Salmeterol, formoterol, and salbutamol in the isolated guinea pig trachea: differences in maximum relaxant effect and potency but not in functional antagonism

Anders Lindén, Anna Bergendal, Anders Ullman, Bengt-Eric Skoogh, Claes-Goran Löfdahl

Abstract

Background—Formoterol and salmeterol are new long acting β₂ adrenoceptor agonists. The maximum relaxant effect, potency and functional antagonism against carbachol induced contraction for salmeterol, formoterol and salbutamol have been compared in the guinea pig isolated trachea. In addition, the possibility of inducing a non-β adrenoceptor mediated relaxation by salmeterol was studied.

Methods—Concentration response experiments were conducted with isolated tracheal preparations (n = 4–6 in all experiments), precontracted by carbachol to cause either 40% (60 nmol/l), 80% (0.3 μmol/l) or 100% (3 μmol/l, supramaximal) of the maximum contraction. Each β agonist was added cumulatively at each level of precontraction. Additional cumulative concentration response experiments were conducted for salmeterol alone at the highest level of precontraction, with and without β blockade by sotalol (1 mmol/l). With the drug concentrations which produced the maximum response and the highest level of precontraction, the relaxation of formoterol (10 nmol/l) and salmeterol (1 μmol/l) was also compared non-cumulatively. Finally, with the corresponding drug concentrations and precontraction, the relaxant effect was compared for formoterol (10 nmol/l) in salmeterol relaxed airways with that of salmeterol (1 μmol/l) in formoterol relaxed airways.

Results—The increase in carbachol concentration from 60 nmol/l to 3 μmol/l induced a rightward shift in the mean (SE) concentration (log steps) causing 50% maximum relaxation for salmeterol (0.73 (0.17)), formoterol (0.85 (0.18)), and salbutamol (1.13 (0.11)). Significant differences in the maximum relaxant effect were shown at the highest level of precontraction only, with a remaining active tension of percentage precontraction of 27% (4%) for 1 μmol/l salbutamol and 35% (3%) for 10 nmol/l formoterol compared with 50% (2%) for 1 μmol/l salmeterol. The rank order of potency was: formoterol > salbutamol ≈ salmeterol at all levels of precontraction (−log EC₅₀: formoterol 9.32 (0.05) for formoterol, 7.82 (0.08) for salbutamol, and 7.50 (0.13) for salmeterol at 80% maximum precontraction). Beta blockade by sotalol (1 mmol/l) significantly inhibited the relaxation induced by salmeterol (1 μmol/l) (remaining active tension: 104% (1%) v 71% (11%) of precontraction) but not the relaxation induced by salmeterol (10 μmol/l) (remaining active tension: 75% (5%) v 71% (12%) of precontraction). In the non-cumulative experiments, formoterol displayed more relaxant effect than salmeterol (remaining active tension: 51% (5%) v 65% (6%) of precontraction). Formoterol significantly relaxed salmeterol relaxed airways (relaxant effect: 22% (8%) of precontraction) whereas there was no significant response to salmeterol in formoterol relaxed airways (relaxant effect: 5% (12%) of precontraction).

Conclusions—In the guinea pig isolated trachea, formoterol and salbutamol produce more relaxant effect than salmeterol, suggesting that salmeterol is a partial β₂ agonist. Very high concentrations of salmeterol may induce non-β adrenoceptor mediated relaxation. Formoterol is more potent than both salbutamol and salmeterol. There is no pronounced difference in the magnitude of antagonism against carbachol induced contractions between salmeterol, formoterol, and salbutamol.

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In acute severe asthma there is a high level of airway smooth muscle contraction. Clinical trials of β₂ adrenoceptor agonists are, however, often performed in subjects with mild to moderate asthma and in vitro studies often examine the relaxant effect of β₂ agonists on airway smooth muscle at a single moderate level of precontraction.

The β₂ agonists salmeterol and formoterol produce bronchodilation of long duration in human subjects as well as in guinea pig isolated airways. It is not known whether the rank order of the maximum relaxant effect and potency of salmeterol and formoterol differ at various levels of airway smooth muscle contraction and are different from salbutamol.
In the present study, the potency and maximum relaxant effect of salmeterol and formoterol was compared with that of salbutamol at various levels of carbachol induced precontraction in the guinea pig isolated trachea. We also compared the rightward shift in the concentration response curve for each drug induced by an increase in precontraction, in order to evaluate differences in functional antagonism. In addition, we evaluated the possibility that salmeterol can produce non-β adrenoceptor mediated relaxation and examined the onset of action for salmeterol and formoterol at a high level of precontraction.

