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The effects of adrenoceptor agonists and antagonists on plasma potassium concentration in anaesthetized guinea-pigs, rabbits and rats

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1 An intravenous K^+-sensitive electrode has been used to monitor plasma $[K^+]$ changes induced by α- and β-adrenoceptor agonists in anaesthetized guinea-pigs, rabbits and rats. The effects of phentolamine and propranolol on these responses were studied.

2 In the guinea-pig both α- and β-adrenoceptor agonists produced a biphasic response consisting of an initial rapid increase in $[K^+]$ which was followed, within 1 min, by a fall below baseline. The antagonist studies indicated that in this species both phases of the response could be elicited by either α- or β-adrenoceptor activation.

3 In the rabbit the responses were both slower and smaller than those seen in the guinea-pig and required larger agonist doses. In addition it was found that the increase in plasma $[K^+]$ was α-adrenoceptor-mediated while the subsequent fall was seen only with β-adrenoceptor activation.

4 In the rat triphasic changes in plasma $[K^+]$ were seen consisting of an initial decrease which was α-adrenoceptor-mediated, followed by an increase and then a second fall which was elicited by β-adrenoceptor stimulation. The increase in plasma $[K^+]$ was only slightly reduced by either α- or β-adrenoceptor antagonists.

5 Apamin, a toxin from bee venom which blocks Ca^{2+}-activated K^+-channels, was found to block the hyperkalaemic phase of the response in the guinea-pig and rabbit but had no effect in the rat.

6 It is concluded that there are marked species differences in the effects of adrenoceptor agonists on plasma $[K^+]$ *in vivo*.

Introduction

It has been known for many years that the intravenous injection of adrenaline causes a rapid and transient increase in the plasma K^+ concentration, often followed by a more prolonged fall below baseline levels (D'Silva, 1934). The major source of the additional K^+ reaching the plasma during adrenaline hyperkalaemia is the liver (D'Silva, 1936; for references to more recent work, see Coats, 1983). Adrenaline-induced K^+-release from the liver is generally considered to be an α-adrenoceptor-mediated phenomenon (Ellis & Beckett, 1963; Ellis & Eusebi, 1965; Kvam *et al.*, 1965; Todd & Vick, 1971; Castro-Tavares & Cardoso, 1974) although in some circumstances a greater release can be elicited by the simultaneous stimulation of α- and β-adrenoceptors (Todd & Vick, 1971; Castro-Tavares, 1975; see also Jenkinson & Koller, 1977; Cocks *et al.*, 1984).

The second (hypokalaemic) phase of the response to adrenaline has been shown to be a consequence of K^+-uptake by both liver and skeletal muscle (Vick *et al.*, 1972). The mechanism by which adrenaline elicits an uptake of K^+ by the liver is not fully understood. Studies using antagonists with differing α- and β-adrenoceptor selectivities has led to a variety of conclusions. It has been suggested (Castro-Tavares & Cardoso, 1974) that K^+-uptake by liver is mediated by β-adrenoceptor stimulation but that previous K^+-release is a prerequisite for this response to occur. Hence, α-adrenoceptor antagonists which block the initial hyperkalaemic response also indirectly inhibit the K^+-uptake. However, more recent work in the guinea-pig

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has shown that apamin, a toxin from bee venom, is able to block adrenoceptor-mediated K^+-release whilst having no effect on the subsequent uptake (Coats, 1983). This work also suggests that in the guinea-pig K^+-uptake could be elicited by α-adrenoceptor stimulation alone since the α_1-adrenoceptor agonist amidephrine caused biphasic changes in plasma $[K^+]$ of the same kind as those seen with adrenaline.

The effect of adrenaline and other adrenoceptor agonists on liver $[K^+]$ can readily be shown *in vitro*. A net loss of hepatic K^+ in response to adrenaline and noradrenaline has been demonstrated using isolated, perfused livers (Craig, 1958) and liver slices (Haylett & Jenkinson, 1972). However, large species variations occur. For example, Haylett & Jenkinson (1973) showed that neither α- nor β-adrenoceptor agonists increased K^+ efflux from rat liver slices under conditions identical to those found effective with guinea-pig and rabbit tissue (see also Burgess *et al.*, 1981). Most of the *in vitro* work performed to date has used liver tissue from the guinea-pig, rabbit and rat, whereas the majority of the *in vivo* studies have been done in the cat and dog. It was decided therefore, in the present work, to compare the effects of adrenoceptor agonists and antagonists on plasma $[K^+]$ in the former three species *in vivo* so that a direct comparison could be made between the *in vivo* and *in vitro* results. The action of apamin was also studied. The work was based on the use of an intravenous K^+-sensitive electrode as described previously (Coats, 1983).

