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Effects of selective β_2-adrenoceptor blockade on serum potassium and exercise performance in normal men

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1 The differential effects of β-adrenoceptor subtypes on potassium fluxes and exercise capacity were compared in eight healthy young men using single oral doses of the selective β_2-adrenoceptor antagonist ICI-118551, the selective β_1-adrenoceptor antagonist atenolol or the non-selective β-adrenoceptor antagonist propranolol. The study was randomized, double-blind and placebo controlled.

2 Potassium in the venous effluent from the exercising muscles increased progressively with increasing exercise intensity. This response was augmented by propranolol, whereas neither atenolol nor ICI-118551 modified the response. After exercise potassium concentration fell exponentially with no difference between the treatment regimens.

3 Cumulative work was significantly reduced by ICI-118551 (6.4%, $P = 0.04$) and by propranolol (12.4%, $P < 0.01$), whereas the reduction with atenolol (5.6%) did not reach statistical significance.

4 Atenolol and propranolol reduced peak heart rate by 23% and 29%, and peak systolic blood pressure by 9% and 11% respectively during maximal exercise. ICI-118551 caused a non-significant reduction in heart rate during submaximal exercise, with a significant reduction at maximum exercise (6% reduction), whereas systolic blood pressure was not different from placebo. Diastolic blood pressures were similar across all treatment regimens.

5 Similar glucose concentrations were obtained at baseline and at exhaustion during all treatment regimens. Lactate concentrations were comparable for any given exercise intensity irrespective of treatment regimens. Propranolol reduced lactate concentrations from the exercising muscles at maximum exercise in proportion to the reduction of maximal exercise capacity.

6 The subjective perception of fatigue was not affected by either β_1- or β_2-adrenoceptor blockade.

7 In a separate study, the effects of selective β_2-adrenoceptor stimulation (terbutaline) in resting men on heart rate, systolic blood pressure, serum potassium and glucose were completely blocked by the doses of ICI-118551 used in the exercise study.

8 We conclude that both β_1- and β_2-adrenoceptors are of importance for maximal short term exercise performance in healthy young men. The decisive mechanism for the reduction in exercise performance during β-adrenoceptor blockade is unclear. The present study suggests that other mechanisms than haemodynamic and metabolic factors are of importance. The lack of effect of selective β_2-adrenoceptor antagonists on serum potassium at rest and during exercise, and the finding that the rate of decline in the potassium concentrations after exhaustion was independent of treatment regimens, suggests that β-adrenoceptors are of minor importance for potassium release or reuptake in the exercising muscle.

Keywords atenolol ICI-118551 muscle fatigue propranolol β-adrenoceptor antagonists heart rate

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Introduction

The sympathetic nervous system has an important role in modulating transmembrane potassium flux, and both α- and β-adrenoceptors seem to be involved.

During resting conditions infusion of adrenaline (Brown *et al.*, 1983; D'Silva, 1934), and pure β_2-adrenoceptor agonists (Leitch *et al.*, 1976; Smith *et al.*, 1983) are known to cause hypokalaemia, suggesting a β_2-adrenoceptor mediated effect, probably by receptors linked to Na-K-ATPase in the skeletal muscles (Clausen & Flatman, 1980). The effect of β_1-adrenoceptor stimulation in the skeletal muscles is of little importance due to their relatively small number, whereas selective β_1-adrenoceptor stimulation in the heart causes a marked reduction in potassium in the coronary venous effluent (Ellingsen *et al.*, 1987). In contrast, stimulation of α-adrenoceptors causes impaired cellular uptake of potassium opposite to the effect of β-adrenoceptor stimulation (Williams *et al.*, 1984).

Exercise causes an increased efflux of potassium from the working muscles, which is the result of increased electrical activity (Hirche *et al.*, 1980; Medboe & Sejersted, 1990). The outward shift of potassium during exercise allegedly is modulated by opposite effects of α- and β-adrenoceptors (Williams *et al.*, 1985).

The rise in potassium during exercise is potentiated by non-selective and to a lesser extent by selective β_1-adrenoceptor antagonists (Carlsson *et al.*, 1978; Gullestad *et al.*, 1988, 1989a; Lundborg *et al.*, 1981; McDonald *et al.*, 1984), which has led to the assumption that the exercise-induced increase in potassium by β-adrenoceptor antagonists is β_2-adrenoceptor dependent.

