A REVIEW OF MAXIMIZING MUSCLE BUILDING CAPABILITIES WITH ANABOLIC ENZYMES

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Abstract

Building muscle at a rate faster than the human body would under normal circumstances is of great importance in skills and activities that require intense muscular effort. Although physical training stands as the backbone of muscle building, physiological variations make it an unfair yardstick in measuring individual efforts. Other methods of muscle building such as specialised nutrition and the use of digestive enzymes in breaking down proteins for quick absorption are also commonly used together with physical training. The use of anabolic substances, however, has proved more successful than any of the aforementioned methods. Nevertheless, with it comes ethical, legal, and clinical issues especially in sports. In spite of this, athletes still find ways of circumventing test protocols which have been a major issue for the World Anti-Doping Agency. However, advancements in science have opened the doorway for anabolic enzymes which are the ultimate muscle growers to be more or less, directly manipulated. One method is gene doping which involves altering gene expressions. The future of muscle building lies in man's ability to decisively alter the functioning of these enzymes directly.

Keywords: Muscle building, anabolic enzymes, mTOR, myostatin

Background

The race for fitness in modern times has with it the backing of advancements in technology and science aimed at maximising the gains that can be made from muscle building exercises. The desire to be 'ripped' in a relatively short time has become a common obsession amongst athletes today. Although the practice of building body physique dates back to ancient times, specialised routines, diets, and chemical formulas effective in producing targeted physiological responses on the body have been developed in more recent times and have been very successful. Nowadays, one can increase not only strength but also determine his or her body composition. Using any of several

fitness techniques currently available, the focus can be put on just muscular hypertrophy without paying attention to strength gain and vice versa; or on carving body contours by exercising select muscle sets; or on simply building up core strength and balance without paying attention to physique or muscle size.

Due to the uniqueness of individual physiology, it is essential to consider one's physiological state in muscle building choices made as no single workout or factor holds the same degree of effect on the entire human race. Several strategies have been employed in achieving these muscle building goals. Physical training which simply involves the use of resistance against the muscles is the most common and widely practised system for muscle building with several therapeutic applications (Darren, Warburton, Nicol, & Bredin, 2006). It is usually backed up with diet restrictions used either independently as in during weight loss or as a follow up on physical training. In addition, the ingestion of digestive enzymes has also been found to quicken the development of muscle tissue through the accelerated breakdown of proteins (Shannon, 2009). Steroids and other hormonal substances which have a more direct impact on the muscle tissue formation are commonly used for muscle building and has also been a major concern in the field of sports (World Anti-Doping Agency, 2016). Research is still ongoing to find better ways of building muscle, and the susceptibility of athletes to physical enhancement techniques puts them at a vulnerable position in the testing of new products and techniques (Momaya, Fawal, & Estes, 2008).

An area that is yet to be conquered in terms of muscle building is through the direct manipulation of the intracellular enzymes that play key roles in the chemical reactions that lead to muscle building. Anabolic steroids and other anabolic hormones may affect nuclear and other intracellular processes that lead to protein synthesis but do not directly influence the functioning of the anabolic enzymes that build up these polypeptides (Kicman, 2008). This study seeks to draw attention to the enormous potentials that are locked up in the physiology and chemistry of these enzymes. If all other muscle building variables that are currently used are kept at maximum efficiency, by altering the anabolic capabilities of these enzymes, there is no telling the magnitude of impact that such can have on muscle building. This can pave the way for a new era in the world of muscle building.

The Science of Muscle Building

Muscle building is a basic requirement for growth. Average day to day activities are usually sufficient in maintaining one's musculature. However, with the demands of sports, technical work and other energy-driven activities, it has become necessary to accelerate the muscle building process beyond what normal activities can accomplish. Thus, machines, pedagogies, drugs, and formulae have been created to accelerate muscle building. The different levels of muscle building techniques can be better understood from the diagram below.

