function, and thus the life of the organism, but variable in the sense that shifts in the conditions affecting the organism are counteracted so that these changes do not damage its delicate structure. Cannon exemplifies this by stating that the heat generated from 20 minutes of maximal muscle effort could denature several of the body's proteins (Cannon, 1949)[20] unless the heat is dispersed.

Selye formulated the GAS theory[21] to describe the body's reaction to stressors imposed on it. According to GAS theory, any stressor imposed on the body will provoke the same response pattern, irrespectively of what the stressor is (Selye, 1976). According to Selye, there are three stages in the GAS reaction (Selye, 1958)[22]. The first stage is the alarm reaction, when the stressor is imposed and the body's or system's level of resistance is diminished. If the stressor is too strong, the body will die at this point. However, if the body is sufficiently strong, it will adapt to meet the increased demands of the stressor. During the second phase, called the resistance phase, the body adapts by increasing resistance toward the stressor. In the third phase, the body's ability to resist the stressor is exhausted, leading to eventual death of the body if the stress persists.

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[18] PP 14

[19] From the greek *homoios* meaning "similar", and *stasis* meaning "position". Explanation by Selye when discussing the work of Cannon. (Selye, 1958) PP 25.

[20] PP 9.

[21] General Adaptation Syndrome

[22] PP 42.

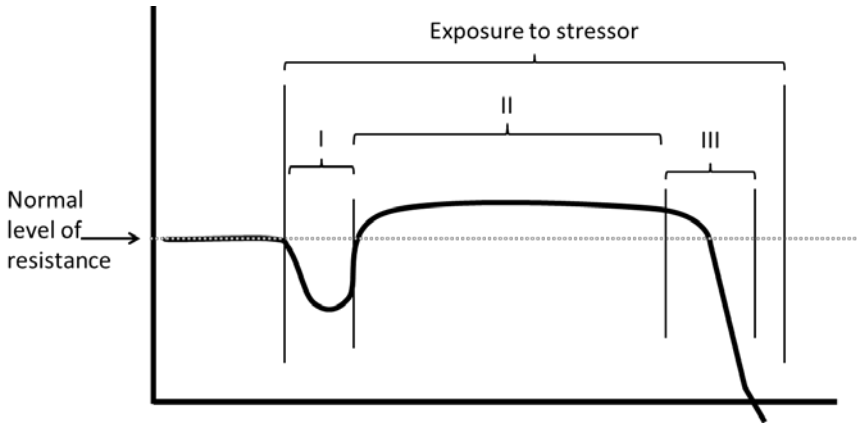

Figure I. GAS diagram. Adapted from Selye (1974). Phase I is the alarm phase when the stressor is first introduced. Phase II is the resistance phase were the body adapts to the stressor. Phase III marks the exhaustion of the body's resistive capabilities.

Selye (1974) elaborated his theory by stating that the seemingly same stressor may elicit different responses in different individuals; even the same degree of the same stressor may elicit different responses in different individuals[23]. He explained this by the term conditioning (Selye, 1958)[24]. Conditioning factors have the ability to enhance or inhibit the stress effects of the body. These conditioning factors may be internal or external to the body. It is together with these conditioning factors that the stress effect induced by the stressor will be determined.

The GAS theory has some interesting features regarding potential uses of stressors to induce a desired stress reaction in the human body. As resistance is enhanced in the second phase of the stress response, one could carefully expose a body to a selected stressor, removing it before resistance is exhausted, and thus maintain the body in an adapted state with enhanced resistance toward the stressor. If the stressor is reapplied at this time, the body should be able to resist it, i.e., the stressor will have a diminished effect on the body, and thus the body has become conditioned to resist the stressor. If further adaptation is desired, the same stressor needs to be applied at a higher degree or intensity, but only at a level that the body can adapt to in order to resist it. Conversely, if there is no stressor or the degree of

[23] PP 44-47.

[24] PP 98-101. Both of Selye´s books mentioned in this thesis explain conditioning factors in the same manner. However, there are some differences in formulations, hence the use of two references.

exposure is very low, the body will maintain a level of resistance that is appropriate to the current level of stress, and hence resistance will decline.

The physical body

"Desire is irrelevant. I am a machine!"

- The Terminator

In a mechanistic sense, in the context of physical activity, the human body is a system for producing mechanical force at the cost of chemical energy. Muscle contractions, instigated by nerve signals, produce force at the cost of stored chemical energy in the muscle and other tissues of the body. An average human body, for example, contains energy deposits in the form of fats and glycogen. This capability is afforded by chemical reactions that release energy. Thus, muscles' chemical properties are interesting, as they will strongly influence muscles' physical properties (Goldsmith et al., 2010).

Human skeletal muscle

As the name suggests, skeletal muscles are distributed around the entire human skeleton, and are typically attached to the bones of the skeleton by tendons composed of bundles of collagen fibers (Tortora & Derrickson, 2005)[25]. The muscle is composed of multiple bundles of muscle fibers bound together by connective tissue. Muscle fibers are the basic component of the muscle tissue, the "muscle cell". The fibers are formed by fusion of multiple progenitor cells, myoblasts, giving rise to long, cylindrical, multinucleated cells called muscle fibers or myofibers (Tortora & Derrickson, 2005)[26]. The myofibers are largely composed of myofibrils. The myofibrils in turn are composed of repeated sarcomeres, the basic functional unit of the muscle, responsible for the machinery of muscle contraction. Sarcomeres placed in parallel displace more volume than sarcomeres placed in series. The parallel orientation also gives the muscle a greater capacity for generating tension than the same number of sarcomeres placed in series.

Skeletal muscle cell biology has a distinctive nomenclature. The cytoplasm is called sarcoplasm and the plasma membrane is named sarcolemma (Tortora & Derrickson, 2005)[27]. The myofibrils are found in the sarcoplasm, with mitochondria interlaced. The rich content of contractile elements presses the nuclei toward the inside of the sarcolemma. Muscle fibers

[25] PP 292-293, text and Figure 10.1.

[26] PP 294-295, text and Figure 10.2.

[27] PP 294-295, text and Figure 10.2.

contain the sarcoplasmatic reticulum, which regulates the calcium reserves required for muscle contraction.

Muscle contraction is caused by cross-binding of actin and myosin in the sarcomeres of the myofibrils. The binding causes tension in the muscle, which can be used to shorten, maintain, or lengthen the muscle. These actions of myosin and actin, or rather the resetting or unbinding, are energy-dependent processes, requiring the presence of ATP[28] (Tortora & Derrickson, 2005)[29]. Voluntary muscle contraction starts with nervous impulses causing release of calcium ions into the myofibrils, and hence a cascade of actin/myosin cross-binding. After contraction, calcium is transported back into the sarcoplasmatic reticulum.

Muscle fibers are sometimes categorized by their content of contractile proteins. Those in adult human skeletal muscle include several isoforms of MyHC[30], in varying proportions, hence muscle fibers are classified as fibers containing mainly MyHCI, MyHCIIa or MyHCIIx (Scott, Stevens, & Binder-Macleod, 2001). As classification is based on the main expressed isoforms, there is also a possibility for hybrid fibers to arise by co-expression of isoforms MyHCI + MyHCIIa or MyHCIIa + MyHCIIx. Properties such as speed of contraction seem to be strongly associated with specific types. Fibers classified as type I fibers are usually called slow fibers, whereas fibers classified as type IIA and IIX are called fast fibers. The myosin molecules themselves have ATPase activity. The ATPase activity of the component myosin molecules is positively correlated with fibers' speed of contraction (Bottinelli, Pellegrino, Canepari, Rossi, & Reggiani, 1999; He, Bottinelli, Pellegrino, Ferenczi, & Reggiani, 2000; Szentesi, Zaremba, van Mechelen, & Stienen, 2001).

Type I fibers in skeletal muscle are typically considered as weak, with low but long-lasting capacity to produce force, whereas type II fibers are stronger but fatigue quickly. The endurance of specific fiber types is largely dependent on the metabolic systems used for refueling ATP: type I fibers mostly utilize aerobic systems to resynthesize ATP, whereas the faster fiber types can use anaerobic pathways to recover ATP (Egan & Zierath, 2013). These metabolic systems are also properties that can be used to describe muscle fibers, as they have specific cellular contents and functions.

As the size of a fiber is related to the amount of filaments it contains, and thus its capacity for force production, the faster and stronger

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[28] Adenosine triphosphate.

[29] PP 299-300, text and Figure 10.7.

[30] Myosin heavy chain, this is only one of the proteins making up the contractile machinery, but due to the nature of the empirical work presented in this thesis, this is the only contractile protein presented.

fibers are usually larger than the slow fibers (Maughan, Watson, & Weir, 1983). Human skeletal muscle is composed of a mosaic of different fiber types. There seem to be differences within individual muscles, between muscles, and between individuals (Henriksson-Larsén, Fridén, & Wretling, 1985). Depending on the functional application of the muscle, it will have or acquire a suitable composition in terms of fiber type and metabolic capabilities.

Muscles called in to action

Groups of muscle fibers are linked through a neuron to form a single motor unit. There are numerous motor units of various sizes in the human body. When the motor unit is stimulated to activate, every single muscle fiber controlled by it is activated. Thus, either all the fibers are activated or none. This is known as the "all or nothing law". Depending on the type and demand of muscle action, different motor units will be stimulated to action (Cannon, 1922)[31]. Muscle fibers and motor units are recruited according to the size principle (Cope & Pinter, 1995; Henneman, Somjen, & Carpenter, 1965), which states that motor units and muscle fibers are recruited from the smallest to the largest and slowest to fastest as the effort and intensity of contraction increases (Carpinelli, 2008). If an external load is resisting the intended movement, the first muscle fibers to be recruited will be the smallest and slowest, but these will quickly be overtaken by bigger and faster fibers, as required to generate at least sufficient force to meet the external load.

There are **s**everal ways to increase the force production capabilities of skeletal muscles. Muscles with high absolute contents of contractile elements have greater capabilities of force production than muscles with lower absolute contents. An increase in muscle fibers' size, through increases in their cross-sectional areas, is called hypertrophy. Hypertrophy and increases in the number of muscle fibers, hyperplasia, will probably lead to increases in whole muscle size (Tortora & Derrickson, 2005)[32]. However, the contribution of hyperplasia to overall increases in whole muscle size is considered small, generally, and may be disregarded for practical purposes of muscle conditioning (Mccall, Byrnes, Dickinson, Pattany, & Fleck, 1996; Zatsiorsky & Kraemer, 2006)[33].

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[31] The "all or nothing law" is attributed to Henry Pickering Bowditch and was published in 1871. Cannon's contribution in this regard lies in writing a biographical memoire of Pickering.

[32] PP 294.

[33] The claim that hyperplasia is of no practical use in strength training comes from Zatsiorsky & Kraemer PP 50. McCall et al. is an example of a study that was unable to substantiate any claims of hyperplasia in humans as a result of resistance training. The method of obtaining muscle tissue for research makes it difficult to quantify any hyperplasia. As tissue is removed in the process, it

From a broader perspective, there are further possibilities for increasing force production in a given movement. Motor units can apparently be trained to coordinate force production more efficiently (Semmler & Nordstrom, 1998). Normally, motor units are activated asynchronously to produce smooth movements. By activating motor units synchronously, conflicting directions of force production can be eliminated, thus increasing the force directed in the intended direction of movement. It may also be possible for the central nervous system to lower inhibitory stimuli on the motor neurons (Weier, Pearce, & Kidgell, 2012). The details of these factors are beyond the scope of this thesis, but it should be noted that many factors play a role in physical preparation for performance and that factors beyond the morphology of muscle fibers affect the intended performance.

Demand and supply

Key elements of muscle bioenergetics, i.e. the energy conversion systems in muscles and associated processes, are the pathways whereby ATP is replenished. ATP stores energy that is released as the molecule is broken down into ADP[34] and P_i[35] (Stryer, Berg, & Tymoczko, 2002)[36]. There are three major energy pathways that supply ATP. The first is the ATP-PC[37] system (Bompa & Haff, 2009)[38]**,** sometimes called the alactic anaerobic system, meaning that there is no involvement of oxygen or glucose/lactate conversion to pyruvate (Stryer et al., 2002)[39]**.** In this system phosphocreatine molecules available in muscle serve as a phosphate source for restoring ADP to ATP. The ATP-PC system is limited by the amount of ATP and PC stored in the muscle. During all-out activation, the ATP-PC source of energy will be depleted in 30 seconds or less (Bompa & Haff, 2009; Meyer & Terjung, 1979)[40]. This system is capable of delivering an immediate and powerful source of energy for contractions that last only a short time.

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becomes difficult to examine how the removed tissue is affected by any training regime that would lead to hyperplasia.

[34] Adenosine diphosphate.

[35] A phosphate molecule, called inorganic phosphate, hence the "i".

[36] PP28-29 text and Figures 2.12 and 2.13.

[37] Phospho-creatine.

[38] While the chemistry is the same as in Stryer, Berg, and Tmoczko, Bompa and Haff use a terminology more suitable for this discussion of exercise metabolism. Therefore, both references are used throughout this section. The term ATP-PC system is found on page 22.

[39] PP380, Stryer, Berg and Tymoczko do not use the term Alactic when describing the said process. The term alactic is from Astrand et al. (2003) PP 248.

[40] PP21, 26-27 and Figures 1.15, 1.17 in Bompa and Haff for an overview of timeframes of energy systems in sport activity.

The next system is anaerobic glycolysis, sometimes called the lactic acid energy source (Bompa & Haff, 2009; Stryer et al., 2002)[41]. Muscle contains stores of fuel in the form of glycogen, which is composed of long chains of glucose moieties. Each glucose moiety can be split into two, thereby releasing energy and two pyruvate molecules. The energy released from each split glucose moiety is used to produce two ATP molecules, or more strictly, phosphorylate two ADP molecules, yielding tow ATP molecules. No oxygen is needed for this process. However, the pyruvate is transformed into lactate. As the concentration of lactate increases, pH in the tissue decreases and ultimately the process of producing ATP will be hindered. The lactic acid system can produce a larger amount of energy than the ATP-PC system, but at a slower rate. The lactic acid system is less powerful than the ATP-PC system, but somewhat longer lasting, until it is eventually limited by its own side effects.

The third system is the oxidative phosphorylation system (Bompa & Haff, 2009)[42], which produces ATP via metabolism of fats and carbohydrates using oxygen (Stryer et al., 2002)[43]. The aerobic metabolism of carbohydrates involves the same initial steps as their anaerobic metabolism, but the pyruvate released can enter a series of chemical reactions called the Krebs cycle and associated electron transfer systems, and eventually be completely metabolized into carbon dioxide and water, both of which are easily excreted by the body. Fat is hydrolyzed into fatty acids, which can undergo a series of reactions called beta oxidation before entering Krebs cycle and electron transport systems. These reactions also produce ATP and leave carbon dioxide and water for the body to excrete.

The oxidative system is limited by the oxygen available. At rest, carbohydrate and fat metabolism are normally responsible for about one third and two thirds of the replenishment of the ATP pool in the human body, respectively. This ratio gradually shifts with increasing energy demand from muscle action until maximal physical effort is reached and the body relies almost exclusively on carbohydrates, if available (Maresh et al., 1992; Maresh, Allison, Noble, Drash, & Kraemer, 1989). The oxidative system is the least rapid of the three systems described, producing the lowest amount of ATP per second. However, as the stores of fats and glycogen exceed ATP and PC stores, and the system generates far fewer problematic by-products than the lactic acid system, the oxygen system can outlast both the former systems, as long as oxygen is available.

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[41] Chapter 16 and 21 in Stryer, Berg, and Tmoczko. PP 22-24 in Bompa and Haff.

[42] PP 24.

[43] Chapters 17 and 18.

The aerobic energy system has yet another function: replenishment of the two anaerobic systems when they are spent or unbalanced (Hermansen & Vaage, 1977). Even after a bout of anaerobic exercise is completed, the body's oxygen uptake remains above resting levels. This excess postexercise oxygen consumption is used to replenish the anaerobic energy systems and remove harmful by-products (Bahr, 1992). The ATP produced by the oxygen system is stored as ATP in the muscles and some of it metabolized to release energy used to replenish PC pools. The extra oxygen taken up at rest can also be used to metabolize lactate accumulated in the tissue during exercise. By oxidation, lactate can be converted back to pyruvate and enter the Krebs cycle. There is also a possibility for lactate to be converted back into glucose, by the Cori cycle, which can then be released into the bloodstream or stored as glycogen (Brooks, Brauner, & Cassens, 1973).

What about the body fat?

An important question is whether the demands made by working muscles extend far enough to affect the adipose tissue distributed around the body. Theoretically, if muscles' oxidative systems require fatty acids as substrates to fuel further contractions, fatty acids stored in adipose tissue could be released into the circulation and transported to the muscles needing them (Harwood, 2012). This could be advantageous as it could enable prolonged contractile activity. There also seems to be a desire among the general populace to reduce amounts of body fat, both to achieve a very lean body composition for esthetic reasons and to reduce levels of obesity and overweight to obtain a healthier body composition. Exercise and training can indeed increase skeletal muscles' oxidative capacity, and again both the extent of the effects and the associated mechanisms seem to be closely related to the stimuli involved (Ruas et al., 2012; Wang, Mascher, Psilander, Blomstrand, & Sahlin, 2011).

In order for fatty acids to be oxidized, they must enter the mitochondria of cells, which is facilitated by enzymatic conversion. The reaction involved, catalyzed by the enzyme CPT1[44], is considered the rate-limiting step in fatty acid oxidation (Jeppesen & Kiens, 2012), and human muscle can seemingly be conditioned by exercise to increase the activity and expression of CPT1 (Berthon, Howlett, Heigenhauser, & Spriet, 1998; Tunstall et al., 2002). The final step in the oxidation of nutrients can also be enhanced by training. Proteins mediating the final reactions of the electron transport chain can be upregulated and downregulated by training and cessation of training, respectively (Burgomaster et al., 2007). Adipose tissue also has endocrine functions.

[44] Carnitine palmitoyltransferase.

Adipocytes produce adiponectin, which acts on target tissues through its receptor, AdiopR1. In muscle, this receptor interaction leads to mitochondrial biogenesis and increased rates of fatty acid oxidation. AdipoR1 regulates the activation and expression of PGC-1α[45] and SIRT1[46](Iwabu et al., 2010). PGC-1α can be stimulated by exercise to increase fatty acid oxidation and mitochondrial biogenesis in skeletal muscle. SIRT1 is involved in activation of PGC-1α by deacetylation (Serra, Mera, Malandrino, Mir, & Herrero, 2012).

