EDITORIAL REVIEW

The role of adrenal medullary catecholamines in potassium homoeostasis

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Introduction

The concentration of potassium in plasma is maintained within the normal range in man by many different physiological factors. The kidney is obviously of prime importance, as demonstrated by the hyperkalaemia which develops in renal failure [1]. Several circulating hormones are, however, also of importance in potassium homoeostasis. Insulin enhances the uptake of potassium in muscle, liver and adipose tissue [2-4]. Mineralocorticoids and glucocorticoids lower the serum potassium, not only by their kaliuretic effect, but also by increasing potassium secretion from gut epithelial tissue [5, 6]. It has been known for a long time that a third group of hormones, namely catecholamines, also influence potassium balance, but it is only recently that this physiological mechanism has been shown to be of clinical relevance. This review concerns the role of adrenomedullary hormones in potassium homoeostasis and the pathophysiological relevance of this in man.

Physiology

Animal studies

The effect of adrenaline on potassium was first noted as far back as 1934 by D'Silva, who found that a rapid injection of adrenaline in cats caused an immediate short-lived increase followed by a prolonged decrease in the plasma potassium [7]. A closer analysis has revealed that the initial hyperkalaemia is due to net release of potassium from the liver [8]; this effect is probably due to stimulation of \( \alpha \)-adrenoceptors as it is inhibited by \( \alpha \)-receptor blockade [9]. The subsequent pro-

longed hypokalaemia is due to net uptake of potassium in skeletal muscle and other tissues: this effect is due to stimulation of \( \beta \)-adrenoceptors and is inhibited by \( \beta \)-receptor blockade [9, 10]. Elegant studies in vitro to characterize this mechanism have been performed by Flatman & Clausen, who used rat soleus muscle as a model of skeletal muscle. They showed that adrenaline stimulates \( Na^+ \) efflux and \( K^+ \) influx in this tissue [11]. Similar results have been reported in frog sartorius muscle, rat diaphragm and cat skeletal muscle [12-14]. Potassium uptake by muscle was found also to occur after isoprenaline and terbutaline [15, 16]. Furthermore, adrenaline-induced \( Na^+,K^+ \)-dependent ATPase activity was blocked by propranolol but not by metoprolol [17]. Overall these experiments suggest that catecholamines stimulate a \( \beta_2 \)-adrenoceptor linked to membrane bound \( Na^+,K^+ \)-ATPase in skeletal muscle causing potassium influx.

Interestingly, Buckler and his colleagues have extended these observations on muscle tissue in vitro. They found that adrenaline and noradrenaline stimulated \( Na^+ \) pump activity in frog skeletal muscle but depressed \( Na^+ \) pump activity in frog hemiventricles [18]. In the frog, therefore, increased circulating catecholamines cause potassium uptake in skeletal muscle but potassium loss from cardiac tissue.

Human studies

Confirmation of the role of adrenaline in potassium homoeostasis in man has depended on other experimental and clinical approaches. In 1960, Lepeschkin infused adrenaline slowly into normal human subjects and noted the electrocardiographic changes of T wave flattening and an increase in U wave amplitude [19]. In retrospect, it seems likely that these electrocardiographic changes were due to hypokalaemia but the plasma
concentration of potassium was not measured in this study. Another β-adrenoceptor agonist, salbutamol, was shown to lower serum potassium when infused into normal man [20]. Overdose of salbutamol tablets causes profound hypokalaemia [21, 22]. Propranolol completely blocked salbutamol-induced hypokalaemia whereas practolol had only a modest inhibitory effect, suggesting that in man as in the animal studies discussed above, Na⁺,K⁺-ATPase is linked, in some tissues at least, to β₂-adrenoceptors [23].

In normal man this mechanism has also been studied by the infusion of potassium chloride in the presence of adrenaline with an without propranolol [24, 25]. When potassium chloride is infused, plasma and urinary potassium concentration both increase. In the presence of adrenaline, both of these increases are markedly inhibited. Propranolol blocks these effects of adrenaline on both renal and extrarenal potassium metabolism.

Further circumstantial evidence for this mechanism comes from observations on plasma potassium concentrations in patients undergoing open heart surgery [26, 27]. In such patients, circulating catecholamine concentrations are elevated and intravenous potassium may be required to maintain normokalaemia. When patients were infused with a standard intravenous regimen, pretreatment with propranolol caused the plasma potassium concentration to rise whereas pretreatment with metoprolol had no effect on plasma potassium.