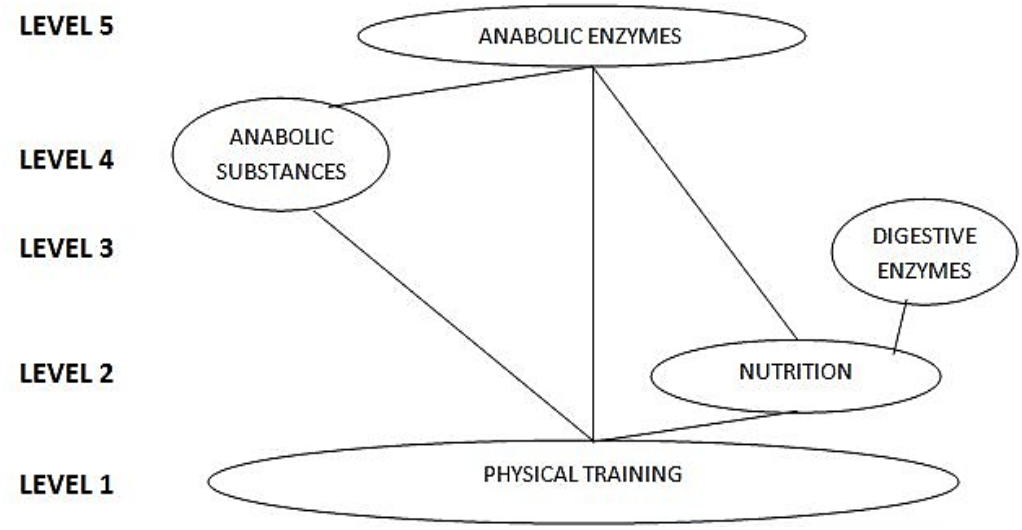

Figure 1: 5-Tier representation of muscle building systems. The lines connect the systems that can influence each other.

The figure above can be viewed as a nominal ranking of the stage at which each technique lies in the muscle building mechanism or pathway. It is important to note that these levels may also depend on one another. For example, abundance of amino acids (level 3) in the body without physical exertion (level 1) will not amount to net increase in muscle mass (Shannon, 2009).

Level	Technique/Method	Impact	Principle	Application
1	Physical Training	Skeletal & Cardiac Musculature	Load Resistance, Stretch	Calisthenics, Yoga, Weightlifting
2	Nutrition	Body Composition	Availability of Nutrients	Dieting, Protein/ Carbohydrate Loading
3	Digestive Enzymes	Nutrient Absorption	Accelerated Nutrient Hydrolysis	Oral Ingestion
4	Anabolic Substances	Intracellular Operations	Accelerated Protein Synthesis Reactions	Oral & Intravenous Administration
5	Anabolic Enzymes	Protein Synthesis	Direct Regulation of Protein Synthesis & Muscle Formation	IGF & Leucine Therapies, Gene Doping

Table 1: Analysis of 5-Tier representation of muscle building systems

Physical Training

Based on the training principle of frequency, intensity, type, and time commonly known as FITT, several activities have been developed that load the skeletal muscles beyond their average capacity. By creating sustained tension in the muscles beyond its optimum

ability, the contractile components experience wear and tear which causes them to partially breakdown. Their breakdown leads to stimulation of signalling pathways which cause more protein to be manufactured and incorporated into the sarcomere units (Phillips, 2014). The net increase in muscle volume is referred to as muscular hypertrophy. Hyperplasia, which involves the addition of extra muscle fibres (cells) to the tissues, has also been suspected to occur during some forms of physical training (Antonio & Gonyea, 1993). However, muscle growth only occurs whenever the rate of muscle protein synthesis is greater than the rate of muscle protein breakdown (Rasmussen & Phillips, 2003).

Nutrition

In recent times, it has been discovered that the timing between training routines and nutritional intake is critical in gaining maximal results in muscle building (Ivy & Portman, 2004). This understanding is widely utilised in endurance training circles where activities last for long hours (Millard-Stafford, Childers, Conger, Kampfer, & Rahnert, 2008). Such long lasting activities have been shown to cause significant breakdown of proteins if left unmitigated which means that working out at maximum intensity, frequency or duration does not necessarily yield maximum results (Smith, 2016). Also, the quality of foods taken remains an important factor in muscle building as it has been shown that different foods of the same nutrient class can have different effects on protein synthesis (Tang, Phillips, 2012).

Digestive enzymes

Digestion of protein is one of the slowest in the gut especially given the fact that it does not begin until it gets to the stomach (Dubois, 2016). Therefore, it takes quite a while for amino acid stores in the body to be replenished. In order to quicken these catabolic reactions, digestive enzymes are orally taken to supplement the naturally secreted proteases in the gut thus increasing the rate of hydrolysis (Shannon, 2009). This proves effective because the steep chemical differential gradient caused by more amino acids in the blood lead to more uptake of amino acids into the cells thus accelerating the rate of intracellular protein formation. Note that the anabolic process of protein building mostly occurs during rest and not during the training itself (Kwon & Kravitz, 2016).

