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The Effects of β2-Adrenergic Agonists on Skeletal Muscle Hypertrophy: A Narrative Review

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ABSTRACT

β2-adrenergic agonists (β2-mimetics) are widely used to treat pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD), yet strong evidence indicates that they also affect skeletal muscle metabolism and growth. This review covers current knowledge of the β2-mimetic effect on muscle mass, its underlying mechanisms, and its clinical application. This review draws on animal and human studies that show differences between them. β2-agonists may have therapeutic potential for elderly patients, who often suffer from muscle loss. However, cardiovascular side effects and receptor desensitization constrain clinical application. Additionally, their anabolic properties have led to misuse in sports. In summary, β2-agonists exhibit clear anabolic effects in experimental models; however, their practical application in humans remains limited and needs further research.

Keywords: β2-agonists, β2-adrenergic agonists, β2-mimetics, β2-adrenergic receptors, skeletal muscle hypertrophy, enhanced regeneration, geriatric patients, osteoarthritis, cachexia, muscle wasting.

1. INTRODUCTION

β2-adrenergic agonists (β2-mimetics) are a class of drugs that selectively stimulate β2-adrenergic receptors, which various tissues, including bronchial smooth muscle and skeletal muscle, widely express. Clinically, they are mainly used to treat respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), where they act as relaxants of airway smooth muscle, causing bronchodilation. However, beyond their therapeutic role, β2-mimetics have attracted growing attention for their effects on skeletal muscle metabolism and growth.

Studies in animal models have shown that certain β2-adrenergic agonists can significantly increase skeletal muscle mass. This effect often leads to reduced adipose tissue, a phenomenon termed repartitioning, and it has raised interest in the potential use of β2-adrenergic agonists in conditions characterized by muscle wasting, for example, in older people. The anabolic properties of β2-adrenergic

agonist medicines lead to their misuse in doping and livestock production, raising regulatory and moral concerns. Some studies showed a potential in increasing muscle mass and reducing oxidation stress (Higashihara et al., 2021). Faster recovery after injury (Beitzel et al., 2004) is a promising finding proving that β2-adrenergic agonists might be useful in sports and accidents.

This review draws on clinical data and experimental evidence from animal and human studies. It aims to determine therapeutic benefits for older people and other patients with muscle loss. It examines the effects of β2-mimetics on skeletal muscle mass, drawing on molecular mechanisms, experimental evidence, and clinical data.

2. REVIEW METHODS

The search consisted of an analysis of β2-agonists' influence on skeletal muscle hypertrophy, enhanced regeneration, and mechanisms of action, animal and human studies, and adverse effects. Articles excluded from the literature search included duplicates, unrelated articles, or those with insufficient data relevant to the topic. The literature search included original research and review articles that examined β2-adrenergic agonists in the context of skeletal muscle hypertrophy and protein metabolism. Selected studies consisted of human and animal studies and in vitro models. The article screening process followed the PRISMA guidelines (Figure 1).