This thesis focuses on muscular hypertrophy as a result of training, rather than the capacity of energy turnover in the body. However, these two processes are inseparable, as the maintenance of body size and activity are energy dependent. Therefore, the content of the following section is limited to hormones and gene products usually associated with physical training and changes in muscle size.

The hormone hypothesis

Briefly, the hormone hypothesis states that transient elevations in certain circulating hormones after training cause some of the adaptations gained from training. Most relevant research has focused on testosterone and IGF1[47] (Schoenfeld, 2013), since these hormones are profoundly associated with muscle hypertrophy. Both of these hormones exert anabolic or anti-catabolic effects on muscle tissue. The interest in these hormones coupled to physical training lies mostly in the benefits sought from increasing muscle mass, which could effectively increase performance if the performing subject is capable of making effective use of the additional muscle mass. There are reports of increased levels of circulating testosterone following resistance training. The response appears to depend on the makeup of the training, the training status, sex, and age of the performing subject (Copeland, Consitt, & Tremblay, 2002; Linnamo, Pakarinen, Komi, Kraemer, & Häkkinen, 2005; McCaulley et al., 2009; Vingren et al., 2008).

There is however some debate regarding the causal relationship between circulating hormones and resistance training results (Schroeder, Villanueva, West, & Phillips, 2013). It has also been suggested that intrinsic factors of the exercised muscles strongly influence the results of training (West, Burd, Staples, & Phillips, 2010).

[45] Peroxisome proliferator-activated receptor γ co-activator-1α.

[46] Sirtuin 1.

[47] Insulin-like growth factor.

Anabolism and the body

The goal of physical training is, in part, to qualitatively and quantitatively change the cellular content of the muscles. For this to happen, there is a need to shift the balance of buildup and breakdown of the proteins in the body. Skeletal muscle hypertrophy is a consequence of net increases in muscles' protein content resulting from gains provided by anabolic activity minus losses due to catabolic activity.

In skeletal muscle, the ubiquitin–proteasome pathway is the main proteolytic pathway. Expression of MuRF-1[48], an ubiquitin ligase, can be used as a measure of ubiquitin proteolytic activity (Bodine et al., 2001; Fuentes, Ruiz, Valdes, & Molina, 2012). The steroid hormone cortisol can be used as a marker of catabolic status, as cortisol can increase rates of protein breakdown in the muscle, and induce increases in both gluconeogenesis and fat mobilization from adipose tissue (Frühbeck, Méndez-Giménez, Fernández-Formoso, Fernández, & Rodríguez, 2014; Judelson et al., 2008; Khani & Tayek, 2001; Lafontan & Langin, 2009; Simmons, Miles, Gerich, & Haymond, 1984). This effectively enables, inter alia, the relocation of substrates from one tissue to another within the body.

Regarding anabolism, possibly the most famous hormone is testosterone, which is converted via several reactions to androgens from cholesterol, via the adrenal secretory products DHEA and DHEAS[49] (Fernand Labrie et al., 2005; Payne & Hales, 2004). DHEA is an important substrate for further androgenic conversion by other tissues, whereas DHEAS is a storage form of DHEA (Allolio & Arlt, 2002). The conversion of DHEA to androgen can be catalyzed by 17β-HSD[50] and 3β-HSD enzymes. The finished product, testosterone, can exert effects via interaction with AR[51] (Georget et al., 1997). However, testosterone may not be the final product of this chain of reactions. Further conversion mediated by the enzyme 5α-reductase results in DHT[52], which have higher affinity for AR than testosterone (Hiipakka & Liao, 1998). Furthermore, testosterone can be converted by the enzyme aromatase to estrogens (Aizawa et al., 2007; Larionov et al., 2003), which affect cells through ESR[53].

Administration of supraphysiological doses of testosterone has been shown to increase strength and muscle mass, and decrease fat mass in

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[48] Muscle ring finger-1.
[49] Dehydroepiandrosterone.
[50] Hydroxysteroiddehydrogenase.
[51] Androgen receptor.
[52] Dihydrotestosterone.
[53] Estrogen receptor.

young healthy men (Bhasin et al., 1996; Woodhouse et al., 2004), even without exercise. Conversely, high levels of visceral fat have been related to low levels of testosterone in men (Kapoor, Aldred, Clark, Channer, & Jones, 2007), and suppression of testosterone may interfere with the results of resistance training (Kvorning, Andersen, Brixen, & Madsen, 2006).

IGF1 is a peptide hormone that exerts anabolic effects by increasing protein synthesis and decreasing catabolic rates by reducing proteolysis (Florini, Ewton, & Coolican, 1996; Sacheck, Ohtsuka, McLary, & Goldberg, 2004). It has been shown that the working musculature in intensive exercise is the primary assimilator of circulating IGF1 (Brahm, Piehl-Aulin, Saltin, & Ljunghall, 1997). IGF1 has an alternative splice variant exclusive to muscle tissue, called MGF[54] (Goldspink, 2005). MGF performs essentially the same functions as IGF1, but MGF transcription is instigated by contractions of working muscles. Training can induce increased expression of MGF, with significant correlation between the increase in MGF expression and resulting muscular hypertrophy after a period of training (Bamman, Petrella, Kim, Mayhew, & Cross, 2007).

One must not forget that amino acids must be acquired from the environment to increase an individual body's protein content (Goldberg, 1968). This occurs through ingestion of substances containing amino acids, either in the regular diet or dietary supplements. This is important for individuals engaged in physical training with the goal of increasing the body's muscle mass, which may be enhanced by increasing protein intake in combination with resistance training (Cermak, Res, De Groot, Saris, & Van Loon, 2012). Further, amino acids should be available to the system post exercise in order to obtain a net positive protein balance so that muscle hypertrophy can be achieved from the training (Rennie & Tipton, 2000). It has been suggested that ingesting 20 g of protein post exercise is enough to maximally stimulate muscle protein synthesis (Moore et al., 2009). However, the quality or type of protein ingested might also affect training results, for example ingesting milk protein reportedly leads to greater muscle hypertrophy than ingesting soy protein (Hartman et al., 2007; Wilkinson et al., 2007). The amino acid leucine seems to have a signaling effect on skeletal muscle, causing activation of similar processes to those possibly activated by physical training (Drummond et al., 2008; Kimball & Jefferson, 2006). Based on such reports, early post-exercise protein ingestion has been recommended to stimulate muscle hypertrophy (Phillips, 2011). However, there have also been reports that ingesting essential amino acids prior to exercise leads to greater net protein synthesis than their ingestion post exercise (Tipton et al., 2001). This could be due to an interactive

[54] Mechano growth factor.

effect of exercising with high levels of amino acids in circulation or to pre-exercise consumption providing a head start in the recovery phase as it takes some time for blood concentrations of amino acids to rise after ingesting beverages. However, there are uncertainties in the length of the interactive protein ingestion and exercise timeframe, whether there really is an effect of timing, or if the total protein intake is most important for the end result of training (Schoenfeld, Aragon, & Krieger, 2013).

As mentioned above, the protein content of muscle depends on the net sum of protein buildup and breakdown. Ingesting protein, or amino acids, seems to play an important role in increasing the buildup of protein. Further increases in the net protein balance could be achieved by decreasing the breakdown of proteins caused by exercise. In addition, the intake of carbohydrates might reportedly reduce the breakdown of protein caused by exercise (Drummond, Dreyer, Fry, Glynn, & Rasmussen, 2009).

Further elucidation of possible interactive effects of protein and carbohydrate intake and physical exercise is important to enhance training results. Any such findings would help performing individuals to maximize these effects in order to achieve the greatest possible net protein balance, and thus training results.

Skeletal muscle as an endocrine organ

In addition to producing force and proteins for its own use, skeletal muscle also produces myokines, which are cytokines and peptides with autocrine, paracrine, and endocrine properties (Pedersen & Febbraio, 2012). Apart from affecting other tissues, these myokines may cause hypertrophy in the muscle itself. Usually, the production of steroid hormones occurs mainly in the gonads. However, many other tissues, such as prostate, brain, and muscle, contain enzymes required for converting steroid hormones. The prostate, for example, can produce testosterone from DHEA even after castration and almost complete depletion of circulating testosterone (F Labrie, Luu-The, Labrie, & Simard, 2001). Regarding muscle, most data available are from experiments performed on animals (Yarrow, McCoy, & Borst, 2012). Rat skeletal muscle expresses all enzymes needed for converting DHEA to testosterone and estrogens, and experiments have shown that cultured rat muscle cells does indeed convert DHEA into testosterone in a dose-dependent manner (Aizawa et al., 2007). Furthermore, exercise has been shown to increase transcription of 17β-HSD, 3β-HSD, and aromatase genes in rat muscle (Aizawa et al., 2008), and increases in both 5α-reductase protein and muscular androgen levels in rats suggest that exercise can induce local biosynthesis of androgens in muscle according to Aizawa et al. (2010).

Experienced powerlifters reportedly have more muscle nuclei containing AR protein than non-training controls (Kadi, Bonnerud, Eriksson, &

Thornell, 2000), suggesting that long-term training accustoms muscles of trained subjects to responding to androgen signaling. Similarly, Wiik et al. (2005) found a difference in ERS subtype composition between muscles of trained cyclists and controls, where the cyclists expressed more of the ESR1-subtype of the estrogen receptor. Estrogens play an important role in regulating the oxidative metabolism pathways of muscle (D'Eon et al., 2005), which could be beneficial for cyclists owing to the nature of the sport.

Conditions for conditioning

Designing resistance training is the craft of selecting appropriate demands or stressors to impose on a given performers' body and musculature. In order to design an appropriate set of stressors for the muscles, one needs to know which stressors lead to which adaptations.

The basis for training skeletal muscle rests on the following assumptions: a) only recruited muscle fibers are trained, b) the recruited muscle fibers must be sufficiently stimulated during recruitment, and c) the order of muscle fiber recruitment follows the size principle described above.

The first assumption clearly implies a need to direct the intended stimuli toward the muscle fibers intended to be trained, essentially exercises/movements must be chosen that will force recruitment of the targeted muscle or part of the muscle. The second and third assumptions have more problematic implications. What constitutes sufficient stimuli in the second assumption and how do we know which muscle fibers are recruited? In order to answer these questions, we must formulate a goal for the physical training. Without stating a desired adaptation, there will be no way of knowing if the training has been sufficient and whether the targeted muscle fibers have been stimulated.

In the empirical work presented in this thesis, also referred to as the present study, the goal was to increase muscle mass as an effect of physical training. In this case, the second and third assumptions are fulfilled if there is an increase in muscle mass of the performing subjects after the training period.

In order to fulfill all three assumptions and meet the goal of increasing whole body muscle mass, exercises that collectively activate as many muscle groups as possible in a reasonable timeframe and external loading sufficient to induce activation of those muscles were used. The size principle states that depending on the external load, only the motor units of appropriate size/strength will be recruited, and thus stimulated. According to this assumption, imposing a load that stimulates the greatest number of muscle fibers with the greatest capacity for increasing size should be the most effective way of increasing muscle size. Usually, type II fibers are larger and stronger than

type I fibers, and have greater capacity for increasing in size (van Wessel, de Haan, van der Laarse, & Jaspers, 2010).

Interestingly, if the biggest muscle fibers have the greatest capacity for contributing to overall muscle size, then stimulating these fibers by using the greatest load one can handle should lead to the greatest increases in muscle size. Empirically, loads that the performing subject is capable of sustaining for 8-15 repetitions[55] of work before fatiguing seem to induce a greater gain in muscle size than performing fewer repetitions[56] at higher loads (Ratamess et al., 2009). The use of repeated effort method training also seems to cause the greatest fluctuations of growth factors and hormones (Linnamo et al., 2005). According to previous assumptions, the repeated effort method leads to a wider range of muscle fibers being recruited during work, not just the biggest fibers needed for maximal effort training. Assuming that the fibers activated by repeated effort training are still large, but more numerous than the biggest fibers, then the growth of each fiber activated by repeated effort training should contribute to a greater overall increase in muscle size.

Contemporary literature states that training programs where exercises are performed in 1-3 sets of 8-12 repetitions with 1-2 minutes of rest between the sets provide the most suitable stimuli for muscle hypertrophy in healthy adults. The loading should be adapted so that the number of repetitions performed is the maximal number that the individual can perform with the given load (De Lorme, 1945; Ratamess et al., 2009; Spiering et al., 2008). The exercise session should be performed several times per week, and each week all muscle groups should be stimulated 2-3 times with appropriate exercises and loads. This can, for example, be achieved by exercising the whole body 2-3 times per week or by splitting the routine into several shorter sessions in which selected parts of the body are exercised during each session, but with a similar total amount of stimulation each week as in the whole body strategy. There is also the possibility of varying the load and volume of the training program in an undulating manner, so that a different number of repetitions are used throughout the week or between weeks. This could potentially stimulate a greater range of muscle fibers, enabling gains of even more muscle mass.

[55] Named repeated effort method (Zatsiorsky & Kraemer, 2006) PP 82

[56] 1-5 repetitions, sometimes called the maximal effort method (Zatsiorsky & Kraemer, 2006) PP 80

Understanding adaptation

"Human beings in a mob.

What's a mob to a king?

What's a king to a God?

What's a God to a non-believer who don't believe in anything?"

-Kanye West & Jay-Z

Adaptation is problem-solving

The theory of evolution applies the term natural selection to explain how changes in a population of individuals of a species may accumulate until they become a new species, distinct from and incapable of mating with members of other populations of the progenitor species (Darwin, 2001). It describes how organisms are selected for survival or demise in the environment in which they compete for survival. By a similar process, statements and theories can be refined based on their ability to handle a problem situation through an error-elimination process of severe testing and criticism according to the scheme presented by Popper (1979)[57] and shown in Figure II.

PS1 → TTa → EE → PS2… etc

Figure II. Poppers tetradic schemae: a problem situation, PS1, is approached with a tentative theory, TTa, which is subjected to an error elimination process, EE, in which TTa is either accepted as a sufficient solution to PS1 or falsified because it fails to solve, survive, or explain PS1. If TTa is rejected another TT is formulated and tested.

The following sections attempt to describe how the problem-solving process of adaptation to the environment, as outlined above and generically in Figure II, can be applied to training in humans.

Complex systems emerge as a result of lower order adaptations

I assume that the human body is a complex system, comprising several orders of highly integrated systems. The complex organization of the human organism is perhaps best described by Alex Novikoff.

[57] Popper's formula appears in many of his works. This reference is from the essay "On the theory of the objective mind" section 6. This is because in this particular essay the discussion is focused in a way that ties in closely to this thesis.

"The concept of integrative levels describes the process of evolution of the inanimate, animate and social worlds. It maintains that such processes are the result of forces which differ in each level and which are unique for each level. Since higher level phenomena always include phenomena at lower levels, one cannot fully understand the higher levels without an understanding of the lower level phenomena as well. But knowledge of the lower level levels does not enable us to predict a priori, what will occur at a higher level. Although it may have validity for the higher level, laws of a lower level are inadequate to describe the higher level. The laws unique to the higher level can be discovered by approaches appropriate to the particular level; to do otherwise is invalid scientifically and, in some instances, dangerous socially." (Novikoff, 1945).

Chemistry may be said to happen largely due to physical processes (Anderson, 1972; Novikoff, 1945). Matter have properties which makes for atoms of different kinds to emerge when it is subjected to certain environmental conditions (Englert & Brout, 1964; Higgs, 1964). Atoms in their turn are subjected to a whole new environment, which enables new conditions and possibilities for change to emerge. Atoms combine to form molecules, new features, and thus new environments. All new molecules and systems that occur in the evolutionary process are selected on the basis of stability. Any system unstable in its environment will break apart and cease to be a system on its own. This view holds for all levels of existence, whether it is atoms or political parties. The theory of natural selections boils down to this - the organism or system which remains most stable is the best adapted, as the degree to which an organism or system remains stable in a changing environment determines its fitness level (Popper, 1979)[58].

Given the right set of conditions, chemistry can be described in terms of biological concepts. There might not be a clear-cut division between inanimate and animate substances, but when there is a sufficient amount of organic chemicals, with an appropriate composition, under the right circumstances, living organisms emerge. From the most basic of organisms, further complexity arises and multi-cellular organisms emerge. At some points, certain combinations of units will lead to a system with whole new levels of complexity (Novikoff, 1945). By integration of parts into a new system, a new level of organization with new features appears.

Complex systems may solve other problems than lower order systems

Adaptation is the process whereby systems maintain stability in an ever-changing environment. Chemicals behave by responding to external and internal stimuli. At some point, the complex organization of chemicals

[58] "The two faces of common sense", Section 16.

becomes biological, as “living cells” emerge. Cells maintain their own internal environment, or more precisely the successful cells have adaptive features that maintain a stable internal environment. More complex cells have a wider array of features that enable them to address problem situations, i.e. greater complexity goes hand-in-hand with greater capability for maintaining homeostasis. If irreversible violations of homeostasis occur, organisms die, their existence is terminated and they are removed by natural selection. In such cases, solutions to the problem situation of maintaining stability in the environment have failed.

The environment constantly changes around all organisms, thus affecting them and presenting new problem situations for them. All responses, successful and unsuccessful, to the problem situations will change the context in which each organism is acting, thus changing the problem situation of all organisms in the environment. This describes interactions between organisms and their environments, which include other organisms engaged in the same processes, thus introducing more fluctuations to the context. The important thing to remember here is that the process will be wholly driven by the context in which the TT is presented or subjected. Theories can only be formulated with the information at hand, as with testing. This means that changes in the context will change the conditions that test and criticize theories. There is no guarantee of future survival because each survived test changes the testing process.

The adaptive trait of homeostasis is what enables an organism to maintain stability in a changing environment. However, it represents only part of the problematic task for the organism of maintaining sufficient stability for survival. Not only must the system be able to resist and counteract stimuli imposed upon it from external sources, it must also respond in such a way that it does not destroy itself in the process The ability to maintain homeostasis is what enables organisms to survive destabilizing challenges posed by their own behavior and the environment. They must fend off threats from both higher level systems and lower level systems. Each organism, in this respect, is continually between a metaphorical hammer and anvil, which may forge it into something better adapted, or smash it.

