

The effects of beta (2)-adrenergic receptors activation on the cardiovascular system and on the skeletal muscle: A narrative review

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ABSTRACT

Beta(2)-adrenergic receptors (adrenoceptors) are activated by the catecholamines norepinephrine and epinephrine. Adrenoceptors are found in different tissues, such as smooth muscle, skeletal muscle and myocardium. Stimulation of adrenoceptors is implicated in several physiological functions in the body, such as bronchodilation, increased perfusion and vasodilation. The latter, together with increased muscular mass and contraction speed, facilitate muscle's motility and contraction. In the cardiovascular system, the activation of adrenoceptors increases heart muscle contraction, cardiac output and heart rate. Some studies also suggested a cardioprotective role of the stimulation of adrenoceptors. Beta(2)-adrenergic receptors agonists, principally divided in long-acting beta(2) agonists (LABAs) and short-acting beta(2) agonists (SABAs), are primarily used to treat asthma and other pulmonary disorders. Beta(2)-adrenergic receptors activation has been correlated with anabolic properties and muscular hypertrophy with the use of oral clenbuterol, as well as intravenous albuterol. Given these anabolic, lipolytic and performance-enhancing effects, LABAs are frequently abused by athletes. For this reason, most of these drugs are banned by the World Anti-Doping Agency, or admissible only with limitations. The aim of this narrative review is to report the results of some recent studies about the effects of beta(2)-adrenergic receptors activation on the cardiovascular system and on the skeletal muscle.

Keywords: Beta(2)-adrenergic receptors; Beta(2)-agonist; Catecholamines; Cardiovascular system; Skeletal muscle; Doping.

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INTRODUCTION

Beta-2 (β_2)-adrenergic receptor (α_r) is a subtype of adrenergic receptors which binds several endogenous hormones such as the catecholamines norepinephrine and epinephrine, resulting in several types of responses. β_2 - α_r is mainly expressed in the airways and in the vascular smooth muscle, but some studies also found its presence in the myocardium, although the β_1 - α_r subtype is the most expressed in heart (Brodde et al., 2006).

β_2 - α_r selective agonists are derived from the chemical structure of adrenaline. They are traditionally used for the treatment of bronchospasm associated with asthma and the treatment of symptomatic patient with chronic obstructive pulmonary disease (COPD) to induce a bronchodilatation by relaxing airway smooth muscle (Cazzola et al., 1997).

Stimulation of adrenoceptors is also implicated in muscle's contraction and motility. This happens through a mechanism of increased perfusion and vasodilation of blood vessels to skeletal muscle, but also through a mechanism of increased mass and contraction speed (Rang et al., 2003).

The skeletal muscle's microvasculature response to β_2 - α_r stimuli was recently found to be diminished with cardiac surgery (Ziegler et al., 2020).

It has been widely accepted that activation of muscle β_2 - α_r s with the use of β_2 - α_r agonists, principally divided in long-acting β_2 -agonists (LABAs) and short-acting β_2 -agonists (SABAs), leads to muscle hypertrophy and skeletal muscle repair in vivo (Chikazawa and Sato, 2018b; Jean-Baptiste et al., 2005; Sato et al., 2011).

LABAs, such as clenbuterol, are frequently abused performance-enhancing drugs for their anabolic, lipolytic, and performance-enhancing effects (Davis et al., 2008). SABAs, such as albuterol, were not found to generate the same impacts on muscle mass if administered orally, suggesting that drugs with a short half-life are not able to achieve these effects unless they are administered by intravenous route (Choo et al., 1992; Kamalakkannan et al., 2008). Indeed, the use by athletes of β_2 - α_r agonists such as clenbuterol is strictly prohibited, and it would be considered a doping violation (Chikazawa and Sato, 2018b), since these drugs are banned by the World Anti-Doping Agency, though some are permissible under a therapeutic use exemption (such as for asthma).

Recent studies reported the correlation of a different expression of β_2 - α_r in the myocardium and heart diseases, potentially allowing to detect new markers of myocardium infarction. Moreover, β_2 - α_r can be a potential therapy target for several heart diseases (Li et al., 2019; Xia et al., 2017). In addition, β_2 - α_r s are also present on endothelial cells where they modulate vasodilation and angiogenesis (Chisholm et al., 2012; Guimarães and Moura, 2001).

