Effects of short-term oral salbutamol administration on exercise endurance and metabolism

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Collomp, K., R. Candau, F. Lasne, Z. Labsy, C. Préfault, and J. De Ceaurriz. Effects of short-term oral salbutamol administration on exercise endurance and metabolism. J Appl Physiol 89: 430–436, 2000.—The present study examined whether oral short-term administration of salbutamol (Sal) modifies performance and selected hormonal and metabolic variables during submaximal exercise. Eight recreational male athletes completed two cycling trials at 80–85% peak O2 consumption until exhaustion after either gelatin placebo (Pla) or oral Sal (12 mg/day for 3 wk) treatment, according to a double-blind and randomized protocol. Blood samples were collected at rest, after 5, 10, and 15 min, and at exhaustion to determine growth hormone (GH), cortisol, testosterone, triiodothyronine (T3), C peptide, free fatty acid (FFA), blood glucose, lactate, and blood urea values. Time of cycling was significantly increased after chronic Sal intake (Sal: 30.5 ± 3.1 vs. Pla: 23.7 ± 1.6 min, P < 0.05). No change in any variable was found before cycling except a decrease in blood urea concentration and an increase in T3 after Sal that remained significant throughout the exercise test (P < 0.05). Compared with rest, exercise resulted in a significant increase in GH, cortisol, testosterone, T3, FFAs, and lactate and a decrease in C peptide after both treatments with higher exercise FFA levels and exhaustion GH concentrations after Sal (P < 0.05). Sal but not Pla significantly decreased exercise blood glucose levels. From these data, short-term Sal intake did appear to improve performance during intense submaximal exercise with concomitant increases in substrate availability and utilization, but the exact mechanisms involved need further investigation.

β2-agonist; performance; submaximal exercise; hormone; free fatty acid

The β2-adrenoceptor agonist salbutamol (Sal) is the most commonly prescribed medication for bronchoospasm and exercise-induced asthma, a clinical entity that affects ~10–20% of athletes, with an even higher prevalence in cycling and mountain biking (21, 22, 33, 35). Since 1985, athletes have been allowed to take a few inhaled β2-agonists, including Sal, but systemic administration is currently banned by the International Olympic Committee because of the concern that it may lend an unfair competitive advantage to the users.

Most of the published studies (20–22) have not been able to demonstrate increased physical performance after acute β2-adrenoceptor agonist inhalation. However, surprisingly little work has been done to determine whether oral Sal administration, which represents doses 10- to 20-fold greater, has a beneficial effect on performance. As a matter of fact, two studies (3, 18) demonstrate that chronic Sal intake at therapeutic doses increases voluntary muscle strength in men, but no published information on endurance performance and on eventual hormone and/or metabolism Sal interaction(s) is available for dynamic exercise after systemic administration.

The present study was designed to test the hypothesis that short-term oral administration of Sal (12 mg/day for 3 wk) improves endurance performance during submaximal exercise in a group of nonasthmatic recreational athletes. Furthermore, given the well-known direct or indirect involvement of β2-adrenoceptors in different metabolic pathways (4, 13, 23, 25, 30), hormonal and/or metabolic effects resulting from Sal intake may be expected to have an influence on exercise endurance. Performance, hormonal [growth hormone (GH), testosterone, cortisol, triiodothyronine (T3), C peptide], and metabolic parameters [blood glucose, free fatty acids (FFAs), lactate, and blood urea] were therefore monitored in the present study.

METHODS

Subjects

Eight recreational male athletes agreed to participate in the study after being informed of the nature of the experiments. All subjects signed a consent form that outlined possible risks due to the protocol, which had been approved by the Ethics Committee of the Montpellier Saint-Eloi Hospital.

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They had been actively cycling and/or running three to five times per week for at least 3 yr. Subjects were screened with a medical history and physical examination to exclude those with a history of bronchospasm or atopy. Exclusion criteria included respiratory tract infection during the previous month, regular use of tobacco, regular use of any medical drug, recognized asthma or allergy during the 5 yr before the study, or a restriction in forced expiratory volume during 1 s after exercise (experimental procedure). Subjects were 23.4 ± 0.8 yr of age and weighed 71.6 ± 2.7 kg (means ± SE). No significant changes in body weight were measured at the end of the experiment.

Experimental Procedure

All the subjects had previously participated in physical exercise experiments in the laboratory. In the month before the first treatment, an incremental test for peak oxygen consumption (VO2peak) was conducted on a Monark cycle ergometer (model 918E, Monark-Crescent, Varberg, Sweden) to select a power output eliciting 80–85% of VO2peak, following a standard laboratory procedure (10). Mean VO2peak was 55 ± 1.7 ml·kg⁻¹·min⁻¹. To increase the reproducibility of time to exhaustion and to habituate themselves to the protocol, they returned for one additional submaximal (80–85% VO2peak) trial ride in the 2 wk before the actual experiment.