A complex system must maintain homeostasis at all levels of organization

Just because a higher organizational level emerges from the complexity of lower order systems, does not mean that the lower systems are absorbed into the new system, thereby losing their own need for stability to maintain functionality (Novikoff, 1945; Selye, 1976). As the higher order system is dependent on functions of the lower order systems, the latter must also retain functionality for the higher order system to function properly. Should any

of the lower order systems be changed, the higher order system will no longer be the same.

Richard Dawkins makes an interesting argument in his books "The Selfish Gene"[59] and "The Extended Phenotype"[60], in which he expounds a "gene-centered" view of biology and evolution. Dawkins proposes that DNA and genes were selected over other molecules in the primordial soup for their ability to replicate and change the dynamics of the environment so as to favor their own survival and stability. Later, genes better able to ensure the survival of cells and organisms were selected, thus promoting survival and replication of those genes too.

What Dawkins did was to force the reader to take a different perspective. Instead of thinking "What is in it for me?" the reader must ask "What is in it for the gene?" (Dawkins, 1999)[61]. To do so, the reader must understand the problem situation that the gene faces, to take the perspective of the gene. Dawkins (2006) explicitly states that he is not suggesting that a gene or DNA molecule has a will of its own[62], but that it may seem that way and that there is perhaps no better word than selfishness to describe what is seen from this perspective.

To extend this line of thinking, I suggest that one should apply this view to more levels of organization. To this we also add the possibility of downward causation, the possibility that higher order systems affect lower order systems (Noble, 2008). If we here accept the view Dawkins presented, when genes are kept stable by a cell, the cell is acting in the interest of the genes. At the same time, cell-level selection processes determine which genes will remain within a population of cells. Any gene that reduces cells' stability or their ability to survive in the environment will be removed by natural selection. Thus, in this sense cells could be regarded as acting selfishly towards their genes.

The cell and its genes are in a somewhat asymmetrical state of balance where failing strategies to resist the environments influences are removed by natural selection. As long as cells are independent from other cells, in the sense that their stability is not compromised by damaging or killing other units in the environment, they can evolve strategies that counteract environmental stresses, which may involve damaging or killing other cells of the

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[59] ISBN: 9780199291151.

[60] ISBN: 9780192880512.

[61] PP 4.

[62] PP 24 "In this, the replicators are no more conscious or purposeful than they ever were."

same or other species and eliminating the genes they carry (Dawkins, 2006)[63]. In cases where cells are part of an organism, there will be an additional level of organization that acts in "its own selfish interests" on the processes occurring.

A multilevel system survives through integrated selfishness

The theories of Selye and Cannon mentioned above can be used to describe the framework and driving forces involved in the adaptation of biological systems, i.e., resistance to irreversible changes to homeostasis. Any system will work at all times to serve its own purpose of maintaining stability. Systems may span several levels of organization and may compete with each other. A mutation or change in behavior may be advantageous for a cell or organism, in its time and place. But this reasoning raises risks of taking the systems out of context because the perspective is too narrow; there will always be other systems in the environment and the environment will always be changing. For any change to persist, it needs to be stable with the environment, while at the same time all surrounding systems have the same objective (Thomas, 1984). Mutation of a cell, which may be deemed beneficial for the cell in terms of raising its immediate prospects of replication, may lead to cancer in the organism and the behavior of a single organism may threaten its entire population, present and future (Dawkins, 2006)[64]. Again, natural selection serves to eliminate strategies that do not lead to a stable environment.

To understand adaptations of integrated systems, we need to consider a perspective of integrated selfishness. Like Dawkins, I do not mean selfishness in the common egoistic sense, it is just a word to describe the process of someone or something acting to maintain oneself or itself. A system that does not maintain itself will cease to be. It is not a matter of desire, it is just that the systems that did not are not.

Physical training is a means to achieve physical fitness

If there is no aim, an activity cannot be considered training (Ericsson, Krampe, & Tesch-Römer, 1993). The aim of physical training is to increase fitness, to become better prepared for what may challenge the physique. There is however, at this time no consensus as to what fitness is in humans, there is no clear answer to the question "which are the marks of the fittest human?". Nevertheless, we have invented games and play in attempts to overcome this problem. As humans we have the capacity to formulate "What if?" scenarios, in which we can "test" theories to approach the problem. The

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[63] PP 45.

[64] PP238. "But we shall now see that the phenotypic effects of a gene need to be thought of as all the effects that it has on the world."

ability to test behaviors before executing them may allow individual organisms to gain an advantage in handling possibly lethal situations (Popper, 1978). Humans have ways of preparing for "What if?" situations, enabling such an adaptation to be naturally selected and thus gaining more possibilities for postponing death (or promoting survival of offspring). According to Popper this is the emergence of world three, and the adaptation of being able to utilize world three, the world of "What if?" among other things. It does not simply involve making mental pictures of possible situations, but also construction of situations similar to the expected "real" situation. This is useful as it enables preparation for the real situation by engaging in a simulated situation (Ericsson et al., 1993). It also helps to reduce risks and dangers associated with the situation, which may make it easier to deal with, both practically and psychologically (Winnicot, 1971)[65]. Eriksson refers, in this context to deliberate practice, deliberate play, while Winnicot applies and discusses the concept of play in an unadulterated matter. Although there seems to be a difference, these concepts vary in purpose, not mechanism. Both are attempts to control the world, in order to integrate it into the self by refining the individual's strategy of approaching the world and particular features of it.

Humans have been aware for a long time that practice and training work. According to Bompa and Haff, physical training has been practiced for at least 3000 years (Bompa & Haff, 2009)[66]. Methods have changed, but the fundamental idea of arranging problem situations for the safe development of skills has remained. By developing skills in a safe environment, the performing subject may be better prepared and fitter to handle circumstances when encountering the corresponding problem situation in an "uncontrolled environment". Sports and sports training are merely attempts to create a controlled environment to make preparation predictable and practical so that fitness levels of individual humans can be measured by their performance in the controlled environment/situation.

However, a sport only measures fitness for that particular sport, and sports are just a set of many human behaviors, subordinate to the whole concept of "being human". A sport is therefore a poor measure of human fitness. There will probably be degrees by which high fitness in any given sport is indicative of high general fitness, i.e. fitness for life as we humans tend to live it, insofar as such definitions are possible or practical.

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[65] Chapters 6 and 7

[66] PP 31

Evaluation of physical fitness is at best a description of an individual's physical fitness in the specific modality designed to test physical fitness

Physical training literature typically falls into one of two categories, focusing on either training or exercise physiology. The training literature is mostly concerned with ways to structure humans' behavior to attain high levels of sports performance. In contrast, exercise physiology literature mainly concerns measurements of the direct, delayed and cumulative effects of exercise on the content of the human body/cells.

In each of these fields, fitness is measured in different ways. In the training field, fitness is measured in terms of sports performance, usually in competition with other contenders. In exercise physiology, fitness is measured in terms of clinical chemistry and clinical physiology parameters. Measuring sports performance provides a measure of fitness that indicates the relative adaptive levels of the participants for the particular behavior and situation presented. The weakness of sports as fitness measures is that the behaviors and skills involved correspond very poorly with skills required for most humans' everyday living. In contrast, exercise physiologists study the physiology of fit or unfit individuals and how they react physiologically to exercise, with the hope of finding patterns of molecular and physiological parameters that correlate with the individuals' current fitness. Application of the findings then involves attempts to induce desired fitness-linked molecular and physiological changes in focal individuals via physical training and appropriate manipulation of training variables (Egan & Zierath, 2013; Kraemer & Ratamess, 2004; Toigo & Boutellier, 2006). Neither of the two perspectives is problem-free. Just as it is unreasonable to say that a person who is the best shot putter in the world is also the fittest person in the world, so too is it to assume that the level of a molecule is the key to fitness.

At the moment, we are poor at predicting the performance of athletes (Astrand, Rodahl, Dahl, & Stromme, 2003; Sands & McNeal, 2000)[67]. There is a lot of knowledge about factors that are deemed "necessary" for athletic performance, but there are no reliable methods for predicting any kind of athletic performance from measurements of these factors. This may be due to a lack of suitable data for constructing robust regression models and/or other confounding factors, for instance, any test of physical performance or fitness will be biased by the context in which it occurs, making the results difficult to extend beyond the testing situation.

[67] Åstrand et al. PP 299, "the thrill of watching athletic competitions is partly caused by the fact that it is impossible to predict who is going to win."

The primary effect of exercise is the physical action taken

Training is behavior, an attempt to prepare for the future and control the environment that will stress the system concerned. The attempt to construct a plan to follow in a hypothetical situation. All training is meant to prepare for "the real situation" corresponding to the training situation. As the difference between the "real" and "corresponding" situations is one of context, training allows us to test different solutions to identify one that may work in the "real situation".

Physical action requires muscular actions to move the body; even in the smallest of actions, muscles are the means by which the body actively moves. In the model of living organisms presented here, mind emerges from biological systems. Both organic mass and mind may influence each other. Minds can make an organism move and take action, to the extent the organism is capable. The organism's capabilities will depend on its current functions. For example, a human who has exercised until fatigue may desire to continue to exercise, but the body will not be able to perform the desired action as it does not currently possess the necessary capacities to chemically convert stored energy to restore the muscles' contracting capabilities. Action will be discontinued due to the body's limitations. The point where the body and mind intersects is in the action, in the case of physical exercise, in the force production performed by muscle. Therefore, any attempt to stimulate, condition and hopefully adapt the skeletal muscle should be aimed at force generation, through practicing skills involving muscular force production. No matter whether it is one repetition of maximal lifting, or sustained activity for running a marathon, force generated by muscles is what makes the movement happen. A maxim in sport and comparison of performances is that increases in force produced during the chosen activity will lead to better performance, assuming that technical and tactical requirements of the activity are met. Different activity, characterized by differences in duration, application and magnitude of force production, will lead to different conditions in the systems affected by muscle contraction.

Secondary effects of exercise are consequences of the primary effect

The primary effect of an action is force production, so changes to any other system are side-effects or secondary effects. Chemical changes occur in the body as the muscles produce force. These chemical changes depend on the type and magnitude of action performed, and the conditioning of the performing individual. Other compensatory or homeostatic processes also occur at various levels of organization.

Selye (1958) [68,69] has proposed a unified theory of biology and medicine using stress as a common denominator, according to which unless a stressed system can alter its own function to cope with the stress it must transmit the effects to other systems, so they can deal with it. The stress caused by action of the kind addressed in this thesis, can be summarized as chemical changes in the body[70]. These first chemical changes are restored by making other chemical changes, which in turn are restored by yet other chemical changes. Sometimes the chemical changes can be restored by relocation of chemicals stored inside the body together with substances from the environment. In other instances, there might be a need to dispose of substances from the body in the external environment to fully restore a stable internal environment. Any transmitted effect or stress may activate many systems and any system may be part of other systems.

Imagine a cocktail party[71], at which humans are spread evenly across a room, each fixed to a specific position on the floor, and interacting by shaking hands with every person within arm's reach. The partygoers never stop greeting and shaking the hand of every individual around them. Eventually, one of them spills a sticky drink on his or her hand, but unfortunately cannot move to the bathroom to wash it off. Even worse, the greeting continues. On a positive note, some of the sticky stuff is transmitted in every handshake, so it starts spreading to other people in the room, through the handshaking process. Eventually, it reaches an individual conveniently standing beside a sink, who is able to wash away the sticky stuff that has been transferred to him/her. After enough time and handshaking, almost all of it is transmitted, little by little, to the sink and the party continues as before the spillage.

The transmission of stress will lead to other changes in the body's position and internal milieu, changing the chemical environment that the body's constituent cells must react to in order to maintain homeostasis.

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[68] Books 4 and 5.

[69] Selye's explanation entails "the smallest biological unit that can respond selectively to stimulus" (Selye, 1958) PP 222, a part that does not have to have mass. This is very close to my own theory. Whereas I take the position that features emerge from the constituent parts, Selye attributes features to the quantity and quality of these small parts. Both theories are similar in that it is hard to find substance in all features seen in biology. The difference is that the emergent perspective can explain where these features come from, without inventing new particles.

[70] Changes at other levels of organization also occur. Mechanical compensations of body positioning to maintain balance, heat dispersion, changes in the environment, etc.

[71] Inspired by David Miller, "A Quasi-Political Explanation of the Higgs Boson; for Mr Waldegrave, UK Science Minister 1993".

Tertiary effects of exercise counter the secondary effects

This is when the tertiary effects of exercise set in. All tertiary effects are homeostasis-restoring responses. Restoration in the context of muscle homeostasis refers to the musculature becoming capable of performing more contractions, thereby enabling the performing subject to take additional action. The tertiary effects of training may influence other tissues than those directly involved in force production, i.e., the muscle/muscles performing the contraction/contractions. Thus, as the body and its cells cannot freely access all the substrates that may be required from the environment, a change anywhere in the body will likely affect the entire body. The tertiary effects of physical action restore homeostasis following the disruption caused by the stress of actions.

The great difficulty here lies in explaining the supercompensation seen in GAS, where the resistance toward a stressor is increased above the initial levels. How can the stress of exercise increase the body's resistance to exercise?

Delayed and cumulative effects of training are a mixture of secondary and tertiary effects caused by the actions performed

If the stresses that result in training adaptations, at least those definable as GAS-related supercompensation, are biological/chemical rather than behavioral, the supercompensation scenario provides a basis for explaining how training adaptation may occur in the recovery phase following activity. This means that the stress to which the body must adapt is not the training itself but the chemical changes induced by the actions taken. The muscles' production of force comes at the cost of stored chemical energy. Chemical energy is made available through chemical reactions, thus changing the chemical environment in the cell/body, which in turn triggers cellular homeostasis-restoring responses to the chemical changes. As the cells are not totally independent of each other but bound together in the milieu of the body, changes to one cell will lead to changes in cells in other tissues and organs. Responses that counter one change will cause other changes that need to be countered. The resulting cascades could potentially continue for some time if sufficient tissue has been sufficiently stimulated.

This could explain phenomena such as excessive post-exercise oxygen consumption and why protein synthesis may be elevated for several hours, if not days, after exercise sessions (Atherton & Smith, 2012; Buitrago, Wirtz, Yue, Kleinöder, & Mester, 2012). Furthermore, and perhaps more importantly, this could explain why resistance training may lead to adaptations more often seen after endurance training (Burgomaster et al., 2008; Pesta et al., 2011). On the other hand, plenty of studies have found that endurance and resistance training activate opposing cellular signaling pathways, making it

inefficient if not impossible to successfully adapt to both of these training modalities simultaneously (Egan & Zierath, 2013; Wilson et al., 2012).

Cells can only interact with the chemical environment in their proximity at the time. If any type of activity or stimulus evokes a chemical change in the body akin to that experienced by the cells of the body during an endurance exercise, the counter measures induced will be the same as those induced by the actual endurance exercise, leading to adaptations that appear to stem from the endurance exercise. To find connections between a behavior and a specific molecular response, the behavior needs to be clearly defined.

Training should strive to optimally stress the targeted system

The purpose of training is to prepare for the future. To achieve this in the realm of physical training, the goal is to stimulate the body's system or systems to progress towards a state of conditioning that is perceived as beneficial or necessary to perform well in the situation being prepared for. The method for doing this is to present the system with a problem situation that must be solved in order to induce an adaptation to counter the problem situation. While the intentional imposition of stress on another's or one's own organism may cause some ethical dilemmas, there is also a problem of selecting the optimal stress to impose.

There are difficulties in controlling the amplitude and duration of the imposed stress and the specificity of adaptation, i.e. modulating the stressor to induce a desired stress response in the targeted system. This can be graphically described by the first depression of resistance seen in the GAS diagram. If the stressor lacks potential, the body or system will resist. The body or system will most likely adapt its resistance capabilities to meet the demands of the lifestyle, which in a sedentary person might be less than ideal for the organism. The stressor needs sufficient potential to provoke the responding system into counteracting the effects of stress. The solution of the problem is to transmit the stress to other systems, diluting it to harmless levels or transmitting it to the external environment. There must be a possibility or opportunity for the body to restore homeostasis when stressed, as imposition of too much stress will depress the resistance beyond recoverable levels, thereby violating homeostasis requirements. While induction of fatal stress by exercise is unusual, it is possible (Kuklo, Tis, Moores, & Schaefer, 2000). When the imposed stress is too great, the transmission chain may collapse and become unable to transmit the stress any further.

There are upper and lower limits to the amplitude of the imposed stress that may lead to a stress response of increased resistance, i.e., increased capabilities of transmitting/translating the stress to other systems and restoring homeostasis. The lower limit can be called the lowest sufficient stress and the upper limit maximal stress. The stress response will depend on

the body's ability to transmit the stress and restore homeostasis; the conditioning of several systems needs to be considered. As the goal of training is to increase resistance toward the stressor, the stress must be manageable by the body[72] and the net result of adaptation should be increased resistance to the stressor.

Any amount of stress between these two limits can be called sufficient stress, at least when it is willfully induced in the hope of increasing resistance. A sufficient amount of stress generates appropriate adaptations, i.e., resistance to the stressor is increased. As maximal stress carries some risks, approaching these levels of stress should be avoided. We can apply ideas of costs versus benefits to the process of training and adaptation. Optimum stimulation lies somewhere between the maximum and lowest sufficient. It is difficult, if not impossible, to know exactly, where, but this does not mean that one should not strive for such an ideal.

Overtraining is caused by a gradual decrease in the capacity of support systems to resist the effects of training

This has to some extent been discussed above. Below, I present a brief discussion of the effects of training perceived as negative. The stress imposed on the body's subsystems may not occur at the same time as a physical activity is performed. If stress is exerted on any given system of the human body, that system will transmit the stress to more systems, thus increasing resistance to the stressor. This is only possible if other systems can sustain the stress being transmitted. This process will extend further to yet more systems. Hopefully, somewhere along the line, there will be some system capable of transmitting the stress out of the body.

