Pharmacology of bronchodilators used in the treatment of COPD

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Introduction

Bronchodilators have beneficial effects in the treatment of COPD (1). Although the most commonly used bronchodilators, anticholinergics and β2-agonists, have been compared in many clinical studies, there is still debate as to which drug is the most effective.

Anticholinergics

Ipratropium bromide is the most commonly used anticholinergic in COPD, though oxitropium bromide is used in some countries. A more long-acting anticholinergic drug, tiotropium bromide, is due to become clinically available in the near future (2-6).

MECHANISMS OF ACTION

Anticholinergics have been used as bronchodilators for several hundred years in western Europe (7). They act by blocking the effects of acetylcholine, which is released from parasympathetic nerves in the airways, and which contributes to bronchoconstriction and mucus secretion in patients with COPD. Acetylcholine causes activation of muscarinic receptors at the level of the target cells, such as bronchial smooth muscle and goblet cells (8). Muscarinic M1 receptors are present in parasympathetic ganglia in the bronchial wall, and M2 receptors are found pre-junctionally on post-ganglionic cholinergic nerves. The most important receptor for the effects of acetylcholine is, however, the M3 receptor, because M3 receptor blockade will reduce all cholinergic bronchoconstrictor responses (9).

EFFECTS OF ANTICHOLINERGICS

Inhaled ipratropium bromide leads to bronchodilation and has a slightly slower onset of action than salbutamol, but a slightly longer duration of effect (10). It is important to remember that anticholinergics will reverse only one endogenous mediator of airflow obstruction, that is the release of acetylcholine from nerves, and will not affect bronchoconstriction induced by other mediators. It is, therefore, possible that functional antagonists of bronchial smooth muscle contraction, such as β2-agonists, will result in more pronounced bronchodilatation, because they reduce the adverse effects of several mediators in the airways. This statement is supported by the results of several published studies (11-13).

Anticholinergics are more effective in patients with COPD than in those with asthma, probably because parasympathetic tone contributes to the airway narrowing to a substantial degree in COPD (14,15). Nevertheless, the maximal bronchodilating effect of a β2-agonist is still more pronounced in most studies and, more importantly, β2-agonists are much more effective in improving bronchial responsiveness in patients with COPD (15-17).

β2-agonists

The relatively short-acting inhaled β2-agonists, salbutamol and terbutaline, have been used in the management of COPD for many years. In the recent guidelines published by the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) (1), inhaled short-acting β2-agonists, either alone or in combination with anticholinergics, are recommended as an alternative to the use of anticholinergics alone in the treatment of COPD (1,18).

The most important recent improvement in bronchodilator treatment has been the introduction of two long-acting inhaled β2-agonists, salmeterol and formoterol (19-21,22 24), both of which have proved to be beneficial in COPD (1). The duration of action of both drugs exceeds 12 h on average, compared with 4-5 h for salbutamol and 6 h for ipratropium bromide. Salmeterol was developed for use by inhalation, but formoterol was initially developed as an oral bronchodilator, and was subsequently shown to have a far longer duration of action when administered by inhalation than by the oral route (21). Interestingly, formoterol has been shown to be more effective than ipratropium bromide in a large population of patients with COPD (25), particularly in terms of quality of life. The different pharmacological properties of ipratropium bromide and formoterol may explain these findings.

MECHANISMS OF ACTION

At the β2-receptor, a β2-agonist forms hydrogen bonds to specific amino acids within the receptor protein, and thus induces a change in the three-dimensional structure of the receptor. This process enables the receptor to interact with intracellular stimulatory G-proteins (Gs) (26-28), which in turn stimulate the production of intracellular cyclic
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adenosine monophosphate (cAMP) (29). Production of cAMP leads to activation of protein kinase A (PKA), which leads to the phosphorylation of several intracellular proteins, resulting eventually in bronchial smooth muscle relaxation by inhibition of myosin–actin interaction (30). Other mechanisms of action of β2-agonists that are independent of cAMP have been proposed, including K+ channel activation via a sub-unit of the Gs (31-35). Importantly, β2-agonists are functional antagonists. Thus, they cause relaxation of the smooth muscle, regardless of which stimulus is causing the contraction.

EFFECTS OF β2-AGONISTS

The pharmacological behaviour of salmeterol and formoterol has several similarities, but also some clear differences. Both drugs are lipophilic (Fig. 1), though salmeterol is more lipophilic than formoterol (36-38). In airway smooth muscle preparations, the onset of action of salmeterol is slower than both salbutamol and formoterol, whereas the onset of action of formoterol is as rapid as salbutamol (39-41). However, salmeterol and formoterol have very similar durations of action in patients with asthma, despite the fact that formoterol has a slightly shorter duration of action than salmeterol in vitro (40-43).

MICROKINETIC DIFFUSION THEORY

The mechanisms of action of formoterol and salmeterol at the tissue and receptor level are considered to be quite different to those of the short acting β2-agonists. Anderson (44) has suggested that lipophilicity may be the most important factor in explaining why formoterol and salmeterol behave differently when given by inhalation. Because of its very high lipophilicity, salmeterol passes very rapidly into different cell membranes in the airway wall, and the cell membranes of all cells are likely to work as a depot of salmeterol (44) (Fig. 2). This is likely to reduce the speed by which salmeterol will reach the smooth muscle layer and the functional β2-receptors, because it will first enter other (non-smooth muscle) cells. In contrast, the more water soluble β2-agonists, such as salbutamol, which are present in high concentrations in the water phase of the airways after inhalation, move rapidly through the tissue to quickly reach the smooth muscle layer and its β2 receptors. Formoterol is not as lipophilic as salmeterol, and therefore a substantial proportion of formoterol molecules remain in the water phase and move rapidly through the airway wall (37,38,45), which may explain its more rapid onset of action (40,46). The long duration of action of both formoterol and salmeterol can be explained by the fact that both drugs are stored in the cell membrane lipid bilayer (Fig. 2), primarily in the smooth muscle, in close proximity to the β2-receptor. This allows the lipophilic long-acting β2-agonists to be available to the receptor over a long period of time (37,45).