Several studies investigated the role of β_2 - α_r agonists as pharmacologic agents aimed at reversing pathological conditions associated with skeletal muscle wasting such as sarcopenia and frailty (Kim et al., 2018, 2020). Even in the case of severe muscle wasting, such as after a spinal cord injury, a role for systemic β_2 - α_r -mediated mitochondrial biogenesis in improving skeletal muscle recovery was found (Scholpa et al., 2019).

In this review we will report the results of some recent studies about the effects of β_2 - α_r activation on the cardiovascular system and on the skeletal muscle.

STRUCTURE AND PATHWAYS RELATED TO THE β 2-ADRENERGIC RECEPTOR'S ACTIVATION

The β 2-ars are a subtype of β -adrenergic receptors, belonging to the superfamily G protein coupled receptors (GPCR). GPCRs have a conserved core of seven transmembrane α -helices that are connected by three extracellular and intracellular loops. Some of these receptors are known as potent inducers of hypertrophy (Berdeaux and Stewart, 2012), and there is evidence about the importance of the regulation of the activation of GPCRs for the maintenance of skeletal muscle function (Chikazawa and Sato, 2018b). They transduce a signal from the extracellular environment to the intracellular ones. The signal transduction starts with the binding of an endogenous hormone (epinephrine and norepinephrine for the adrenergic receptors) leading to a conformation change that activate the intramembrane protein G, an heterotrimer with three subunits: α , β , γ . The activation of G protein leads to a loss of affinity of GDP for GTP with the consequently dissociation of the heterotrimer $G\alpha$ and $G\beta\gamma$ active subunits, mediating the intracellular signal transduction. $G\alpha$ subunits are grouped in 4 subfamilies: $G\alpha_s$, $G\alpha_i$, $G\alpha_q$ and $G\alpha_{12}$. These different subunits modulate the release of a second messenger in the cytoplasm. β -ars are mainly associated with G stimulating (G_s), leading to the activation of adenylate cyclase with the consequent increasing of cyclic adenosine monophosphate, cAMP, which activates cAMP dependent-kinases protein kinase A (PKA). PKA phosphorylates troponin I and Ca^{2+} channel, activating it, and finally inducing organism response (Freedman and Lefkowitz, 2004).

Intracellular cAMP enhances cAMP-response element binding protein (CREB) phosphorylation and CREB target gene expression, which is assumed to be critical for myogenic differentiation and myofiber survival. $G\alpha_i$ -coupled receptors activate both the PI3K–AKT and mTOR signalling pathway, resulting in an increase in muscle protein synthesis (Minetti et al., 2011). The 3'-phosphoinositide–dependent kinase 1 (PDK1), a key component of PI3K signalling pathway, was found to regulate skeletal muscle mass under the static condition and that it contributes to mechanical load–induced muscle hypertrophy, at least in part by mediating signalling from β 2-ar (Kuramoto et al., 2021).

A common genetic variant in the β 2-ar, the Arg16Gly genotype was found to have a significant effect on fat-free mass, muscle strength and motor unit behaviour in recreationally trained men (Jenkins et al., 2018). These data might have important clinical and exercise-related implications. For example, β 2-AR (rs1042713) genotype might influence the responsiveness of skeletal muscle to clinical or exercise-based interventions or β -ar agonist treatment (Jenkins et al., 2018).

RELATIONSHIP BETWEEN LOCALIZATION AND FUNCTION OF β 2-ADRENERGIC RECEPTORS IN THE CARDIOVASCULAR SYSTEM

β 2-ars are estimated to be the 25% of all adrenergic receptors in myocardium, while β 1-ars are the most expressed adrenergic receptors in the heart (75%) (Brodde et al., 2006). β 1-ars are the most expressed adrenergic receptor in the cardiomyocyte, while β 2-ars are mainly expressed in cardiac fibroblasts, where they modulate collagen secretion and fibroblast autophagy, although the mechanism is still not totally understood (Bristow et al., 1986; Meszaros et al., 2000).

New findings were available in the last two decades for β -ar signalling. In the classic linear model, β -ars were thought to primarily mediate cardiac functions such as inotropy, chronotropy, and lusitropy through the activation of stimulating G_s pathway, activating the adenylate cyclase which increases cAMP's intracellular concentration (Guimarães and Moura, 2001; Xia et al., 2017). Increased cAMP's concentration leads to the activation of PKA, which phosphorylates several downstream proteins like calcium ATPase enhancing intracellular calcium concentration with a consequent increase of heart contractions and blood flow rate

(Bernstein et al., 2011). The presence of both β_1 and β_2 adrenergic receptors in the heart generates a difference in the cAMP local concentration depending on the spatial localization of adrenergic receptors. β_2 -ar was also found to be localized in caveolae, an invagination of plasma membrane enriched in cholesterol, glycopospholipids, so this could be associated to a cardioprotective effect of β_2 -ars (Agarwal et al., 2011; Bernstein et al., 2011; Head et al., 2005; Woo and Xiao, 2012; Xiang et al., 2002; Zhu et al., 2001).