Subjects were asked to maintain similar exercise patterns and normal food intake throughout the duration of the experiments and to abstain from intense exercise and any caffeine and alcohol for 24 h before each trial.

Drug

The double-blind, randomized crossover study consisted of two 3-wk treatments for each subject separated by a 4-wk drug-free washout period: gelatin placebo (Pla) and salbutamol (Sal). Pla and Sal (trade name Salbumol, 2 mg, tablet, Glaxo-Wellcome Laboratory, Paris) were packaged in identical capsules. During the experimental periods, the subjects received three capsules daily of either Pla or Sal (4 mg, i.e., 2 tablets per capsule), one capsule at 8:00 AM, one at 12:00 noon, and one at 5:00 PM. When questioned as to their knowledge of which of the two treatments they received first, subjects were unable to report any difference except one, who mentioned some overexcitement after Sal treatment.

Trials to exhaustion were performed on the 22nd day of each treatment after a final capsule ingestion of either Pla or Sal with an additional submaximal trial performed after the drug-free washout period.

Experimental Protocol

The protocols for each trial were identical. Trials were held at the same time of day (10:30 AM–11:30 AM) for each subject to prevent diurnal variations in hormonal responses (14). On the actual testing days, subjects reported to the laboratory at 8:30 AM–9:30 AM, 1 h after ingestion of a small meal, which was identical for each trial. Dietary consistency (~500 kcal) was confirmed through self-reported diet records and questioning before each trial. Subjects then ingested one capsule containing either Pla or Sal (4 mg) and rested quietly for 90 min. After insertion of a catheter into a superficial forearm vein (10:00 AM–11:00 AM), subjects warmed up with light cycling. An accurate record was kept of the duration and intensity of the warm-up on the first trial (~5 min), which was identical for all trials and was not considered to be part of the total exercise time.

The subjects then rested and at 10:30 AM–11:30 AM exercised to exhaustion at 80–85% VO2peak after a resting blood sample was obtained. Blood samples were taken every 5 min during the first 15 min of exercise. No samples were taken between 15 min and exhaustion so that subjects could not count samples as a crude time device. Exhaustion was determined by the investigators when cadence could no longer be maintained at a rate of 90% of the subject’s set rate. Water was given ad libitum during exercise. Subjects did not have access to any indication of time after the initial 15-min sampling period during the exercise, and results were disclosed only on completion of the entire study.

Blood Analyses

Blood samples (12 ml) were immediately separated into three aliquots, promptly centrifuged for 10 min at 4°C and 3,000 rpm, and stored at −72°C until assayed. Four milliliters were transferred to a nontreated tube for GH, T3, and blood urea analysis; 4 ml were placed in a chilled sodium-heparinized tube for FFA, cortisol, and total protein determination; and the last 4 ml were placed in a chilled EDTA-aprotinin tube for blood glucose, lactate, testosterone, and C peptide analysis.

ELISA tests were used for the hormone analyses: cortisol, GH, testosterone, C peptide, T3, and TSH (kits from Elitech, IBL, and NeoGen). Total protein, blood glucose, lactate, FFA, and blood urea were determined by enzymatic colorimetric assays on two automatic analyzers (Dimension, Dade Behring and Cobas Mira +, Hoffman La Roche). All assays were made in duplicate. Coefficients of variation (inter- and intra-assay) for all parameters were always <10%.

Statistics

Data are presented as means ± SE.

Paired t-test was used to determine whether significant differences existed 1) between Pla and Sal cycling time to exhaustion and 2) between the first habituation trial and the final Pla trial to verify the lack of training effect during the experiment.

All the measured blood variables were statistically analyzed for effects of time (0, 5, 10, and 15 min and exhaustion) and treatment (Sal vs. Pla) by use of a two-way ANOVA (one between, one within). When a significant F ratio was observed, a Newman-Keuls multiple-comparison test was performed to determine the location of the differences.

The null hypothesis was rejected at P < 0.05.

RESULTS

Performance Responses

No training effect was found in this study. Indeed, times to exhaustion for the first habituation trial (22.8 ± 1.8 min) and for the final Pla trial (23.5 ± 1.7 min) were not significantly different.

