THE ROLE OF $\alpha_1$-ADRENOCEPTORS IN ADRENALINE-INDUCED HYPERKALAEMIA

H. ENSINGER, B. DIRKS, K. H. ALTEMEYER AND A. GRÜNERT

SUMMARY

The hyperkalaemic action of adrenaline was investigated in 44 anaesthetized domestic pigs. Plasma and epicardial concentrations of $K^+$ were measured, in the latter case with an ion-selective electrode. Adrenaline $10 \mu g kg^{-1}$ caused a rapid increase in the plasma concentration of $K^+$ from 4.2 to 5.9 mmol litre$^{-1}$. The magnitude and the time course of epicardial concentration of $K^+$ were similar. Alpha-adrenoceptor block with either phentolamine $5 mg kg^{-1}$ (non-selective block) or prazosin $0.1 mg kg^{-1}$ (selective $\alpha_1$-adrenoceptor block) abolished the hyperkalaemic effect of adrenaline in the plasma and on the epicardium. The $\alpha_1$-adrenoceptor agonist phenylephrine increased the $K^+$ concentration, but the $\alpha_2$-adrenoceptor agonist UK 14.304 did not cause any change in concentration. These results suggest that the hyperkalaemia induced by adrenaline occurs in the interstitial fluid of the myocardium and is mediated by $\alpha_1$-adrenoceptors. These findings may be important in patients at risk of hyperkalaemia, with implications, for example, in the use of suxamethonium during induction of anaesthesia.

KEY WORDS


Sympathetic nerve activity has been shown to play a role in the external homeostasis of $K^+$. Beta-adrenoceptor block [1] or $\alpha$-adrenoceptor stimulation [2] is known to impair extrarenal deposition of infused $K^+$ in humans and to attenuate the increased plasma $K^+$ associated with physical exercise [3]. Adrenergic mechanisms also cause a rapid biphasic change in the plasma concentration of $K^+$ [4].

Rapid changes in the myocardial concentration of $K^+$ may be one reason for electrophysiological disturbances [5]. Such changes may occur in patients whose sympathetic nervous systems are activated, for example by painful surgical procedures, tracheal intubation, hypcapnia or hypoxia or after injection of adrenaline. Administration of suxamethonium increases the plasma concentration of $K^+$ [6] and $K^+$ deposition may be disturbed in patients with $\alpha$-adrenoceptor stimulation or $\beta$-adrenoceptor block. We therefore investigated the effects of adrenaline on plasma $K^+$ and on the epicardium with a $K^+$-selective electrode [7], as an index of myocardial $K^+$.

METHODS

Animal preparation

Approval from the Federal Government was given for the study. Domestic pigs (28–30 kg) were premedicated with azaperone 100 mg and atropine 2.5 mg i.m. and anaesthetized with metomidate 100 mg i.v. The trachea was intubated, and positive pressure ventilation commenced with 60% nitrous oxide in oxygen using a Siemens Servo 900 ventilator and adjusted to achieve normoxia and normocapnia. After tracheal intubation, the animals were given metomidate 150 mg, buprenorphine 0.6 mg and alcuronium 5 mg i.v. Anaesthesia was maintained with a continuous infusion of metomidate 3 mg min$^{-1}$ and alcuronium 0.04 mg min$^{-1}$. Ringer's lactate solution was infused at a rate of 120 ml h$^{-1}$. The right and left femoral arteries and the left
femoral vein were cannulated. Rectal temperature was maintained at 38 °C with a heating pad. Sternotomy was performed and the pericardium opened. The K$^+$-selective electrode was attached to the epicardium near the apex. After preparation the pig was placed in a Faraday cage and allowed to stabilize for 15 min.

**Measurements and chemical analysis**

K$^+$-selective electrodes were constructed and calibrated by the method of Hirche and colleagues [7]. Arterial pressure was recorded via the left femoral artery and heart rate derived from the ECG. The amplified output of the K$^+$-selective electrode was registered on a chart recorder. Blood samples for chemical analysis were centrifuged and the supernatant analysed for Na$^+$ and K$^+$ with a flame photometer (Beckman).

**Experimental programme**

Eight differently treated groups were studied: a control group and animals given adrenaline, phentolamine, phentolamine plus adrenaline, prazosin, prazosin plus adrenaline, phenylephrine and a selective $\alpha_1$-adrenoceptor agonist, UK 14.304 (5-bromo-6-(2-imidazolin-2-ylamino)-quinoxaline) [8].

