Effect of β-adrenoceptor blockade on exercise performance and metabolism

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Summary

1. Carbohydrate and lipid metabolism and the capacity to perform prolonged submaximal physical exercise were studied in six young healthy subjects treated in a randomized double-blind fashion for 2 days with either placebo, the non-selective β-adrenoceptor antagonist propranolol (80 mg b.i.d.) or the cardioselective agent metoprolol (100 mg b.i.d.). On day 3, 1 h after the last dose, the subjects exercised for 30 min periods followed up 10 min rest up to the point of exhaustion.

2. The capacity to perform exercise was decreased with both β-adrenoceptor antagonists. However, at an equal degree of β1-adrenoceptor blockade, all subjects could exercise for a longer period of time on the cardioselective agent as compared with the non-selective drug.

3. Blood glucose levels decreased during exercise irrespective of the type of treatment, but the attenuation occurred most rapidly on propranolol. At exhaustion the average non-esterified fatty acid levels had increased 256% on placebo, 148% on metoprolol and 65% on propranolol. A significant positive correlation was found between changes in non-esterified fatty acid levels during exercise and total working time. It is concluded that β-adrenoceptor blockade diminishes the capacity for prolonged submaximal exercise at least in part by reducing the availability of substrates to the working muscles.

Key words: β-adrenoceptor blockade, carbohydrate metabolism, catecholamines, lipid metabolism, physical exercise.

Introduction

Muscle fatigue is a common complaint of patients treated with β-adrenoceptor antagonists [1, 2]. This is of particular importance in young or middle-aged physically active subjects. There are several ways in which β-adrenoceptor blockade could impair physical performance. For instance, an effect on neuromuscular transmission may be possible, leading to reduced muscular contractility. However, in a previous study no difference in muscular strength after treatment with either a cardioselective or a non-selective β-adrenoceptor antagonist was found [3]. The circulatory effects of these drugs may lead to a reduced physical performance. During exercise, heart rate is reduced but the stroke volume unchanged or increased, the overall effect being a reduction in cardiac output [4]. This effect is a likely reason for the diminished capacity for maximal work noted in some studies [4, 5]. However, during the more commonly performed submaximal work this effect appears less relevant, since direct measurements of the blood flow to the working muscles have not revealed any clear changes with β-adrenoceptor blockade, probably due to a redistribution of the blood flow to the muscles [6]. Other known effects of β-adrenoceptor blockade which should be considered include inhibition of the β2-adrenoceptor-mediated muscle glycogenolysis [7, 8] or an influence of β-adreno-
ceptor blockade on the potassium flux across the muscle cell membranes [9, 10].

Even though these latter effects may contribute to muscle fatigue, it appears clear that during prolonged submaximal physical exercise the supply of substrates, such as glucose and non-esterified fatty acids, are limiting physical performance [11]. It has been shown, for instance, that prolonged carbohydrate feeding [12] or glucose ingestion [13] immediately before work increases performance.

β-Adrenoceptor antagonists may influence the metabolism of both carbohydrates and lipids (for review see [14]. Thus, a non-selective β-adrenoceptor antagonist reduces the recovery of blood glucose levels after hypoglycaemia [15-17], probably in part due to a diminished glucose production in the liver [18]. Additionally, adrenergic non-esterified fatty acid mobilization from the adipose tissue is strongly inhibited by β-adrenoceptor antagonists although less so by the cardioselective drugs [17, 19]. These effects of β-adrenoceptor blockade on carbohydrate and lipid metabolism may be of decisive importance during long-term submaximal physical exercise and impair the working capacity. Support for this is obtained from the study by Galbo, Christensen & Holst [20] showing that propranolol decreased the capacity to perform moderately heavy work. This reduction in physical capacity was associated with a rapid fall in blood glucose levels.

The present study was carried out to investigate the influence of two β-adrenoceptor antagonists, metoprolol (cardioselective) and propranolol (non-selective), on the capacity for physical exercise as well as on associated metabolic changes.