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[72] Bartley argues that when one is trying to impose natural selection upon ideas by the use of critical rationalism, criticism (stress against statements [abstract systems]) must be optimum rather than maximum (Bartley, 1982). Popper on the other hand says that we must hold nothing back when we criticize a statement and you should not hold back when trying to defend the theory or criticize the critique (Popper, 1979), "A Realist View of Logic, Physics, and History." Section 4. Popper's method suggests that there are no fatal consequences involved in stressing a statement and that there are no limitations in the measures of defense. Popper has a point in that this will truly test the fitness of a statement. The difference between the two may be that Popper is looking for nature's way of testing fitness, whereas Bartley is interested in the human endeavor of improving fitness ("Criticism must be optimum rather than maximum, and must be deftly applied. Second, my initial formulation overemphasizes matters intellectual such as beliefs, conjectures, ideas, and such like. I want explicitly to include for review not only beliefs, conjectures, ideas, ideologies, policies, programmes, traditions, but also institutions, and even etiquette, manners and customs, and unconscious presuppositions and behavior patterns that may pollute the econiche and thereby diminish creativity, criticism, or both."- W. W. Bartley).

Looking at this from the other way around, we can ask the question, where does the response cascade end when the stress is overwhelming? This corresponds to the system in the chain that is unable to resist the imposed demands. This will start a chain reaction that runs in the opposite direction, shutting down systems depending on the support from the failed systems until overall activity is minimal. Hopefully, systems are able to regain some level of capacity after a failure event. The consequences of such a failure should not be overlooked and are as important as the positive effects. If systems downstream of the failed system receive less conditioning due to the cessation of transmission, the failing system will be more likely to fail again if the same stressor is applied. This could slowly move the weakest link closer to the initial stress responder. This could explain the phenomena of overtraining. If the resistance capacity in support systems is lowered, then the supported systems will be unable to transmit the stress further, eventually leading to decreased performance. In the long run, this may present similar effects to increases in performance, but the other way around. In cases of small initial changes, support systems are located far away in the chain of events giving in, leading to substantially decreased performance as the failing effects move closer to the source. As the support system furthest away from the cause is likely to be where the last adaptations have occurred in the evolution of the systems, it is liable to be the weakest because it has not been adapted by natural selection to the same degree as older more basic systems. This may partly explain why there are shorter recovery times for short-term overtraining or overreaching than for long-term overtraining (Bompa & Haff, 2009)[73].

The effects of training depend on the previous conditioning of the performing subject

Currently, probably the most reliable method for determining a sufficient amount of training stimulus is to monitor the performing subject for an extended period of time while applying the principle of progressive overload (Zatsiorsky & Kraemer, 2006)[74]. Overload in this context refers to a stimulus sufficient to evoke adaptation, and progressive to the stimulus being adjusted according to the progress of adaptation. By trial and error, one can probe precisely how progressive and overloading the training program should be to provide sufficient stimuli, and by continually testing the performing subject one can gauge whether the training program has the intended effects.

There are well-proven guidelines for achieving the desired effects of training, based on data gathered regarding successful training

[73] PP 99-104.
[74] PP 4-5.

methods (Garber et al., 2011; Ratamess et al., 2009). By conforming to these guidelines when planning training, one will be more likely to achieve the desired effects and adaptations. However, these guidelines are quite shallow and have not changed much since the 1940s (De Lorme, 1945). There are currently no good tests to determine the ideal type of training for any given individual to reach any given goal. The best way is still to expose the individual to a training program and evaluate the results. There have been some interesting attempts to elucidate what determines a person's susceptibility to training stimuli (Bamman et al., 2007). However, this is complex given the many permutations of training variables, wide variation in the duration of training programs and huge variations in performers' physiological, psychological and demographic factors. Hence, there may be infinite numbers of options for training programs.

Whether we are trying to determine a genetic profile or track the history of a performing subject, it is all about trying to understand the underlying conditioning factors, i.e., what is the level of preparation? The conditioning factors are the current resistance capabilities or stress transmission capabilities of the subjects' systems, which will determine the capacity to deal with effects of a given load of a stressor. More understanding of these factors will increase our knowledge about training and adaptation. The most important thing is to focus on the problem situation, which problems are the systems of the body selfishly solving (*sensu* Dawkins and Popper)? Which problems are the performing subjects trying to solve?

The outcome of performance will depend on the amount of conditioning in the four categories. But how does one decide when a performing subject has the proper conditioning of technique, tactics and psychological factors for any given task? What are the potential effects of the task? What will be the stress reactions of the body's systems? Can we predict a path for the performing subject or are we testing what the subject is capable of at the time of testing?

The process of planning and executing training should involve matching the perceived stress of the intended activity to the level of preparation of the performing subject

Creating a training program or strategy may appear to be more an art than a science as it is difficult to analyze conditioning factors to determine what the performing subject is prepared for and hence an appropriate level of stress to impose during training. In sports training, conditioning factors can be divided into four categories, each of which can be further differentiated into sub-categories (Bompa & Haff, 2009; Matveyev,

1981)[75]. Another difficulty lies in weighting the categories against each other and deciding the contribution of each to the performance outcome of the subject. As fitness is measured in performance and it is impossible to disentangle any of the categories from performance, one must assume that they all contribute to the performance. The main question is the relative importance of each category at any given time or fitness level. An athlete may be more and better prepared compared to all competitors in three out of four categories but still finish last, for any combination of the three categories.

In physical preparation, a popular strategy is to identify the limiting factor of the performance and attempt to increase preparation in terms of that factor in order to increase overall performance (Zatsiorsky & Kraemer, 2006)[76]. Questions asked include the following. What was the limiting factor for the subject, what was it that made the subject fail to perform beyond what was already achieved? Was it a lack of physical preparation? If so, does the subject lack strength, stamina, flexibility, endurance or power? Was the problem technical? If so, does the subject have suboptimal movement patterns or lack coordination of movement patterns? Was the deficiency tactical? If so, does the subject know how to perform in a way that minimizes disadvantage and maximizes environmental or equipment advantages? Was the factor psychological? If so, was the subject hesitant to perform due to previous experience or does he/she lack motivation to perform? The subject or coach must then analyze which of these factors are limiting performance and subsequently apply appropriate training to increase preparation in terms of that factor. There may be many factors that need improving, each needing to be addressed in specific ways.

A critical approach to training consists of formulating a plan that takes the available knowledge and current state of the subject's conditioning factors into account. This plan must then be tested. Does it hold up to the test of being put into practice? Is the strategy leading to increased performance? The strategy formulated must be put into practice and tested severely. This does not imply maximal training stimulus, it is the training strategy that needs testing. One difficulty here is the adherence to the strategy, i.e., is the formulated strategy really being tested? The performed strategy will in all likelihood differ from the formulated one, partly because a formulated strategy cannot cover and describe every aspect of the subject's life. Nevertheless, the strategy will affect the actions of the subject, in the same manner as theories affect observations (Ajzen, 1991).

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[75] Chapter 1 Section 3 Figure 2 in Matveyev. Chapter 1 Figure 1.1 in Bompa and Haff.

[76] The Peak-Contraction Principle, PP 118.

One difficulty in formulating and evaluating a strategy for any training honestly and critically is that the topic is vast. The performance of actions depends on shifting permutations of huge numbers of physical, technical, tactical and psychological factors of the subject. Determining which factors are in need of training requires elaborate testing to disentangle the role of each category in any given situation. With such diverse options, disentangling which part of a plan has failed is complicated. The process of eliminating errors is only needed if the theory has failed to meet the problem situation. The theory must then be reformulated with better content and power of explanation. As long as training yields expected effects, there is no need to change the current training theory/strategy. It is when effects are lacking or counter-productive that the theory must be reformulated.

Exercise must be consistent with the strategy of the training program

The literature on training periodization to maximize performance suggests that one should plan backwards from the point of the intended performance to the current day (Bompa & Haff, 2009; Zatsiorsky & Kraemer, 2006)[77], i.e., the goal of training is the most important part of the planning. All choices lead somewhere, not just toward the goal. One difficulty in the training process is that all choices and actions taken will affect preparation, regardless of the training goal. To be successful in preparation, all choices and actions should be oriented toward reaching the goal.

There is a big difference between a training program and a single exercise session. A training program calls for progressive stress in order to provide sufficient stimulus to gain positive effects beyond a certain point. According to GAS theory, one type of stressor at specific amplitude will provoke a stress response to the stressor. Once resistance has been increased, the same stressor will be resisted, so the level of resistance will not be increased any further. The stressor needs to be applied to a higher degree in order to overload the resistance and induce a stress reaction.

By this reasoning, the stressor and stress of a progressive training program will never be exactly the same as the stressor and stress during each session of that training program. This constitutes a major difficulty if one is trying to determine the type of stressor, amplitude of stress, and level of resistance induced by an exercise session. This was the aim of the empirical work the thesis is based upon — to examine the stress reaction of human skeletal muscle and its adaptation to long-term training. Bearing in mind the difficulties of this type of research, as stated above, efforts were made to produce a model of resistance training, based on data acquired from

[77] Bompa and Haff chapter 6. Zatsiorsky and Kraemer Chapter 5.

observations of the degree to which desired adaptations were induced by a training program formulated according to a designed table of exercises and volumes of exercise in a periodization scheme. However, the process of creating the training program also led to a description of how the exercises were to be performed and how effort was to be exerted by the subject undertaking the training.

Theories and previous research findings have suggested that lifting moderate to heavy weights for several repetitions in multiple sets to failure or close to failure, at a deliberately restrained angular velocity, with a relatively short time for inter-set recovery, is optimal, or at least highly efficient, for stimulating muscle hypertrophy (Ratamess et al., 2009; Wernbom, Augustsson, & Thomeé, 2007). The postulated reason for this is that application of such training behavior will require tremendous exertion and effort from the performing subject. More than just performing recommended repetitions, sets, rest and exercises, the description of the training program needs to convey that the exercise performed requires an effort of free will to maintain a level of exertion that is most likely painful (Borg, 1982).

Theory into practice

In the empirical work this thesis is based upon, the training focused on what is usually called resistance training, i.e. participants overcoming gravitational resistance to move objects via muscle actions, through lifting them either on their own or using levers and pulleys. The eight-week training program comprised a series of planned sessions of deliberate effort to perform the prescribed physical exercises combined with nutritional intervention and general lifestyle guidelines aimed at conditioning the body to specific responses to the imposed environment and any wanted or unwanted consequences conveyed as a result of the said environment (Ericsson et al., 1993). The exercises used in the training program were selected for the purpose of developing whole body muscle mass of the subjects, with the aim to distribute gains of mass above and below the waist roughly equally. The training program was based on contemporary guidelines designed to result in maximal increases in subjects' lean body mass after the program (Ratamess et al., 2009; Wernbom et al., 2007).

Empirical aims

"Creative minds have always been known to survive any kind of bad training."

-Anna Freud

The empirical work was aimed at stimulating muscular hypertrophy in human males as a result of resistance training. Measurement of size and bio-chemical composition of the muscle was seen as a more objective outcome than performance, as cellular events are not directly influenced by psychological states. Hence, purely biological aspects of human training were of primary interest rather than the performance aspects. A comprehensive overview of the experimental design is presented in Figure XI, in the Materials and Methods section.

As a first step, the method for obtaining biological samples was tested. By sampling tissue in a resting state, spatial and temporal effects of the chosen physiological factors were analyzed to evaluate the following;

- Differences in skeletal muscle gene expression associated with variations in timing and location of sampling in the vastus lateralis.
- Correlations between gene expression and muscle fiber type in samples taken at rest at different sites and times from the vastus lateralis.

The results from the method tests are presented in Paper A, *Gene expression and fiber type variations in repeated vastus lateralis biopsies*.

The exercise training experiment consisted of two parts. The first of these was aimed at studying immediate and delayed effects of one exercise session combined with intake of a beverage containing either a mixture of protein and carbohydrates or carbohydrates alone. Specific aims were to evaluate:

- Exercise-mediated changes in levels of transcripts associated with selected anabolic and catabolic pathways in skeletal muscle.
- Exercise-mediated changes in levels of anabolic and catabolic hormones.

The observed immediate and delayed effects of exercise are presented in Paper C, *Effects of protein ingestion on the hormonal response to resistance exercise and increases in lean body mass after eight weeks of training*.

The second part was aimed at studying cumulative effects after eight weeks of training combined with intake of a beverage containing either a mixture of protein and carbohydrates or carbohydrates alone during every single session. More specific aims were to evaluate:

- Exercise-mediated changes in levels of transcripts associated with selected anabolic, catabolic and oxidative metabolism pathways in skeletal muscle and adipose tissue.
- Exercise-mediated changes in levels of circulating anabolic and catabolic hormones and adipokines.
- Pre- and post-training differences in body composition and physical performance.

The cumulative effects of exercise are presented in Papers B and C, *Metabolic adaptations in skeletal muscle, adipose tissue, and whole-body oxidative capacity in response to resistance training* and *Effects of protein ingestion on the hormonal response to resistance exercise and increases in lean body mass after eight weeks of training*.

Empirical findings

Results were regarded as significant if $p < 0.05$. All units are SI, unless specified otherwise, for example units of gene expression are arbitrary. All means are geometrical and standard deviation is presented in parentheses whenever means are used. All error bars represent standard deviation.

Method test

The purpose of this part of the project was to explore the method of skeletal muscle biopsy sampling as an option for gathering data by examining whether the biopsy sampling procedure would cause changes to subsequent samples taken from the same individual. The baseline was set by a biopsy from a vastus lateralis muscle. One hour later, biopsies were obtained from the opposite leg and an additional biopsy from the first leg a few centimeters away from the first incision. Time and site effects were evaluated using univariate and multivariate methods of statistical analysis.

Results from RNA expression and muscle fiber type analysis are displayed in Table I. One-way ANOVA revealed no significant differences in RNA levels or fiber type composition between opposite legs of individual subjects. Expression of CKM[78] was lower an hour later than at baseline, however, further analysis of the whole dataset by RM-ANOVA[79] indicated there were no significant time or site effects, although fractions of type I and type I+II muscle fibers tended to differ across the biopsies ($P = 0.083$ and 0.063, respectively). Pairwise comparison showed a significant difference in the fraction of type I fibers between biopsies taken from the same leg.

The data were further analyzed using multivariate statistical methods. No significant differences in gene expression associated with differences in sampling sites or timing were detected by Orthogonal Partial Least Squares-Discriminant Analysis, OPLS-DA. However, as shown in Figure III, OPLS-DA of co-variation of gene expression between the subjects explained 90.3%[80] of the variation in the gene expression data and 82.3%[81] of between-subject variation and cross-validation indicated that the model could predict 49.8%[82] of the between-subject variation. OPLS regression was used to investigate the correlation between gene expression and fiber type. Again, the dominant variation seen in Figure IV was between-subject differences. The

[78] creatine kinase, muscle.

[79] repeated measures Analysis of Variance.

[80] R2X = 0.903.

[81] R2Y = 0.823.

[82] Q2Y = 0.498.

calculated regression model accounted for 52.1%[83] of the variation in the gene expression data and 51.0%[84] of the variation in the fiber type data, and cross-validation estimated the goodness of prediction to be 13.1%[85] of the variation detected between subjects.

Table I. Gene expression and proportions, in percentages, of fiber types in repeated vastus lateralis biopsies (n=6)

	First biopsy	+1 h same leg	+1 h other leg
IGF1R	0.73 (0.18)	0.69 (0.20)	0.76 (0.30)
IGF1	0.58 (0.24)	0.63 (0.23)	0.76 (0.39)
TRIM63	0.56 (0.25)	0.43 (0.21)	0.48 (0.29)
ESR1	1.32 (0.16)	1.20 (0.32)	1.20 (0.36)
HSD17B10	2.06 (0.85)	1.66 (0.54)	2.02 (0.87)
SRD5A1	1.22 (0.15)	1.15 (0.22)	1.05 (0.22)
AKR1C3	1.15 (0.49)	1.63 (1.53)	1.54 (0.87)
AR	1.29 (0.28)	1.32 (0.23)	1.25 (0.24)
CKM	0.95 (0.16)*	0.81 (0.21)	0.74 (0.09)
PFKM	0.71 (0.15)	0.64 (0.19)	0.68 (0.29)
MYH1	0.38 (0.44)	0.34 (0.32)	0.24 (0.25)
MYH2	1.03 (0.22)	0.94 (0.20)	0.98 (0.26)
MYH7	1.95 (0.71)	1.72 (0.78)	1.88 (0.89)
Type I	48.8 (16.12)	39.82 (14.45)†	45.45 (9.69)
Type IIA	40.18 (10.46)	46.82 (8.52)	40.70 (12.61)
Type IIX	0.93 (1.8)	1.18 (1.30)	0.43 (0.67)
Type IIAX	7.87 (6.74)	10.45 (8.25)	7.45 (7.54)
Type I+II	2.2 (1.65)	1.78 (2.44)	5.93 (5.62)

*= significant effect of time, †= significantly different from first biopsy. Adapted from Boman, Burén, Antti, & Svensson (2015).

[83] R2X = 0.521.
[84] R2Y = 0.51.
[85] Q2Y = 0.131.

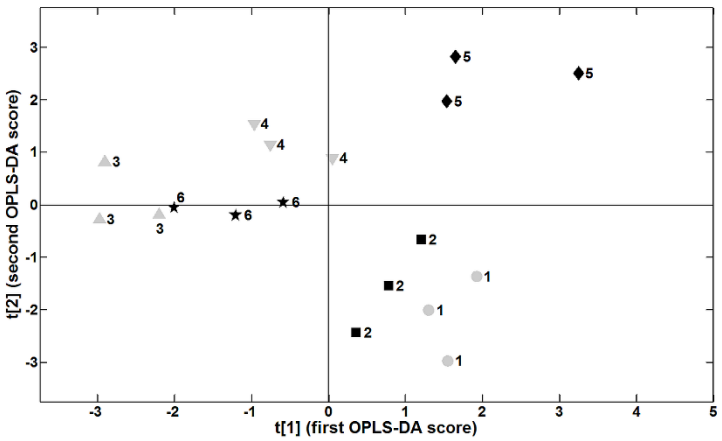

Figure III. Score plot of OPLS-DA analysis of the relationship between gene expression levels[86] and study subjects[87]. Each symbol in the plot refers to one biopsy sample described by the combination of all measured gene expression levels. Each set of symbols is labeled with a number unique to each subject. The plot of the first two OPLS-DA components[88] shows a clear separation between the six individual study subjects based on the measured gene expression levels. Adapted from (Boman et al., 2015).

[86] *X*.
[87] *Y*.
[88] *t*2 versus *t*1.