To verify the *in vivo* function of the K$^+$-selective electrode, a bolus of 5-mmol potassium chloride (1 mmol ml$^{-1}$) was injected. Before and 45 s after the injection, blood samples were taken and the increase in plasma and epicardial concentrations of K$^+$ measured. Another 15 min elapsed until the start of the experiment. When phentolamine or prazosin was used for receptor-subtype classification, these drugs were administered during the 15 min before the experiment, together with 6 % hydroxyethyl starch 300 ml. A blood sample to determine Na$^+$, K$^+$, pH, $P_{CO_2}$ and $P_{O_2}$ was taken (time $t = 0$ min). A bolus of adrenaline 10 μg kg$^{-1}$, phenylephrine 100 μg kg$^{-1}$, UK 14.304 3 μg kg$^{-1}$ or an equal volume of saline (3 ml) was injected during a period of 30 s. At $t = 1, 2, 4$ and 8 min after completion of the injection, blood samples were taken to determine Na$^+$, K$^+$ and, at $t = 8$ min, pH, $P_{CO_2}$ and $P_{O_2}$ also. As the experiments with UK 14.304 were carried out 1 year after the experiments with adrenaline, we measured only the plasma concentration of K$^+$. In preliminary experiments it was shown that UK 14.304 reached the maximum pressure effect without decreasing heart rate at a dose of 3 μg kg$^{-1}$.

**Statistical analysis**

Analysis of variance was performed for the statistical treatment of the data using the SAS program [9]. Results are expressed as means and SEM. $P < 0.05$ was taken as significant. If the analysis of variance showed a significant difference (treatment used as independent variable) $t$ statistics modified by the Bonferroni method were calculated by comparing each treated group with the control group.

**RESULTS**

**In vivo function of the ion-selective electrode**

Baseline plasma and epicardial concentrations of K$^+$ in the control experiments were both 4.0 (0.2) mmol (n = 8). The injection of potassium chloride 5 mmol increased the plasma concentration of K$^+$ to 5.1 (0.2) mmol and the epicardial concentration to 5.3 (0.4) mmol (n = 8). Heart rate and mean arterial pressure were not affected by the injection of potassium.

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**Fig. 1. Typical recordings from the potassium selective electrode.**

A: A control experiment; the withdrawal of blood caused artefacts at $t = 0, 1, 2, 4$ and 8 min. B: Adrenaline. C: Prazosin plus adrenaline.
Typical tracings of the output of the ion-selective electrode from three experiments (control, adrenaline, prazosin plus adrenaline) are shown in figure 1. In the control experiment, the epicardial concentration of K\(^+\) remained constant. After injection of adrenaline, there was an increase in the epicardial concentration, followed by a decrease to less than the original value. In the experiment with the antagonist, only the decrease was detected.

**Control studies**

At \( t = 0 \) min, plasma concentration of Na\(^+\) was 142 (1) mmol litre\(^{-1}\), pH was 7.45 (0.02), \( P_{CO_2} \) 4.8 (0.15) kPa and \( P_{O_2} \) 18.8 (1.2) kPa \((n = 8)\). Both plasma and epicardial concentrations of K\(^+\) were 4.2 (0.2) mmol litre\(^{-1}\) at \( t = 0 \) min. These parameters remained constant at \( t = 1, \) 2, 4 and 8 min after the injection of saline 3 ml. Comparison of all groups did not show any difference for any of the parameters determined at \( t = 0 \) min.

**Adrenaline**

The absolute values for plasma and epicardial concentrations of K\(^+\) are shown in tables I and II. The maximal effect in the plasma concentration of K\(^+\) was reached after 1 min. The time course was similar in the epicardium, but the rapid decrease in K\(^+\) concentration did not begin until 2 min after the injection of adrenaline.

Adrenaline increased mean arterial pressure from 64 (3) to 122 (5) mm Hg and heart rate from 120 (8) to 229 (10) beat min\(^{-1}\).