Time to exhaustion was significantly increased (Fig. 1) over Pla after the Sal treatment: 30.5 ± 3.1 vs. 23.7 ± 1.6 min for Sal vs. Pla, respectively (P < 0.05). Chronic ingestion of Sal increased the time to exhaustion in seven subjects and decreased it in one.

Metabolic Data

Plasma volume was significantly decreased during exercise because there was a significant increase in plasma protein concentration (P < 0.05; see Table 1...
and Fig. 2). At rest and during exercise, total protein tended to decrease after Sal administration but not significantly compared with after Pla administration. Because we did not see any significant differences in plasma protein shifts between Pla and Sal (Table 1), we have chosen to present the direct measured values.

Blood glucose. Preexercise blood glucose concentration was not altered after Sal treatment. During exercise, blood glucose level remained constant after Pla compared with rest but decreased significantly after Sal (Fig. 2). The statistical significance appeared after 5 min of exercise.

Lactate and FFAs. Preexercise lactate and FFA concentrations were quite similar in Pla and Sal trials. However, whereas no significant difference during exercise was found for lactate between the two treatments, exercise FFA concentrations were significantly higher after Sal treatment at any time of exercise ($P < 0.05$).

Blood urea. Resting and exercise blood urea levels were significantly decreased by Sal vs. Pla ($P < 0.05$).

**Table 1. Mean total protein and blood urea concentrations at rest and during exercise after Pla and Sal intake**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rest</th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>Exhaustion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pla</td>
<td>73.0 ± 1.4</td>
<td>77.2 ± 1.2†</td>
<td>81.2 ± 2.3†</td>
<td>78.4 ± 1.6†</td>
<td>81.3 ± 3.3†</td>
</tr>
<tr>
<td>Sal</td>
<td>71.6 ± 1.9</td>
<td>75.1 ± 1.1†</td>
<td>78.3 ± 1.6†</td>
<td>77.6 ± 1.3†</td>
<td>79.0 ± 1.3†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urea, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pla</td>
</tr>
<tr>
<td>Sal</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Significant difference between placebo (Pla) and salbutamol (Sal) ($P < 0.05$); †Significant difference between rest and exercise ($P < 0.05$).
No significant change was found after exercise compared with rest.

**Hormonal Concentrations**

GH, testosterone, cortisol, and C peptide basal values were not significantly different after Pla and Sal (Table 2; Fig. 3). However, T3 concentrations were significantly higher at rest after Sal intake (P < 0.05). All these hormones were significantly increased during exercise (P < 0.05) except C peptide concentrations, which were significantly lower compared with rest (P < 0.05). The increases in testosterone and cortisol concentrations were not significantly different after Sal compared with after Pla, and, because of the high interindividual variations, only end-exercise GH levels were significantly increased by intake of Sal vs. Pla (P < 0.05). Higher T3 concentrations were found after Sal at any time of the test (P < 0.05).

**DISCUSSION**

In this study, the effects of short-term oral administration of Sal during submaximal exercise on hormonal, metabolic, and endurance responses were examined. To our knowledge, the present study is the first to investigate the potential ergogenic effects of oral Sal intake during dynamic exercise, and it is unique in the examination of the influence that chronic Sal use may have on hormonal and metabolic responses during exercise. Our major finding is significant improvement in exercise performance after oral Sal intake with concomitant changes in hormonal and metabolic parameters.

Sal (albuterol) is a β2-selective adrenoceptor agonist, which accounts for its pronounced bronchodilatory, vascular, uterine, and metabolic effects (23). The mechanism of action of Sal is thought to be mediated via stimulation of cAMP production by activation of the enzyme adenyl cyclase (16, 23). cAMP is then capable of triggering a sequence of intracellular events that ultimately leads to the pharmacological effects associated with Sal therapy. Direct and indirect metabolic actions of β2-agonists include stimulation of hepatic glucose production (both glycogenolysis and gluconeogenesis) and glucose release, stimulation of glycogenolysis and glycolysis with increased lactate and pyruvate release from tissues such as muscle, stimulation of lipolysis with increased glycerol and fatty acid release and lipid oxidation, and stimulation of insulin secretion (4, 13, 23, 25, 30).