In order to define the role of the β-adrenoceptor subtypes on potassium and working capacity, exercising healthy subjects were examined during administration of selective β_1- and β_2-adrenoceptor antagonists, as well as a non-selective agent.

Methods

Eight moderately trained healthy male subjects, mean age 27 years (range 20–31 years), mean height 186 (range 178–194) cm and mean weight 87 (range 75–95) kg participated. All consented to participate after being fully informed. The experimental protocol was approved by the Hospital Medical and Ethics Committee.

An oral dose of either 80 mg propranolol, 50 mg atenolol, 25 mg ICI-118551 or placebo was given in a randomized fashion on separate occasions using a double-dummy technique.

There was at least a 7 day wash-out period between each test. Atenolol 50 mg is considered equivalent to 80 mg propranolol in decreasing exercise-induced tachycardia (McGibney *et al.*, 1983). ICI-118551 is a potent and highly selective β_2-adrenoceptor antagonist (Bilski *et al.*, 1980; Harry *et al.*, 1982).

On the day of the experiments the subjects had a light breakfast. Caffeine, alcohol and nicotine were withheld for at least 12 h. A thin polyethylene catheter was introduced into the right femoral vein by percutaneous technique. Thereafter the subjects rested for at least 30 min.

Ninety minutes after the medication an exercise test was performed in the upright position on an electrically braked cycle ergometer (Siemens Elema Schønander), pedalling at 60 rev min^{-1}. Exercise began at a workload of 40 watt for 3 min. Thereafter the exercise intensity was increased stepwise by 40 watt every third minute until exhaustion (defined as the inability to pedal at 60 rev min^{-1}). After exercise the subjects were monitored for 6 min.

All participants had previously been exposed to the exercise test used in the present study, and the test has been found to be reproducible for all participants (Gullestad *et al.*, 1989a). Blood pressure were recorded by a Criticon Dinamap automatic blood pressure recorder, and heart rate from a standard 12 lead ECG at rest, every 3 min during exercise, at exhaustion, and at 30 s, 1, 2, 4 and 6 min in the post-exercise period. Blood was sampled at the same time points from the catheter in the femoral vein for analysis of plasma sodium, chloride and potassium by flame photometer. Lactate was determined by a standard enzymatic method (Boehringer), and glucose was analysed at rest and at exhaustion using a hexokinase method.

Effect of β_2-adrenoceptor stimulation

A separate study was performed to define the effect of the selective β_2-adrenoceptor blocker ICI-118551 on changes in potassium and haemodynamic variables during infusion of the selective β_2-adrenoceptor agonist terbutaline. Seven healthy male volunteers, of whom six had participated in the exercise study, were examined in the supine position on 2 separate days with at least 4 days in between. They received an oral dose of either 25 mg ICI-118551 or identical looking placebo tablets according to a randomized double-blind protocol. After 90 min terbutaline was given as a bolus dose of 0.25 mg i.v. followed by an infusion of 5 μg min^{-1} for 40 min. After terbutaline infusion, the subjects were studied for 20 min.

Heart rate and blood pressure were determined as described, before terbutaline infusion and at 10 min intervals during and after the infusion. Blood was sampled from a catheter in an antecubital vein at the same time as heart rate and blood pressure were recorded, and analyzed for potassium and glucose.

Statistics

All results are expressed as mean with 95% confidence interval. The Bernoulli-Wilcoxon procedure was used to calculate the confidence interval (Kendal & Stuart, 1977). Results from baseline and exhaustion were analyzed separately. During exercise and in the recovery period the analysis was based on the area under the curve (trapezoid method). The Wilcoxon signed mid-rank test was used for comparison within groups (Kendal & Stuart, 1977).

The half-time of the decrease in potassium concentration was calculated by linear regression on the log-transformed data. All tests used in this analysis were one tailed. Differences were considered significant when the *P* values were less than or equal to 5%.

