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Letter to the Editor

BETA2-ADRENERGIC AGONISTS ARE SYMPATHOMIMETIC DRUGS WITH A MYOLYTIC-SPASMOGENIC ACTION

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INTRODUCTION

Selective β2-adrenergic agonists are very important sympathomimetic drugs which have been used for thousands of years and today, remain the one of the first-line treatments for asthma and chronic obstructive pulmonary disease (1). In addition to being the most powerful bronchodilator drugs (with myolytic action) currently available, these compounds can prevent bronchospasm (anti-spasmogenic action) induced by various types of agents. Another favorable prerogative is constituted by the notable flexibility of use of these drugs, due to the availability of short-acting and long-acting compounds that can be used respectively for the symptomatic treatment of asthma episodes and the prolonged control of the bronchospasm (2).

DISCUSSION

Three β receptors have been identified, called β1, β2, and β3, which are located respectively in the heart, in the smooth muscle of the airways, and in adipose tissue (3). Upper airway smooth muscles contain mostly β2 adrenergic receptors, while in the terminal respiratory tracts and alveoli, β1 and β2 receptors are both present. Additionally, the bronchial epithelia and mucous glands contain β2 receptors which are vital for regulating secretions. In the airways, inflammatory cells such as alveolar macrophages have β2 receptors (4).

β2-adrenergic receptors are membrane receptors coupled to stimulatory G proteins and consist of a single polypeptide chain having an extracellular N terminus and an intracytoplasmatic C terminus (5).

β2-agonists bind to their specific receptors, causing a conformational modification at the level of the fifth and sixth transmembrane domain, after which there is the activation of stimulatory G proteins made up of three α β γ subunits, which can directly activate the Ca^{2+} positive dependent potassium flux or stimulate adenylate cyclase by increasing the concentration of intracellular cAMP (6). Intracellular cAMP determines the activation of protein kinase A (PKA) and protein kinase G (PKG), and the subsequent phosphorylation of numerous substrates which initiate or modulate various cellular responses that are responsible for the myolytic and anti-spasmogenic action (7).

Three fundamental mechanisms for cellular responses can occur: (i) there can be a reduction in the cytosolic free Ca^{2+} concentration which can occur due to the extrusion of Ca^{2+} outside the cell due to activation of the ATP-dependent Ca^{2+} pump, (ii) an increase in Ca^{2+} uptake within intracellular stores; or (iii) an inhibition of Ca^{2+} release from intracellular stores sensitive to the second messenger inositol 1,4,5-triphosphate (IP3). There can be a hyperpolarization of the cell

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membrane or a decrease in the efficiency of the contractile apparatus through direct inhibition of the kinase at the level of the myosin light chain.

Therefore, β2-agonists act as functional antagonists causing bronchodilation independently of the contracting agent (Table I). β2-agonists can also cause bronchodilation indirectly by inhibiting the release of bronchoconstriction mediators, such as histamine and leukotrienes, that are generated by specific antigen-activated mast cells (MCs).

Table I. *Positive features of β2-agonists.*

- Powerful and rapid onset of the bronchodilation effect.
- Action on large and small caliber airways.
- High efficacy by inhalation with consequent selective activity on the target organ.
- Stimulation of mucociliary clearance.
- Inhibition of cholinergic and non-cholinergic neurotransmission.

However, it should be noted that while disodium cromoglicate, which is less powerful in inhibiting the release of histamine from MCs compared to β2-agonists, also prevents the late inflammatory phase of the response, and a pre-treatment with β2-agonists only prevents the immediate phase without any effect on macrophages.

β2-agonist activation also stimulates surfactant secretion by type II alveolar cells (8). The increase in surfactant secretion reduces the adhesiveness of bronchial secretions, which is increased in the case of bronchial asthma, and improves the transport of mucus through the lumen of the airways. This effect is also related to an improvement in mucous clearance, resulting in both improved ciliary function and the transport of ions and water across the epithelium. Finally, it is important to remember the modulatory effect of β2 receptor activation on cholinergic transmission. The activation of β2-receptors located on the post-ganglionic cholinergic nerves at a prejunctional level reduces the release of acetylcholine and may contribute to the bronchodilator effect by reducing reflex bronchoconstriction.