Anabolic substances

Doping legalities are very common in the sporting world (World Anti-Doping Agency, 2016). When these performance enhancement substances are used in competitions, results become biased because the actual capability of the athlete is not expressed. Nevertheless, they are still used legally especially under the premises of health challenges. Growth hormone, insulin, steroids such as testosterone including synthetic steroids like Oxymetholone (Anadrol) and other testosterone derivatives are among the common anabolic substances used for performance enhancement. They stimulate muscle building by binding to receptors which trigger signals that increase protein synthesis and decrease protein degradation (Fahey, 1998). Thus, they tend to yield greater results in building muscle mass. However, the downside to their use is due to their effects on other

organs of the body like the heart, liver, and brain which leads to pathological responses like liver injury (Supasyndh, Satirapoj, Aramwit, Viroonudomphol, Chaiprasert, Thanachatwej, & Kopple, 2012) especially when taken beyond recommended doses. The practice of taking steroids is usually discouraged by many sports and health bodies because of the social, physical, and health issues it brings along.

Protein Synthesis Mechanisms

The two major signalling pathways that control protein synthesis and degradation are the IGF1–Akt–mTOR pathway which acts as an up-regulator, and the myostatin–Smad2/3 pathway, which down regulates protein synthesis (Schiaffino, Dyar, Ciciliot, Blaauw, & Sandri, 2013). Despite extensive studies that have been conducted to understand how these pathways function and the roles the component molecules play, a lot of ground still needs to be covered as much of these pathways remain undeciphered.

IGF1–Akt–mTOR Pathway

Found in almost all cells of the body, the IGF1–Akt–mTOR pathway begins from processes originating at the inner surface of the plasma membrane of the cell, from the binding of IGF1 (Insulin-like growth factor 1) to its receptor, to inhibition of protein degradation by Akt (protein kinase B, PKB) and its stimulation of protein synthesis through the mechanistic (or mammalian) target of rapamycin (mTOR) and glycogen synthase kinase 3β (GSK3β). Akt indirectly activates mTOR signalling by inhibiting a certain chain of reactions that will not be dealt with in this paper (Schiaffino & Mammucari, 2011).

mTOR is a protein encoded by the mTOR gene. mTOR integrates both intracellular and extracellular signals and serves as a central regulator of cell metabolism, growth, proliferation and survival (Laplante & Sabatini, 2009). It also directly controls protein synthesis (Hay & Sonenberg, 2004). It is the catalytic subunit of the mTOR complex 1 (mTORC1), a complex consisting of mTOR itself, regulatory-associated protein of mTOR (Raptor), mammalian lethal with Sec13 protein 8 (mLST8, also known as GβL), proline-rich AKT substrate 40 kDa (PRAS40), and DEP-domain-containing mTOR-interacting protein (Deptor) which together control protein synthesis (Peterson, Laplante, Thoreen, Sancak, Kang, Kuehl, & Sabatini, 2009).