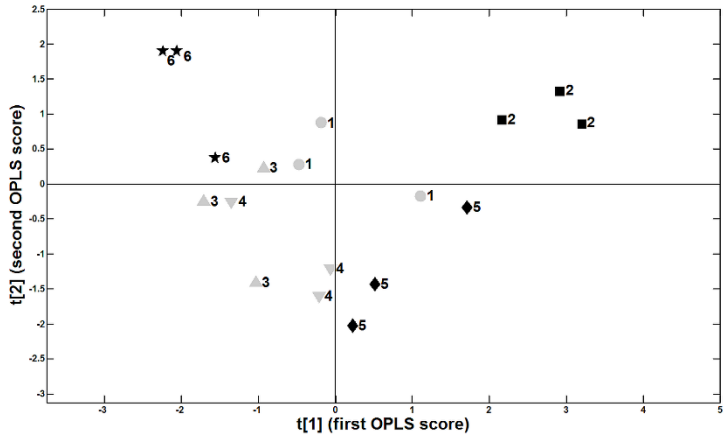

Figure IV. Score plot from OPLS regression analysis of the relationship between gene expression levels and percentage of fiber type. Each set of symbols is labeled with a number unique to each subject. Between-individual differences clearly account for most of the variation, particularly in the first latent vector, t[1]. Adapted from (Boman et al., 2015).

Immediate and delayed effects of exercise

Subject characteristics

The groups of subjects who ingested isoenergetic beverages containing carbohydrates alone, shortened CHO, and carbohydrates plus protein, shortened CHO:P, had similar characteristics and there were no significant differences between them in age, weight or height, as shown in Table II. Note on Table II; Biopsies for the study of immediate and delayed effects were not obtained from all the subjects in the exercise-training experiment, hence the differences in characteristics described for each experiment. Both groups reported a similar extent of resistance exercise activity in their current training schedule as screened in the recruitment process[89].

[89] Data not shown.

Table II. Age, height and weight of subjects in the CHO (n=10) and CHO:P (n=9) groups in the exercise experiment

	CHO	CHO:P
Age	25.5 (3.7)	25.2 (3.2)
Weight	79.5 (9.3)	77.7 (5.9)
Height	182.4 (6.8)	182.4 (6.1)

Muscle gene expression

Immediate effects of resistance exercise combined with ingestion of the isoenergetic beverages containing either carbohydrates and protein or carbohydrates alone on levels of transcripts associated with selected anabolic and catabolic pathways in sampled muscles are shown in Figure V.

No significant differences in gene expression between the groups were observed at baseline. AR mRNA levels were significantly lower 45 minutes after the resistance exercise session than immediately afterwards, while ESR1 and SRD5A1 mRNA levels tended to be lower (p=0.096 and 0.078, respectively). Levels of AKR1C3[90] appeared to be unaffected by the exercise.

To further investigate these trends, data pertaining to each group were separately evaluated by one-way ANOVA. In the CHO group, SRD5A1 mRNA levels were significantly lower 45 minutes post-exercise. However, no apparent effects on expression levels of SRD5A1 were detected in the CHO:P group 45 minutes after the exercise session.

Levels of TRIM63[91] mRNA were significantly and roughly two-fold higher 45 minutes post-exercise than immediately afterwards, and there was no significant between-group difference in them. No differences in IGF1 and IGF1R[92] expression proved to be significant, either between groups or between time points.

[90] Encoding HSD17B5.

[91] Encoding MuRF-1.

[92] Encoding IGF1 receptor.

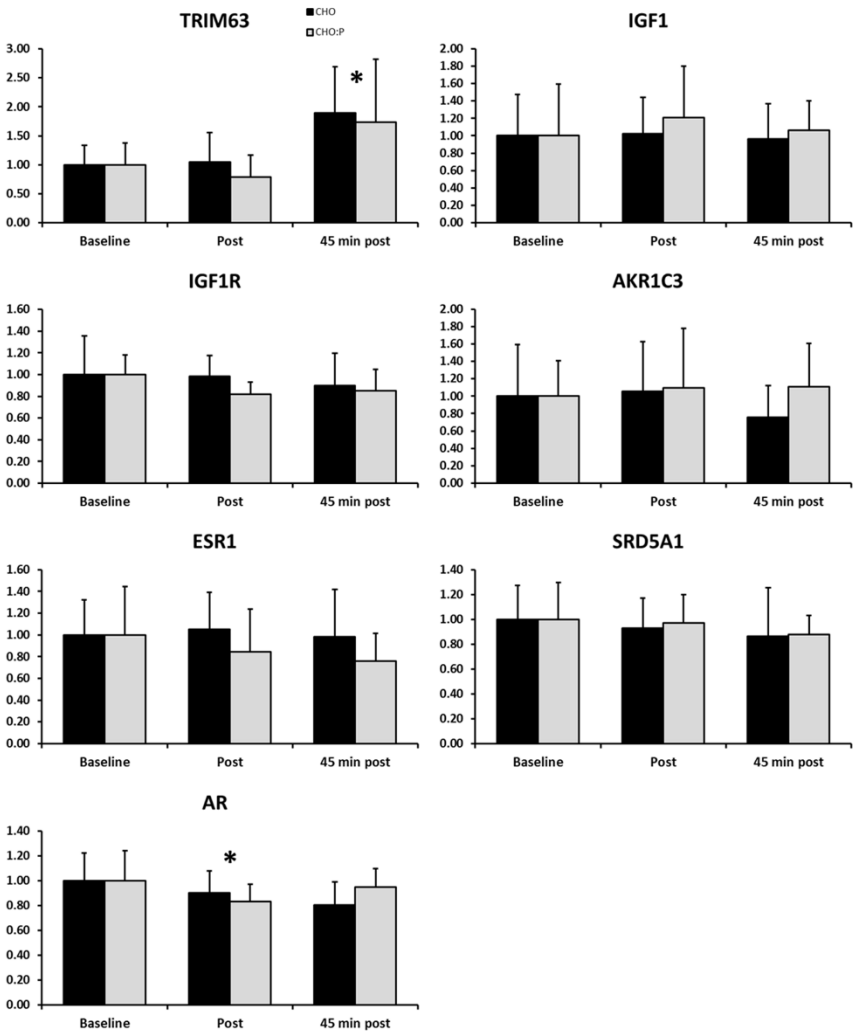

Figure V: Transcript levels as fractions of baseline values for groups CHO (n=8) and CHO:P (n=6), of selected genes immediately and 45 minutes after exercise. There were no significant differences between the groups. Hence, all statistically significant differences indicated are for the pooled subjects treating them as a single population. *= significantly different from pre exercise values.

Serum hormone levels

There was a continuous decline in serum levels of testosterone in both groups as the exercise session and subsequent recovery progressed, as displayed in Figure VI together with the results of DHEAS, IGF1, and cortisol measurements. Significantly lower levels of testosterone were reached 15 minutes after exercise in group CHO, and only after 45 minutes in group CHO:P, but there were no significant between-group differences in this respect according to two-way ANOVA.

DHEAS levels were significantly increased directly after the training session according to one-way analysis, but the increase was not significant according to two-way analysis taking the nutritional intervention into consideration.

According to pairwise comparison, levels of IGF1 were significantly lower 45 minutes post exercise than immediately afterwards. Separate analysis of the groups showed was no significant reduction in IGF1 in the CHO:P groups, while IGF1 levels tended to decline from peak levels during the 45 minutes following exercise in the CHO group ($p=0.062$).

Cortisol levels were increased at all time points after the onset of exercise but only significantly increased during the exercise session and immediately after the last exercise. Separate analysis of the groups showed that levels of cortisol were significantly increased only in the CHO group at these time points.

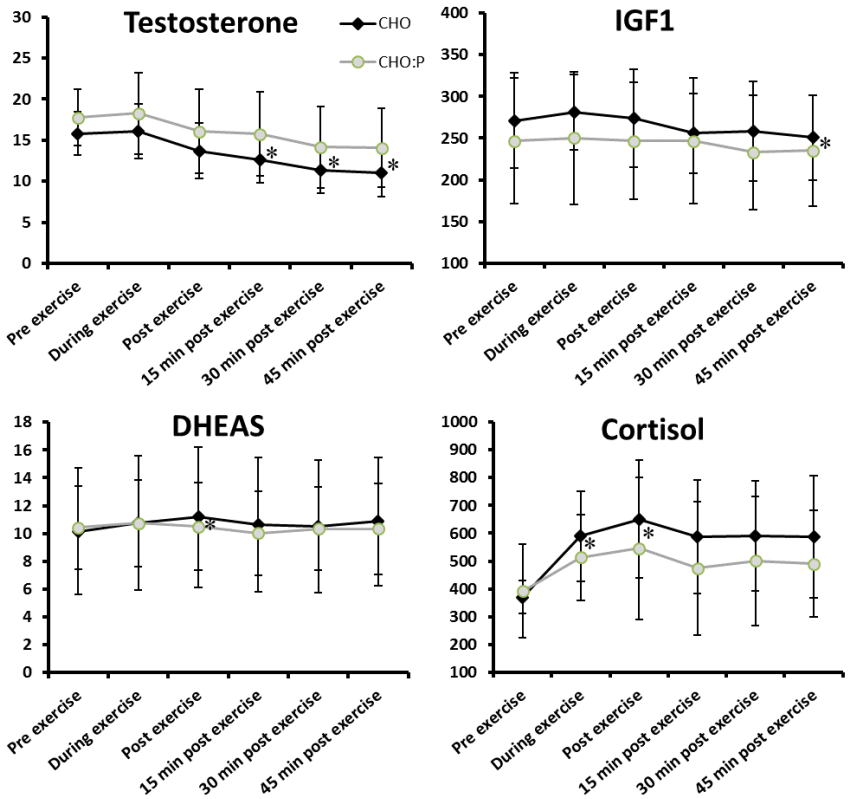

Figure VI Immediate and delayed effects of exercise on levels of selected serum hormones; testosterone (nmol/l), IGF1 (µg/l), DHEAS (µmol/l), and cortisol (nmol/l); CHO (n=10), CHO:P (n=9). There were no significant differences between the groups. Hence, all statistically significant differences indicated are for the pooled subjects treating them as a single population.*= significantly different from pre exercise values.

Cumulative effects of eight weeks of training

Anthropometrics and performance

There were no differences between the groups in terms of any of the characteristics presented in Table III. Analysis of the subjects' dietary records (n=13), summarized in Table IV, showed that the CHO group had a significantly higher E% from protein than the CHO:P group. By the end of the training period, subjects in both groups had a higher proportion of fat in their macro nutrient composition than during the beginning of the training program (34.4 ±5.56 and 31.2 ±6.11 E% from fat, respectively).

Table III. Age, height, weight and BMI of subjects at time of recruitment in the CHO (n=8) and CHO:P (n=8) groups in the exercise experiment, and numbers of sessions performed during the eight-week training program

	CHO	CHO:P
Sessions	27.1 (3.6)	24.8 (4.6)
Age	25.9 (3.7)	24.8 (1.8)
Weight	77.1 (8.8)	80.2 (6.5)
Height	179.3 (5.3)	183.0 (6.4)
BMI	23.9 (1.8)	24.0 (1.9)

Table IV. Dietary records, body composition and performance of subjects.

	CHO (n=8)		CHO:P (n=8)	
	Pre-training	Post-training	Pre-training	Post-training
E% Protein	22.0 (7.2)#	19.2 (3.0)#	17.1 (4.6)	15.3 (2.6)
E% Fat	29.5 (5.2)	33.3 (5.0)*	32.7 (6.8)	35.3 (6.3)*
E% Carbohydates	48.8 (5.7)	47.5 (4.5)	50.1 (6.2)	49.4 (4.7)
Body fat[c]	19.0 (3.4)	18.5 (3.3)	21.2 (3.5)	20.8 (3.8)
Lean body mass[d]	59.7 (6.6)	62.1 (7.2)*	60.4 (6.0)	62.5 (5.7)*
VO_{2peak}[e]	3.92 (0.7)	4.56 (0.5)[b]*	3.96 (0.7)	4.72 (0.6)*
Peak power[f]	1188.8 (213.5)	1321.0 (327.7)[b]	1270.8 (136.9)	1304.9 (204.2)
Benchpress 3RM[g]	81.6 (16.5)	88.1 (16.1)*	77.2 (17.8)	79.7 (20.2)
CMJ[93,h]	39.7 (4.4)	41.4 (5.7)	36.4 (3.8)	38.9 (5.4)[b]
Squat jump[h]	33.8 (3.5)	36.8 (4.0)[a]*	34.2 (4.2)	34.7 (5.4)[a]

*= statistically significant change from pre-training values, #= statistically significant difference between groups, the group with the highest value is indicated. 13 subjects reported diet composition, CHO n=6, CHO:P n=7. a= 1 lost to follow-up. b= 2 lost to follow-up, c= percentage, d= in kg, e= l/min, f= in watt, g= in kg RM (repetition maximum), h= in cm.

To accommodate the need for individualization of training stimulus, subjects chose a training program in consultation with the training and experimental staff. The factors taken into consideration were the subject's previous training history, exercise experience, training frequency, and motivation[94]. Subjects were instructed to be consistent in their fulfillment of the chosen training program and adhere to the program as best as possible. The difference in frequency of training sessions, seen in Table III, between the groups was not significant. Although the training had the strongest effect on the endpoint measurements, the difference in training frequency did not affect differences between the groups in any of the outcome variables.

The subjects' body composition and physical performance before and after the training period are presented in Table IV. There were no significant differences between the groups before or after the training period. There were significant gains of lean body mass in both CHO and CHO:P groups,

[93] Counter-movement jump. I apologize for the use of this acronym as it is not congruent with the rest of the thesis - it was used to fit the table to the printing format.

[94] What was taken into consideration was the subjects "willingness" to train, the intention, and possibility to allocate time each week to train.

but no difference between the groups. The percentage body fat did not change significantly from the baseline. 3RM bench press improved significantly in the CHO group, whereas there was no significant improvement in the CHO:P group's bench press performance. Squat jump performance improved, but only significantly in the CHO group. Changes in fat oxidation and work performed, together with significant observed increases in maximum oxygen consumption rates following the training period, are shown in Figure VII. The highest performed cycle effect measured during the ten second all-out test did not increase significantly in either group.

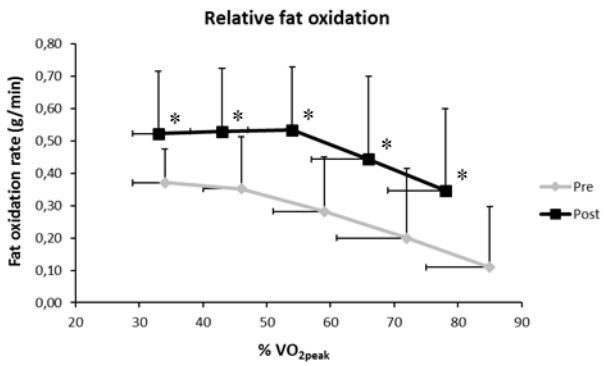

Figure VII. Changes in fat oxidation and sub-maximal work performance after the training program. A vertical shift of the curve indicates a change in fat oxidation rate and a horizontal shift indicates a change in the amount of work performed during the incremental cycle test. There were no significant differences between the groups. Hence, all statistically significant differences indicated are for the pooled subjects treating them as a single population.*= significantly different from pre exercise values.

Circulating hormones

Levels of cortisol, IGF1, testosterone, SHBG[95], and DHEAS did not differ significantly between groups before or after the training, shown in Figure VIII. In contrast, circulating levels of adiponectin were significantly lower after the training program.

[95] Sex-hormone binding globulin.

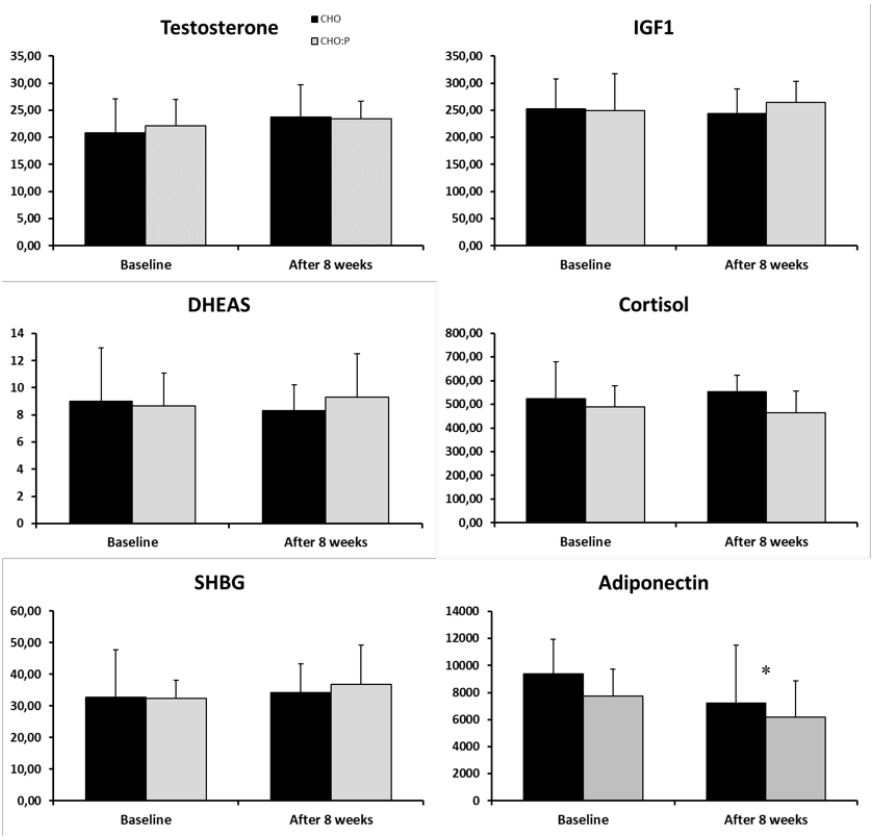

Figure VIII. Resting serum hormone levels selected serum hormones; testosterone (nmol/l), IGF1 (µg/l), DHEAS (µmol/l), and cortisol (nmol/l); CHO (n=7), CHO:P (n=8) before and after the training program. There were no significant differences between the groups. *= significantly different from pre-training values for the pooled subjects treating both groups as a single population. Adapted in part from Alvehus, Boman, Söderlund, Svensson, & Burén (2014).