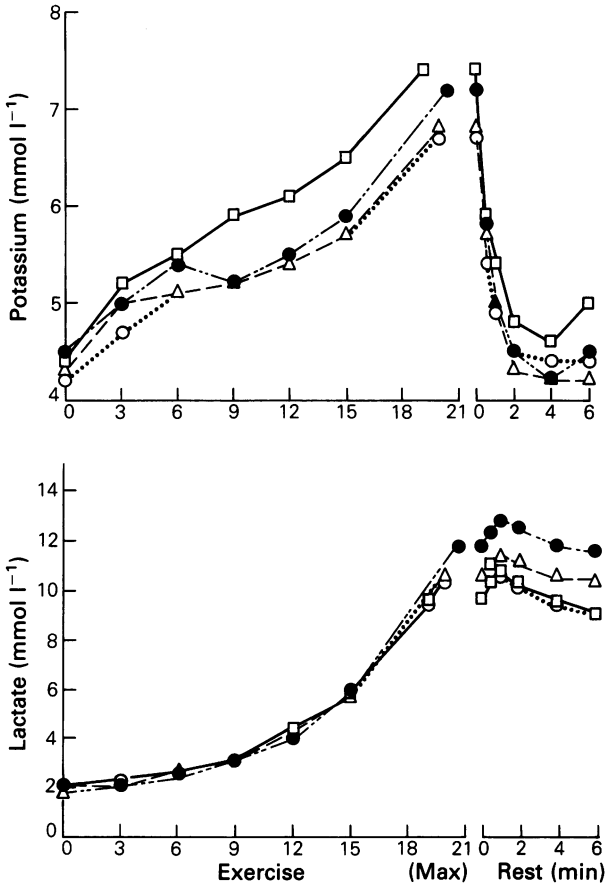

Figure 1 Mean potassium and lactate concentrations during the treatment regimens. Observations according to marks on the x axis. For significance, see text. □ propranolol, △ atenolol, ○ ICI 118551, • placebo.

Results

Effects of exercise and recovery on plasma potassium (Figure 1)

In the control study the plasma potassium from the femoral venous effluent increased progressively from 4.5 (4.3–4.7) to 7.2 (6.7–7.7) mmol l^{-1} ($P \ll 0.01$) at exhaustion (Figure 1). When exercise stopped it fell exponentially with a half-time of 28 (25–31) s to levels equal to basal level.

Baseline plasma potassium concentration was slightly reduced with ICI-118551 ($P < 0.05$), as compared with placebo. During exercise propranolol caused significantly higher potassium concentrations for any given exercise intensity, whereas this relationship with atenolol and ICI-118551 was not different from that with placebo.

However, at exhaustion there were no differences in potassium levels between placebo and the three β-adrenoceptor antagonists, but peak potassium concentration after propranolol, 7.4 (6.9–7.9) mmol l^{-1}, was significantly higher than with ICI-118551, 6.6 (6.1–7.1) mmol l^{-1}, or atenolol, 6.8 (6.6–7.0) mmol l^{-1} ($P < 0.01$).

The rate of decline in potassium concentrations after exercise was not influenced by β-adrenoceptor blockade, but the potassium levels remained higher with propranolol than with the other treatment regimens ($P < 0.05$) in the post-exercise period (Figure 1).

Effect of exercise and recovery on lactate concentrations (Figure 1)

Lactate increased in a biphasic fashion from a basal level of 1.98 (1.35–2.62) to 11.80 (10.62–12.98) mmol l^{-1} ($P \ll 0.01$) at exhaustion. Similar lactate levels were obtained at each level of exercise for all treatment regimens, and the breaking point (anaerobic threshold) for the four curves was identical (Figure 1).

Propranolol reduced lactate concentrations at exhaustion to 9.65 (8.14–11.16) mmol l^{-1} ($P < 0.05$), which was proportional to the reduction in maximal exercise capacity.

Effect of exercise on haemodynamic variables (Figure 2)

Baseline heart rate was reduced by atenolol and propranolol ($P < 0.05$), but not by ICI-118551.

The exercise induced increases in heart rate and systolic blood pressure were blunted after atenolol and propranolol ($P \ll 0.01$), whereas ICI-118551 had no effect on these parameters at submaximal exercise intensities. However, at exhaustion all three β-adrenoceptor antagonists reduced peak heart rate, by 6%, 23% and 29% respectively with ICI-118551, atenolol and propranolol.