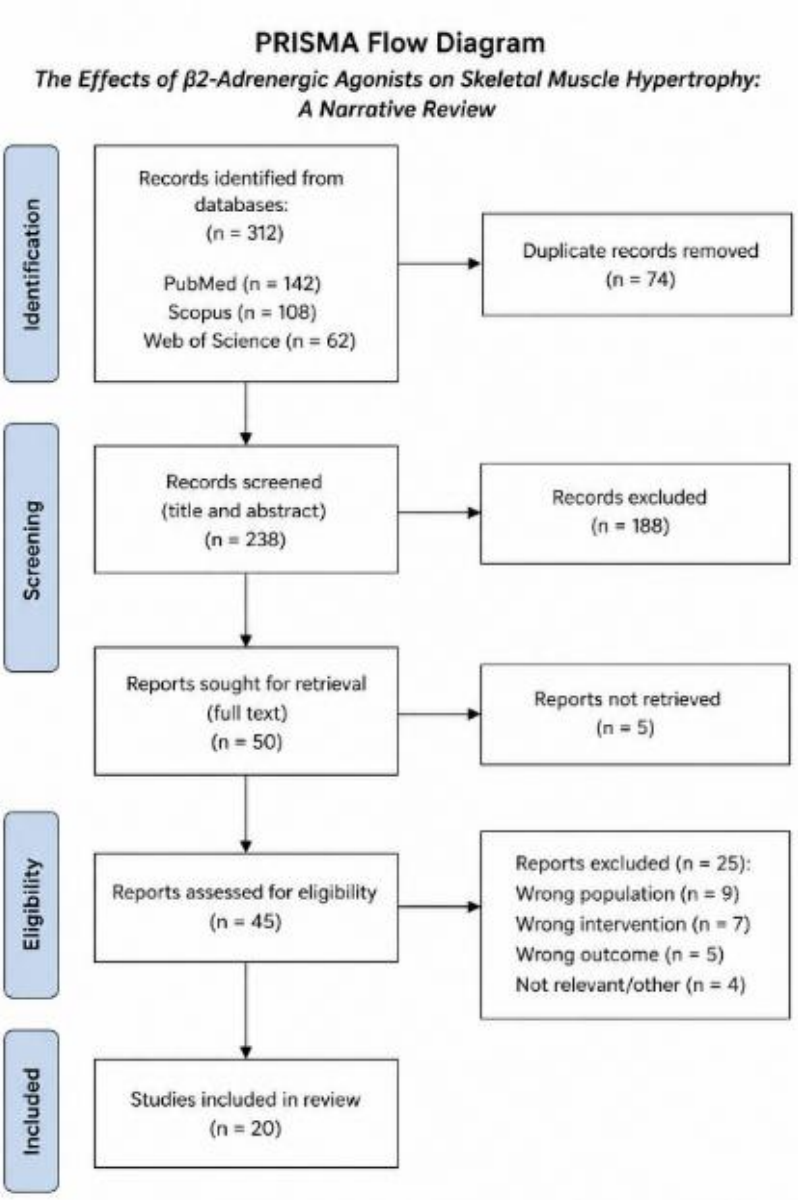

Figure 1. PRISMA flow diagram.

3. RESULTS AND DISCUSSION

β2-Adrenergic Receptors and Mechanisms of Action

β2-adrenergic receptors (β2-ARs) are G protein-coupled receptors (GPCRs) that mediate the physiological effects of β2-adrenergic agonists. Bronchial smooth muscles, vascular endothelium, cardiac muscle, and skeletal muscle contain these receptors.

β2-adrenergic receptors are transmembrane proteins. G proteins (Gs) couple to these receptors and initiate the intracellular signaling cascade when a ligand binds. β2-ARs are the most common subtype of β-adrenergic receptors in skeletal muscle. The expression of β2-ARs is higher in fast-twitching (type II) fibers than in slow-twitching (type I) fibers. This distribution is relevant for their role in muscle hypertrophy. Upon binding of a β2-agonist, the receptor undergoes a conformational change that activates the Gs protein, which leads to stimulation of adenylyl cyclase, and as a result, the intracellular level of cAMP. Elevated cAMP activates protein kinase A (PKA), which in turn stimulates metabolism and gene expression. It leads to smooth muscle relaxation, modulation of ion channels and calcium handling, and regulation of transcription factors that are involved in muscle growth.

β2-adrenergic stimulation impacts both anabolic and catabolic processes in skeletal muscle. The interaction with the mechanistic target of rapamycin (mTOR) results in increased protein synthesis. At the same time, β2-agonists inhibit proteolysis (the enzymatic breakdown of proteins) through downregulation of the ubiquitin–proteasome system (e.g., atrogin-1 and MuRF-1). Both of these effects contribute to net positive protein balance, resulting in muscle hypertrophy.

In addition to the classical cAMP/PKA pathway, β2-adrenergic signaling can also involve alternative mechanisms, such as β-arrestin–mediated pathways. These non-canonical pathways contribute to receptor desensitization but may also independently regulate gene expression and cellular growth processes.

Chronic stimulation of β2-adrenergic receptors leads to adaptive changes, including desensitization and downregulation of β2-ARs. Desensitization is an important factor limiting the prolonged effectiveness of β2-agonists, both in clinical use and within their potential anabolic applications. The extent of desensitization depends on the dose, duration of exposure, and specific agonist used.

Common β2-Mimetics used in medicine

We classify beta-2 agonists by their onset and duration of action. We divide these classes into short-acting beta-agonists (SABAs), long-acting beta-agonists (LABAs), and ultra-long-acting beta-agonists (ultra-LABAs). SABAs have the shortest half-life and immediately alleviate negative symptoms. LABAs and ultra-LABAs offer much longer and sustained treatment due to their long duration (Wannenes et al., 2012). The differences in properties between these classes arise from modifications to the molecular structure of the drugs.

Short-Acting β2-Agonists (SABA): Short-acting β2-agonists have an immediate onset of action (within minutes) and a relatively short duration (3–6 hours). They are primarily used to relieve acute bronchospasm and as rescue medications. The most common SABAs include salbutamol, fenoterol, and terbutaline.

Long-Acting β2-Agonists (LABA): Clinicians prescribe long-acting β2-mimetics, which have a prolonged duration of action (≥12 hours), for maintenance therapy rather than acute symptom relief. The most common LABAs include salmeterol and formoterol.

Ultra-Long-Acting β2-Agonists (Ultra-LABA): These drugs have a prolonged duration of action (up to 24 hours) and are mainly used to manage COPD. The most common Ultra-LABAs include indacaterol, olodaterol, and vilanterol.