Skeletal muscle and adipose tissue gene expression

Displayed in Figure IX, muscle tissue gene expression data showed that AKR1C3, AdipoR1, and COX4[96] were significantly higher after than before the training program, whereas the expression of TRIM63 decreased significantly. Adipose tissue gene expression analysis, shown in Figure X, revealed that levels of both SIRT1 and CPT1B[97] mRNA decreased significantly after eight weeks of resistance training, with no between-group differences.

[96] Cytocrome c oxidase 4.

[97] B indicates a CPT1 type specific to skeletal muscle.

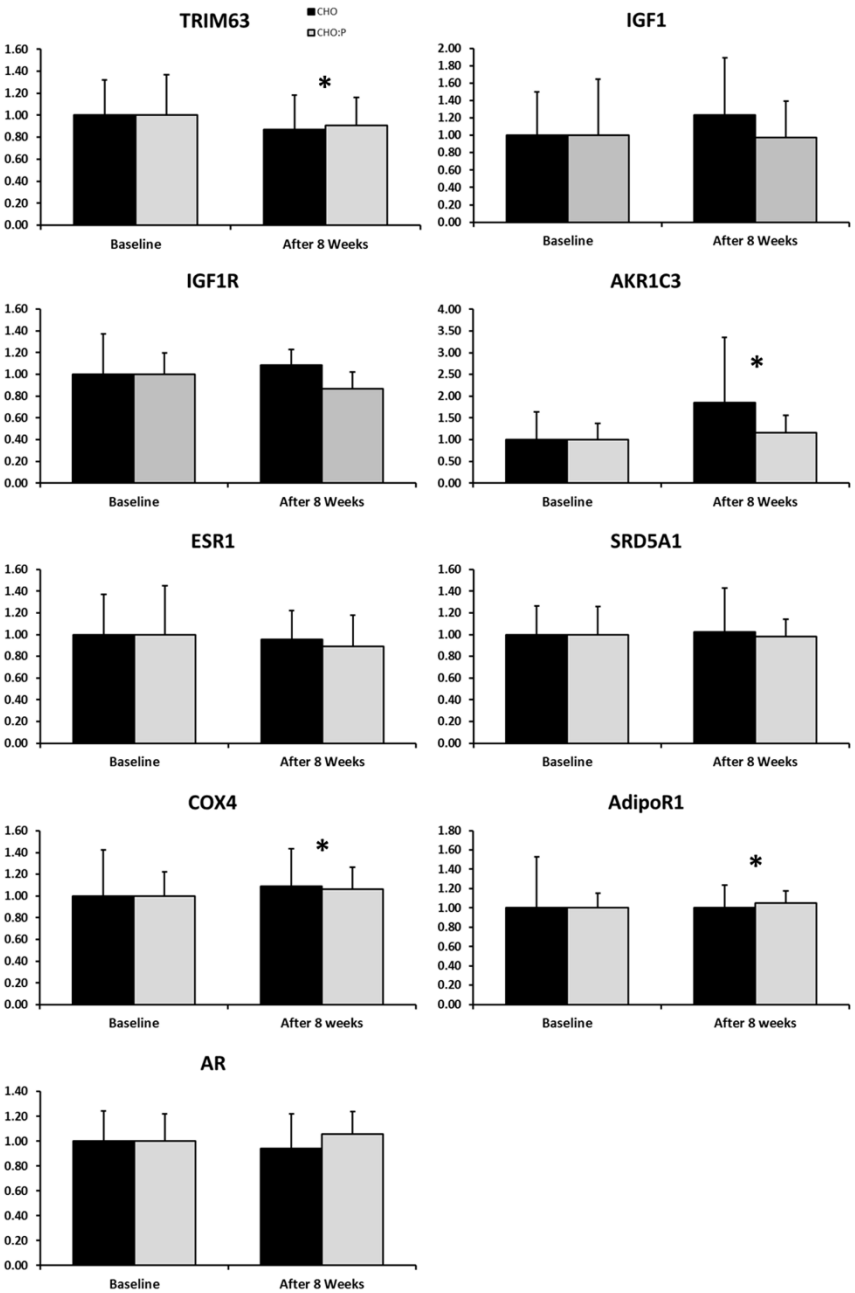
TRIM63
CHO
CHO:P
*
Baseline
After 8 Weeks
IGF1
Baseline
After 8 Weeks
IGF1R
Baseline
After 8 Weeks
AKR1C3
*
Baseline
After 8 Weeks
ESR1
Baseline
After 8 Weeks
SRD5A1
Baseline
After 8 Weeks
COX4
*
Baseline
After 8 weeks
AdipoR1
*
Baseline
After 8 weeks
AR
Baseline
After 8 Weeks

Figure IX. Fold-changes from baseline values in levels of transcripts of selected genes from skeletal muscle biopsies before and after the training program. CHO n=8, CHO:P n=8. There were no significant differences between the groups. *= significantly different from pre-training values for the pooled subjects treating both groups as one population. Adapted in part from Alvehus et al. (2014).

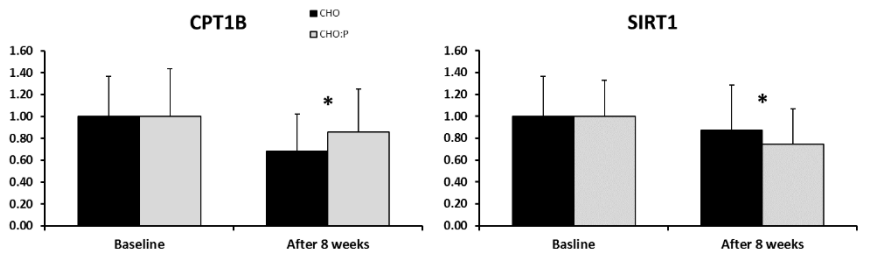

Figure X. Fold-changes from baseline values in levels of transcripts of selected genes from adipose tissue biopsies before and after the training program. CHO n=8, CHO:P n=8. There were no significant differences between the groups. *= significantly different from pre-training values for the pooled subjects treating both groups as one population. Adapted from Alvehus et al. (2014).

Discussion of empirical findings

The two groups in the study consumed a nutritional supplement, consisting of a carbohydrate beverage with or without protein, at quarterly intervals during each exercise session. The difference in intake between the two groups, i.e., the carbohydrates and proteins in the beverages, did not result in any significant differences between the groups in the in the measured response variables. In some cases, changes were significant in the CHO group, while the CHO:P group showed a similar trend that was not statistically significant. This may be interpreted as the CHO beverage increasing the stress on the systems affected, thus leading to greater training results, or the protein content in CHO:P reducing the stress of exercise (Howatson et al., 2012).

The small difference, detailed in Table V, in the composition of the beverages consumed during the exercise sessions may have been insufficient to yield any major differences between the groups. The administration of a post-exercise recovery beverage was intended to control and standardize the subjects' peri-exercise nutritional intake, to hopefully eliminate some effects of differences in the subjects' lifestyle factors. This post-exercise supplementation meant that subjects ingested approximately 20 g of protein after each exercise session. Intake of such an amount of protein post-exercise has been suggested to be sufficient for maximal stimulation of protein synthesis (Phillips, 2014). Although it might have been a successful attempt to control for effects of lifestyle factors, the post-exercise recovery nutrition may have eliminated any differences that could have been accumulated by ingestion of the two different beverages consumed during each exercise session. However, the exercise experiment, in which the post-exercise recovery beverage was omitted, showed there was little or no difference between the groups. These results provide little support for the hypothesis that small differences accumulated over eight weeks may have resulted in significant differences between the groups if the post-exercise recovery beverage had not been used at all.

There may have also been a problem with weak statistical power due to the low number of subjects, and the results may have been due more to the effects of the training performed than the nutritional intake. Therefore, the discussion below focuses on interpreting the results as effects of training rather than nutritional composition.

Gene expression in vastus lateralis muscle tissue samples is not affected by location or timing of the sampling

The preliminary biopsies were intended to determine whether the sampling procedure itself may induce stress that affects subsequent samples, which could have severely compromised attempts to detect effects of

the exercise as a stressor, rather than the method used to obtain tissue samples. The setup was aimed at testing the local and contralateral effects of sampling muscle from the vastus lateralis. The first sample provided baseline values, and an hour later samples from the same and the contralateral leg were obtained. The results showed that expression of genes associated with the selected pathways was only marginally affected by the timing and location of sampling.

In line with previous research, there were significant differences in fiber type composition among samples taken from the same muscle (Henriksson-Larsén et al., 1985). Samples taken from corresponding contra-lateral sites showed less between-sample differences than samples taken from the same leg.

This tells us that each individual has a unique set of conditioning factors, which depend on their genetic factors and history of environmental exposure. It also has further implications for analysis of acquired data and interpretation of results. The statistical tools used should be able to account for within and among individual variations in the measured attributes and responses. They should also be able to handle missing values. Thus, a mixed method model was applied, which met the mentioned criteria (Field, 2013)[98].

Although these findings may provide some validation of the method chosen for obtaining muscle samples, there are some limitations to consider. Notably, the number of genes analyzed was limited, samples were only obtained from one muscle, and the sampling timeframe was short. Further studies exploring effects of these variables in greater detail could help to validate or just as importantly, falsify, results.

The study of physiological training adaptation should consider all exposures during the time period, not just the training

When studying adaptation, one tries to understand the problems that the different levels of biological systems have faced. In the context of this thesis these problems will be sums of all the environmental challenges that the subject has been exposed to during the focal time period, not just the stress intentionally imposed through the training program. The results from any period of training should be evaluated in this light. Perhaps more importantly, one should consider this when planning the training period so that the environment and behavior of the subject can be influenced toward

[98] Chapter 15.

fulfilling the said purpose (Matveyev, 1981)[99]. The subject performing the training must also be aware of this.

First and foremost, the training implemented in the empirical study seems to have led to improvements in characteristics usually targeted by physical training. Subjects' lean body mass and $VO_{2\ peak}$ values increased, and their aerobic energy utilization during sub-maximal work improved. All the subjects' strength, $VO_{2\ peak}$, and body composition tests were conducted during the last week of training, following the study design, but there was enough time in the training program for adaptations to occur. However, there is a risk that the peak potential of the measured parameters in the subjects may have been clouded by accumulated fatigue induced by the training (Bompa & Haff, 2009)[100]. While this is paramount in sports, it was less important in the empirical study reported here. To allow for some recovery, all retesting procedures were performed 48 h after a session of exercise in the study. This hopefully meant that some of the delayed effects of the preceding exercise session, which could have negatively affected performance, would have dissipated and that detraining effects, if any, would still be weak, but there is no way of knowing to what extent this was achieved. However, the primary aim was to study adaptation due to training in this experiment, not to optimize the training program used.

In terms of human behavior, the changes in performance could be explained by the nature of the training performed. A consequence of the training program was that subjects knew that they were expected to increase performance weekly. More than just conditioning the body, the idea of always reaching further and making an extra effort may also have been achieved during progression in the training program, which may have contributed to improvements in performance.

The method of physical training used was that of general preparation using sub-maximal repeated effort (Zatsiorsky & Kraemer, 2006)[101]. As seen in the results, the performance in tests similar to the training practices improved the most. The stepwise incremental cycle time increased, together with effectiveness of oxygen utilization. However, maximum power cycle test results did not improve significantly, possibly because the training did not focus on fast contraction speeds or high rates of force development. Bench press performance also increased, but this was not surprising as the training program involved the subjects performing bench press. The subjects performed no less

[99] PP 55.
[100] Chapter 7.
[101] PP 82-85.

than eight repetitions of bench press per set, which probably had a significant carryover to a three repetition effort in bench press for a novice bench presser. The study protocol did not take the Hawthorne effect[102] into consideration (McCarney et al., 2007), which could account for some changes in performance seen.

Increases in strength and lean body mass after physical training may not result in changed resting testosterone levels

It has been suggested that testosterone is a master key to increasing muscle size and strength in humans (Zatsiorsky & Kraemer, 2006)[103]. This may have led to the hormone hypothesis, that transient elevations in levels of anabolic hormones after exercise are needed to gain strength and muscle mass (Schoenfeld, 2013). However, there is some evidence that this is not the case as plenty of studies have shown that elevations may not occur after exercise although training still results in hypertrophy (Schroeder et al., 2013).

In the empirical study reported here, subjects' lean body masses were increased after the training program although their testosterone levels were significantly depressed after the studied exercise session and resting testosterone levels were unchanged after the training period. However, immediate and delayed effects of exercise on testosterone levels were only measured after one session at the beginning of the program, and there would be a large difference between the stress induced by one session of exercise and an eight-week training program.

The timing of measurements was both a difficulty and weakness in the empirical study. If the body responds to the stress of exercise by increasing resistance to the stress exercise (Nosaka, Sakamoto, Newton, & Sacco, 2001), the exercise at the end of the program may have been provided insufficient stress for any effects to be apparent in the endpoint measurements. Furthermore, the relatively long period of the exercise program of eight weeks, with just two sampling points, only provides low-resolution snapshot indications of how adaptation to training occurs. If more samples had been obtained at more time points during the program, the resolution could have been improved but at the expense of increased costs of resources and pain of the subjects. In addition, excessive removal of tissue could potentially have impaired the subjects' training performance and results.

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[102] The Hawthorne effect is described as the increase in performance stemming from the psychological stimulus as a consequence of being singled out and made to feel important (McCarney et al., 2007). The act of observation causes the changes rather than the intervention.
[103] PP 202.

Testosterone may have very potent anabolic effects, but inducing such effects should not necessarily be considered its function. Schoenfeld (2013) has suggested that testosterone is a metabolic hormone responsible for mobilization of stored energy reserves rather than an instigator of tissue anabolism. This might seem like a minor distinction, but the master key theory suggests that testosterone activity is increased when the body senses that it or some of its tissues need hypertrophy after training. In contrast, theory based on the energy reserve-mobilization function suggests that tissues may respond to stressors by increasing their energy acquisition capacities, and signaling their needs for more nutrients, while higher order regulatory systems prevent excessive use of stored fuel. To this, I suggest an addition from the oxygen handicap hypothesis, presented by Zahavi & Perel (2011), postulating that production of testosterone is a side effect of oxidative metabolism in the mitochondria and that there must be sufficient oxygen pressure in the synthesizing cells in order to produce testosterone. Testosterone may in turn increase mitochondrial efficiency of ATP production (Starkov et al., 1997). This could offer some explanation as to how supraphysiological doses of testosterone can increase muscle mass without training or the connection between testosterone levels and body composition. This suggests that testosterone levels might limit anabolic activity in the muscle. In such cases depressions in testosterone levels would offer a mechanism to limit anabolism when the body is under metabolic stress. The opposite situation, when testosterone is added to the system, may then offer a way to circumvent the limits imposed by "normal" testosterone levels.

Cumulative effects of training may not be apparent from immediate and delayed effects

The changes in mRNA expression observed in the empirical study were similar to those of testosterone levels, in that cumulative effects differed from immediate and delayed effects. For example, expression of AR genes was decreased directly after exercise. Hulmi et al. (2008) found that AR mRNA levels in the muscle of older men receiving protein supplementation increased 48 h after a resistance exercise session, although the effect was not statistically significant 1 hour after exercise. This is consistent with the results of the empirical study reported here, as the group receiving protein supplementation showed a similar tendency for AR expression to increase with time after the exercise session finished. However, the subjects in the study by Hulmi et al. also trained three months longer than the subjects in the present study and performed exercises targeting the sampled muscles 48 h prior to tissue sampling. The findings of Hulmi et al. and other studies using greater training volumes targeting the sampled muscles (Willoughby & Taylor, 2004) suggest that the training program used in the present study may have been insufficient to induce changes in AR expression. The previous training history of

participants has been shown to affect increases in androgen and estrogen receptor content and expression (Kadi et al., 2000; Wiik et al., 2005), further highlighting the importance of conditioning factors for stress responses. It is possible that the amount of stimulus needed for elevating AR mRNA levels is greater than the levels of stimulus provided in the present study (Willoughby & Taylor, 2004). Kadi and colleagues also reported that experienced powerlifters have more muscle nuclei expressing AR than subjects with less training experience. Further, doped individuals engaged in power sports reportedly have even more muscle nuclei expressing AR than non-doped powerlifters. It should be noted that mRNA levels are not necessarily correlated with protein contents, and I am not arguing that they are. The hypothesis that exercise increases muscle's testosterone sensitivity is based on the notion that post-exercise elevations in circulating testosterone are highly important for achieving the desired training effects of increasing muscle size and strength. If the muscles themselves could, as a result of training, become more adapted at responding to the stimulus evoked by training, then the training is likely to be much more efficient. Although the exercise session led to lower levels of testosterone in the subjects in the present study, there was no significant change in levels of AR mRNA indicating that the muscle tissue was inclined to compensate for this change in the environment. In future studies, the recovery time of testosterone levels could be examined to elucidate whether severe fluctuations are needed to evoke responses in the muscle tissue.

Other gene products important for the production of testosterone are AKR1C3 and SRD5A1 (Luu-The & Labrie, 2010). The general trend observed during the exercise session in the present study was toward a reduction in mRNA levels of SRD5A1, while those of AKR1C3 remained relatively stable. Similar results have been reported. For instance, Aizawa et al. (2010) found that levels of 5alfa-reductase[104] mRNA in the skeletal muscle of male rats was unaltered or lower after an exercise session. These rats performed a session of endurance exercise, in contrast to the subjects in the present study. Although there are methodological differences between resistance and endurance training, the results presented here indicate that reduction in SRD5A1 expression could be a common response to stressors associated with "endurance-type training" as the oxygen uptake of the subjects was found to be increased after the training. However, AKR1C3 expression was increased in muscle tissue after eight weeks of resistance training. The expression levels were elevated in both intervention groups, although only significantly in one of the groups. Likely, the observed increase was an effect of the training rather than the nutritional intervention, and the differences in significance were

[104] Encoded by SRD5A1.

probably due to power issues. The differences between observed responses in both SRD5A1 and AKR1C3 mRNA levels at the different time points indicate that the muscle may have been in very different states at the different times. This could indicate a cumulative effect of the training caused by the chemical changes taking place during the training.