**Alpha-adrenoceptor block**

Phentolamine 5 mg kg\(^{-1}\) and prazosin 0.1 mg kg\(^{-1}\) affected neither the basal values at \( t = 0 \) min nor the plasma or the epicardial concentrations of K\(^+\) at \( t = 1, \) 2, 4 and 8 min (tables I, II). Both drugs abolished the increases in plasma and epicardial concentrations of K\(^+\) caused by adrenaline and completely antagonized the in-

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**Table I.** Mean (SEM) plasma concentrations of K\(^+\) before \((t = 0)\) and at 1, 2, 4 and 8 min after administration of the study drugs. *P < 0.05 compared with \( t = 0 \)

<table>
<thead>
<tr>
<th>Study drug</th>
<th>( n )</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8</td>
<td>4.2 (0.2)</td>
<td>4.2 (0.2)</td>
<td>4.2 (0.2)</td>
<td>4.2 (0.2)</td>
<td>4.2 (0.2)</td>
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<tr>
<td>Adrenaline 10 µg kg(^{-1})</td>
<td>13</td>
<td>4.2 (0.2)</td>
<td>5.9 (0.3)*</td>
<td>4.6 (0.2)</td>
<td>3.8 (0.2)</td>
<td>4.0 (0.1)</td>
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<tr>
<td>Phentolamine 5 mg kg(^{-1})</td>
<td>4</td>
<td>4.3 (0.3)</td>
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<tr>
<td>Phentolamine 5 mg kg(^{-1})</td>
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<td>3.8 (0.2)</td>
<td>4.0 (0.1)</td>
<td>3.8 (0.1)</td>
<td>4.1 (0.3)</td>
<td>3.9 (0.3)</td>
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<tr>
<td>+ adrenaline 10 µg kg(^{-1})</td>
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<tr>
<td>Prazosin 0.1 mg kg(^{-1})</td>
<td>4</td>
<td>4.4 (0.2)</td>
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<tr>
<td>Phenylephrine 100 µg kg(^{-1})</td>
<td>5</td>
<td>4.1 (0.1)</td>
<td>4.7 (0.4)</td>
<td>4.2 (0.3)</td>
<td>3.9 (0.1)</td>
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<td>UK 14.304 3 µg kg(^{-1})</td>
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<td>4.0 (0.1)</td>
<td>4.1 (0.1)</td>
<td>4.1 (0.1)</td>
<td>4.0 (0.1)</td>
<td>4.1 (0.1)</td>
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</table>

**Table II.** Mean (SEM) epicardial concentrations of K\(^+\) before \((t = 0)\) and at 1, 2, 4 and 8 min after administration of the study drugs. *P < 0.05 compared with \( t = 0 \)

<table>
<thead>
<tr>
<th>Study drug</th>
<th>( n )</th>
<th>0</th>
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<th>2</th>
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<td>4.2 (0.2)</td>
<td>5.9 (0.5)*</td>
<td>5.6 (0.4)*</td>
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<td>3.8 (0.2)</td>
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<tr>
<td>Phentolamine 5 mg kg(^{-1})</td>
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<td>4.3 (0.3)</td>
<td>4.2 (0.3)</td>
<td>4.3 (0.4)</td>
<td>4.4 (0.3)</td>
<td>4.5 (0.8)</td>
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<tr>
<td>Phentolamine 5 mg kg(^{-1})</td>
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<td>3.8 (0.2)</td>
<td>4.1 (0.1)</td>
<td>3.7 (0.2)</td>
<td>3.6 (0.2)</td>
<td>3.8 (0.2)</td>
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<tr>
<td>+ adrenaline 10 µg kg(^{-1})</td>
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<tr>
<td>Prazosin 0.1 mg kg(^{-1})</td>
<td>4</td>
<td>4.4 (0.2)</td>
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</tr>
<tr>
<td>Phenylephrine 100 µg kg(^{-1})</td>
<td>5</td>
<td>4.1 (0.1)</td>
<td>5.7 (0.9)</td>
<td>6.1 (1.3)*</td>
<td>4.0 (0.1)</td>
<td>3.9 (0.2)</td>
</tr>
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</table>
increase in arterial pressure without affecting the adrenaline-induced tachycardia.

**Alpha-adrenoceptor activation**

Phenylephrine 100 μg kg⁻¹ increased the plasma concentration of K⁺ (not significantly) and the epicardial concentration. Arterial pressure increased to a greater value with phenylephrine than with adrenaline, and the increase persisted for longer.

With UK 14.304 3 μg kg⁻¹ min⁻¹, there was no change in the plasma concentration of K⁺ (tables I, II).