Materials and methods

Six healthy male volunteer subjects were studied. Clinical data for the subjects are given in Table 1. None of the subjects was on any concomitant medication. Informed consent was obtained from each individual. The study was submitted to and approved by the local Ethics Committee of the University of Göteborg.

The physical working capacity was tested stepwise on an ergometer bicycle with continuous ECG recordings. The work load giving a heart rate of around 130 beats/min, corresponding to about 50% \( \dot{V}O_2 \) max., was thus determined. The individuals were randomized in a double-blind fashion to one of three treatments: placebo tablets (b.i.d.), metoprolol (100 mg b.i.d.) or propranolol (80 mg b.i.d.). The subjects were given the medication for 2 days before the experiment. On day 3 the individuals came to the laboratory in the morning having been told not to eat after 22.00 hours or to smoke or drink alcohol for 24 h before the experiment.

Venous blood samples were drawn from a cannula in the cubital vein with subjects in the supine position. The morning dose of the respective medication was then given and blood samples were again drawn in the supine position after 55 min rest.

Physical exercise was then started on an ergometer bicycle at the work load tested previously to give a heart rate around 130 beats/min and ECG was followed regularly. After 28 min blood samples were again drawn and the exercise was maintained to complete the 30 min interval which was then followed by a 10 min rest. This sequence was again repeated; i.e., a total of 30 min work with 10 min rest up to the point of exhaustion (defined as inability to perform any further work). After each 28 min period of exercise venous blood samples were drawn. Samples were also drawn at exhaustion and 15, 30 and 45 min after exhaustion while the subjects were recovering.

At least 2 weeks after the exercise the subjects were randomly switched to one of the two remaining treatments for 2 days and the study was repeated in an analogous way on day 3. Consequently, each subject underwent treatment with each agent after a 'wash-out' of at least 2 weeks.

The following blood analyses were performed; concentrations of propranolol and metoprolol were determined in blood samples drawn before exercise [21]. Glucose levels were determined with hexokinase (Gluc-o-quant, Boehringer Mannheim GmbH, West Germany) and analyses performed of non-esterified fatty acids [22], glycerol [23], lactate [24], potassium (by flame photometry), insulin (Phadebas, Pharmacia, Uppsala, Sweden), noradrenaline and adrenaline (Cat-a-kit, Upjohn Diagnostics, Kalamazoo, MI, U.S.A.). Glucagon was measured by radioimmunoassay with carboxy-terminal-directed antiserum E7 which has similar characteristics to

<table>
<thead>
<tr>
<th>Table 1. Clinical data</th>
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<tbody>
<tr>
<td>Working intensity was chosen to give a heart rate of 130 beats/min.</td>
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<tr>
<td>Subject</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>
P-Adrenoceptor blockade and physical exercise

TABLE 2. Individual heart rates before and after 30 min exercise

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Placebo</th>
<th>Propranolol (80 mg b.i.d.)</th>
<th>Metoprolol (100 mg b.i.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start 30 min</td>
<td>Start 30 min</td>
<td>Start 30 min</td>
</tr>
<tr>
<td>1</td>
<td>62 130</td>
<td>46 105</td>
<td>47 102</td>
</tr>
<tr>
<td>2</td>
<td>59 139</td>
<td>52 105</td>
<td>62 101</td>
</tr>
<tr>
<td>3</td>
<td>53 118</td>
<td>52 108</td>
<td>49 104</td>
</tr>
<tr>
<td>4</td>
<td>40 138</td>
<td>39 101</td>
<td>40 116</td>
</tr>
<tr>
<td>5</td>
<td>53 130</td>
<td>40 97</td>
<td>44 96</td>
</tr>
<tr>
<td>6</td>
<td>56 122</td>
<td>42 96</td>
<td>42 98</td>
</tr>
<tr>
<td>Mean</td>
<td>54 130</td>
<td>45* 102*</td>
<td>47 103*</td>
</tr>
<tr>
<td>± SEM</td>
<td>± 3 ± 3</td>
<td>± 2 ± 2</td>
<td>± 3 ± 3</td>
</tr>
</tbody>
</table>

Significance of differences from comparable placebo groups: *P < 0.05. No significant differences were found between propranolol and metoprolol treatment.

antiserum $^{30}$K [25]. Alanine was assayed in deproteinized plasma by liquid chromatography combined with postcolumn derivatization and fluorimetric detection [26].