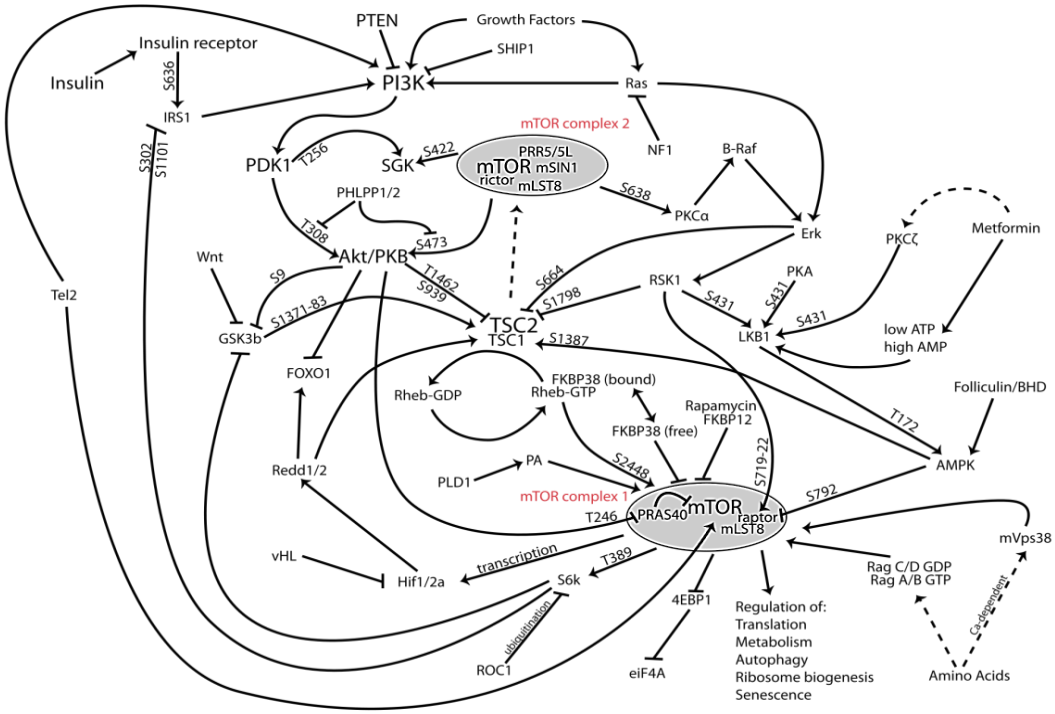

Figure 2: mTORC1 pathway. Source: Wikipedia

The mTORC1 is a vastly researched bio-complex due to its far reaching effects on other body processes (Johnson, Rabinovitch, & Kaeberlein, 2013). Basically, mTORC1 functions in activating the translation of proteins from mRNA and its activities are regulated by rapamycin, insulin, growth factors, phosphatidic acid, certain amino acids, mechanical stimuli and oxidative stress which do so through different couplings and pathways (Bond, 2016). Being a nutrient/energy/redox sensor, it is only activated by the abundant presence of nutrients (especially amino acids), oxygen, ATP, and certain growth factors (Wullschleger, Loewith, & Hall, 2006).

When all the requirements for the activation of mTORC1 are met, it accelerates several reactions in the translational process of mRNA to protein. mRNA is generated from the transcription of DNA through other mechanisms (Campbell, Reece, Urry, Cain, Wasserman, Minorsky, & Jackson, 2005). Protein synthesis occurs in three stages: initiation (of the polypeptide chain), elongation (through the addition of more amino acids) and termination. So far, it is known that mTORC1 controls several processes in the initiation and elongation stages of protein synthesis including the binding of mRNA to ribosomes (Wang & Proud, 2006). Increased translation of mRNA is mediated by increased number of ribosomes involved. This is because the translation occurs in the ribosomes where amino acids brought by tRNA are coupled with the aid of some components of the ribosome. The RNAs attached to ribosomes function as enzymes which make the RNA-ribosome complex to be referred to as ribozyme (Campbell et al., 2005). Thus, ribozyme is the key anabolic enzyme that synthesises proteins. Wang and

Proud (2006) also maintained that the biogenesis of ribosomes is conducted by mTORC1 which causes translation of the mRNA coding for the ribosomes.

Note that protein synthesis regulation is necessary to prevent the development of anomalies like gigantism and cancers. The activities of steroids and other hormones influence the processes leading up to protein syntheses such as activation of transcription and several pathways. However, the activity of ribosomes is directly affected by mTORC1. mTOR itself is actually an enzyme belonging to the phosphatidylinositol 3-kinase-related protein family and functions as a serine/threonine protein kinase (Mitra et. al, 2015).