EFFECT OF β_2 - ADRENERGIC RECEPTOR'S ACTIVATION ON THE CARDIOVASCULAR SYSTEM

Recent studies found that, unlike β_1 -ar, β_2 -ar can activate both G_s and G_i pathways, decreasing cAMP concentration, and activating another pathway inhibiting cardiomyocytes apoptosis with a cardioprotective effect (Santos and Spadari-Bratfisch, 2006). Another study underlined the cardioprotective effect of an overstimulation of β_2 -ars, regulating macrophage activation and decreasing the possibility to develop heart injuries (Noh et al., 2017). The role of extracellular matrix (ECM) has been shown to be pivotal in cardiac regeneration and repair after cardiac injury (Castaldo et al., 2013; Belviso et al., 2020a; Belviso et al., 2020b), and a recent study discovered that β_2 -ars are also involved in the maintenance of the cardiac matrix's homeostasis, modulating collagen secretion and fibroblast autophagy, so that might contribute to prevent fibrosis due to pathological adrenergic stimulation (Aránguiz-Urroz et al., 2011). Another study underlined the cardioprotective effect of β_2 -ar stimulation, activating pro-survival kinases and reducing mitochondrial dysfunction; in fact, β_2 -ar knock up enhances cardiotoxicity downregulating survival kinases and damaging the mitochondrial membrane (Fajardo et al., 2011).

In contrast with the β_2 cardioprotective effect, some studies revealed a relationship between heart failure and over-stimulation of β_2 -ar in subject with type-2 diabetes, since β_2 -ar antagonists were found to reduce heart complications in type-2 diabetes. These findings could contribute to discover a new therapeutic target in β_2 -ar preventing and treating type-2 diabetes associated cardiac dysfunction (Rybin et al., 2000; Spadari et al., 2018; Wang et al., 2017; Wright et al., 2014). β_2 -ar was found to be involved in the modulation of vasodilation via $G_{as}/AC/PKA$ pathway trough the activation of the endothelial nitric oxide synthase. Furthermore, β_2 -ar stimulation was found to be related to the activation of the vascular endothelial growth factor and the basic fibroblast growth factor, both activating proangiogenic pathways (D'Angelo et al., 1997; Iaccarino et al., 2005; Storch and Hoeger, 2010). A recent study has revealed that β_2 -ar is overexpressed in infantile haemangioma, so it might be used as predictive marker and a preventive therapy target of vascular cancer (Chisholm et al., 2012).

EFFECT OF β_2 - ADRENERGIC RECEPTOR'S ACTIVATION ON THE MUSCULOSKELETAL SYSTEM

Skeletal muscle mass is controlled by balancing protein synthesis and degradation (Chikazawa & Sato, 2018a). Decreased protein synthesis and/or increased protein degradation for a prolonged period of time, which may be caused by inactivity, inadequate diet, reduced hormone levels or disease, contribute to a decrease in skeletal muscle mass and the onset of atrophy (Chikazawa & Sato, 2018a; Toledo et al., 2016).

The hypertrophy and anti-atrophy effects of β_2 -ar-agonists can be explained by their actions on the balance between protein synthesis and protein degradation (Joassard et al., 2013). Previous studies indicate that chronic administration of β_2 -ar-agonists not only increases muscle protein synthesis, but also decreases muscle protein degradation (Busquets et al., 2004; Koopman et al., 2010; Navegantes et al., 2000, 2001, 2004).

β 2-ar agonist clenbuterol administration was found to improve skeletal muscle atrophy induced by hindlimb unweighting, denervation, and dexamethasone treatment through the activation of protein synthesis and inhibition of protein degradation by controlling lysosomal and proteasomal activity in animal models (Chikazawa and Sato, 2018a; Gonçalves et al., 2011; Pellegrino et al., 2004; Yimlamai et al., 2005).