Non-Selective or Off-Label β2-Agonists: Some β2-mimetics are not commonly used in standard medical therapy but researchers frequently study for their anabolic effects, such as clenbuterol, which is not approved for human use in many countries but researchers widely investigate its effects on muscle hypertrophy and fat metabolism (Hinkle et al., 2002).

Effects on Skeletal Muscle Mass

β2-adrenergic agonists researchers have thoroughly tested for their effects on skeletal muscle mass increase. These effects have a greater impact on animal models than on humans. In humans, the effects of these drugs are more variable and often depend on the dose. Evidence shows that these compounds can induce skeletal muscle hypertrophy, alter fiber type composition, and reduce adipose tissue mass through a metabolic process known as repartitioning.

Evidence from animal studies

Animal studies provide the most consistent evidence for the anabolic effects of β2-mimetics on skeletal muscle hypertrophy. In rodents, studies have shown that clenbuterol administration increases muscle mass across multiple muscle groups. For example, chronic

administration of clenbuterol in rat studies have shown that it increases muscle mass in certain muscles while simultaneously reducing fat tissue content (Ryall et al., 2006). In uremic mice, clenbuterol increased muscle mass and myosin expression and reduced oxidative stress, but did not restore strength (Higashihara et al., 2021). Researchers have observed similar increases in muscle mass in livestock species, which has commonly led to illegal use of β2-agonists as growth promoters.

β2-agonists mainly affect glycolytic fibers, thus enhancing force production and altering endurance. They also facilitate a faster recovery after injury and increase muscle mass, protein content, and fiber cross-sectional area (Beitzel et al., 2004). As for skeletal muscle hypertrophy, chronic administration of β2-agonists increases muscle fiber cross-sectional area, particularly in fast-twitch (type II) fibers. This hypertrophy often increases overall lean body mass. For example, low systemic doses of formoterol in rats significantly cause hypertrophy of fast and slow muscles, with relatively small cardiac effects (Ryall et al. 2006).

Evidence from human studies

The effects of β2-agonists in humans are far more limited and less consistent than in animals. Some studies show that β2-adrenergic agonists slightly increase protein synthesis and degradation, with an advantage in protein production after exercise. It is highly dependent on dose and the route of administration. Results regarding muscle strength are inconsistent. Some studies report slight improvements in maximal force output, while others show no significant performance enhancement.

Some clinical studies have shown small but measurable increases in lean body mass following terbutaline administration, particularly when combined with resistance training. In healthy young men, 4 weeks of near-therapeutic inhaled terbutaline increased lean body mass by ~1 kg compared with placebo in both habitual and resistance-training groups (Jessen et al., 2018). The same dose of terbutaline enhanced insulin-stimulated glucose disposal. As a result, lean muscle mass increased, suggesting that muscle hypertrophy enhances insulin sensitivity, which is vital for preventing diabetes (Jessen et al., 2022). Administration of salbutamol per os for 3 weeks in young men increased quadriceps strength by ~12% and hamstring strength of the dominant leg by ~22% without measurable changes in body composition (Martineau et al., 1992). Inhaled salbutamol in healthy volunteers has been shown to increase markers of muscle protein turnover, but only minor changes in actual muscle hypertrophy. It implies that although β2-agonists can influence muscle metabolism in humans, their practical anabolic potential is limited compared to findings in animal models. Short-term salbutamol administration during resistance training increased myofibrillar protein synthesis and leg protein balance (Hostrup et al., 2018).

As for adverse effects, the doses required to produce anabolic effects in humans commonly are close to those causing adverse cardiovascular and metabolic side effects, such as tachycardia, tremor, and hypokalemia. Chronic administration leads to downregulation of β2-adrenergic receptors, reducing responsiveness over time and limiting long-term efficacy (Sato et al., 2011).

In summary, Studies have shown that β2 agonists increase skeletal muscle mass and can prevent or even reverse atrophy (Table 1). Clinically effective doses of β2 agonists result in small but noticeable increases in lean muscle mass, strength, and protein synthesis. Some studies have also reported positive effects on glucose disposal. Although these effects are weaker in humans than those observed in animal models. They also raise safety concerns.

Table 1. The summary of the article.

Aspect	Summary
Main Findings	Studies in animals suggest that β2-adrenergic agonists can increase skeletal muscle mass and improve muscle strength.
Mechanisms of Action	These effects are associated with alterations in metabolism and changes in gene expression involved in muscle growth and protein synthesis.
Potential Clinical Applications	β2-adrenergic agonists may potentially help treat conditions associated with muscle wasting, including cancer cachexia, osteoarthritis in older adults, and movement impairments.
Metabolic Benefits	They may also contribute to diabetes prevention, which could indirectly reduce cardiovascular risk.