Diastolic blood pressure remained virtually unchanged during exercise and across the treatment regimens.

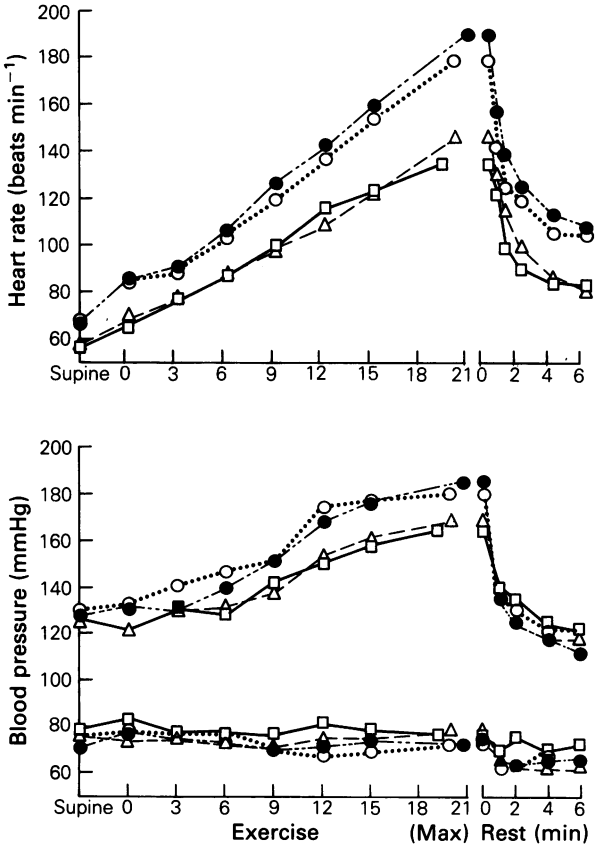

Figure 2 Heart rate, systolic and diastolic blood pressure during the different treatment regimens. Observations according to marks on the x axis. Results are given as mean. For significance, see text. □ propranolol, △ atenolol, ○ ICI-118551, • placebo.

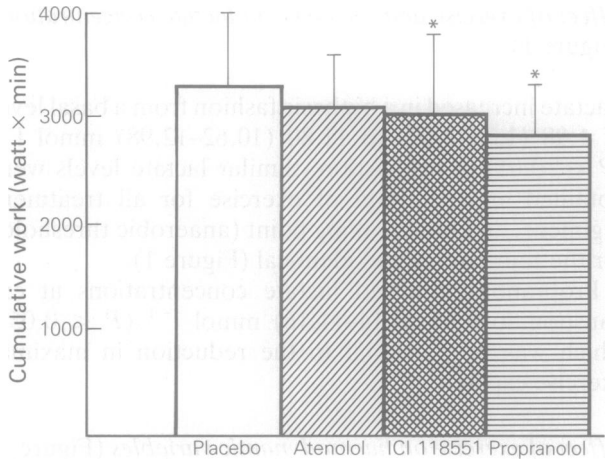

Figure 3 Accumulated work (total work), watt × min (joules), during the different treatment regimens. Results are given as mean ± s.d. Asterix denotes $P < 0.05$ as compared with placebo.

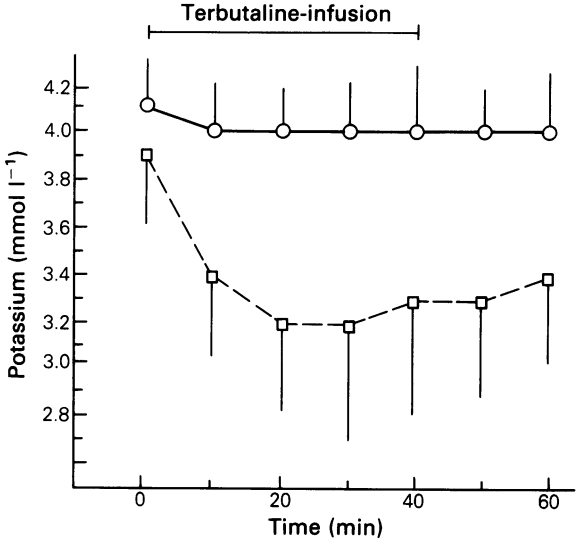

Figure 4 Potassium during ICI-118551 (○) and placebo (□) after stimulation with terbutaline. Results are given as means ± s.d.