Similarly to testosterone, IGF1 has anabolic and anti-catabolic effects (Sandri, 2008), and both its effects and functions are debated. It has been suggested that both the quantity and composition of diets strongly influence serum IGF1 levels (Allen et al., 2002; Miura, Kato, & Noguchi, 1992), especially protein quality, notably amounts of essential amino acids may play important roles. As most serum IGF1 is produced by the liver, this could mean that IGF1 functions as a central sensor of amino acids available for tissue anabolism. Muscular expression of IGF1 could have similar functions, increasing tissues' capacities to absorb amino acids and/or signaling to tissues in the immediate vicinity that amino acids are available for de novo synthesis of proteins.

IGF1 may reduce the expression of TRIM63 (Sacheck et al., 2004). However, levels of circulating IGF1 were unchanged in the present study, but TRIM63 transcript levels still increased directly after exercise. This could have been due to the changes in testosterone levels concurrently observed, as testosterone deprivation may lead to increased TRIM63 expression (Serra et al., 2013). Cortisol levels increased during exercise and remained elevated after the session. However, there was no change in resting cortisol levels following the eight weeks of training, or difference in its levels between the groups. This is in line with the notion that cortisol levels reflect current metabolic demands of the body (Viru, Litvinova, Viru, & Smirnova, 1994), as well as downward causation. This would explain the increased cortisol levels seen in response to exercise and the return to baseline levels at the endpoint measurement. Since the blood samples for endpoint measurements were obtained after at least 48 h rest preceding training session, it would seem that the metabolic demands of the subjects were similar at both measuring times.

The training appeared to induce increases in lean body mass, VO_{2peak} and fat oxidation in the performing subjects. After the training program, their bodies had adapted toward increased fat oxidation during sub-maximal exercise. However, no signs of such adaptation were seen in the adipose tissue. On the other hand, serum adiponectin levels were decreased by about 20%. It has been suggested that adipokines are metabolic hormones for preserving adipose tissue levels in the body and that adiponectin is a starvation signal (Kubota et al., 2007). The results from the present study could imply that the adipose tissue may not experience starvation at the same time as the musculature does. If there is no starvation of the adipose tissue, it probably will not excrete additional adiponectin. On the other hand, if the musculature

becomes adapted toward increased oxidative metabolism, increased AdipoR1 expression may be an adaptive response triggered by the increased energy turnover in the musculature, and accompanying need to absorb as much adiponectin signal as possible. This could explain the discrepancy between the current study and reports of weight loss in obese subjects associated with reductions in adiponectin levels, as the subjects in the present study did not lose weight or fat mass during the training period.

In future research, attention should be paid to the context of the studied systems, i.e., concentrating on both the environment and history of interactions that have shaped them. Investigation of all interactions between the studied systems and their environments could lead to new insights into how cells/tissues/organisms maintain homeostasis under different conditions.

Concluding summary

Iron enough to make a nail,
Lime enough to paint a wall,
Water enough to drown a dog,
Sulfur enough to stop the fleas,
Poison enough to kill a cow,
Potash enough to wash a shirt,
Gold enough to buy a bean,
Silver enough to coat a pin,
Lead enough to ballast a bird,
Phosphor enough to light the town,

Strength enough to build a home,
Time enough to hold a child,
Love enough to break a heart.

- Terry Pratchett

The poem quoted from Terry Pratchett is called “These are the things that make a man” from the book “Wintersmith”[105]. The poem comes into play when the Wintersmith, a mystical-magical deity who is an anthropomorphication of winter, falls in love with Tiffany, a young woman who is a human. The Wintersmith reasons that it must fashion itself a human body in order to be with Tiffany. At the climax of the story when the Wintersmith and Tiffany meet, the Wintersmith explains how it observed children building a snowman while singing the poem and it then used the components to make

[105] ISBN: 9780060890339.

itself a human. But the Wintersmith only used the first ten lines of the poem because it could not find the last three, they had no substance, no meaning for the Wintersmith. Tiffany explains that without the last three lines, a nail is nothing but a nail, it may be what humans are made of but it is not what humans are.

This is very close to what I wish to accomplish with this thesis. Not to make the mistake of the Wintersmith, but improve where it failed. I wish to make a human, a model of a human anyway, a way of thinking about the whole human. I wish to do this because I wish to better explain the world we live in and to make it easier and more effective to plan and perform training.

There is a need to understand how different organizational levels have acquired different properties, and hence these differences may require a different set of conceptual structures (Novikoff, 1945). Although everything in the world may have a common origin, it does not mean that all things must follow the same rules of causality as that original event. Rather, every level of increased complexity will need different or additional sets of explanations. In other words, you can gather the ingredients but the trick is putting them together. All organisms on earth represent an unbroken chain back to the first bio-chemo replicator, all evolved from that into current forms. The crux is that systems are pushed around and selected for their ability to sustain the pushing. It would be a great achievement to build a human from a nail, but somehow I think that the result would fall apart at the slightest nudge. It may look human, but only to someone with a sufficiently bloodless idea about a human.

"In spite of all imperfection I'm a fan of man"

"The stage is set, you pull your own strings now
Like butterfly wings
Once they're touched they never leave the ground
No, I don't make things happen here!"

-Entombed

The perspective described in this thesis is of a world in which all systems have some properties that cause them to be stable and some that allow them to change. This is the world of systems integrated at multiple organizational levels that selfishly seek (*sensu* Dawkins) to solve the problem (*sensu* Popper) of maintaining stability in an environment full of other entities engaged in the same activity.

The difficult part of training or any action/intervention intended to modulate the current state of being is in perceiving its full ramifications. Our choice of perspective affects how we evaluate the consequences of our actions.

With a limited perspective, consequences become easier to perceive, but the concepts relevant to that perspective may not apply at all to other levels, at which the consequences may be far less desirable, or undesirable. The perspective needs to be sufficiently broad and deep to encompass sufficient consequences for the focal purposes. In physical training, this mostly means reconciling the demands for homeostasis of the body and its constituent cells while at a behavioral level striving to maximize performance. Human conscious behavior is to a large extent lived out in Popper's world three, an abstract world of statements. Most of the systems of the human body on the other hand, have no direct contact with world three; they or it knows nothing of plans or schemes. The systems of the body can do but one thing, try to maintain the stability needed for survival. The world of the physical body has boundaries and limits regarding what and how much can be changed. The domains within these boundaries in living matter can be summarized as homeostatic regimes. The plasticity of the body and cells allows them to resist changes to homeostasis, to resist changes in the internal and external environment, to certain degrees. If we are to understand the changes made to the systems of the human body, we must apply concepts that are relevant to the corresponding levels of organization.

This is one of the main points of my thesis, the translation of conceptual structures from several levels into a model that can be used for understanding how adaptation occurs in any given situation. The model is rooted in the view that properties emerge with increased level of organization and that higher order systems may affect lower order systems. All systems and levels of the world are integrated, not separated. In a complex field such as physical training, one must therefore consider the concepts of several levels in order to explain the effects seen. In the field of training, Matveyev (1981) has proposed four categories of preparation to enhance human performance. As we cannot separate the categories from the performing subject, we have to treat the subject as a whole. This can only be done by examining the evolution of life (Dobzhansky, 1973), to understand how the same process we are trying to exploit has given rise to the conditions we are subjected to.

I end my thesis with an appeal to openness. Dawkins suggests in "The Selfish Gene"[106] that we have the possibility to rebel against the tyranny of the genes by using our rationality. I rephrase this as an appeal to rebel against ourselves, against our structures of thinking, to always be on the lookout for our own limitations of perspective, to always be critical of our formulated solutions to problems. We have the possibility of taking perspectives to the extent that we are willing to accept. If you take the

[106] PP 201, 331-332

perspective that you are forced into an existence that you accept as real and deal with that existence in the best possible way while the world mutually accepts you as real and deals with you in every possible way. Put in the context of this thesis, seeking to build muscle, all you need to do is to apply a rational and critical approach to any given method of physical training. This can be summarized as: impose change according to method/strategy→ evaluate effects→ eliminate errors from strategy→ impose changes according to new strategy→ repeat until desire to build muscle is lost. The body will do all that it can to resist the changes imposed on it, via homeostatic mechanisms, as it has been honed by evolution to do. The first difficulty will be in translating your desire to build muscle into something that the muscle can respond to appropriately, some problem for the tissue to overcome, a problem that produces a solution analogous to your desire. The second difficulty will be to understand your desire. Where does the problem come from? Which problems am I solving and creating by trying to build muscle? However, the real difficulty lies in understanding how little that desire means to the muscle.

Materials and methods

Experimental design

The empirical part of the work this thesis is based upon consisted of three experiments, one stand-alone and two linked together. The "method test" was performed separately from the "exercise-training experiment" in the sense that different subjects were included. In the "exercise-training experiment", the subjects were recruited to participate in both parts of the experiment, which consisted of one "exercise experiment" and one "training experiment".

Briefly, the protocol for the exercise-training experiment was as follows. Subjects were recruited and screened for inclusion before they were accepted for the baseline testing procedure. The first session of testing was conducted in the morning after overnight fasting; subjects were instructed to refrain from strenuous exercise for 48 hours and not to use any "snus" for 24 hours before each testing session. The subjects´ body composition was measured before a fasting blood sample was drawn and a maximum oxygen test was performed. After a brief rest, the subjects performed a ten second all-out cycle sprint. Strength assessments were performed in the afternoon on a different day; again, participants were to abstain from strenuous physical activity and testing for 48 hours before the testing. After strength testing, subjects were provided with a familiarization session of the exercise protocol for the exercise session experiment.

Subjects first participated in the exercise experiment. The session began in the early afternoon; subjects were asked to refrain from training and testing for 48 hours before the session, eat a light meal two hours before arriving at the facility and abstain from snus for 24 hours. After giving consent, biopsy areas were anaesthetized and baseline biopsies were obtained. A baseline blood sample for the acute session was also drawn. Subjects then performed the exercise protocol while consuming their allocated nutritional beverage, consuming one quarter of the beverage per completed quarter of exercise volume in the session. There was a brief pause in the exercise session after two thirds of the exercise protocol in order to administer anesthesia for the post-exercise biopsies, a mid-exercise blood sample was also drawn at this point. The exercise session was completed and biopsies were obtained at time points 0 and 45 minutes post-exercise. Blood samples were drawn at time points 0, 15, 30, and 45 minutes post-exercise.

After the exercise session experiment, the training program began. Subjects were asked to adhere to their training program as best as possible and exert great effort in their training. Trainers and research personnel were present during each session to provide technical support and encouragement for the subjects. During the last week of the eight-week

program, subjects repeated the first two testing sessions with the same demands for resting, fasting and snus abstinence.

End-point biopsies marked the end of the experiment and were obtained the week after subjects had completed eight weeks of training. Participants arrived at the facility in the early afternoon. No exercise or testing was performed during the last 48 hours leading up to this session. Subjects were instructed to eat a similarly light meal as for the acute training session.

The method test was performed under similar conditions to those in the exercise session, except no exercise was performed and no beverage was consumed. After giving consent, anesthesia was administered and biopsies were obtained from the vastus lateralis of one leg and abdominal subcutaneous fat of each participating subject. After 60 minutes of rest, biopsies were obtained from the vastus lateralis of both legs and from another part of the abdominal subcutaneous fat of each subject.

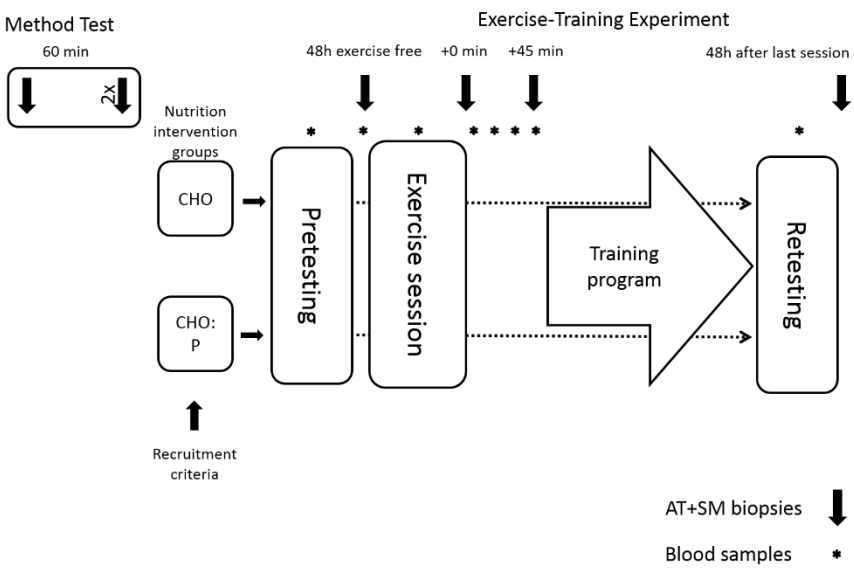

Figure XI. Overview of the experimental protocol for the empirical work, with symbol explanations in the lower right corner, AT+SM: adipose tissue and skeletal muscle. In the upper left corner is a description of the method experiment. In this study, the subjects donated tissue at two time points, 60 minutes apart. There was no other intervention or treatment performed on the subjects, which is why the intervention is circled. The rest of the figure schematically illustrates the process from recruitment of subjects for the exercise and training experiments to the end of the training experiment. At the time of recruitment, i.e., the invitation to participate in pretesting, volunteers were given a designation in the form of a letter from the Swedish alphabet, A for the first who appeared, B for the second, etc. At the same time, subjects were alternately assigned to the CHO:P or CHO nutritional intervention groups. The pretesting consisted of two

sessions of performance and measurements. After pretesting and at least 48 h of rest from the last strenuous activity, subjects performed the exercise session for the exercise experiment. Tissue samples obtained for the exercise experiment were as follows: three tissue biopsies (first three samples from the left in Figure XI) and six blood samples (sample numbers 2-7 from the left in Figure XI). During the exercise experiment, the subjects consumed their assigned beverage. After the exercise experiment followed the training program, where subjects performed training combined with the intake of their respective beverage. During the last week of training, subjects performed the same two sessions of performance and measurements, with the same requirements of rest between exertions as in the pretesting. After 48 h of rest from the last exercise session, the final biopsy was obtained. The first and last tissue and blood samples were used to assess effects of the interventions in the training experiment.

Subjects in exercise and training

Young healthy men, between the ages of 20 and 35, were recruited through advertisements placed in the campus and the training facility located in the campus area of Umeå University. Applicants were to be apparently healthy, free from previous injuries, normotensive, have no history of using hormone-altering medications, and tolerant of lactose, milk protein and local anesthesia. All subjects participating in the exercise and training were to be non-smokers and have some to moderate experience of resistance training. Defined as performing regular recreational resistance training 1-5 times per week for the last year. Subjects were to have some experience in resistance exercise to speed up the learning curve of exercises, but not possess a level of conditioning that could resist the demands imposed by the training program. It was deemed possible to conduct, within the limits of the current project, a training program that would impose desired adaptations onto individuals of all backgrounds, who met the inclusion criteria.

Applicants were first interviewed by phone to screen fulfillment of the inclusion criteria. Applicants were also asked about their motivation for participating in a training program that would most likely be taxing and time consuming. They were also informed about the study protocol and all testing and sampling procedures. Written information about the study and procedures was sent to the applicants. As applicants signed up for baseline testing, they were randomly divided into two groups for the nutritional intervention.

A total of 29 people were recruited for baseline testing, three did not show up for their appointment or declined to participate further after the first testing session. The remaining 26 completed baseline testing.

Subjects in method-test experiment

To evaluate the effects of the method of tissue sampling on the outcomes measured in the exercise-training experiment, a group of control

individuals were recruited to a method-test experiment. Subjects were recruited through advertisements placed in the campus and the training facility located in the campus area of Umeå University. Healthy, physically active male volunteers aged 20-35 years were included. Applicants were excluded if they were smokers, had any recent medical procedures, any current medication or had any known allergies toward local anesthesia. Applicants were informed over the phone and were also given written information. Six men were included in the control study.

Design of training program

In the exercise-session experiment, subjects performed the same six exercises regardless of prior experience. Prior to the session, the participants were familiarized with the exercises and equipment, and were instructed in the proper technique for each exercise. As a part of the technical instructions, the participants were asked to perform each movement at a 2/2 second eccentric/concentric tempo. The load was adjusted so that participants could reach local fatigue but not failure by the last few repetitions of the last set for each exercise. The session began with ten minutes of warm-up on an exercise bike at ≈75W resistance, this warmup was used throughout the training program. The exercises, in the order performed, were lateral pull down, triceps pushdown, twisting crunch, leg press, seated leg curl and seated leg kick. Each exercise during this session was performed for three sets of 12 repetitions with a 2/2 seconds concentric/eccentric tempo, except for the twisting crunch, which was performed for two sets of 12 RM. The participants were assigned 90-120 seconds of rest between sets and as close to 90-120 seconds as possible for transition between exercises and recovery between exercises. Two thirds of the way through the session, there was a brief break in the exercise in order to administer local anesthesia and insert an antecubal vein catheter. The entire exercise session was supervised by research personnel.

The eight-week training program was designed in the same fashion as the exercise experiment, using the same tempo and rest intervals. All design choices in the process of formulating the training program were targeted toward producing a program that would result in increases in lean body mass after eight weeks of training (Ratamess et al., 2009; Wernbom et al., 2007). Repetitions and number of sets were varied in a systematic manner throughout the training program to provide the participants with a varied exercise stimulus for the muscles and to alleviate monotony. The systematic variation followed an undulating model of periodization of eight cycles, where odd numbered cycles were designated for higher numbers of repetitions, fewer sets and less emphasis on maximal exertion. The even numbered cycles consisted of slightly fewer repetitions, more sets and high focus on more load and effort. The even numbered weeks also involved performing exercises to concentric failure, achieved by increases in load from previous weeks.

Each individual was subjected to a training program of two, three or four sessions per week, according to his level of experience, previous training frequency and level of ambition. One of the main principles of the training program was that each muscle group was to be stimulated twice a week; so programs with fewer sessions had to include more exercises per session. Also, recommendations state that relatively inexperienced resistance training practitioners should use less training intensity than more experienced users. Thus, the program was suitable for the slightly less experienced by including more repetitions per set in order to achieve the desired effort at a lesser intensity (Ratamess et al., 2009).

Each session started with ten minutes warm-up. During the exercise experiment, all subjects used the same equipment, whereas during the eight-week training program there were possibilities to perform exercises with different equipment. For example, at the time of the experiment, the training facility had five different machines for leg press. Subjects were free to use any of the equipment available or preferred by them. Subjects were also allowed to change the order of exercises within a session if the equipment needed was occupied. All training was performed in the gym at the Sport Medicine unit at Umeå University or the adjacent training facility, IKSU Sport Center.