Statistical analysis

Conventional statistical methods were used. Significance of differences were analysed with Student's t-test.

Results

Heart rate (Table 2)

Heart rates were equally reduced by propranolol and metoprolol both in the resting state and after the first 30 min exercise period. This latter point was used for the comparisons, since it was the only observation point during the exercise period where all subjects could be compared. These data suggest that an equal degree of $\beta_1$-adrenoceptor blockade was obtained with the two drugs.

Duration of exercise

As shown in Table 3 the duration of the submaximal exercise was generally longer during placebo than with either $\beta$-adrenoceptor antagonist. However, it is also clear that all subjects could perform work for a longer period of time while treated with metoprolol compared with propranolol ($P < 0.05$).

Metabolic variables

Blood glucose. During the initial exercise period (28 min) only slight changes in blood glucose levels were found while the subjects were treated with placebo or $\beta$-adrenoceptor antagonists (Fig. 1). Subsequently, the glucose levels decreased to about the same levels at exhaustion irrespective of the type of treatment. However, the attenuation in glucose during exercise occurred most rapidly on propranolol treatment followed by that on metoprolol and placebo respectively (Fig. 1). At the exhaustion point on propranolol significantly higher glucose levels were found while on either placebo or metoprolol treatment.

Non-esterified fatty acids and glycerol levels. The plasma non-esterified fatty acid (Fig. 2) as well as glycerol levels (results not shown) increased during exercise. This increase was considerably less on propranolol treatment (65%
FIG. 2. Changes in plasma non-esterified fatty acid levels during exercise. The figures on the x-axis represent the number of 30 min exercise periods performed up to exhaustion (arrow). After work samples were taken at 15 min intervals (I, II, III). Significance of differences: *P < 0.05; **P < 0.01. ○—○, Placebo; ●—●, propranolol; △—△, metoprolol.

FIG. 3. Relationship between maximal non-esterified fatty acid increase during exercise and duration of work. Correlations for all three treatment groups (---, r = 0.73, P < 0.01) and for only the β-adrenoceptor-blocked groups (—, r = 0.68, P < 0.01) are shown. ○—○, Placebo; ●—●, propranolol; △—△, metoprolol.

TABLE 4. Lactate and potassium concentrations during exercise

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lactate concn. (mmol/l)</th>
<th>Potassium concn. (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Start</td>
<td>0.88 ± 0.14</td>
<td>0.80 ± 0.09</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 min</td>
<td>1.66 ± 0.41</td>
<td>1.47 ± 0.25</td>
</tr>
<tr>
<td>68 min</td>
<td>1.17 ± 0.24</td>
<td>1.11 ± 0.16</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>1.30 ± 0.13</td>
<td>1.17 ± 0.18</td>
</tr>
<tr>
<td>Post exercise</td>
<td>15 min</td>
<td>1.01 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>1.02 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>45 min</td>
<td>0.88 ± 0.10</td>
</tr>
</tbody>
</table>

increase in non-esterified fatty acid level over basal) than on placebo (256% increase). Metoprolol also attenuated the rise in non-esterified fatty acid and glycerol during exercise as compared with placebo, the average increase in the former being 148% over basal (Fig. 2). Significant positive correlations were found between the rise in non-esterified fatty acid over basal levels in the three treatment groups (Fig. 3) as well as the fasting levels (results not shown) and the duration of exercise up to exhaustion. A similar correlation was found when the rise in non-esterified fatty acid in only the two β-adrenoceptor antagonist groups was analysed (r = 0.73, P < 0.01 and r = 0.68, P < 0.01 respectively).