Maximum exercise capacity (Figure 3)

Total exercise capacity, expressed as the cumulative product of exercise intensity and exercise duration was reduced by ICI 118551 (6.4%, $P = 0.04$), by atenolol (5.6%, NS), and by propranolol (12.4%, $P < 0.01$). The differences in total amount of work between the three β-adrenoceptor blocking agents were not statistically significant.

Other variables

In the placebo period sodium increased from 142 (138–146) to 149 (145–153) mmol l^{-1} at maximum exercise. Similar levels were obtained with the three β-adrenoceptor antagonists. Whereas baseline chloride levels were similar, chloride concentrations at maximum exercise were reduced after placebo and ICI-118551, 99 (97–101) mmol l^{-1}, compared to atenolol 103 (101–105) mmol l^{-1} and propranolol 104 (100–108) ($P = 0.02$).

Plasma glucose concentrations decreased slightly during exercise from 5.6 (4.7–6.5) to 4.6 (3.9–5.3) mmol l^{-1} ($P < 0.001$) with placebo, and from 5.2 (4.9–5.5) to 4.5 (3.8–5.1) mmol l^{-1} ($P < 0.05$) with ICI-118551, whereas unchanged values were observed after atenolol and propranolol.

The subjective perception of fatigue (Borg scale rating; Borg, 1970) increased with increasing exercise intensity up to 19 at maximum exercise, with no difference between the treatment regimens.

Effects of β_2-adrenoceptor stimulation on potassium disposal at rest (Figure 4)

During terbutaline infusion potassium decreased significantly from 3.9 (3.7–4.1) to a nadir of 3.2 (2.9–3.5) mmol l^{-1} after 20 min infusion. ICI-118551 completely abolished this response.

Effect of β_2-adrenoceptor stimulation on other variables

Terbutaline infusion increased heart rate significantly from 64 (58–70) to a maximum of 80 (69–91) beats min^{-1} after 30 min infusion and systolic blood pressure from 119 (111–127) to 131 (119–143) mm Hg, whereas diastolic blood pressure decreased slightly from 75 (68–83) to 70 (63–77) mm Hg. ICI-118551 completely abolished the haemodynamic effects caused by terbutaline.

Glucose concentration increased significantly from 4.1 (3.5–4.7) to 6.6 (5.9–7.3) mmol l^{-1} during terbutaline infusion, but remained unchanged during ICI-118551.

Discussion

The principal findings in the present study were that β_2-adrenoceptor blockade did not modify exercise induced increase in potassium concentrations, but reduced maximal exercise performance and peak heart rate.

Potassium

Intravenous infusion of adrenaline in animals increases plasma potassium due to α-adrenoceptor mediated release from the liver followed by sustained hypokalaemia due to an increased uptake of potassium by skeletal muscles (D'Silva, 1934; Vick *et al.*, 1972). A lower dose infusion in man produces hypokalaemia with no initial hyperkalaemia (Struthers *et al.*, 1983).

The fall in potassium concentration seen after catecholamine stimulation has been attributed to stimulation of the β_2-adrenoceptors in skeletal muscles (Clausen & Flatman, 1980). This notion was supported in the present study by the finding that the haemodynamic and metabolic effects of the selective β_2-adrenoceptor agonist terbutaline were blocked by ICI-118551.

During exercise the relative hyperkalaemia caused by non-selective β-adrenoceptor blockade has been thought to be due to an increased release of potassium from working muscles (Linton *et al.*, 1984), or to blockade of cellular uptake of potassium (Carlsson *et al.*, 1978).

Furthermore, as shown in animal experiments (Todd & Vick, 1971) and in humans during exercise (Williams *et al.*, 1985), α-adrenoceptors act to enhance hyperkalaemia, and the opposite effect occurs with β-adrenoceptor stimulation.