Diet and nutritional supplements

Subjects were screened for diets in the recruitment process to exclude applicants adhering to a conceptual diet, such as a low-carb high-fat diet, the zone, etc. None of the applicants or subjects reported adhering to a diet. All subjects were also instructed to refrain from any self-administered dietary supplementation and maintain their regular diet during the study period.

Subjects recorded their dietary intake for four consecutive days before starting their training and once during the training period. Furthermore, the subjects were instructed in how to keep records and were equipped with a kitchen scale, protocol for registration and a document explaining how to keep records and how to use the scale. Diet composition was analyzed using the Dietist XP program[107].

The nutritional intervention in this experiment involved the ingestion of protein in combination with carbohydrates during exercise. The CHO:P group consumed a beverage containing carbohydrates and protein, whereas the CHO group consumed a beverage containing carbohydrates alone. The beverages were isoenergetic and both were flavored with citric acid and

[107] Kost och Näringsdata, Bromma, Sweden.

delivered in red or blue containers. All subjects consumed a body-weight equated amount, 8.5 g of beverage per kg body weight, of their allocated beverage during each exercise session. Participants were given their beverage in their own semi-transparent bottles. Each bottle was marked in quarters according to the subject´s specific volume, to facilitate consumption of one quarter of beverage per completed quarter of the training session. Subjects were allowed water *ad libitum* during training and recovery.

After each training session, subjects were asked to remain at the unit of Sports Medicine's facility for 25 minutes. When the 25 minutes had passed, subjects were given an amount of a commercially available recovery beverage equivalent to 0.5 g of carbohydrates and 0.24 g of protein per kg body weight. The content of the post-exercise recovery beverage is specified in Table V.

Other guidelines

Subjects were instructed to maintain their general lifestyle but to refrain from any strenuous endurance training or other resistance training activity. In addition, subjects were instructed to maintain their diet, diurnal rhythm and be consistent in their training.

Body composition analysis

The first part of the baseline testing was performed after an overnight fast. Subjects were instructed not to eat after 7 pm on the day before the test. Body composition was analyzed using dual energy X-ray absorptiometry[108]. After the body-composition analysis, subjects consumed a volume of the beverage used for post-exercise recovery, equivalent to 1 g of carbohydrates per kg body weight, and rested for one hour to prepare for the ergometer cycle test.

Measurements of performance

After the rest period, an ergometer cycle[109] test was performed. The test started at 80 W with an increment of 40 W every third minute until exhaustion. $VO_{2\ peak}$, calculated as the highest average of one minute during the test was determined and gas exchange was measured using indirect calorimetry[110] and the fat oxidation rate was calculated according to $1.695*VO_2 - 1.701*VCO_2$ (Smith et al., 2011). After a brief rest, peak cycle power

[108] DXA: Lunar iDXA, GE Healthcare, Waukesha WI, US.

[109] Monark 839E, Monark Exercise AB, Vansbro, Sweden.

[110] Jaeger Oxycon Pro system, Intramedic AB, Bålsta, Sweden.

was assessed by a 10 seconds all-out sprint on an Ergomedic 894E Peak Bike[111] at a constant workload of 7.5% of the subject's body weight.

Strength was assessed on a different day, in the afternoon, after ten minutes of warm-up. For the first test, subjects performed squat jumps and countermovement jumps, with three repetitions of each jump, under supervision of a technician and the jump height was recorded using a MuscleLab 4020e with a contact mat[112]. For each type of jump, the mean of the three attempts was calculated.

After the jumps, participants performed a 3RM bench press test. The test was defined as the maximum weight participants could bench press three times without a pause, through a full range of motion and using an estimated 2/2 seconds eccentric/concentric tempo. Subjects were allowed a short warm-up with an unloaded barbell to prepare for the test. The load was progressively increased by the participant under the guidance of technicians until an estimated 3RM was reached. Subjects were allowed two attempts at performing the lifts at the estimated load or to change load after a failed or successful first attempt. Rest between warm-up sets and attempts were unrestricted; research personnel advised the participants so that rest intervals did not become too short and gave verbal encouragements during the attempts.

Tissue biopsies

Prior to the first biopsy, subjects were again informed about the study and the procedure. The consent document was signed by subjects after this information session.

Subjects assumed a supine position on the procedure table while a surgeon identified the vastus lateralis muscles on both legs and marked the sites intended for sampling. Areas for subcutaneous adipose tissue biopsies in the periumbilical region were also marked in the same fashion. Each area was cleaned and shaved before local anesthetic, Carbocain + adrenaline[113], was injected under the skin and down toward the muscle fascia. Muscle tissue samples were obtained using a conchotome, after making a small incision through the skin and muscle fascia with a surgical scalpel. The surgeon inserted the conchotome into the incision, closed the mouth of the instrument and rotated the instrument 180 degrees before subtracting the tissue sample. Adipose tissue biopsies were obtained by needle aspiration. The surgeon

[111] Monark Exercise AB, Vansbro, Sweden.

[112] Ergotest Innovation, Porsgrunn, Norway.

[113] 5 mg/ml + 5mkg; AstraZeneca.

inserted the needle through the anesthetized area into tissue unaffected by the drugs, from which the samples were obtained. All samples, fat and muscle tissue, were dissected free of any visible connective tissue and blood was washed away with saline before samples were frozen in liquid nitrogen prior to storage at -80° C.

Sample designations in the exercise and training experiments

Tissue was collected to study the immediate, delayed and cumulative effects of exercise and training. Samples were labelled according to the code for each subject and the time point in the experiment at which they were obtained, as follows.

Pre: the first biopsy serving as a baseline for the exercise session and training experiment. Muscle and adipose tissue samples for biochemical analyses were obtained.

Post- and 45 minutes post-exercise: the second and third biopsies for the exercise experiment, obtained directly after the first exercise session and approximately 45 minutes later, respectively. Muscle tissue samples for biochemical analyses were obtained.

Post-training: the last biopsy, serving as the endpoint for the training experiment. Muscle and adipose tissue samples for biochemical analyses were obtained.

Sample designations in the method test experiment

Tissue samples collected during the method test were used to study effects induced by the spatial and temporal differences in tissue sampling. Samples were named according to the code representing the subject and the order in which they were obtained, as follows.

1: First biopsy. Muscle tissue samples for IHC[114] and biochemical analyses were obtained.

2: Biopsy taken approximately 1 hour after the first biopsy from the same leg as the first biopsy. Muscle tissue samples for IHC and biochemical analyses were obtained.

3: Biopsy taken approximately 1 hour after the first biopsy from the opposite leg as the first biopsy. Muscle tissue samples for IHC and biochemical analyses were obtained.

[114] Immunohistochemistry.

Fiber type classification and morphometric analysis

The muscle tissue samples for IHC were oriented according to the direction of the fibers and embedded in an OCT compound[115] on a thin piece of cardboard, then rapidly placed in liquid propane chilled with liquid N_2 and stored at -80°C.

Using a Leica CM 3050 cryostat microtome[116], transverse muscle cross-sections, 7-8 µm thick, were serially cut at -23°C. The sections were placed on gelatin-coated glass slides and kept at -23°C. The samples were fixed with 2% PFA[117] for 6 minutes before rinsing for 3 x 5 minutes with 0.05% Tween in 0.01 M PBS[118] at room temperature. After the rinsing step, sections were incubated in normal serum for 15 minutes, before addition of the first primary antibody; samples were then left for overnight incubation at 4°C. The following day, the rinse step was repeated and sections were again incubated in normal serum for 15 minutes, before the first secondary antibody was added and incubated for 30 minutes at 37°C.

The analysis required sections to be dual-stained, necessitating repetition of all steps performed after fixing the sections, except that incubation with the second primary antibody was for 60 minutes at 37°C, instead of overnight at 4°C. After rinsing with the second secondary antibody, the sections were mounted using Vectashield mounting medium[119]. Nuclear DNA was stained using Vectashield containing DAPI[120].

The fiber content of contractile MyHC isoforms was assessed by IHC staining using mAbs[121] A4.74[122], N2.261[123], and A4.840[124]. Muscle fiber borders were identified by staining laminin α2-chain using mAb NCL-merosin[125]. All other antibodies were obtained from the Developmental Studies Hybridoma

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[115] Tissue Tek®, Miles laboratories, Naperville, IL, USA.

[116] Leica, Nussloch, GER.

[117] Paraformaldehyde.

[118] Phosphate buffered saline together with Tween (PBST).

[119] Vector Laboratories Inc, Burlin-game CA, US.

[120] 4', 6-diamidino-2-phenylindole.

[121] Monoclonal antibodies.

[122] Strong affinity for MyHCIIa.

[123] Strong affinity for MyHCIIa, weak affinity for MyHCI, no affinity for MyHCIIx.

[124] Strong affinity for MyHCI.

[125] Nova Castra Lab, Newcastle, UK.

Bank[126]. The secondary antibodies used were Alexa Fluor 594 Goat Anti-Mouse IgG1 and Alexa Fluor 488 Goat Anti-Mouse IgM[127].

To estimate fiber size and classify fiber types, areas of each muscle cross-section stained for laminin α2-chain and the different MyHC isoforms were arbitrarily chosen and scanned by a light microscope[128] equipped with a color CCD camera[129] and digital high-speed fluorescence CCD camera[130]. Morphometric analyses were performed using image analysis software[131] to estimate the fiber area by tracing the outline of each fiber basement membrane using the image of sections stained for laminin α2-chain. The staining pattern obtained by staining the MyHC isoforms using different mAbs was used to classify fiber types in the analyzed images. Briefly, fibers were classified as containing slow MyHCI, fast MyHCIIa or fast MyHCIIx or hybrid fibers co-expressing MyHCI+MyHCIIa or MyHCIIa+MyHCIIx. To ensure robustness in the analysis of muscle fiber composition, 50 or more fibers were analyzed (McCall, Byrnes, Dickinson, & Fleck, 1998). All subjects in the current work were individually analyzed, with an average of 164 fibers[132] from each biopsy.

Gene expression and RNA extraction

Total RNA from muscle and adipose tissue biopsies was extracted using a RNeasy lipid tissue mini kit[133] according to the instructions supplied by the manufacturer. The yield and purity of RNA samples was determined using a spectrophotometer[134]. The integrity of RNA was assessed by 1% agarose gel electrophoresis with GelRed nucleic acid gel stain[135] following by inspection of the gels under UV light. cDNA was synthesized by reverse transcription of RNA samples using TaqMan reverse transcription reagents[136]. Muscle RNA samples were reverse-transcribed with the addition of 0.2 U/ml RNase inhibitor[137]. Relative mRNA levels of target genes were measured in triplicate using an ABI Prism 7000 sequence detection system and Taqman

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[126] Developed under the auspices of the NICHD and maintained by the University of Iowa, Iowa, USA.

[127] A21125 and A21042, Molecular Probes, Life Technologies.

[128] Leica DM6000B, Leica Microsystems CMS GmbH, Wetzlar, GER.

[129] Leica DFC490.

[130] Leica DFC360 FX.

[131] Leica, QWin plus.

[132] Range 129-219.

[133] QIAGEN, Hilden, Germany.

[134] ND-1000, NanoDrop Technologies, Wilmington DE, USA.

[135] Biotium, Hayward, US.

[136] High Capacity cDNA Reverse Transcription kit, Applied Biosystems, Foster City, CA, USA.

[137] Applied Biosystem.

universal PCR master mix[138] , then calculated using the ΔΔCt method (Schmittgen & Livak, 2008). Reference genes were evaluated by analyzing coefficients of variation. For muscle tissue, the genes B2M[139], ACTB[140] and GAPD[141] were the selected candidates (Mahoney et al., 2004), while for adipose tissue the genes ACTB, GAPD and RPLP0[142] were the selected candidates. Using the NormFinder algorithm (Andersen, Jensen, & Ørntoft, 2004), the most stable reference gene for normalization was identified. For muscle tissue, a combination of ACTB and B2M appeared to be the most stable choice for normalization. For adipose tissue, RPLP0 proved the most stable. Reference genes were evaluated by running candidate genes on the full study cohort and using the NormFinder algorithm (Andersen et al., 2004).

For each gene expression analysis, a TaqMan gene expression assay[143] was used. To control for DNA contamination, two controls were used for each assay: one where the cDNA was substituted for nuclease-free water and one without reverse transcriptase.

Collection and analysis of blood samples

Blood samples were obtained from an antecubal vein. For each blood sample drawn from the catheter, the first few ml of blood were discarded to rid the sample of stale blood. Samples were centrifuged and the resulting plasma or serum was aliquoted and stored at -80°C until analysis. All plasma and serum samples, except for adiponectin, were analyzed at the Department of Clinical Chemistry[144], University Hospital of Uppsala, using an automated immunoassay system[145] with Cobas Elecsys reagent kits. Circulating adiponectin levels were analyzed using a radioimmunoassay according to the manufacturer's instructions at the Department of Public Health and Clinical Medicine of Umeå University[146].

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[138] Both from Applied Biosystem.

[139] β 2- microglobulin,part number 4333766F, Applied Biosystems.

[140] Human β –actin, part number 4352935E, Applied Biosystems.

[141] Human glyceraldehyde-3-phosphate dehydrogenase, part number 4352934E, Applied Biosystems.

[142] Large Ribosomal Protein, Hs99999902_m1, Applied Biosystems

[143] AKR1C3 (Hs00366267_m1), ESR1 (Hs00174860_m1), SRD5A1 (Hs00971643_g1), AR (Hs00171172_m1), TRIM63 (Hs00261590_m1), IGF1 (Hs01547656_m1), IGF1R (Hs00609566_m1), PKFM (Hs00175997_m1), CKM (Hs00176490_m1), HSD17B10 (Hs00189576_m1), MYH1 (Hs00428600_m1), MYH2 (Hs00430042_m1), and MYH7 (Hs01110632_m1), Adiponectin (Hs00605917_m1), adipoR1 (Hs01114951_m1), PGC1-α (Hs01016719_m1), COX4I1 (Hs00971639_m1), Tfam (mitochondrial transcription factor A), (Hs00273372_s1), Sirt-1 (Hs01009005_m1), CPT1b (Hs03046298_s1), fndc5 (Hs00401006_m1). All from Applied Biosystems.

[144] ISO 15189 certified

[145] Cobas 8000, e602, Roche Diagnostics, Mannheim, Germany.

[146] Electra-box Diagnostica AB, Tyresö, Sweden.

Statistics

All univariate statistical analyses were performed using the SPSS software package[147]. For all performed tests, results were considered to be statistically significant if $P < 0.05$. All data are presented as arithmetical means with standard deviations, unless otherwise specified. All units used were SI, except units for gene expression, which were arbitrary.

Subject characteristics and gene expression data before and after resistance exercise were compared using the Wilcoxon signed rank test, RM-ANOVA and ANOVA. Two-way ANOVA and RM-ANOVA were used to determine possible interactions between the beverages and training program[148]. To account for multiple testing, Bonferroni correction was applied in all such procedures. In the RM-ANOVA analysis, Maulchy's test of sphericity was used to test the sphericity of the data. The Greenhouse-Geisser adjustment of degrees of freedom was applied to any test with a significant violation of sphericity.

For multivariate analyses, OPLS and OPLS-DA were used to explore relations between the input data *X*, gene expression data in this case, and the treatment or class used in the experiment, *Y*. The model seeks the latent vector/vectors in the multidimensional space *X* that maximize/maximizes the co-variation with *Y* by projection onto a lower dimensional line, plane or hyperplane for graphical interpretation. This method enables identification of the regression or discriminant line, plane or hyperplane in which the observations are best correlated to one or many continuous responses or separated by class. This interpretation of latent structures by OPLS can be improved by the separation of variation correlated and uncorrelated to *Y* in the data as the uncorrelated variation will be orthogonal to the projected predictive variation, thus reducing systematic noise. In fitting the model, a number of latent variables are assumed as components containing the underlying

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[147] SPSS Inc 20.0 and 22.0, Chicago, IL, USA.

[148] Different statistical tests were used for different purposes depending on the data analyzed. ANOVA and two-way ANOVA were mostly used for exploratory purposes, whereas Wilcoxon tests and RM-ANOVA were used to obtain "the results" of the study. Both Wilcoxon tests and RM-ANOVA can deal with measurements from the same subject at different time points (Field, 2013), Chapters 6, 14-15. In the study reported in *Metabolic adaptations in skeletal muscle, adipose tissue, and whole-body oxidative capacity in response to resistance training*, effects of the beverages were unnoticeable and therefore not used as variables in the analysis. Therefore, Wilcoxon tests were used when data were analyzed as before and after training. In the study reported in *Effects of protein ingestion on the hormonal response to resistance exercise and increases in lean body mass after eight weeks of training*, there was an attempt to explore some differences between groups seen after the training period. Therefore, RM-ANOVA was used when the variables training and nutrition were used in the analysis. Upon verification of the results in this thesis, it would seem that both methods, the Wilcoxon signed rank test and RM-ANOVA, yielded similar results.

structures of variable correlation. The sample distribution of *X* in relation to *Y* can be viewed and interpreted in the model scores, t_i. Models are evaluated by their ability to reproduce variation in *X* and *Y* and ability to predict variation in *Y*. The fit, ranging from 0-1, of the model is expressed as R2 for both X and Y, whereas the estimated goodness of prediction is expressed as Q2, also ranging from 0-1, for Y alone. In the work this thesis is based upon, all multivariate analyses were performed using SIMCA-P software[149].

Nutritional supplements

Table V. Composition of beverages allocated to the CHO:P and CHO groups, and the post-exercise recovery beverage.

per 100g		CHO:P	CHO	Gainomax Recovery
Energy	kJ	130	130	400
	kcal	30	30	95
Fat	g	0	0	0.5
Carbohydrates	g	5.9	7.9	15
Protein	g	2.0	0	7.3

Ethics

All procedures and protocols in this study were approved by the Regional Ethics Committee[150]. All subjects signed informed consent documents before participating.

[149] Version 12. Umetrics AB, Umeå, Sweden.

[150] DNR:2010-71-31.

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Appended papers

A

B

c

The game of science is, in principle, without end. He who decides one day that scientific statements do not call for any further test, and that they can be regarded as finally verified, retires from the game.

- Karl Popper