Methods

The procedures with guinea-pigs have already been described in detail (Coats, 1983). Briefly, male Hartley guinea-pigs (340–510 g) were anaesthetized with pentobarbitone sodium (25–30 mg kg^{-1}), fentanyl (0.1 mg kg^{-1}) and droperidol (10 mg kg^{-1}), all administered intraperitoneally. The left carotid artery and the left jugular vein were cannulated to record blood pressure and for drug injections respectively. A K^+-sensitive electrode was inserted into the right jugular vein so that its end was normally positioned in the suprahepatic portion of the inferior vena cava. (The final electrode position was always confirmed *post mortem*.) The indifferent electrode took the form of an agar-filled butterfly needle inserted under the skin of the chest in all three species. Drugs were given at 7–8 min intervals, as boluses of 0.05–0.2 ml washed in with 0.3 ml saline. All solutions contained 4 mM K^+ to avoid dilution artifacts.

Male New Zealand White rabbits (2.3–3.4 kg) were anaesthetized with pentobarbitone sodium (40–50 mg kg^{-1}) via a butterfly cannula inserted in the right marginal ear vein. It was found that insertion of the needle into the ear vein became easier if the animal was given diazepam (5 mg kg^{-1}) into the muscle of the thigh about 5 min beforehand. In several experiments the base of the ear was found to become swollen and the injected agents became less effective. If this occured the butterfly cannula was relocated in the left marginal ear vein. In the final experiments the drug injection cannula was routinely placed in the right jugular vein to avoid this problem. The K^+-sensitive electrode was inserted about 8 cm into the left jugular vein and was normally found to be in the inferior vena cava. Drugs were given via the butterfly cannula in the ear vein (or via the cannula in the jugular vein if used) in volumes of 0.05 to 0.3 ml and washed in with 0.4 ml of saline (0.3 ml if using the jugular vein) at 10–12 min dose intervals.

Male Sprague-Dawley rats (300–550 g) were anaesthetized with pentobarbitone sodium (20–25 mg kg^{-1}) supplemented with fentanyl and droperidol as for guinea-pigs. The K^+-sensitive electrode was inserted for the appropriate distance into the right jugular vein and its end was found to be in the suprahepatic portion of the inferior vena cava in every experiment. Adrenoceptor agonists were administered at 10–12 min dose intervals.

K^+-sensitive electrodes were constructed by forming valinomycin-containing PVC membranes on the ends of 15 cm lengths of narrow PVC tubing (0.96 mm o.d.), as previously described (Coats, 1983). The sensitivity and calibration of the electrode was checked before and after each experiment using standard solutions containing 1 to 20 mM K^+ in isotonic NaCl. Only electrodes which gave at least 95% of the expected Nernstian response were used.

Materials

The following materials were used: pentobarbitone sodium (Sagatal; May and Baker), fentanyl citrate (Sublimaze; Janssen), droperidol (dehydrobenzperidol; Droleptan, Janssen), diazepam (Valium; Roche), (±)-amidephrine mesylate (Mead and Johnson), (−)-adrenaline bitartrate (B.D.H.), (−)-isoprenaline bitartrate (Ward-Blenkinsop), oxymetazoline hydrochloride (Allen and Hanburys), methoxamine hydrochloride (Burroughs Wellcome), (−)-phenylephrine hydrochloride (Koch Light), angiotensin II (Sigma), phentolamine hydrochloride (CIBA), propranolol hydrochloride (Sigma), valinomycin (Sigma) and sebacic acid dibutyl ester (dibutyl sebacate; Sigma). Polyvinylchloride (PVC; Corvic S71/102) was a kind gift from ICI Plastics Division.

I am most grateful to Dr B.E.C. Banks (Dept of Physiology, University College London) for a supply of purified apamin. Apamin can be obtained commercially (Serva, Sigma).

Results

The baseline values for the K^+ concentration in plasma of the three species were found to be 4.4 ± 0.2 mM ($\pm$ s.e.mean; $n = 24$) in the guinea-pig, 3.9 ± 0.2 mM ($n = 15$) in the rabbit and 4.8 ± 0.1 mM ($n = 19$) in the rat.