In the present study neither selective β_1- nor β_2-adrenoceptor blockade modified the potassium concentrations in the venous effluent during or after exercise. Furthermore, there was no difference in the rate of decline in potassium concentrations between the different treatment regimens after exercise, which may suggest that the β-adrenoceptor subtypes in skeletal muscle are of less importance for modification of potassium during exercise. This notion is in accordance with exercise tests in humans showing no effect on arterial-femoral venous difference for potassium with non-selective β-adrenoceptor blockade although a systemic elevation of potassium concentration was observed (Katz *et al.*, 1985). This strongly suggests that the working muscle is not the source of the elevated potassium levels. In addition stimulation of β_2-adrenoceptors with terbutaline during exercise seems to decrease both arterial and venous potassium concentrations and does not prevent potassium loss from the exercising muscles (Rolett *et al.*, 1990). Thus, the relative importance of β-adrenoceptors seems to diminish during exercise, as has also been demonstrated in animal studies showing that the stimulating effect of adrenaline on the Na-K-pump is reduced by concomitant electrical stimulation of the muscles (Everts *et al.*, 1988).

If β-adrenoceptors in skeletal muscles are not involved in potassium regulation of the exercising muscles, what is the explanation for the increased potassium concentrations following non-selective β-adrenoceptor blockade with propranolol? The possibility that non-selective β-adrenoceptor blockade may reduce peripheral blood flow is not likely because propranolol does not seem to reduce leg blood flow significantly during exercise (Katz *et al.*, 1985), and in accordance with this lactate concentrations are not increased as shown in the present study.

β-adrenoceptor blockade generally causes a higher potassium level in both arterial and venous blood. It has been suggested that the relative hyperkalaemia with propranolol is due to a diminished uptake of potassium by inactive skeletal muscles (Katz *et al.*, 1985; Rolett *et al.*, 1990), or alternatively due to unopposed α-adrenoceptor stimulation (Williams *et al.*, 1985).

β_1-adrenoceptors may also be involved in potassium homeostasis. Atenolol only partially blocks potassium influx caused by adrenaline (Struthers *et al.*, 1983), and the number of β_1-adrenoceptors in the skeletal muscle is less than 20% of the total β-adrenoceptor number, which may explain why no effect with atenolol could be detected in the present study. In contrast to skeletal muscle β_1-adrenoceptors are the dominant receptor in the myocardium and have been shown to increase myocardial potassium uptake during cathecolamine infusion (Ellingsen *et al.*, 1987).

The physiological importance of the elevated potassium is not known, but it may be responsible for the post-functional increase in muscle blood flow, may locally depolarize nerve endings and muscle cells (Hnik *et al.*, 1976), and by its effect on the membrane potential reduce force of contraction leading to muscle fatigue (Jones, 1981; Medboe & Sejersted, 1990). From clinical experiments it is known that muscular weakness progressing to flaccid quadriplegia occurs at plasma concentrations exceeding 7 mmol l^{-1} (Epstein, 1980). It is therefore possible that the increase in serum potassium during exercise may be a limiting factor for the maximal exercise capacity following β-adrenoceptor antagonists (Carlsson *et al.*, 1978; Gullestad *et al.*, 1989a).

We anticipated that a pure β_2-adrenoceptor antagonist would enhance potassium concentration during exercise and reduce exercise capacity. However ICI-118551 did not modify the exercise induced rise in potassium concentration, and the reduction in exercise capacity was less than with propranolol. This does not rule out the importance of high levels of extracellular potassium as a limiting factor during exercise. It is possible that a difference in cellular transmembrane potassium concentrations is not reflected in the venous effluent from the working muscles. However, alternative mechanisms may be involved during selective β_2-adrenoceptor blockade, like interference with cellular calcium regulation (Vøllestad *et al.*, 1988).

Heart rate

The reduction in peak heart rate obtained with selective β_1-adrenoceptor blockade accounted for 80% (44 beats min^{-1}) and β_2-adrenoceptor blockade for 20% (11 beats min^{-1}) of the reduction obtained with β_1, β_2-adrenoceptor blockade (55 beats min^{-1}). This is in accordance with the known proportions of β_1- and β_2-adrenoceptors in the heart (Stiles *et al.*, 1983) and with a previous study (Pringle *et al.*, 1988) where combined effects of selective β_1- and β_2-adrenoceptor blockade equalled the haemodynamic effects obtained with non-selective β-adrenoceptor blockade during isoprenaline infusion.