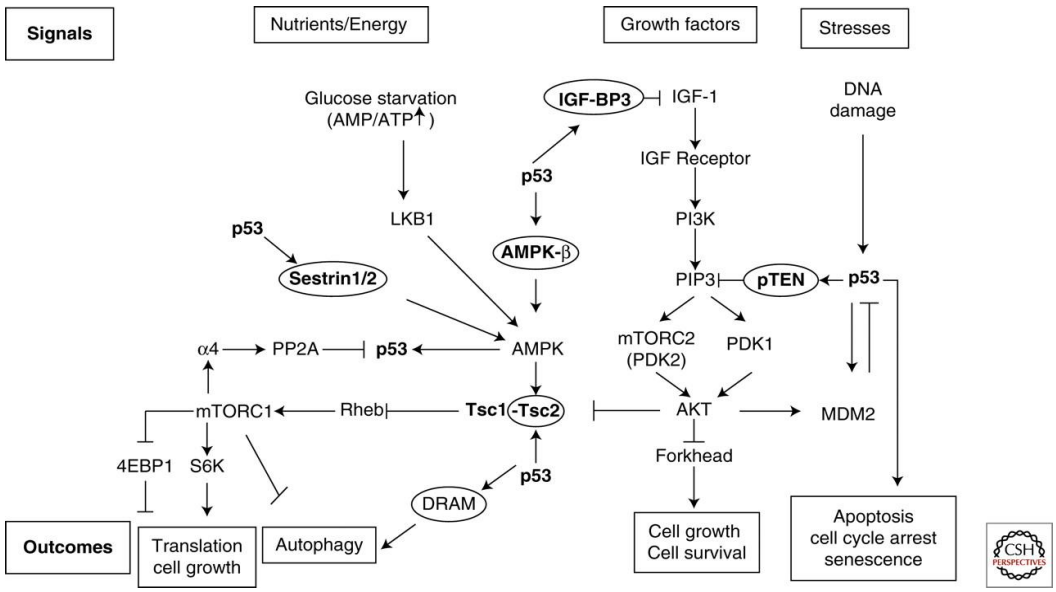

Figure 3: How signals drive the mTORC pathway. Source: http://cshperspectives.cshlp.org/

The activities of mTOR are regulated by several other pathways and molecules in different cell types due to its ubiquity and multiple functions. Thus, a comprehensive understanding of mTOR processes and that of the IGF1–Akt–mTOR pathway as a whole is practically impossible as much of it remains unknown. However, ribozymes are solely involved in protein synthesis (Campbell et al., 2005). Thus, the direct control of mTORC1 over ribosome function can be seen as one of the limiting factors in the production of proteins that help to build up muscle. Therefore, ribosome activity can be indirectly altered by controlling the signals that are integrated by mTORC1 which include growth factors, energy status, oxygen, and amino acids (Laplante & Sabatini, 2009).

Myostatin–Smad2/3 pathway Pathway

Myostatin is popularly known for its muscle wasting properties and the frustrating limit it places on muscle size. Though an extracellular cytokine, myostatin initiates a cascade of numerous reactions that ultimately signal the breakdown of muscle tissues (Elkina,

Haehling, Anker, & Springer, 2011). Many naturally occurring genetic defects of the coding of myostatin as well as induced defects have revealed the delimiting function of myostatin (Tsuchida, 2008). However, much of its mechanism of action is still unknown and less understood compared to mTOR.