An additional mechanism has been proposed to explain the long duration of action of salmeterol. It has been suggested that the long lipophilic arm of salmeterol interacts with a specific binding region within the β2-receptor. This reduces the likelihood of salmeterol leaving the receptor and enables the active portion of the salmeterol molecule to re-engage with the active site of the receptor region (the anchored-binding hypothesis) (45,47-49). However, the addition of excessive amounts of the salmeterol side chain, which according to pharmacological principles should block the binding of salmeterol to this anchored-binding site, does not influence the duration of effect of salmeterol (50). This argues against the anchored binding hypothesis for salmeterol.

FULL V.S. PARTIAL AGONISM

Salmeterol and formoterol also differ in efficacy (their maximal effect). Salmeterol has been shown to be a partial agonist. Although salmeterol has some intrinsic activity at the β2-receptor level, it does not have the ability to fully reverse a severe smooth muscle contraction, unlike the more effective β2-agonists, such as salbutamol or formoterol (42). Formoterol is a full agonist, and has been shown to be more effective and have a greater maximal effect than salmeterol in vivo (51) (Fig. 3).

In a randomized, double-blind study of patients with asthma, high doses of formoterol were shown to confer greater protection against methacholine-induced bronchoconstriction than salmeterol (51). The maximal broncho-protective effect of salmeterol, 250 µg, was approximately 2.5 doubling doses of methacholine, with no additional

![Fig 1. The chemical structure of formoterol and salmeterol. Salmeterol is more lipophilic than formoterol.](image-url)
FIG. 2. Salmeterol, because of its very high lipophilicity, is likely to enter cell membranes to a greater degree than formoterol, which may slow its diffusion through tissues. However, both salmeterol and formoterol are present in the cell membranes, which also could work as a depot of drug, explaining the long duration of action (redrawn from Anderson. Agents Action Suppl. 1993; 43: 253–269.)

FIG. 3. The shift in methacholine responsiveness after treatment with formoterol or salmeterol (data for placebo day is subtracted from each active treatment), shown as doubling doses of methacholine (DD). Formoterol causes a greater shift of methacholine responsiveness than salmeterol in these asthma patients, proving higher efficacy in vivo in man. (From Palmqvist et al. Am J Respir Crit Care Med 1999; 160: 244–249, with permission.)

effect when the dose was increased to 500 μg. In contrast, formoterol showed dose-related protective effects of at least 4-7 doubling doses, with no evidence of a maximum being reached after administration of 120 μg. The higher maximal efficacy of formoterol compared with salmeterol was associated with a slightly higher tremor score on the days formoterol treatment was given (formoterol, 120 μg, vs. salmeterol, 500 μg). This study confirmed the findings of the in vitro models that salmeterol is a partial agonist in relation to formoterol in human airways in vivo (42,52–55).

Although the clinical relevance of the differences in efficacy between formoterol and salmeterol remains unclear, several theoretical consequences of using a partial agonist have been noted. Firstly, it is possible that, in some patients, a full agonist is required to have sufficient clinical effect. Several such cases have been described in asthma (56), but it is still not clear how common this problem is in larger groups of asthmatic patients, or whether such cases can be found in a population with COPD.

Secondly, a partial agonist (e.g. salmeterol) could theoretically block the bronchodilating effects of a fuller agonist (e.g. salbutamol) (55). However, one study published as an abstract found no such blocking effect of salmeterol on fenoterol-induced bronchodilation (57). Furthermore, in patients with acute exacerbations of asthma treated regularly with salmeterol, the bronchodilating effect of salbutamol is maintained compared with patients not treated with salmeterol, again arguing against any blocking effect of salmeterol on the bronchodilating effects of a full agonist in the clinical situation (58). It therefore seems likely that patients treated regularly with the partial β2-agonist salmeterol still have enough spare β2-receptors on the smooth muscle for rescue β2-agonists to have sufficient effect.

Thirdly, it may be hypothesized that a full agonist would be more effective in patients with severe asthma, and perhaps also in patients with severe COPD. However, no study with sufficient size and power has evaluated whether there are any differences between formoterol and salmeterol in their ability to effectively treat such patient populations.

Conclusions

Bronchodilators, such as anticholinergics and β2-agonists, are clearly beneficial in the treatment of COPD, and evidence is emerging to suggest that long-acting β2-agonists may have additional benefits (1). Importantly, the two available long-acting β2-agonists, formoterol and salmeterol, have quite different pharmacological properties. Formoterol has a faster onset of action than salmeterol, but the two compounds have a similar duration of effect. Formoterol also has greater efficacy than salmeterol (Fig. 1). The pharmacology of formoterol suggests that it may be beneficial as rescue medication in COPD, as has already been shown in asthma (59). Further studies are required to evaluate the clinical relevance of the pharmacological differences between formoterol and salmeterol in patients with COPD.

References