Massara et al. showed that adrenaline infused at high doses into normal volunteers caused systemic hypokalaemia and this was blocked by propranolol [28]. We have performed similar studies whereby adrenaline was infused into normal volunteers but, in our studies, we used lower infusion rates than Massara et al. We aimed for and achieved steady state plasma adrenaline levels which were very similar to those found during pathophysiological states such as acute myocardial infarction [29, 30] or hypoglycaemia [31]. In normal volunteers, these plasma levels of adrenaline (3-5 nmol/l) cause profound hypokalaemia [32]. This was accompanied by the electrocardiographic changes of T wave flattening, U waves and Q-T interval prolongation. Timolol, a non-selective β-adrenoceptor blocker, completely inhibited adrenaline-induced hypokalaemia, whereas atenolol, a β₁-selective antagonist, had only a small effect [33]. In a subsequent study, a selective β₂-antagonist (ICI 118551) completely blocked adrenaline-induced hypokalaemia [33a].

Changes in potassium also occur during physical exercise. Exercise causes marked efflux of potassium from muscles. This is balanced by potassium influx into muscles, owing to raised circulating catecholamines [34]. The importance of β-receptor mediated potassium influx is demonstrated in the observation that pretreatment with non-selective β-blockers causes the plasma potassium concentration to rise markedly during exercise [35]. A possible teleological rationale for catecholamine-induced potassium influx is to prevent life-threatening hyperkalaemia during prolonged exercise. Additionally, in the resting state, basal levels of circulating catecholamines may help to restore the intracellular potassium which is lost during the repeated action potentials involved in normal tonic muscular activity.

The human studies quoted above help to confirm that catecholamines cause hypokalaemia in man by the stimulation of β₂-adrenoceptors. However, several other possible mechanisms have to be excluded. It is conceivable that catecholamines would stimulate the renin-angiotensin system, causing aldosterone release and subsequent kaliuresis. Although plasma renin increases two- to three-fold during the infusion of adrenaline, there is, however, no increase in plasma aldosterone [36]. Furthermore, during the infusion of adrenaline the urinary concentration of potassium falls in parallel with the plasma potassium [33]. Another possible mechanism is that β-adrenoceptor stimulation causes the release of insulin [23], which is known to stimulate potassium influx [2, 3]. However, adrenaline is not only a β-agonist but has in addition α-adrenoceptor stimulating properties. As insulin release is influenced more by inhibitory α-adrenoceptors than by stimulatory β-adrenoceptors [37], insulin release is in fact inhibited during the infusion of adrenaline [38]. It is, therefore, unlikely that adrenaline-induced hypokalaemia in man is caused by kaliuresis or by the release of insulin or aldosterone. It appears rather to be due to the shift of potassium from the extracellular to the intracellular space. It is tempting to extrapolate from animal studies that adrenaline causes potassium uptake into skeletal muscle in man. There is, however, no direct evidence for this. The erythrocyte is the only cell in which catecholamine-mediated potassium influx has been demonstrated in man [39].

Clinical significance

In normal volunteers profound hypokalaemia develops at plasma adrenaline levels which are similar to those found during pathophysiological states such as acute myocardial infarction or hypoglycaemia [32]. Are there any observations which confirm this in clinical practice?
Transient hypokalaemia has been noted during the endocrine investigation of an insulin tolerance test [40]. In this particular case, it is uncertain whether systemic hypokalaemia is due to insulin itself or to the increases in catecholamines or cortisol which also occur. \(\beta\)-Adrenoceptor agonists are used in the suppression of premature labour and may cause falls in serum potassium [41]. The hypokalaemic effect of \(\beta\)-adrenoceptor agonists also has a clinical application. In familial periodic paralysis the plasma concentration of potassium increases considerably after exercise, leading to paralytic attacks. This hyperkalaemia can be prevented by \(\beta_2\)-adrenoceptor agonists like salbutamol [42, 43].

**Myocardial infarction**

Several studies report that hypokalaemia is frequently observed in the acute phase of myocardial infarction [44-48]. The incidence of hypokalaemia ranged from 15 to 31% in different studies. Ventricular arrhythmias occurred more frequently in the hypokalaemic patients than in the normokalaemic ones. In one study, 23 out of 90 patients with acute myocardial infarction had plasma potassium concentration < 3.5 mmol/l [44]. Ventricular tachycardia and/or fibrillation occurred in 12% of the normokalaemic and 35% of the hypokalaemic group. Hospital mortality in the normokalaemic and the hypokalaemic groups was 15% and 35% respectively. Furthermore, of the 23 hypokalaemic patients, only seven were on diuretic therapy before admission to hospital. Hypokalaemia was not due to haemodilution or to increased urinary excretion of potassium and it resolved spontaneously without potassium supplementation. Plasma catecholamines are raised in acute myocardial infarction. As hypokalaemia occurs at these plasma adrenaline levels in normal subjects, it is possible that the transient hypokalaemia of acute myocardial infarction is due to increased circulating catecholamines. Another possible arrhythmogenic effect of catecholamines may be the Q-T interval prolongation caused by adrenaline [32]. Q-T interval prolongation has often been associated with a predisposition to ventricular arrhythmias [49]. It remains unknown whether the association between hypokalaemia and arrhythmias is a direct one or is indirect, mediated by adrenaline itself or adrenaline-induced changes in ventricular repolarization. It is likely that a low extracellular potassium is at least contributory to ventricular arrhythmias, since spontaneous ectopic activity can readily be suppressed in isolated cardiac muscle preparations by an increase in the concentration of potassium in the perfusate [50].