Lactate, alanine and potassium levels. Lactate levels rose during exercise irrespective of the type of treatment (Table 4). The levels measured were somewhat lower on propranolol than on either placebo or metoprolol treatment although the differences were not statistically significant. During the 45 min recovery period after exhaustion, however, significantly lower lactate levels were found on propranolol treatment.

Alanine levels increased during exercise in all three groups. During the recovery period the


TABLE 5. Noradrenaline and adrenaline concentrations during exercise

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Noradrenaline concn. (mmol/l)</th>
<th>Adrenaline concn. (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Propranolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>1.31 ± 0.19</td>
<td>1.41 ± 0.18</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>6.53 ± 1.06</td>
<td>6.93 ± 1.97</td>
</tr>
<tr>
<td>Postexercise 30 min</td>
<td>2.03 ± 0.30</td>
<td>1.48 ± 0.15</td>
</tr>
</tbody>
</table>

RESULTS are means ± SEM for six subjects. *Significance of differences (P < 0.05) from respective data on placebo.

levels declined, but no significant difference was found between the treatment groups (results not shown).

Potassium levels rose during exercise irrespective of treatment, but the levels reached were higher on either of the β-adrenoceptor antagonists (Table 4). At exhaustion significantly higher potassium levels were found on propranolol as compared with placebo and the rapid normalization after exercise in the placebo group was delayed by both β-adrenoceptor antagonists.

**Hormone levels.** Insulin levels decreased during exercise irrespective of the type of treatment and no significant differences were found between the groups (results not shown).

Glucagon levels increased during exercise in all groups to about the same levels, but the increase occurred most rapidly on propranolol followed by that on metoprolol and placebo respectively (Fig. 4).

Plasma adrenaline and noradrenaline levels were similar before exercise in the three groups (Table 5). The increase in noradrenaline levels during exercise was similar. However, adrenaline levels at exhaustion were higher on either β-adrenoceptor antagonist although statistical differences were achieved only for propranolol.

**Discussion**

The capacity to perform submaximal physical exercise was greatly reduced by propranolol in the present study as also found by Galbo et al. [20]. In our study all subjects could perform less work on propranolol than on placebo; on average the exercise duration was only 58% of that on placebo. On the cardioselective β₁-adrenoceptor blocker metoprolol the working capacity was also reduced, the average exercise duration being 78% of that on placebo. However, a difference was found between the two β-adrenoceptor antagonists as evidenced by the observation that all subjects could perform exercise for a longer time-period on metoprolol.

The reduced capacity for long-term physical exercise on β-adrenoceptor blockade may be associated with the mechanisms leading to the frequently described sensation of muscle fatigue. If this is the case, a cardioselective β₁-adrenoceptor blocker may cause less muscle fatigue than a non-selective agent. However, specific studies are warranted to resolve this question. In this context it is important to emphasize that the work load used in the present study was moderately heavy even though the exercise duration was prolonged up to exhaustion, which is rarely reached in normal life. This design, however, represents one way to measure objectively the working capacity.

There are several possible reasons for the diminished capacity for physical exercise with β-adrenoceptor blockade. As pointed out previously, it appears unlikely that haemodynamic reasons are responsible for changed submaximal working capacity, since the redistribution of blood ensures an essentially unchanged blood flow to the working muscles [6]. This concept is supported by the present findings of differences in work performance between two β-adrenoceptor
antagonists in spite of a similar blockade of the \(\beta_1\)-adrenoceptors measured as reduction in exercise-induced tachycardia. Furthermore there was no correlation between the reduction in heart rate during \(\beta\)-adrenoceptor blockade and the concomitant reduction in exercise endurance.

Although difficult to evaluate, it seems unlikely that the rather small differences in plasma potassium levels between propranolol and metoprolol can explain the recorded differences. Changed potassium levels would mainly influence repolarization and, thus, the ability to elicit muscle contractions.