The changes in arterial blood pressure and plasma [K^+] produced by adrenaline in each species are shown in Figure 1. It can be seen that the responses differ considerably. In the guinea-pig there was a rapid hyperkalaemic phase followed by a slower hypokalaemia, returning to baseline by about 4 min. In the rabbit the K^+-release was considerably slower and the hypokalaemic phase was either absent or very small. The reponse in the rat was triphasic, consisting of an initial rapid fall in plasma [K^+] followed by a rise and then a second, slow hypokalaemic phase. In all three species the changes in arterial blood pressure normally preceded any changes in plasma K^+-concentration. Neither the magnitude, nor the direction of the changes in blood pressure were correlated with the subsequent alterations in plasma K^+-concentration.

In the guinea-pig and the rabbit the response to the α_1-adrenoceptor agonist amidephrine was similar to that seen with adrenaline (see Figure 2.). In the rat, however, this agonist had no effect on plasma [K^+] at doses up to $68\,\mu g\,kg^{-1}$, although a small pressor response was seen with this dose. Another α_1-selective agonist, methoxamine, was also without effect on plasma [K^+] in the rat. Two other α-adrenoceptor agonists, phenylephrine and oxymetazoline, were tested in the rat and found to give K^+-uptake followed by release though there was no subsequent hypokalaemic phase (see Figure 3).

The β-adrenoceptor agonist isoprenaline was also

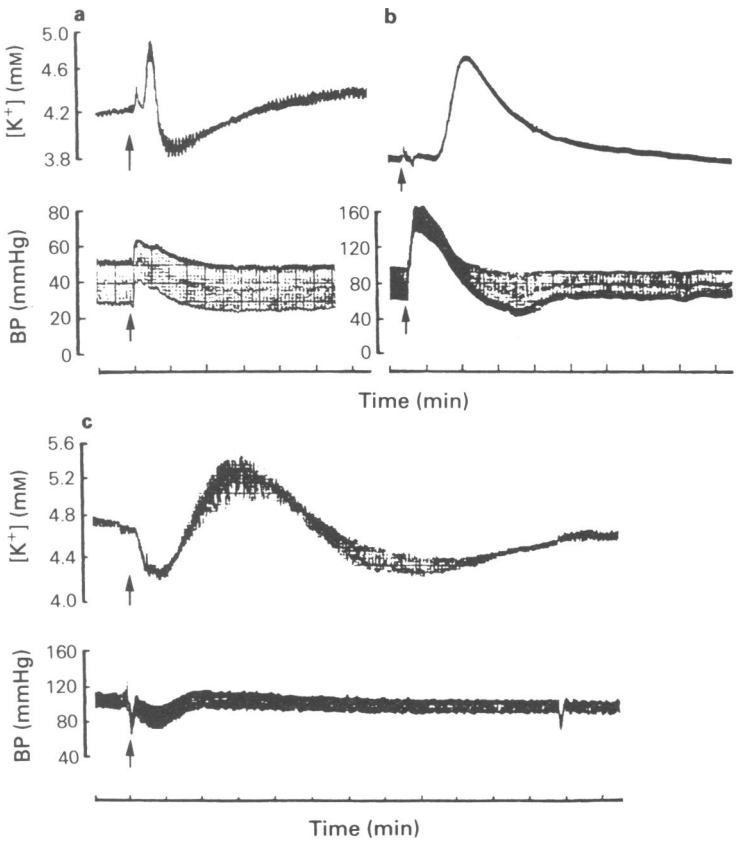

Figure 1 Examples of responses to adrenaline in (a) the guinea-pig ($3.4\,\mu g\,kg^{-1}$) (b) the rabbit ($6.7\,\mu g\,kg^{-1}$) and (c) the rat ($1.3\,\mu g\,kg^{-1}$). In each case the upper curve is the plasma [K^+] and the lower trace the arterial blood pressure. All responses are shown on the same time scale.