Methods
Tissue Preparation
Forty two female Dunkin-Hartley guinea pigs (350-500 g) were killed by cervical dislocation and exsanguination. The thoracic contents were placed in a 200 ml oxygenated (94% O₂; 6% CO₂) dissection bath filled with Krebs-Ringer solution (mmol/l: NaCl 118; KCl 5-9; CaCl₂ 2-5; MgSO₄ 1-2; NaH₂PO₄ 1-2; NaHCO₃ 25-5; glucose 5-6) at room temperature. The cervical trachea was dissected free and 3-4 air rings were then cut transversely, each containing four cartilaginous rings. The air rings were opened longitudinally along the anterior, cartilaginous part and connected to steel hooks as isolated strips. These preparations were mounted in temperature controlled (37°C) and oxygenated 8 ml organ baths which could be flushed with fresh Krebs-Ringer solution (0-33 ml/min). This method of handling leaves the airways histologically intact.

Tension Recordings
The isometric tension was recorded via Grass force transducers (FP30) connected to an NB-MIO-16 analogue/digital converting board and a Macintosh II computer with the LabVIEW signal processing software (National Instruments, Austin, Texas, USA). The difference in tension between the precontraction induced by carbachol and the level during the theophylline induced relaxation (below) was regarded as 100% active tension (precontraction).

Experimental Design
In all the experiments the spontaneous active tension was initially abolished by adding 10 μmol/l indomethacin which was continuously present in the Krebs-Ringer solution. The applied, passive tension was then adjusted to 1-4 g. After the decline during the 45 minutes of equilibration, the tension was readjusted to 1-4 g. At the end of all the experiments the remaining active tension was abolished by 2-2 mmol/l theophylline which produces a maximum relaxation in the guinea pig isolated trachea.

Concentration response curves for salmeterol, formoterol, and salbutamol
These experiments were conducted to compare the maximum relaxant effect and the potency of formoterol and salmeterol and salbutamol at various levels of precontraction. For these drugs the rightward shift in the concentration response curve induced by an increase in precontraction was also compared.

Three different levels of carbachol induced precontraction were established by flushing the organ baths with Krebs-Ringer solution containing carbachol, causing 40% (60 mmol/l) or 80% (0-3 μmol/l) or 100% (3 μmol/l, supramaximal concentration) of the maximum carbachol induced contraction. The induced precontraction stabilized over 20 minutes and the flushing was then stopped. The concentration of the β₂ agonists was increased cumulatively every 30 minutes (formoterol and salbutamol) or 60 minutes (salmeterol). This was because separate experiments showed that these drugs produce a maximum relaxant effect during these incubation times (unpublished data). The concentration of salmeterol was increased in full log steps, whereas the concentration of formoterol and salbutamol was increased in semi log steps in order to obtain a similar time course for the experiments, as the time of onset was longer for salmeterol in a recent study.

Effects of β-blockade on salmeterol induced relaxation
Separate, preliminary experiments showed a plateau on the concentration response curve from 1 to 10 μmol/l salmeterol at the highest level of precontraction whereas 0-1 mmol/l salmeterol produced an additional relaxation (data not shown). The present experiments were conducted because of this atypical, biphasic concentration response curve as an evaluation of the possibility that high concentrations of salmeterol produce non-β adrenoceptor mediated relaxation.

Beta adrenoceptor blockade was initially established by flushing the preparations with sotalol, using preparations within the same guinea pig as controls. One series was performed with 0-1 mmol/l sotalol and another with 1 mmol/l sotalol. A precontraction was induced by 3 μmol/l carbachol and, after the flushing was stopped, salmeterol was cumulatively added every 60 minutes.

Time course of maximum relaxant effect for salmeterol and formoterol
These experiments were conducted to examine whether there is any difference in maximum relaxant effect between formoterol and salmeterol using a non-cumulative design. By doing this, we also examined the onset of action for formoterol compared with salmeterol at a high level of precontraction.