The preclinical data reported in a study by Koziczak-Holbro et al. (Koziczak-Holbro et al., 2019) showed that a novel 5-hydroxybenzothiazolone (5-HOB) derived β 2-ar agonist is a strong, selective β 2-ar agonist that is effective in promoting skeletal muscle growth, displaying tissue selectivity and reduced cardiovascular effects, compared with the well-described formoterol. Hence, their results suggested that 5-HOB may provide a new valuable treatment option for muscle atrophy conditions (Koziczak-Holbro et al., 2019).

Therefore, β 2-ar agonists clearly have the potential to augment skeletal muscle mass and function (Jenkins et al., 2018). Kamalakkannan et al. (Kamalakkannan et al., 2008) observed a significant increase in lean mass and maximal strength after clenbuterol administration in chronic heart failure patients. Jessen et al. (Jessen et al., 2018) observed a 1.03 kg increase in lean body mass after only four weeks of daily inhaled terbutaline compared with placebo administration in healthy young men. Le Panse et al. (Le Panse et al., 2005) observed important increases in peak power during maximal cycling exercise after three weeks of salbutamol ingestion in trained and untrained males.

Hostrup et al. (Hostrup et al., 2015) observed a significant 1.95 kg increase in lean body mass, in addition to increased cross-sectional area of type I and type II fibres of the vastus lateralis, and an increase in maximal strength and in peak power during maximal cycling exercise after four weeks of twice daily oral terbutaline versus placebo administration in trained, healthy young men.

Kim et al. (Kim et al., 2018) found out that the increase in skeletal muscle fibre size with chronic clenbuterol-induced β 2-ar stimulation was β -arrestin 1-dependent, indicating that β -arrestin 1 is a critical signalling molecule regulating skeletal muscle growth and function downstream of the β 2-ar.

The role of β -arrestin 1 was also studied with the use of carvedilol, a β -ar antagonist, widely used for the treatment of chronic systolic heart failure and hypertension. In a murine model, Kim et al. (Kim et al., 2020) showed that chronic treatment with carvedilol enhanced contractile force in skeletal muscle, and this process was mediated by β -arrestin 1. Carvedilol enhanced skeletal muscle contractility despite a lack of effect on skeletal muscle hypertrophy. So, these findings suggested a potential unique clinical role of carvedilol to stimulate skeletal muscle contractility while avoiding the adverse effects with β -ar agonists.

A couple of recent studies by Chikazawa and Sato (Chikazawa and Sato, 2018a, 2018b) showed that it is also possible to increase muscle β 2-ar expression by dietary improvement, so this was thought to be a promising strategy for the maintenance of healthy skeletal muscle and for achieving muscle hypertrophy. Resveratrol (a polyphenolic compound) and genistein (an isoflavone found in soybean) were shown to increase the β 2-ar mRNA levels in skeletal muscle cells (Chikazawa and Sato, 2018b). Gramine (a natural indole alkaloid) and hordenine (an alkaloid of the phenethylamine class), if administered by intramuscular route, were shown to increase the expression of hypertrophic genes in mice quadriceps, which was suggested to have been mediated, at least in part, by the β 2-ar activation, giving new possible therapeutic options (Chikazawa and Sato, 2018a).

DISCUSSION AND CONCLUSIONS

Collectively, there is a strong evidence supporting the importance of the β_2 -ar in the heart. Although β_1 -ar is the main modulator of the cardiac muscle's contraction, this mechanism is also involved in several heart disfunctions (Noh et al., 2017). β_2 -ar was found to potentially enhance heart contractions without the negative effects seen through the overstimulation of β_1 -ar (Bernstein et al., 2011).

The data reviewed here suggested that β_2 -ar's activation has some beneficial effects on the heart, such as a cardioprotective effect due to the alternative activation of β_2 -ar/Gi/PI3K pathway that leads to a decrease in cardiomyocyte apoptosis (Li et al., 2019). Therefore, β_2 -ars represent a potential therapeutic target for the treatment of cardiac diseases and vascular tumours (Aránguiz-Urroz et al., 2011; Rybin et al., 2000; Storch and Hoeger, 2010). However, further studies are needed to understand the intracellular signalling regulated by β_2 -ars, so then its use could be extended to treat a variety of cardiovascular diseases.

Maintaining skeletal muscle mass and function is vital for ameliorating the quality of life of elderly people (Chikazawa and Sato, 2018b). The data from the reported studies suggested that β_2 -ar agonists could be used as pharmacologic agents to prevent skeletal muscle wasting, increasing muscle mass and preventing atrophy (Chikazawa and Sato, 2018a).

Anyway, since most of those studies were performed in vitro, further studies are needed before they could be effectively proposed to be used in vivo.

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