Both β-selective and non-selective β-adrenoceptor antagonists augment adrenaline levels during exercise (Gullestad *et al.*, 1989b; Irving *et al.*, 1971), and this may stimulate β_2-adrenoceptors in the myocardium directly at maximal exercise. Accordingly, the reduction in peak heart rate response by non-selective β-adrenoceptor blockers may be due to blockade of the β_2- as well as β_1-adrenoceptors (Friedman *et al.*, 1987). This may be a limitation in the use of exercise induced tachycardia for comparison of equipotent doses of β-adrenoceptor antagonists with respect to β_1-mediated responses.

Exercise performance

β-adrenoceptor antagonists are known to cause muscle fatigue and reduced exercise performance in hypertensive and healthy subjects (Epstein *et al.*, 1965; Gullestad *et al.*, 1988, 1989a,b; Lundborg *et al.*, 1981; Pearson *et al.*, 1979; Sklar *et al.*, 1982), more pronounced with non-selective than with β_1-selective agents (Gullestad *et al.*, 1988; Lundborg *et al.*, 1981). The present study demonstrates that the reduction in exercise performance with each of the β_1- and β_2-adrenoceptor blockers amounted to 50% of that obtained with the non-selective agent. The relative reduction in exercise capacity with the selective β-adrenoceptor blockers therefore does not reflect the relative distribution of β-

adrenoceptor subtypes in the myocardium and is not related to their differential effects on heart rate.

The reason for the reduction in exercise capacity with β-adrenoceptor antagonists is unclear, but factors such as chronotropic and inotropic stimulation, reduced cardiac output and peripheral blood flow (Epstein *et al.*, 1965; McSorley & Warren, 1978; Pearson *et al.*, 1979), lack of substrate for the working muscles (Lundborg *et al.*, 1981), increased levels of potassium and direct effect on muscle contraction (Bowman, 1980; Carlsson *et al.*, 1978; Gullestad *et al.*, 1989a), and mental factors such as subjective perception of fatigue (Gullestad *et al.*, 1988; Pearson *et al.*, 1979) have been suggested. In the present study, the reduction in heart rate and blood pressure was not proportional to the reduction in maximal exercise performance obtained with the different β-adrenoceptor antagonists. Atenolol resulted in significantly greater reduction in heart rate and inotropic stimulation than ICI-118551, but caused less reduction in exercise performance. The same differential effect with respect to heart rate and cardiac output with atenolol and ICI-118551 has recently been observed (Vanhees *et al.*, 1986). No difference in diastolic blood pressure was observed with any of the treatment regimens, despite allegedly different effects on peripheral resistance between β_1- and β_2-adrenoceptor blockade. Lactate concentrations and anaerobic threshold were the same for placebo and the three β-adrenoceptor blockers during graded exercise. It is therefore not likely that haemodynamic variables (Sklar *et al.*, 1982) or lactate release (Juhlin-Dannfelt, 1983) are the sole important factors for maximal exercise performance in healthy normal subjects.

In conclusion non-selective β-adrenoceptor blockade, in contrast to selective β_1- and β_2-adrenoceptor blockade, caused marked increase in potassium concentrations during exercise to levels which may interfere with muscle contraction. The higher levels are probably not caused by inhibition of potassium influx in the working muscles. The reduction in maximal exercise performance with separate blockade of β_1- and β_2-adrenoceptor subtypes was close to 50% of that obtained by combined β_1- and β_2-adrenoceptor blockade. The reduction in maximal exercise performance with non-selective β-adrenoceptor blockade is therefore completely accounted for by an equal contribution by blockade of β_1- and β_2-adrenoceptor subtypes, despite the different proportions of the two subtypes in skeletal muscle and in the myocardium. The reduction in maximal exercise performance with the different β-adrenoceptor antagonists was not consistently related to their effect on heart rate, blood pressure, substrate or lactate- and potassium concentrations in the effluent from the exercising muscles.

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