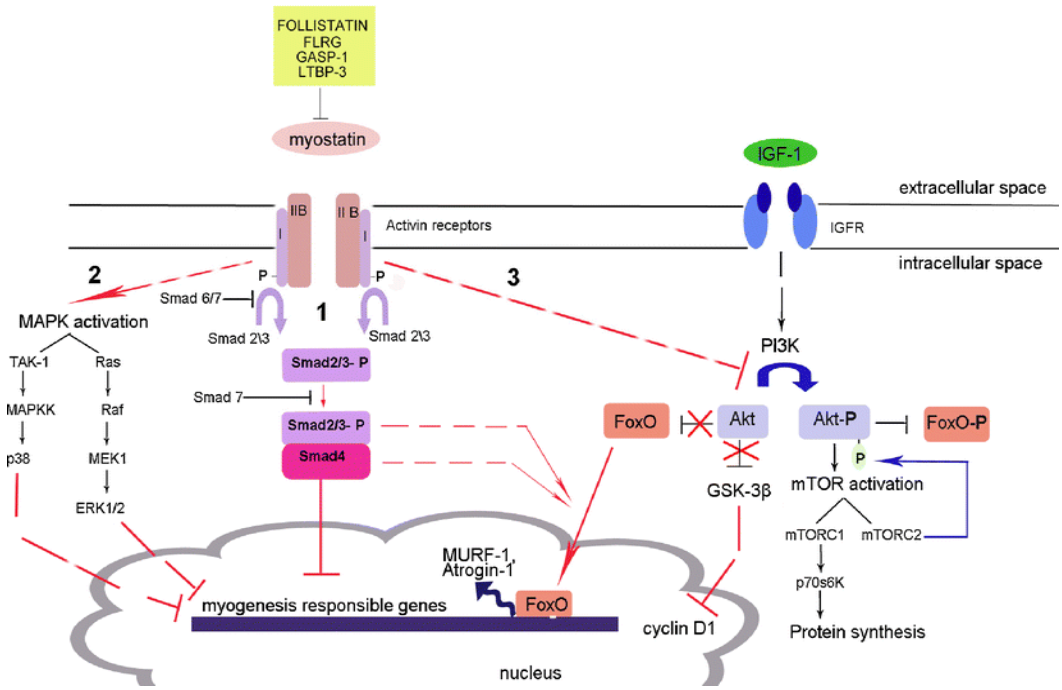

Figure 4: How myostatin inhibits mTOR signalling and other pathways thus inhibiting protein synthesis. Source: The role of myostatin in muscle wasting: an overview. Journal of Cachexia, Sarcopenia and Muscle. 2011.

Myostatin binds extracellularly to its receptors, Activin Receptor II A or B (ActRIIA or B) and Activin-Like Kinase-4 or 5 (ALK-4 or 5), and initiates intracellular signalling through phosphorylation and activation of the transcription factors Smad2 and 3. These protein coding genes (smad2 & 3) then translocate to the nucleus and activate target genes (McCroskery, Thomas, Maxwell, Sharma, & Kambadur, 2003). Myostatin has also been discovered to act through other pathways which are still been researched (Philip, Lu, & Gao, 2005). Also, several mechanisms are known to regulate the activities of myostatin physiologically (Egerman & Glass, 2013). Some of these mechanisms are Smad7 (another coding gene) and Growth and Differentiation Factor-Associated Serum Protein-1 (Hill, Qiu, Hewick, & Wolfman, 2008). Thus, myostatin basically inhibits protein synthesis by regulating the pathways leading up to mRNA translation in the ribosomes. These pathways exert negative feedback on one another and mainly influence the activities of mTOR both in mTORC1 and mTORC2 pathways (Schiaffino et. al, 2013).

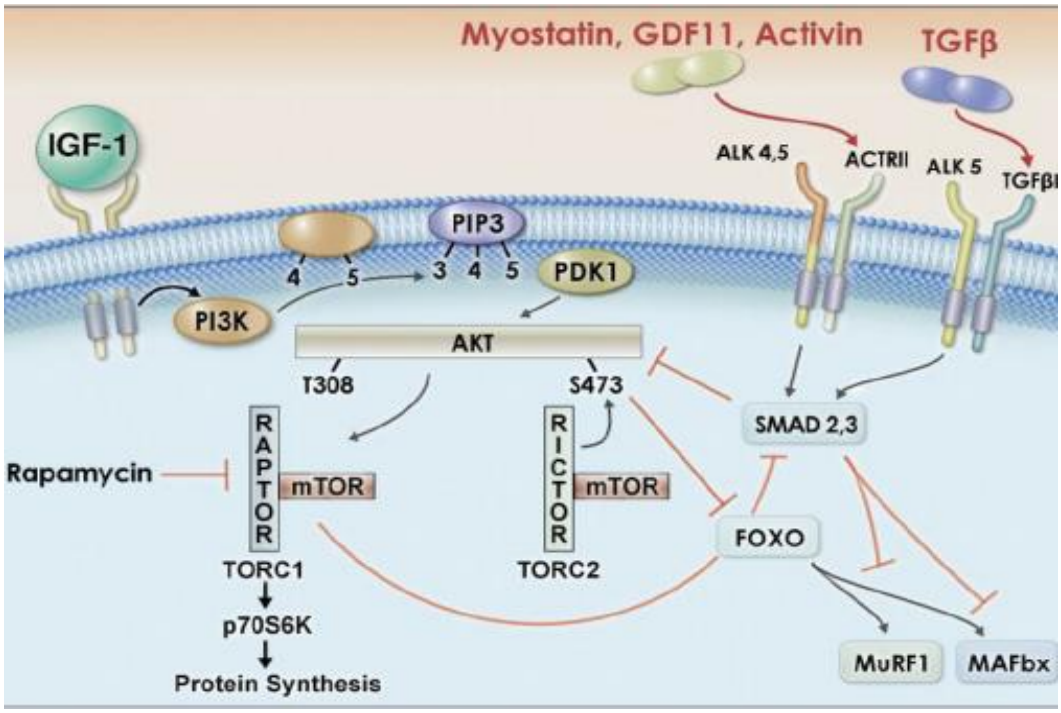

Figure 5: Myostatin–Smad2/3 Pathway. Source: researchgate.net

Maximising Muscle Building Capabilities of Anabolic Enzymes (Level 5)

So far, ribosomes (or ribozymes) have been implicated as the principal anabolic enzymes involved in protein synthesis. The next on the list is mTOR which directly influences the availability and functioning of ribozyme. Thus, it is impractical to discuss the potentials of ribozyme without mTOR. There are currently no scientific ways of directly altering ribozyme function. This is because of several challenges facing this approach.