Risks and Adverse Effects	The use of β2 agonists may cause cardiovascular and neurological side effects, and beneficial effects may diminish after discontinuation.
Ethical and Sports Concerns	β2 agonists may be misused as performance-enhancing substances in sports.
Current Limitations	Existing evidence is still insufficient to fully determine the therapeutic value and long-term safety of β2-adrenergic agonists in humans.
Future Directions	Further clinical and experimental research is necessary to better understand their efficacy, safety, and potential medical applications.

Clinical and Practical Consequences

In diseases that cause progressive loss of skeletal muscle mass, such as chronic heart failure, chronic obstructive pulmonary disease, post-stroke, and cancer, preclinical studies show that β2-agonists may, to some extent, counteract the decrease in muscle mass. In uremic mice, clenbuterol increased muscle mass and reduced oxidative stress. However, it did not restore strength, and its arrhythmogenic and cardiac enlargement risks make it problematic in patients with chronic kidney disease (Higashihara et al., 2021). Some animal studies suggest that β2-agonists may improve muscle regeneration after injury by stimulating satellite cell activity and improving muscle repair. Data from animal studies conducted on rats showed that fenoterol enhanced functional repair after muscle injury, increasing muscle mass, fiber area, protein content, and maximal force during regeneration (Beitzel et al., 2004). Despite these data, translation into clinical practice remains experimental.

Although β2-agonists theoretically offer therapeutic potential in muscle-wasting conditions, systemic adverse effects and insufficient clinical evidence limit their use in humans. Sarcopenia causes decreased muscle mass and function. Experimental data suggest that β2-agonists may help preserve lean body mass in elderly populations; however, cardiovascular side effects and a lack of long-term safety data limit their therapeutic applicability. Low dose β2 agonists (formoterol, fenoterol, clenbuterol) can reverse muscle wasting and improve strength in aged rats, suggesting that "small (10–15%) increases in muscle mass and strength may improve daily function of an elderly person (Ryall et al., 2006).

Chronic use of β2-agonists results in receptor downregulation; long-term treatment of geriatric patients could prove ineffective. Pulse drug administration could address this concern, but more clinical studies are needed.

Adverse Effects and Safety Concerns

The main concern includes the effect β2 agonists have on the cardiovascular system. Chronic β2 agonist use may cause tachycardia, cardiac hypertrophy, left ventricular collagen infiltration, and reduced left ventricular pressure in rodents. Some cardiac hypertrophy appears reversible after stopping clenbuterol or formoterol in rats (Joassard et al., 2013). For example, salbutamol used in humans caused acute side effects such as tremor and heart palpitations during the first day of treatment (Hostrup et al., 2018); earlier work also noted hyperactivity and mild hand tremor (Martineau et al., 1992).

β2 receptor downregulation argues against chronic high-dose therapy for muscle wasting in the geriatric population and cachexia-causing diseases (Sato et al., 2011). Formoterol and salmeterol both induce hypertrophy in rats but cause β-adrenoceptor downregulation in human skeletal muscle at effective doses (Ryall et al., 2006). Significant safety concerns include arrhythmia risk, tremor, and loss of benefit due to β-adrenoceptor downregulation.

Future Directions

Further dissection of downstream signaling is needed: reviews call for deeper study regarding signaling pathways and "downstream effectors that regulate protein synthesis and protein degradation", especially CREB-regulated genes and other cAMP-driven pathways. The scientists will have to focus on minimizing systemic exposure by identifying more β2-selective drugs and developing more targeted delivery routes and avoiding receptor downregulation and desensitization, which currently blunt long-term efficacy. Reviews emphasize a need for controlled human trials in muscle wasting states (sarcopenia, cancer cachexia, neuromuscular disease) to move beyond animal data.

The next generation of β2-adrenergic agonists should be more selective for β2-adrenergic receptors, thereby minimizing or eliminating adverse effects. Additionally, the range of studies on patients should be widened to provide more data on how these drugs work in geriatric patients, who often have chronic conditions. Studies should also consider the pulse therapy, which could help with the downregulation of β2-adrenergic receptors. Many ideas need further testing to prove useful.

4. CONCLUSION

Studies in animals have shown that β2-adrenergic agonists can increase muscle mass and strength by altering metabolism and gene expression. It gives us hope that further research could benefit humans in conditions that cause muscle loss, such as in cancer patients, older people, or people with movement impairment. Additionally, it can be used to prevent diabetes, thereby reducing cardiovascular risk. The data we have today are not sufficient to fully exploit the benefits of β2-adrenergic agonists, but further research may be beneficial for humans.

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All authors have read and agreed with the published version of the manuscript.

Informed consent

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Ethical approval

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Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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