A precontraction was established by flushing with 3 μmol/l carbachol and thereafter the flushing was stopped before the addition of salmeterol and formoterol. Each of these β₂ agonists was then used in the concentration producing the maximum β adrenoceptor mediated response. Salmeterol, 1 μmol/l, was
thus added to every second preparation while 10 nmol/l formoterol was added to the other preparations. Because these experiments also served as controls for the subsequent ones, we ascertained that the theophylline induced reference relaxation was performed under constant conditions. We therefore performed crosswise additions of 10 nmol/l formoterol to the salmeterol treated preparations after 60 minutes and of 1 μmol/l salmeterol to the formoterol treated preparations after 30 minutes.

Partial agonism: salmeterol v formoterol
In these experiments we evaluated the possibility that salmeterol is a partial β2 agonist compared with formoterol.

A precontraction was established by flushing with 3 μmol/l carbachol. The flushing was stopped and 1 μmol/l salmeterol was then added to every second preparation and 10 nmol/l formoterol was added to the other preparations. After 15 minutes, when the maximum relaxant effect was obtained, this was followed by crosswise additions of 10 nmol/l formoterol to the salmeterol treated preparations and 1 μmol/l salmeterol to the formoterol treated preparations. The time course experiments served as controls.

DATA ANALYSIS
Calculations of the drug concentration causing 50% of the maximum drug effect (EC50 value)
A concentration response curve was calculated for each drug and preparation using the maximum relaxation, whenever it occurred, during the incubation time. At each level of precontraction the calculation of EC50 values was made by linear interpolation between the nearest value above and below 50% of the maximum drug response on the concentration response curve for each guinea pig. Two preparations from the salmeterol group were excluded during these calculations as the first drug concentration produced more than 50% of the maximum drug response and thus made it impossible to calculate the EC50 value.

Statistical evaluation
The results are presented as mean (SE). Student's t distribution (one or two tailed) for differences between data (paired or unpaired) was determined at 95% confidence intervals for comparisons including data compared once or twice and at 99% confidence intervals for comparisons including data compared three or four times.25

DRUGS
Formoterol fumarate (racemate, pure R and S enantiomers) (Ciba-Geigy), salbutamol sulphate (Glaxo), and salmeterol base (race-mate) (Glaxo) were dissolved in acetic acid and thereafter diluted in Krebs-Ringer solution. Carbachol (Sigma) was dissolved and diluted in Krebs-Ringer solution only. Indomethacin (Dumex, Confortid, 5 mg/ml) and sotalol hydrochloride (race-mate) (Bristol; Sotacor, 10 mg/ml) were diluted in Krebs-Ringer solution only.

Results
CONCENTRATION RESPONSE CURVES FOR SALMETEROL, FORMOTEROL AND SALBUTAMOL
There were small differences in the absolute levels of precontraction (in grams) induced by 60 nmol/l, 0-3 μmol/l, and 3 μmol/l carbachol, for preparations treated with salmeterol, formoterol, and salbutamol (table 1). We found no systematic, drug related difference in precontraction which could have explained the present results. Table 1 also shows the maximum relaxant response for each β2 agonist and theophylline.

At the highest level of precontraction (fig 1) but not at the two lower levels, salmeterol

![Figure 1](https://example.com/figure.png)

**Figure 1**: Cumulative concentration response curves for salmeterol, formoterol, and salbutamol at various levels of carbachol induced precontraction (60 nmol/l = small filled symbols, 0-3 μmol/l intermediate open symbols, 3 μmol/l large filled symbols) in the guinea pig isolated trachea. The remaining active tension (mean (SE)) is presented as a percentage of the difference between the precontraction level and the level in the presence of 2-2 mmol/l theophylline (n = 4–6). The airways were pretreated with 10 μmol/l indomethacin.

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**Table 1**: Mean (SE) maximum cumulative relaxant responses (change in tension in grams) for salmeterol, formoterol, salbutamol and 2-2 mmol/l theophylline at different levels of carbachol induced precontraction (total tension in grams) in the guinea pig isolated trachea (n = 6)