However, although hyperglycemia and hyperinsulinemia have been reported to be associated with the acute use of β-adrenergic agonists (26, 31, 34), development of tolerance or reduced sensitivity to β-receptor stimulation after chronic administration of β-receptor agonists is well established, and biochemical and metabolic parameters such as the generation of cAMP, secretion of insulin, and production of glucose and fatty acids in response to an acute challenge with β-receptor-stimulating agents are blunted after chronic administration (6, 12, 17, 18). The results of this study seem to confirm the phenomenon of reduced sensitivity to the metabolic effects of acute β-receptor stimulation after short-term Sal administration. Indeed, no significant changes in blood glucose, C peptide, or FFA concentrations were found at rest between the two treatments. However, this study adds the new observation that the metabolic effects of chronic Sal intake are not completely blunted during exercise. Indeed, no significant change was found between Pla and Sal in exercise lactate and C peptide concentrations, but our results show a significant fall in blood glucose concentrations after Sal but not after Pla during the trial ride, suggesting that chronic Sal intake induced changes in carbohydrate availability or utilization during exercise. Without measurements of substrate turnover or gas exchanges, we can only speculate that chronic β-receptor stimulation may increase exercise glycolysis either directly or indirectly via a greater insulin action in peripheral tissues (29), but the exact mechanism(s) remains to be determined. Generally, a fall in glucose is detrimental to endurance performance, so it appears difficult to relate this decrease in blood glucose after Sal intake to the improvement in performance. However, a previous study by Carlson et al. (2) indicates that physiological changes in blood glucose concentration could make an important contribution to lipid fuel homeostasis and that a reduction in blood glucose concentration would magnify FFA release independent of changes in plasma hormones. According to these data, our study shows, in addition, significantly higher exercise FFA concentrations after 3-wk Sal administration compared with after Pla administration. This greater exercise FFA level may be attributed to an increase in fatty acid mobilization from adipose tissue.

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**Table 2. Mean cortisol and testosterone concentrations at rest and during exercise after PLA and SAL intake**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rest</th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>Exhaustion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pla</td>
<td>152 ± 15</td>
<td>150 ± 15</td>
<td>172 ± 21*</td>
<td>168 ± 16*</td>
<td>220 ± 23*</td>
</tr>
<tr>
<td>Sal</td>
<td>153 ± 23</td>
<td>148 ± 22</td>
<td>159 ± 26</td>
<td>168 ± 25*</td>
<td>234 ± 20*</td>
</tr>
</tbody>
</table>

**Cortisol, ng/ml**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rest</th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>Exhaustion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pla</td>
<td>5.8 ± 0.6</td>
<td>6.3 ± 0.6</td>
<td>6.5 ± 0.7*</td>
<td>6.7 ± 0.7*</td>
<td>6.7 ± 0.6*</td>
</tr>
<tr>
<td>Sal</td>
<td>5.2 ± 0.4</td>
<td>5.9 ± 0.4</td>
<td>6.5 ± 0.5*</td>
<td>6.9 ± 0.5*</td>
<td>7.4 ± 0.5*</td>
</tr>
</tbody>
</table>

**Testosterone, ng/ml**

Values are means ± SE. *Significant difference between rest and exercise (P < 0.05).
fat during exercise after Sal administration, as described at rest after acute administration (30). It is therefore tempting to suggest that this significant increase in FFA after Sal administration may be coupled to a greater FFA utilization by exercising muscle. Care must be taken, of course, in interpreting the results presented here because of the relative insensitivity of venous blood, but, despite the need for more detailed studies, including ventilatory kinetics and turnover data to ascertain the greater lipid utilization, there are reasonable internally consistent data to suggest that \( \beta_2 \)-adrenoceptor stimulation would activate both glycolysis and lipolysis during exercise, even after chronic administration. Previous studies on caffeine have been directed toward establishing a causal relationship between prolonged exercise endurance and serum FFA on the basis of the hypothesis that caffeine ingestion resulted in a rise in circulating catecholamines that mobilized FFAs from adipocytes, thus increasing the amount of fat available for active muscle (5, 11), and that the resulting increase in substrate availability may contribute to the improvement in performance. It appears doubtful, however, that FFA availability is the main performance-limiting factor in the present work because the exercise used in our study is of shorter duration and higher intensity. It is then unlikely that the increased exercise FFAs after Sal administration represents the primary explanation for the improvement in performance, and it is impossible at the present time to couple this parameter to the performance.

One of the consistent hormonal effects of short-term Sal administration found in this study was a significant increase in serum T\(_3\) both at rest and during exercise. In the same way, a previous study (28) has shown that terbutaline sulfate administered orally for 2 wk increases resting T\(_3\), probably by an increase in peripheral conversion of thyroxine to T\(_3\). The authors speculate that this alteration in thyroid hormone metabolism after \( \beta_2 \)-adrenoceptor agonist treatment results from an improvement in insulin-mediated glucose metabolism during chronic-receptor stimulation (29). Further studies are needed to clarify the interaction between T\(_3\) concentrations and carbohydrate and lipid metabolism during exercise.

