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Review Article

# Why use long acting bronchodilators in chronic obstructive lung diseases? An extensive review on formoterol and salmeterol

P. Santus [a], D. Radovanovic [a], P. Paggiaro [b], A. Papi [c], A. Sanduzzi [d], N. Scichilone [e], F. Braido [f,*]

[a] Dipartimento di Scienze della Salute. Pneumologia Riabilitativa Fondazione Salvatore Maugeri, Istituto Scientifico di Milano-IRCCS. Università degli Studi di Milano, Italy
[b] Cardio-Thoracic and Vascular Department, University Hospital of Pisa, Italy
[c] Respiratory Medicine, Department of Medical Sciences, University of Ferrara, Ferrara, Italy
[d] Section of Respiratory Diseases, Department of Surgery and Clinical Medicine, University of Naples, Italy
[e] Department of Internal Medicine, Section of Pulmonology (DIBIMIS), University of Palermo, Italy
[f] Allergy and Respiratory Diseases Clinic, DIMI, University of Genoa, IRCS AOU San Martino-IST, Genoa, Italy

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ABSTRACT

Long-acting $\beta_2$-adrenoceptor agonists, formoterol and salmeterol, represent a milestone in the treatments of chronic obstructive lung diseases. Although no specific indications concerning the choice of one molecule rather than another are provided by asthma and COPD guidelines, they present different pharmacological properties resulting in distinct clinical employment possibilities. In particular, salmeterol has a low intrinsic efficacy working as a partial receptor agonist, while formoterol is a full agonist with high intrinsic efficacy. From a clinical perspective, in the presence of low $\beta_2$-adrenoceptors availability, like in inflamed airways, a full agonist can maintain its bronchodilatory and non-smooth muscle activities while a partial agonist may be less effective. Furthermore, formoterol presents a faster onset of action than salmeterol. This phenomenon, combined with the molecule safety profile, leads to a prompt amelioration of the symptoms, and allows using this drug in asthma as an "as needed" treatment in patients already on regular treatment. The fast onset of action and the full agonism of formoterol need to be considered in order to select the best pharmacological treatment of asthma and COPD.

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## 1. Introduction

Since the 1990s, Long-Acting $\beta_2$-adrenoceptor Agonists (LABAs) have been considered as milestones in the treatment of Chronic Obstructive Pulmonary Disease (COPD) and asthma. In COPD, LABAs, formoterol and salmeterol, reduce airways obstruction, lung hyperinflation and exacerbations, improve exercise tolerance, ameliorate symptoms, enhance health-related quality of life [1–4] and offer a potential survival advantage [5]. In asthma, where LABAs are strictly recommended to be used in association with inhaled corticosteroids (ICS) [6], as results of the above mentioned effects, LABAs increase the probability of achieving disease control with a lower concomitant exposure to ICS as compared to ICS alone [7,8]. Although no specific indications concerning the choice between salmeterol or formoterol are provided by COPD and asthma guidelines [4,9], these drugs differ in pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body).

The aim of this paper is to review formoterol and salmeterol pharmacological properties and related different clinical employment possibilities.

## 2. Formoterol and salmeterol: differences in pharmacokinetics

A great advantage of inhalation drug therapy is the possibility to reach directly the target organ, reducing the systemic drug exposure and related adverse effects. LABAs have well-known pharmacological and clinical profiles with a few but essential differences [10,11] (Table 1).

The bronchodilatory effect of a LABA is a function of drug concentration at the bronchial smooth muscle cells and the degree of activation of the $\beta_2$-adrenoceptor. The onset and duration of bronchodilation are influenced by the time it takes for an inhaled LABA to achieve and maintain effective concentration at the receptor site [11]; both of these are related to physicochemical characteristics of the LABAs. Differences in physicochemical properties between formoterol and salmeterol may explain faster onset of action of formoterol [12]. Relatively high water solubility and moderate lipophilicity ensure rapid access of inhaled formoterol to the $\beta_2$-adrenoceptor on bronchial smooth muscle cells and rapid

* Corresponding author.
*E-mail address:* fulvio.braido@unige.it (F. Braido).

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**Table 1**
Effects of LABAs.

| | Stimulating effect | Inhibitory effect |
|---|---|---|
| Airway smooth muscle | | |
| Relaxation | + | |
| Proliferation | | + |
| Mucociliary clearance | + | |
| Ciliary beat frequency | + | |
| Alveolar fluid clearance | + | |
| Neutrophil adhesion | | + |
| Neutrophil chemotaxis | | + |
| Neutrophil apoptosis | + | |
| Eosinophil apoptosis | | + |
| Neutrophil activation | | + |
| Neutrophil ROS production | | + |
| Eosinophil ROS production | | + |
| Mast cell mediator release | | + |
| Eosinophil mediator release | | + |
| T-lymphocyte cytokine release | | + |

bronchodilation. In contrast, low water solubility and high lipophilicity of salmeterol results in its slower onset of action [12]. Additionally, the uptake of formoterol by airway smooth muscle cells is dependent on organic cation transporter 3 (OCT3); in contrast, the uptake of non-charged lipophilic salmeterol is independent of OCTs transporters. Importantly, corticosteroids inhibit OCT3 and by that may increase the presence of formoterol at cell membrane $\beta_2$-adrenoceptor thus potentiating formoterol effect [13,14].