The incidence of hypokalaemia in patients with acute myocardial infarction (15-31%) may appear low when compared with the profound hypokalaemia which can be demonstrated in normal volunteers. However, several factors should be borne in mind. The figure quoted above represented the incidence of hypokalaemia on a single blood sample in those patients who reach hospital. In view of the transient nature of adrenaline-induced hypokalaemia, one single blood sample may underestimate the numbers with transient hypokalaemia. Furthermore, this figure does not include the important group of patients who die suddenly, presumably from ventricular arrhythmias, before arrival at hospital. Another important factor is that some patients with acute myocardial infarction may have poor tissue perfusion and metabolic acidosis, which would cause the plasma potassium concentration to rise and offset the hypokalaemia caused by circulating adrenaline. In severe cardiogenic shock, plasma catecholamines may be very high but the plasma potassium concentration normal, owing to the marked acidosis.

There is increasing evidence of the beneficial effects of \(\beta\)-blockade in the secondary prevention of myocardial infarction [51-53]. The beneficial effect is likely to be due to a reduction in arrhythmias, resulting in a reduction in sudden death. There is also some evidence that intravenous \(\beta\)-blockers administered immediately after myocardial infarction are useful [54, 55]. The effects of \(\beta\)-blockade are likely to be multifactorial. The direct anti-arrhythmic actions via \(\beta\)-adrenoceptor antagonism or even to a membrane stabilizing effect may be of importance, as also would be the reduction in oxygen demand with its resulting decreased infarct size [56, 57]. The action of \(\beta\)-blockers on the transmembrane flux of potassium and the prevention of hypokalaemia may be an additional factor.

**Acute ly ill patients**

In a study of acutely ill hospital patients in a 2 months period Morgan & Young identified 45 acutely ill patients with plasma potassium concentrations of less than 2.8 mmol/l, although only 25% of them had been on diuretic therapy [58]. Plasma potassium concentrations returned to the normal range within days although no potassium supplementation was given. This transient acute hypokalaemia observed in acutely ill patients could be due to an intracellular flux of potassium, mediated by increased catecholamines.
**Diuretic therapy**

Several large studies have demonstrated that antihypertensive therapy reduced the incidence of cerebrovascular accidents but have failed to show any corresponding benefit in coronary heart disease [59-61]. In the recent MR FIT TRIAL [62], hypertensive men with initial ECG abnormalities had a higher coronary heart disease mortality (+65%) and total mortality (+55%) when their blood pressure was treated than the control untreated group. Treatment was usually with thiazide diuretics and it has been suggested that these drugs might predispose to cardiac arrhythmias or sudden death by reducing the concentration of plasma potassium [63, 64]. There is, however, no conclusive evidence to confirm this. However, several studies have demonstrated even in patients without cardiac disease an increase in ventricular ectopic activity and atrioventricular conduction disturbances in those patients with hypokalemia [65-68]. The frequency of ventricular ectopic beats is increased the lower the plasma potassium [69]. It may be more relevant to consider the concentration to which plasma potassium falls during increased sympatho-adrenal activity rather than the plasma potassium at rest. In our studies, normal volunteers were pretreated with either bendrofluazide (5 mg daily) or placebo for 7 days and then infused with adrenaline [70]. After the diuretic, plasma potassium concentration was lower than after placebo (3.40 vs 3.83 mmol/l) and fell still lower after the adrenaline infusion (2.73 vs 3.08 mmol/l). Routine monitoring of the plasma potassium at rest may therefore underestimate the extent of hypokalaemia at times of increased sympatho-adrenal activity.

**Conclusions**

The kidney is primarily responsible for chronic potassium balance but, in the short term, the plasma concentration of potassium is regulated not only by insulin, aldosterone and other corticosteroids but also by circulating levels of catecholamines. Circulating adrenaline in man causes hypokalaemia by stimulating a $\beta_2$-adrenoreceptor-linked $\text{Na}^+,\text{K}^+\text{-ATPase}$ causing potassium influx into skeletal muscle, erythrocytes and possibly other tissues. Profound hypokalaemia occurs at plasma levels of adrenaline which are found in pathophysiological states such as acute myocardial infarction or hypoglycaemia. This mechanism may be a contributory factor in the association between ventricular arrhythmias and hypokalaemia in acute myocardial infarction.

Antihypertensive treatment has not had a significant effect on coronary heart disease statistics. It is possible that this may be due in part to diuretic-induced hypokalaemia and its exacerbation at times of increased sympatho-adrenal activity.

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**References**