Previous data on the effects of Sal on GH are quite limited (7, 9, 15, 27) at rest and were investigated only once during exercise in adult patients with asthmatic bronchitis (8). Rest studies in experimental animals or in humans have found acute Sal administration either to decrease GH secretion (7, 9), probably through hypothalamic somatostatin stimulation, or not to affect GH secretion at all (27). In the same way, Giustina et al. (8) found that acute \( \beta_2 \)-receptor stimulation blunts the physiological GH response to maximal exercise. In contrast to this finding, we demonstrate here that there is a quite similar increase in GH in response to Sal vs. Pla with even significantly higher values at exhaustion. The most probable explanation for the lack of decrease in the Sal trials would be the tolerance effect after chronic use. Indeed, the effects of more prolonged Sal use (3 mo) on GH secretion have apparently been investigated at rest in one study, which suggested that its suppressive effect is not maintained with long-term use (15). An alternative explanation for the increase in GH concentrations at exhaustion in the Sal trials would include a positive relationship between time to exhaustion (increase 6–7 min longer) and GH secretion rather than a Sal effect.

In animal experiments, \( \beta_2 \)-agonist administration leads to skeletal muscle hypertrophy (1, 24). Only two studies support such an effect in humans after chronic Sal administration (3, 18). This anabolic effect has been postulated to be mediated through \( \beta_2 \)-adrenoceptor stimulation. However, the subsequent events leading to anabolic actions in muscle protein deposition remain unclear. Hypothesized mechanisms include al-

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Fig. 3. Growth hormone (GH, A), triiodothyronine (T\(_3\); B), and C peptide responses (C) (means \( \pm \) SE) at rest and during cycling to exhaustion after Pla and Sal intake. *Significant difference between Pla and Sal (\( P < 0.05 \)); ! start of significant difference between rest and exercise after Pla intake (\( P < 0.05 \)); $ start of significant difference between rest and exercise after Sal intake (\( P < 0.05 \)).
terations in resting potential, Ca^{2+} myosin ATPase, and contractile properties (36), and several indirect mechanisms such as changes in hormonal profile and in protein synthesis or reduction in muscle protein degradation (19) have been proposed. To our knowledge, the pharmacological properties of Sal, regarding cortisol and testosterone response, have not been considered. The submaximal exercise performed in this study significantly increased plasma testosterone and cortisol concentrations, as described previously (32), but we did not find any effect of Sal compared with Pla, either at rest or at exhaustion. Thus it appears that Sal did not play any anabolic or catabolic role through modulation of these hormones. However, a decrease in blood urea was found after Sal. In this context, the decrease of this parameter may be related to a number of factors, but it could be suggested that the lower blood urea concentrations after Sal might reflect an eventual reduction in muscle protein degradation (19). Whatever the case, the exact mechanism(s) cannot be ascertained from the present study and may not be linked at present to the improvement in performance. It is, however, necessary to verify in further studies the Sal-induced gains in muscle strength after such a treatment. Indeed, it is not impossible that the prolonged time to exhaustion may have resulted simply from increased strength and its effect on enhancing the ability to maintain a relatively high power output.

The results show that short-term oral Sal administration improves cycling performance during submaximal exercise as shown by the significant increase in time to exhaustion. The ergogenic effect of Sal observed in the present study is in disagreement with the results of most of the investigations conducted during dynamic exercise after acute Sal inhalation (20–22). The most plausible explanation is the difference in the dosage (10- to 20-fold greater per os vs. by inhalation) and in the mode of administration (acute vs. chronic). In addition, the preliminary experiments presented here were designed to investigate potential metabolic or hormonal contributors to this improvement in performance, and several possible explanations have been offered. The higher T_{3} levels found in this study, together with the increased exercise FFA and decreased exercise blood glucose concentrations, could lend support to their involvement in Sal mechanism(s) of action, i.e., increase in lipolysis and/or glycolysis. Other phenomena are probably involved, especially with regard to blood urea decrease or to the two previous studies (3, 18), which show an increase in voluntary muscle strength in men. However, the mechanisms proposed to account for the performance gain are as yet only speculative and will have to be demonstrated in further work with focus in particular on expired gas, turnover data, and strength-enhancing effect to clarify the influence of short-term β_{2}-agonist administration on performance, substrate availability, and utilization.

We thank Dr. Olivier Costes for excellent medical assistance, Dominique Bernard for expert technical assistance, and the subjects for dedicated performance. In addition, we likewise acknowledge Glaxo-Wellcome, Evreux, France, for providing the salbutamol medication and the Recherche Clinique of the Hôpital Arnaud de Villeine in Montpellier for its assistance.

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