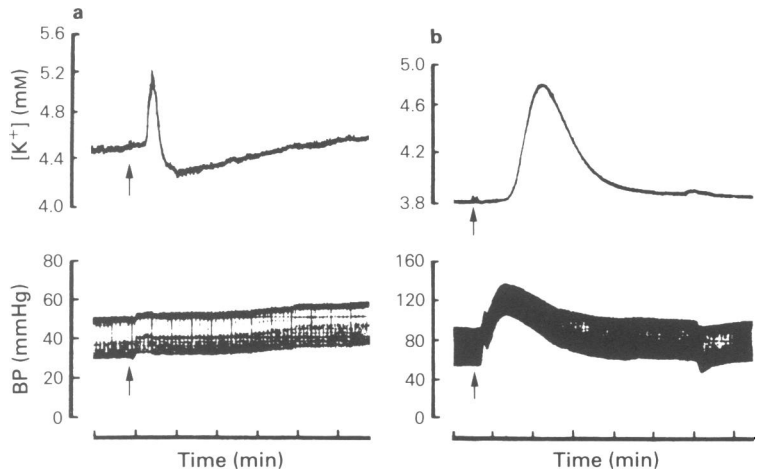

Figure 2 Examples of responses to amidephrine in (a) the guinea-pig (34 $\mu g\,kg^{-1}$) and (b) the rabbit (68 $\mu g\,kg^{-1}$). Upper traces are plasma $[K^+]$ and lower traces arterial blood pressure.

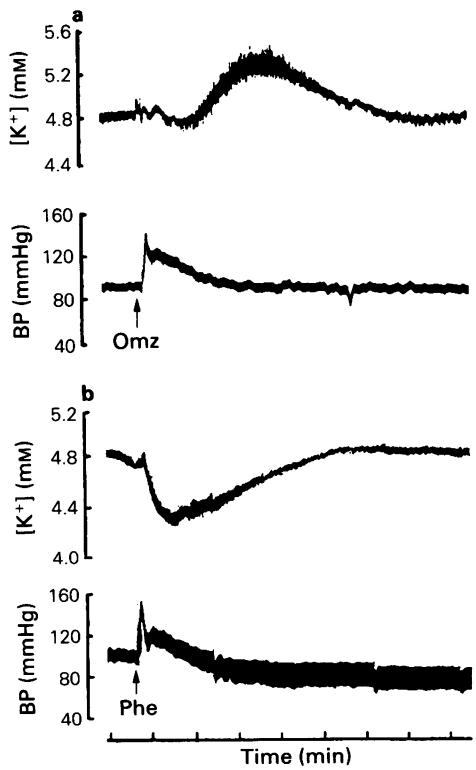

Figure 3 Examples of responses to (a) oxymetazoline (Omz; 6 $\mu g\,kg^{-1}$) and (b) phenylephrine (Phe; 40 $\mu g\,kg^{-1}$) in the rat. In each case the upper trace is the plasma $[K^+]$ and the lower trace the arterial blood pressure.

tested in the three species and the responses obtained are shown in Figure 4. In the guinea-pig the change in plasma $[K^+]$ was once again biphasic, similar to that seen with adrenaline and amidephrine. In the rabbit the response to isoprenaline was also biphasic with a small K^+-release followed by uptake. In the rat the response to isoprenaline was similar to that seen with adrenaline except that the initial uptake phase was absent, the response consisted of a delayed rise in plasma $[K^+]$ followed by a fall.

In the guinea-pig the peptide angiotensin II was also found to elicit biphasic changes in plasma $[K^+]$ similar to those seen with adrenoceptor agonists but the changes in K^+ were small in magnitude compared with the blood pressure increase. An example is shown in Figure 5.

The effects of the α- and β-adrenoceptor antagonists phentolamine and propranolol on these responses were tested in the three species. In the guinea-pig and rabbit it was found, in preliminary experiments, that the block produced by phentolamine was short-lived, being maximal approximately 2 min after administration of the antagonist. The agonist was therefore administered at this time. By about 20 min the responses had returned to control levels. In the rat, however, where lower doses of phentolamine were required, the recovery was also slower. In contrast, the block produced by propranolol was long-lived in all three species, there being no appreciable recovery of the response for at least 30 min. The effects of phentolamine (10 $mg\,kg^{-1}$) on the averaged time course of responses to amidephrine, adrenaline and isoprenaline in the guinea-pig are shown in the upper half of Figure 6. As might be expected, phentolamine blocked the