Lipophilic characteristics of salmeterol and formoterol also explain prolonged duration of bronchodilation by these drugs [12], with a somewhat shorter duration of action for fomoterol than salmeterol in *ex vivo* experiments in small airways [12], however with no difference in duration of effect shown in a clinical study in asthmatic patients [15]. The lipophilicity of both formoterol and salmeterol is sufficient to allow them to easily enter and be stored in cell membranes, making a depot from which drugs are available to $\beta_2$-adrenoceptors on bronchial smooth muscle cells for a prolonged period of time [11]. This is in contrast to short-acting $\beta_2$-adrenoceptor agonists (such as salbutamol and terbutaline) which after inhalation are cleared from the tissue more rapidly due to their high water solubility. This was clearly demonstrated by Jeppsson et al. who showed that the relaxing effect of formoterol and salmeterol on isolated guinea pig tracheal smooth muscle pre-contracted with carbachol was less readily reversed by washing procedure than that of hydrophilic and short-acting salbutamol [16].

## 3. Formoterol and salmeterol: differences in pharmacodynamics

### 3.1. Bronchodilatory effects

The $\beta_2$-adrenoceptor agonists are the most effective bronchodilators because they are functional antagonists of airway smooth muscle contraction irrespective of the constricting stimulus. The $\beta_2$-adrenoceptors are distributed along the entire bronchial tree, in both large and small airways. Smooth-muscle relaxation results from coupling of the $\beta_2$-adrenoceptor, through the stimulatory Gs protein alpha subunit to adenylate cyclase in airway smooth muscle, which in turn increases the concentration of intracellular cyclic adenosine monophosphate (cAMP) [17]. cAMP acts through an intracellular network that is primarily related to protein kinase A (PKA) that leads to a down regulation or an up regulation of different molecular pathways that have smooth muscle relaxation as the principal endpoint. These mechanisms are complex [18,19], and some aspects are not completely understood in airway cells [19]. However, it is known that stimulation of β2-adrenoceptor by structurally different agonists results in stabilisation of different active states of the receptor and this may lead to activation of several different signalling pathways [20], including activation of inhibitory Gi protein which opposes Gs activation [21,22], resulting in decreased cAMP accumulation and the impairment of β2-adrenoceptor-mediated bronchodilation [23]. Thus, the degree of β2-adrenoceptor activation by structurally different agonists may be determined by the extent of Gi activation [22]. The differences in molecular structure of formoterol and salmeterol are responsible for differences in the interaction of these drugs with $\beta_2$-adrenoceptor and therefore differences in intrinsic efficacy that is high for formoterol and low for salmeterol (Fig. 1).

Formoterol binds to $\beta_2$-adrenoceptor with high affinity and triggers effective signal transduction while salmeterol does not lead to full signal transduction and therefore salmeterol is a partial agonist, i.e. has a lower intrinsic efficacy, compared to formoterol.

This explains higher extent of maximal dilation by formoterol of severely contracted tracheobronchial smooth muscle than that by salmeterol (independent of concentration applied) shown in isolated guinea pig trachea and in human bronchus [23,24]. Significantly, the differences in intrinsic efficacy between formoterol and salmeterol have implications for the bronchodilatory effects of these LABAs under inflammatory conditions. Accordingly, while a full agonist can show a full effect both in normal airway smooth muscles (where there is a reserve of $\beta_2$-adrenoceptors) and in inflamed tissues (where the number of fully functioning $\beta_2$-adrenoceptors may be limited), partial agonist may be not able to reach full effects in inflamed tissue, disregarded of how high doses are used. Adner et al. [25] showed that the maximal relaxation of carbachol-contracted mouse trachea segment by salmeterol was decreased by 40% by 4-day pretreatment with proinflammatory cytokines (TNFα and IL-1β) while this decrease was only 16% for formoterol. One likely mechanism involved is the cytokine-induced increased expression of cyclooxygenase (COX-2) leading to heterologous desensitisation of $\beta_2$-adrenoceptor impairing to a greater extent effects of a partial agonist, salmeterol, than those of full agonist, formoterol. Another possible mechanism is that receptor stimulation by salmeterol activates Gi protein to a greater extent, and that pro-inflammatory cytokines – through the up-regulation of the Gi signalling [26] – attenuate salmeterol responses to a greater extent than responses of formoterol. Interestingly, the concomitant treatment with a glucocorticosteroid, budesonide, blocked the cytokine-induced increased expression of COX-2 and prevented the

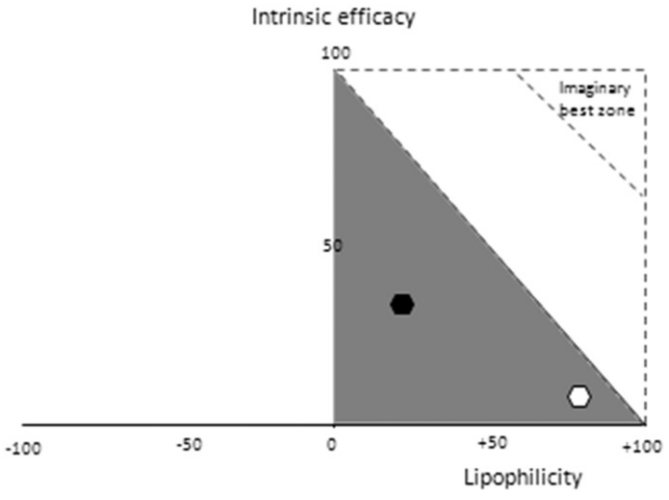


**Fig. 1.** The bronchodilator gray playing field. The black hexagon represents formoterol and the white hexagon salmeterol. The imaginary zone (upper right triangle) identifies the drugs with high power expressed by intrinsic efficacy and duration of action underline by lipophilicity; of course, the onset of action is related to water solubility which is not presented in this figure. However, it's worth considering that while lipophilicity per se does not guarantee a long duration of action, on the other hand may have several disadvantages too.

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