Pharmacological action of β2-agonists

the β2-agonists currently in use derive from chemical manipulations made to the structure of natural catecholamines, with the dual purpose of obtaining increasingly selective molecules and minimizing unwanted side effects, especially at a cardiovascular level (9).

Adrenaline, the precursor of β2-agonist drugs, stimulates both α and β receptors (2). The short half-life of the molecule, which is taken up by the terminal nerves, and the metabolization by catechol-O-methyltransferases distributed throughout the body, make adrenaline administered orally ineffective. Furthermore, its therapeutic interest, even when administered by aerosol, is limited by the non-negligible side effects deriving from α and β stimulation.

The β2-agonist research process began in the 1940s with the development of isoproterenol, the first compound with exclusive activity on β receptors, obtained by replacing the terminal methyl group of the adrenaline side chain with an isopropyl group. Despite the advantage due to the lack of α-adrenergic activity (vasoconstriction), isoproterenol, however, retains the β1/β2 activity of adrenaline and the bronchodilation effect profile characterized by a powerful and rapid, but extremely fleeting action.

Subsequent modifications of the catechol nucleus and/or the side chain of isoproterenol led to the synthesis of resorcinol derivatives (orciprenaline, terbutaline, fenoterol) and saligenin derivatives (salbutamol, carbuterol) with a longer duration of action as they are resistant to degradation operated by catechol-O-methyltransferases and of greater selectivity for the β2-receptor (10).

In resorcinol derivatives, the hydroxyl groups of the aromatic ring, compared to the catechol derivatives, are located in positions 3 and 5, instead of 3 and 4. This modification has made these compounds resistant to catechol-O-methyltransferases, prolonging the duration of the broncho-dilating effect. Metaproterenol, the first synthetic resorcinol derivative, retains the side chain of isoproterenol, while in fenoterol, the latter was modified by adding a hydroxyphenyl group. The β2 selectivity of resorcinol is not very high.

The salbutamol prototype of saligenin was obtained through a dual chemical manipulation with the addition of a methyl radical to the hydroxide group in position 3 of the catechol ring and the addition of a tertiary butyl group to the ethanolamine side chain (11). These modifications have allowed the acquisition of notable resistance against catechol-O-methyltransferases and greater selectivity for the β2 receptor subtype, respectively.

The newer generation of long-acting selective β2 agonists includes salmeterol and formoterol. Both drugs are potent and highly selective β2-agonists and salmeterol may be a partial agonist at β receptors in some tissues. Their long duration of action (about 12 hours) appears to be due to their lipid solubility rather than resistance to metabolic inactivation. Their remarkable lipid solubility allows these drugs to dissolve in high concentrations in the smooth muscle cell membrane. It is assumed that when they are dissolved in this way, they act as a slow-release depot that supplies active ingredients to the adjacent β receptors for a prolonged period.

β2-agonist drugs are classified based on their pharmacodynamic and pharmacokinetic characteristics: β2-agonists as background drugs, including long-acting inhaled β2-agonists and long-acting oral β2-agonists, and β2-agonist symptomatic drugs, including inhaled β2-agonists with rapid onset of action and short-acting oral β2-agonists (which are recommended for patients who are unable to use inhaled drugs). Inhaled β2-agonists with a rapid onset of action result in a prompt and immediate improvement in symptoms, and include salbutamol (albuterol), terbutaline, fenoterol, reproterol, and pirbuterol. Formoterol has both rapid onset and a long duration of action.

The dose administered and the dose of drug present systemically determines the frequency and importance of unwanted side effects. The main side effects are cardiovascular stimulation (tachycardia, extrasystoles), muscle tremors, and hypokalemia. However, the inhalation route of β2-agonists is the most advantageous method of administration, as it enhances the efficacy of bronchodilation while limiting unwanted side effects.

CONCLUSIONS

β2-agonists are historical bronchodilators which have an anti-spasmogenic and myolytic action, and today, still remain the first-line treatment for asthma and chronic obstructive pulmonary disease. Compared to other drugs, β2-agonists have the advantage of acting quickly and being highly effective. The biological action of these drugs is exerted after binding to their β1, β2, and β3 receptors located on the cells of the target tissue, such as smooth and cardiac muscles. Despite the widespread use of these drugs, their side effects must be considered, which include hypokalemia, tachycardia, extrasystoles, and muscle tremors.

Conflict of interest

The author declares that they have no conflict of interest.

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