<table>
<thead>
<tr>
<th>Carbachol concentration</th>
<th>Salmeterol</th>
<th>Theophylline</th>
<th>Formoterol</th>
<th>Theophylline</th>
<th>Salbutamol</th>
<th>Theophylline</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 nmol/l</td>
<td>1.90 (0.10)</td>
<td>1.21 (0.11)</td>
<td>1.42 (0.19)</td>
<td>1.42 (0.20)</td>
<td>1.90 (0.10)</td>
<td>1.01 (0.07)</td>
</tr>
<tr>
<td>0.3 μmol/l</td>
<td>2.31 (0.17)</td>
<td>1.42 (0.19)</td>
<td>3.42 (0.52)</td>
<td>3.42 (0.52)</td>
<td>3.42 (0.52)</td>
<td>3.42 (0.52)</td>
</tr>
<tr>
<td>3 μmol/l</td>
<td>2.85 (0.34)</td>
<td>3.55 (0.14)</td>
<td>2.85 (0.34)</td>
<td>2.85 (0.34)</td>
<td>2.85 (0.34)</td>
<td>2.85 (0.34)</td>
</tr>
</tbody>
</table>

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Salmeterol, formoterol and salbutamol in isolated airways
displayed less maximum relaxant effect than the other two $\beta_2$ agonists; this difference was significant for salmeterol compared with formoterol (99% confidence interval for difference: 1–27% of precontraction, n = 6) and for salmeterol compared with salbutamol (99% confidence interval for difference: 6–39% of precontraction, n = 6). There was no significant difference in maximum relaxant effect at the highest level of precontraction for formoterol compared with salbutamol (99% confidence interval for difference: −11–27% of precontraction, n = 6).

As shown in table 2, formoterol was more potent than salbutamol. This difference in potency was significant at all levels of precontraction (99% confidence interval for difference, in log steps: 0.78±2.16 at 60 mmol/l, 1.26±1.73 at 0.3 mmol/l, and 1.30±2.19 at 3 mmol/l carbachol, n = 6). Formoterol was also more potent than salmeterol and this difference was also significant at all levels of precontraction (99% confidence interval for difference, in log steps: 1.06±2.59 at 60 mmol/l, 1.48±2.16 at 0.3 mmol/l, and 1.32±2.20 at 3 mmol/l carbachol, n = 4–6). There was no significant difference in potency between salbutamol and salmeterol at any level of precontraction (99% confidence interval for difference, in log steps: −0.59±1.30 at 60 mmol/l, −0.04±0.69 at 0.3 mmol/l, and −0.15–0.59 at 3 mmol/l carbachol, n = 4–6).

In terms of $EC_{50}$ value, there was a rightward shift of the concentration response curve for the three $\beta_2$ agonists as the carbachol concentration was increased from 60 mmol/l to 3 mmol/l (shift in log steps: 0.73 (0.17) for salmeterol, 0.85 (0.18) for formoterol, and 1.13 (0.11) for salbutamol, n = 4–6), (fig 1, table 2). No significant difference in the magnitude of this shift was found for salmeterol compared with salbutamol (99% confidence interval for difference, in log steps: −0.25–1.05, n = 4–6), for formoterol compared with salbutamol (99% confidence interval for difference, in log steps: −0.41–0.95, n = 6), or for salmeterol compared with formoterol (99% confidence interval for difference, in log steps: −0.75–1.01, n = 4–6), (fig 1, table 2).

### Table 2

<table>
<thead>
<tr>
<th>Carbachol concentration (mmol/l)</th>
<th>$-\log EC_{50}$ (mol/l) Salmeterol</th>
<th>Formoterol</th>
<th>Salbutamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>8.30 (0.18)</td>
<td>10.13 (0.11)</td>
<td>8.66 (0.16)</td>
</tr>
<tr>
<td>0.3</td>
<td>7.90 (0.05)</td>
<td>9.02 (0.08)</td>
<td>7.75 (0.08)</td>
</tr>
<tr>
<td>3</td>
<td>7.51 (0.08)</td>
<td>9.28 (0.10)</td>
<td>7.53 (0.08)</td>
</tr>
</tbody>
</table>

### EFFECTS OF $\beta$ BLOCKADE ON SALMETEROL INDUCED RELAXATION

Beta blockade by sotalol inhibited the relaxant effect produced by 0.1 mmol/l salmeterol (95% confidence interval for difference: −25–20% of precontraction, n = 4). At 1 mmol/l sotalol, however, there was no significant inhibition of the relaxant effect produced by 0.1 mmol/l salmeterol (95% confidence interval for difference: −20–29% of precontraction, n = 6).