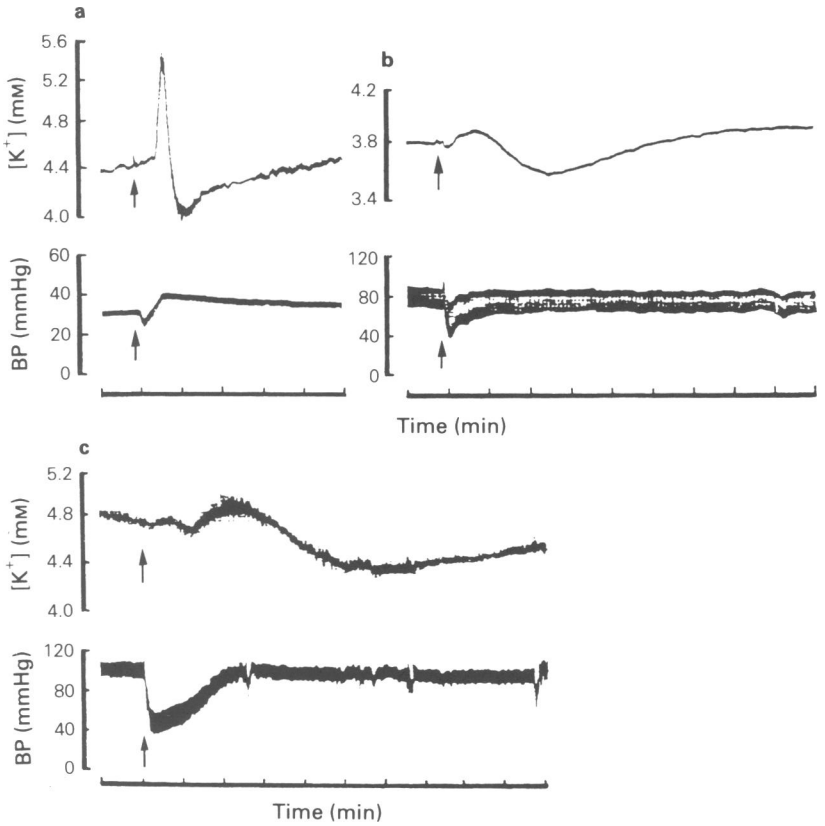

Figure 4 Examples of responses to isoprenaline in (a) the guinea-pig (0.4 μg kg^{-1}) (b) the rabbit (1.6 μg kg^{-1}) and (c) the rat (0.4 μg kg^{-1}). Upper traces are plasma [K^+] and lower traces arterial blood pressure.

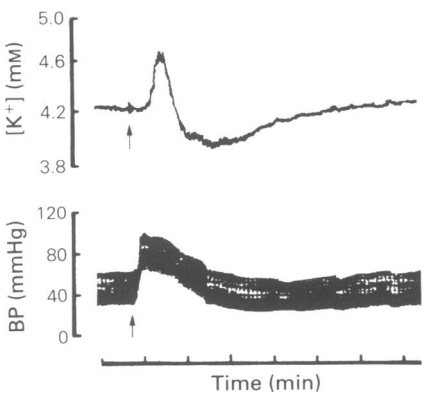

Figure 5 An example of the response to angiotensin II (0.4 μg kg^{-1}) in the guinea-pig. The upper trace is the plasma [K^+] and the lower trace the arterial blood pressure.

response to amidephrine. The hyperkalaemic phase was reduced by 85.8 ± 4.7% (n = 5) and the hypokalaemic phase by 83.8 ± 8.5%, whereas phentolamine had no effect on the hyperkalaemic response to isoprenaline. The results with propranolol (0.3 mg kg^{-1}) are shown in the lower section of Figure 6. The response to amidephrine was not affected but the hyperkalaemic response to isoprenaline was reduced by 92.1 ± 1.7% (n = 5) and the hypokalaemic phase by 82.6 ± 9.0%. However, when adrenaline was used as the agonist, both antagonists significantly blocked the response; phentolamine (10 mg kg^{-1}) blocked the hyperkalaemic response by 61.9 ± 8.8% (n = 5) and the hypokalaemic response by 47.9 ± 13.6%. The equivalent figures for propranolol (0.3 mg kg^{-1}) were 61.9 ± 9.6% (n = 5) and 72.0 ± 9.2%, respectively.