**DISCUSSION**

In our experimental model, adrenaline caused an increase in the plasma concentration of K⁺ followed by a short-term decrease. Time course and extent of the change were similar in plasma and epicardium. Treatment of the pigs with phentolamine 5 mg kg⁻¹ abolished the hyperkalaemic and the pressor effect of adrenaline. As phentolamine has no β-adrenoceptor blocking properties, the receptor causing the hyperkalaemia is an α-adrenoceptor. For receptor subtype classification, experiments with the α₁-adrenoceptor antagonist prazosin were carried out [10]. A low dose of prazosin 0.1 mg kg⁻¹ abolished the pressor response and the adrenaline-induced hyperkalaemia. These results suggest that adrenaline causes the hyperkalaemia by stimulation of α₁-adrenoceptors. The organ most likely to release K⁺ upon adrenergic stimulation is the liver [11]. In an in vitro preparation of guineapig hepatocytes, prazosin blocked the K⁺ efflux evoked by adrenaline [12]. In contrast, the preferential α₂-adrenoceptor antagonist yohimbine [13] only partially antagonized the efflux.

Phenylephrine is a selective α₁-adrenoceptor agonist [14]. The increase in the plasma concentration of K⁺ evoked by phenylephrine was only about 50% of the increase seen after adrenaline. This finding is confirmed by previous observations [15, 16]. Only a combination of α- and β-adrenoceptor stimulation caused a similar increase in the plasma concentration of K⁺ [15]. The explanation for this phenomenon may be a decrease in the hepatic blood flow by α-adrenoceptor stimulation [17] and hence a delayed washout of K⁺ from the liver. The more pronounced increase in the K⁺ concentration on the epicardium may be caused by relative hypoxia of the myocardium, where the oxygen supply is reduced by coronary artery constriction induced by phenylephrine [18] and the oxygen demand of the heart is increased by the increased afterload.

UK 14.304 is a selective α₂-adrenoceptor agonist [8]. The absence of any increase in the K⁺ concentration after UK 14.304 further strengthens the concept that the hyperkalaemia found after injection of adrenaline is caused by α₁-adrenoceptor stimulation.

K⁺-selective electrodes have been used in vivo to determine the K⁺ concentration in the plasma and on the epicardium [7]. The epicardial concentration of K⁺ was taken as an index for the K⁺ concentration of the interstitial fluid of the myocardium. Downey [19] showed that under steady state conditions there is no difference between the K⁺ concentration in the coronary sinus blood and in the coronary lymph, which is the drainage fluid of the extracellular compartment of the myocardium. Hirche [7] reported that after an i.v. injection of K⁺, the time course and the amplitude of the K⁺ fluctuation are similar, both in the coronary sinus blood and on the epicardium.

Hyper- and hypokalaemia are thought to be adverse conditions for general anaesthesia. As the major side effects are disorders of heart rhythm and conduction, the K⁺ concentration of the myocardial extracellular fluid is of interest. Our experiments show that, after i.v. injection of K⁺ or the administration of α-adrenoceptor agonists, there is an increase in the K⁺ concentration of the myocardial extracellular fluid.

An increase in the plasma concentration of K⁺ of 1.9 mmol litre⁻¹ is usually without effect or only causes minor acceleration of cardiac conductance. However, if the plasma concentration of K⁺ is at the upper limit of or slightly above the physiological range, profound and rapid depression of conduction may occur with a 2-mmol litre⁻¹ increase in K⁺ concentration [20]. The α-adrenergic mechanisms leading to hyperkalaemia may be important under conditions in which other mechanisms cause increases in K⁺ concentration and in which the sympathetic nervous system is activated, especially in the presence of β-adrenoceptor block. In anaesthetized dogs, suxamethonium 1 mg kg⁻¹ caused hyperkalaemia, prolonged and intensified by β-adrenoceptor block [21]. Another study [22] failed to confirm these results. β-adrenoceptor block had only a minor effect.
There are no reports on any adverse effects of hyperkalaemia in patients with β-adrenoceptor block. Cardiac arrhythmias during administration of suxamethonium are thought to be the result of the stimulation of vagal and sympathetic ganglia. However, the rapidly occurring changes in plasma concentration of K⁺ caused by adrenergic stimulation have not been investigated in patients during induction of anaesthesia using depolarizing neuromuscular blocking drugs.

ACKNOWLEDGEMENT

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REFERENCES