### TIME COURSE OF MAXIMUM RELAXANT EFFECT FOR SALMETEROL AND FORMOTEROL

At the highest level of precontraction, the relaxant effect induced by 1 mmol/l salmeterol and 10 mmol/l formoterol showed a similar time course, with the mean maximum effect after 15 minutes. In these experiments formoterol also produced more relaxant effect than salmeterol and this difference was significant (95% confidence interval for difference: 7–21% of precontraction, n = 4), (fig 3).

### PARTIAL AGONISM: SALMETEROL VS FORMOTEROL

In the airways which were initially relaxed by 1 mmol/l salmeterol, 10 mmol/l formoterol displayed less maximum relaxant effect than the other two $\beta_2$ agonists; this difference was significant for salmeterol compared with formoterol (99% confidence interval for difference, in log steps: −0.25–1.05, n = 4–6), for formoterol compared with salbutamol (99% confidence interval for difference, in log steps: −0.41–0.95, n = 6), or for salmeterol compared with formoterol (99% confidence interval for difference, in log steps: −0.75–1.01, n = 4–6), (fig 1, table 2).
produced an additional relaxation which proved significant 15 minutes after the addition (after a total of 30 minutes, fig 4A) in comparison with the control (95% confidence interval for difference: 6–38% of precontraction, n = 4–6). In contrast, in the airways which were initially relaxed by 10 mmol/l formoterol, 1 mmol/l salmeterol failed to produce any additional relaxation which proved significant 15 minutes after the addition (after a total of 30 minutes, fig 4B) in comparison with the control (95% confidence interval for difference: −19–29% of precontraction, n = 4).

Discussion
Conducting cumulative concentration response experiments, we found that formoterol and salbutamol produce more relaxant effect than salmeterol at a very high level of precontraction in the guinea pig isolated trachea. This unexpected finding was evaluated with several experimental approaches in order to exclude methodological confounding factors.

In separate cumulative concentration response experiments the salmeterol concentration was increased to very high levels, with and without preincubation with the β blocker sotalol. The control groups in these experiments confirmed our preliminary observation of an atypical, biphasic concentration response curve by displaying a plateau between 1 and 10 μmol/l and a second relaxant phase at 0-1 mmol/l salmeterol. Unexpectedly, β blockade by sotalol did not inhibit the relaxation induced by 10 μmol/l salmeterol. Amplifying the competitive antagonism by increasing the sotalol concentration from 0-1 to 1 mmol/l substantially increased the inhibition of the relaxation produced by 0-1 and 1 μmol/l salmeterol. The amplified competitive antagonism did not, however, inhibit the relaxation produced by 10 μmol/l salmeterol. Clearly this makes competitive antagonism a less credible explanation of the sotalol resistant relaxation produced by salmeterol and there are other data to support this.

In another study on our airway model, 10 μmol/l sotalol did inhibit a relaxation induced by 1 μmol/l intermediate acting salbutamol whereas the effect of 1 μmol/l salmeterol was only partially inhibited. As indicated by their similar potency in our airway model, salbutamol and salmeterol should have had a similar ability to overcome the effect of a competitive antagonist but this was not the case. It also appears unlikely that the high β2 adrenoceptor affinity of salmeterol should be the sole explanation of the sotalol resistant relaxation for two reasons. Firstly, formoterol and salmeterol have a similarly high β adrenoceptor affinity in rat lung membranes and, secondly, when used in the concentration producing the maximum effect in our model, formoterol produced a relaxation which was inhibited by sotalol, in contrast with that of the corresponding concentration of salmeterol. These data also make competitive antagonism a less credible explanation of the sotalol resistant relaxation produced by salmeterol. Our interpretation of the present data is therefore that, in high concentrations, salmeterol produces a non-β adrenoceptor mediated relaxant effect which explains the biphasic concentration response curve.

It is also possible that 1 μmol/l salbutamol and 10 mmol/l formoterol could produce non-β adrenoceptor mediated relaxation which would confuse the interpretation of differences in maximum relaxant effect. With the same or higher concentrations of formoterol and salbutamol in another study on our airway model, however, these β agonists induced a relaxation which was inhibited by sotalol in a 10–100 fold lower concentration than in the present study. The present effects of formoterol and salbutamol cannot therefore be attributed to a non-β adrenoceptor mediated relaxation.

In human airways in vivo little is known about the local drug concentration surrounding the smooth muscle cells. Based on calculations, however, it has been suggested that the topical concentration of an inhaled drug could be as high as 0-1 mmol/l in smaller bronchi. If this is true, salmeterol could produce a non-β adrenoceptor mediated relaxation in vivo in addition to its β adrenoceptor mediated effect.