One of these is that ribosomes are intracellular organelles located in the cell cytoplasm. They cannot be gotten to without passing through several interconnecting pathways. Thus regulating them extraneously is dependent on how well the pathways leading up to them can be controlled.

Also, a lot that pertains to intracellular signalling is yet to be deciphered. The numerosity of these pathways can be daunting to imagine and has led to devote research programmes dedicated to understanding them. Pending when much of these signalling pathways will be known, an indefinite embargo remains on a thorough manipulation of these enzymes. However, current knowledge about these pathways is already being utilised in genetic alterations leading up to the successful deregulation of these intracellular pathways (Patrick, 2008). This has led to another concern known as gene doping (Gronde, Hon, Haisma, & Pieters, 2013).

Gene Doping

Following the successful genetic alteration of mice in laboratory experiments, there has been a massive movement for the application of such therapy on human subjects in spite of the lethal risks involved (Reynolds, 2007). Gene doping involves modifying DNA in order to alter the expression of the affected genes which could lead to increased or decreased function or production of a certain biomolecule. It can be executed using other genetic agents such as myostatin, IGF1, erythropoietin, amongst others. (Birzniece, 2015). Gene doping is the non-therapeutic version of gene therapy and is currently still a hypothetical procedure according to Momaya et al. (2008).

Gene doping is one of the level 5 methods of physical enhancement (as seen in figure 1) because it takes advantage of the ultimate role of gene expression in controlling protein synthesis. The many concerns it raises in the world of sports and fitness are not much different from that generated by drug doping. Successful gene doping can lead to increased muscle strength and endurance without exercise! This plays down the foundational basis for ranking in sports competitions. Consequently, world agencies have made it a top priority in their anti-doping programmes should it become a reality (World Anti-Doping Agency, 2016).

Conclusion

Muscle building expresses itself in several forms such as sarcoplasmic and sarcomere hypertrophy, hyperplasia, recruitment of muscle fibres and elasticity (flexibility). All these depend on intracellular events triggered or amplified by muscle building stimuli in the form of mechanical (physical), chemical (nutrients, anabolics, and enzymes) or procedural (genetic/laboratory) interferences as described above. The effectiveness of each depends on its ability to influence protein synthesis pathways while being opposed or aided by the individual's genetic predispositions.

Massive effects have been produced from just physical training alone. Now, advances in science have exposed the potential of performing procedures that alter genetic factors thus accelerating muscle growth. There is much interest in mTOR signalling and other protein synthesis pathways which have yielded successful therapeutic applications. Being able to directly affect anabolic enzymes will birth a new era of muscle building that can lead to the reappearance of historical giants that beat one's imagination.

Recommendations

1. Given the sensitive nature of level 5 applications (refer to table 1), care must be taken in managing the knowledge, reproducibility and availability of these methods to prevent them from being used for sinister purposes. For example, with successful manipulation of protein synthesis pathways, the concept of a 'perfect soldier/bodyguard' or hulk becomes feasible; referring to someone with no natural limitations in strength. Though the sporting world may not readily

accept this, it will definitely be of interest in the military, political, and entertainment circles.

2. Also, more research has to be done to ascertain the long term effects of such applications in the later years of users. Being that the human body will be experiencing a strange physiological condition, how it adapts, in the long run, is of great importance. For example, an unrestricted increase in muscle mass will result in enormous weight gain which in turn will require more energy to maintain and carry about. Knowing how the heart, skeleton, and regulatory systems cope will shed more light on human physiology and its capabilities.
3. Furthermore, acquired traits get stored in DNA. This is responsible for family traits and conditions like sickle cell and albinism. It is imperative that research further delves into understanding how present manipulations in body physiology will affect future generations of subjects lest a genetic pandemic is created.

Scientific inquiry must go on. Certainly, gene doping will one day become a reality. How it affects us depends on how we respond to it.

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