More likely reasons for the diminished physical performance are the various effects of \(\beta\)-adrenoceptor antagonists on metabolism. There are several reports of differences in the metabolic effects between cardioselective and the non-selective agents both with respect to lipid and carbohydrate metabolism [14–19, 27] which are in accordance with the present findings.

During prolonged submaximal exercise circulating substrates such as glucose and non-esterified fatty acids account for the major part of the energy required [28]. Muscle glycogen is degraded initially, but during prolonged work splanchnic glucose output increases to provide substrate for the working muscles. Splanchnic glucose production, however, cannot keep pace with the greatly augmented muscle uptake leading to reduced blood glucose levels. Non-esterified fatty acid release from the adipose tissue is increased and this, in turn, leads to a greater utilization of these substrates during prolonged work, since non-esterified fatty acid uptake is dependent on the ambient blood levels [28].

Adrenergic muscle glycolysis appears to be a \(\beta_2\)-adrenoceptor-mediated process [7] and, consequently, reduced glycolysis by \(\beta\)-adrenoceptor antagonists could contribute to the feeling of muscle fatigue. It is uncertain, however, whether this factor is of major importance for the reduced physical performance found in the present study, since exercise-induced muscle glycolysis may not be dependent on adrenergic receptors.

The supply of non-esterified fatty acids was greatly inhibited by propranolol making the body more dependent on glucose as fuel. The more rapid fall in blood glucose during exercise probably reflects this as well as reduction in the supply of the gluconeogenic substrate glycerol and, possibly, lactate produced by propranolol.

Although muscle glycolysis during exercise may not be dependent on adrenergic receptors and, thus, not primarily influenced by \(\beta\)-adrenoceptor blockade an intracellular accumulation of lactate associated with lower plasma levels has been reported [6]. In the present study the plasma lactate levels were not significantly lower during exercise on \(\beta\)-adrenoceptor blockade, but this was the case during the recovery period on propranolol. Further studies, including direct measurements of intracellular glycogen and lactate levels, will have to be made to evaluate possible effects of \(\beta\)-adrenoceptor blockade on muscle glycolysis and lactate metabolism during exercise. In this context it should be pointed out that we also measured the alanine levels in the present study, but no differences were found for this important gluconeogenic precursor with or without \(\beta\)-adrenoceptor-blocking therapy.

The more rapid rise in glucagon levels on propranolol is due to the relative hypoglycaemia rather than to a direct adrenergic effect on glucagon release [12]. Similarly, the more rapid rise in adrenaline levels on propranolol (higher levels in spite of shorter exercise duration) probably represents another response to compensate the relative hypoglycaemia.

The cardioselective \(\beta_1\)-adrenoceptor antagonist metoprolol inhibits lipolysis and, thus, glycerol and non-esterified fatty acid release less than propranolol. This is probably due to the presence of a small, but important, pool of \(\beta_2\)-adrenoceptors in human adipose tissue [29]. Consequently, muscle non-esterified fatty acid utilization and liver gluconeogenesis are less hampered leading to a slower fall in blood glucose during exercise as also observed. The present observation of a positive correlation between changes in non-esterified fatty acid levels and exercise duration should not necessarily be taken as evidence for the exclusive importance of these substrates, but rather as an index for the importance of suitable substrate availability at a time when muscle glycogen deposits and blood glucose levels are reduced.

The present observations are also in accordance with the concept that \(\beta\)-adrenoceptor blockade may contribute to the precipitation of severe exercise-induced hypoglycaemia as reported by Asknes [30] and by Uusitupa, Aro & Pietikainen [31] in cross-country skiers treated with propranolol or pindolol. After having become aware of the possibility we have also seen severe symptomatic hypoglycaemia after long-term exercise in a patient treated with alprenolol. Patients performing endurance exercise while on \(\beta\)-adrenoceptor-blockade treatment should be encouraged to ingest suitable substrates for the muscles to prevent the development of symptom-producing hypoglycaemia.
Acknowledgments
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References