The difference in maximum relaxant effect in favour of formoterol over salmeterol was confirmed in the time course experiments with these drugs in the concentrations producing the maximum β adrenoceptor mediated drug response. We also found that a significant additional relaxation was produced by adding formoterol to airways already relaxed by salmeterol. In contrast, no significant additional relaxation was produced by adding salmeterol to airways already relaxed by formoterol, again with the corresponding concentrations of the long acting β agonists. Three experi-
Formoterol and salmeterol are not indicated as therapy for acute severe asthma. However, acute severe asthma can occur during long-term treatment with long-acting β agonists as illustrated by a recent case report in a one-year study on patients with asthma taking formoterol. In this case, one patient stopped taking steroids and seriously deteriorated. Hypothetically, a β agonist with partial agonism would produce less bronchodilator effect in this situation, in comparison with a full agonist. It is, however, uncertain whether the extreme level of smooth muscle contraction which we produced in the guinea pig isolated trachea also occurs in human asthmatic airways.

We examined the potency of β agonists at various levels of precontraction. In our model, formoterol was 30–60 times more potent than salbutamol, depending on the level of precontraction. Compared with salmeterol, formoterol was 60–70 times more potent, also depending on the level of precontraction. The result revealed no pronounced difference in potency between salmeterol and salbutamol and, consequently, the rank order of potency was the same at all levels of precontraction. The higher potency of formoterol compared with salmeterol and salbutamol is consistent with most previous data on the guinea pig isolated trachea. There are also preliminary data on formoterol and salbutamol in the human isolated bronchus, at an increased, acetylcholine induced tone, which agree with our findings. Data from asthmatic subjects also support the finding that formoterol is more potent than salbutamol. In the case of salmeterol, some authors have claimed that this β agonist is more potent than salbutamol in the guinea pig isolated trachea. Although we observed a similar trend, there was no pronounced difference in potency for salmeterol and salbutamol in our study. We find it likely that this type of minor discrepancy could be due to different means of inducing the precontraction.

The functional antagonism between contractile and relaxant responses may be important in the control of airway smooth muscle contraction. However, as the carbachol induced precontraction was increased, no pronounced difference was found in the magnitude of the rightward shift in the drug concentration causing 50% of the maximum drug response (EC50) for salmeterol, formoterol, and salbutamol. This could not be explained by the fact that two salmeterol treated preparations were excluded (see Methods), since there was a trend towards a more pronounced rightward shift in the concentration response curves in those preparations. The somewhat lower mean rightward shift for salmeterol compared with salbutamol would therefore have been somewhat increased by the excluded preparations. We conclude that the potency of long acting and intermediate acting β agonists is similarly decreased by an increased level of airway smooth muscle tone.

The present time course experiments suggested a similar onset of action within 15 minutes for both long acting β agonists at a very high level of smooth muscle contraction. In this respect our in vitro data are consistent with clinical data, both for formoterol and salmeterol, although no comparative clinical study of the onset of action for salmeterol and formoterol is available. In two recent in vitro studies salmeterol did, however, show a slower onset of action than formoterol and salbutamol in the guinea pig trachea. These studies were performed with a lower concentration of salmeterol and a lower level of precontraction than in the present study. At least for salmeterol, it is thus possible that the drug concentration and the level of smooth muscle contraction affect the onset of action.

In conclusion, this in vitro study indicates that formoterol and salbutamol produce more relaxant effect than salmeterol during severe airway smooth muscle contraction, suggesting that salmeterol is a pronounced β agonist. This study also indicates that high concentrations of salmeterol may produce non-β adrenoceptor mediated relaxation. Formoterol appears to be more potent than salbutamol and salmeterol at all levels of airway smooth muscle contraction. The relationship between the potency and the degree of airway smooth muscle contraction is probably similar for all three β agonists. The clinical relevance of these findings is not yet established and should be addressed in further studies.

This study was approved by the Animal Ethics Committee at the Medical Faculty, University of Göteborg (Dnr 92/89). The data in this paper were in part presented at the first meeting of the European Respiratory Society in 1991. Financial support was obtained from Ciba-Geigy, Glaxo, Hermann Krefting’s Foundation, and the Swedish Heart-Lung Fund. We thank Lena Berntsen for her excellent technical assistance.

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