The results of similar experiments in the rabbit are depicted in Figure 7. In this case phentolamine (10 mg kg^{-1}) reduced the K^+-release elicited by amidephrine by 81.9 ± 5.5% (n = 3) and that

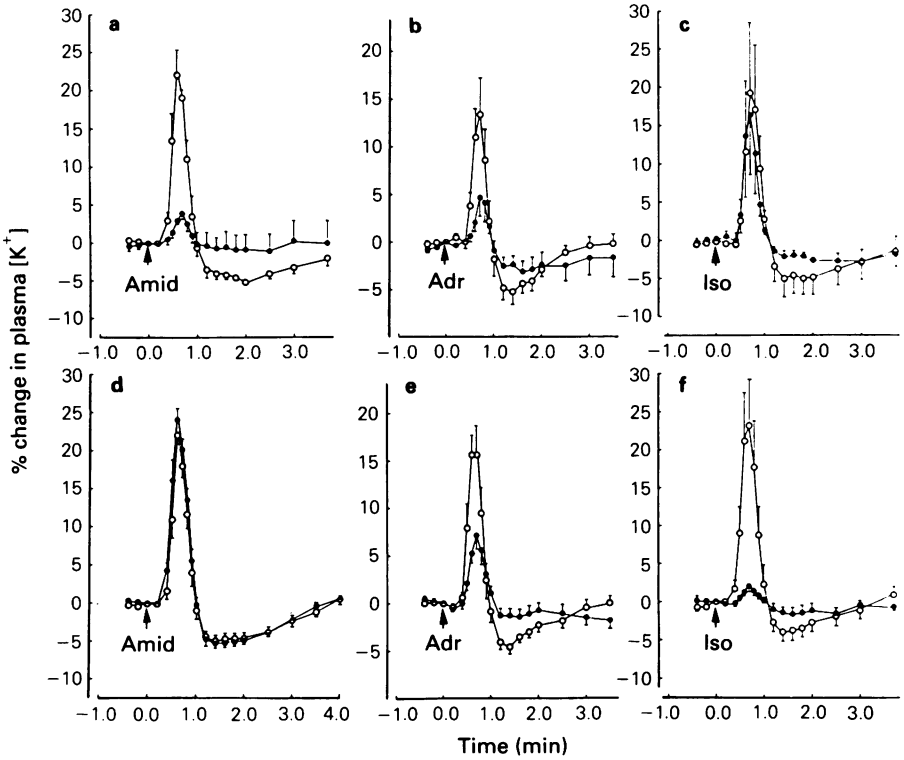

Figure 6 The effect of phentolamine (10 mg kg^{-1}; a,b and c) and propranolol (0.3 mg kg^{-1}; d, e and f) on the meaned time course of changes in plasma [K^+] after amidephrine (Amid, 34 mg kg^{-1}; a and d), adrenaline (Adr, 1.3 μg kg^{-1}; b and e) and isoprenaline (Iso, 0.4 mg kg^{-1}; c and f) in the guinea-pig. In this and subsequent figures the open circles are the control responses and the closed circles those obtained in the presence of the antagonist. The values plotted are the K^+ concentrations expressed as the % change from the moment of drug injection (at arrow). Points are means of 5 responses from 3 experiments in each case; vertical lines indicate s.e.mean.

produced by adrenaline by 83.7 ± 8.9% (n = 3). As in the guinea-pig, propranolol (0.3 mg kg^{-1}) had no effect on the amidephrine-mediated K^+-release but it reduced both phases of the response to isoprenaline by 60.0 and 77.6% respectively. Propranolol also reduced the hyperkalaemic response to adrenaline by 43% (41 and 45%, n = 2).

In the rat, the response to adrenaline was studied in most detail. The results are shown in Figure 8a and b. Phentolamine (1 mg kg^{-1}) abolished the initial hypokalaemic phase of the response while only slightly reducing the subsequent K^+-release and second uptake phases. Propranolol (0.3 mg kg^{-1}), however, had no effect on the initial K^+-uptake or the K^+-release but abolished the second hypokalaemic phase. Propranolol was also tested against the isoprenaline-induced response in the rat and both phases of the response were inhibited (Figure 8c).

It was found that in both the guinea-pig and the rabbit the pressor responses to amidephrine and adrenaline were blocked to a greater extent than were the effects on plasma [K^+] and that the former responses recovered more slowly from the block. This was especially marked in the rabbit where the initial block of the amidephrine induced pressor response was 98.3 ± 1.1% (n = 3) and the response was still blocked by approximately 90% after 30 min.

Effects of apamin

The effect of apamin (40 μg kg^{-1}) on the response to isoprenaline is shown in Figure 9a. As previously found with adrenaline and amidephrine (Coats, 1983) apamin blocked the hyperkalaemic phase of the response while having no effect on the subsequent hypokalaemic response. This dose of apamin blocked the isoprenaline-induced K^+-release by 65.3 ± 2.3% (n = 4). This was between the values found for the block of the amidephrine and adrenaline-induced responses. Isoprenaline normally had a biphasic effect

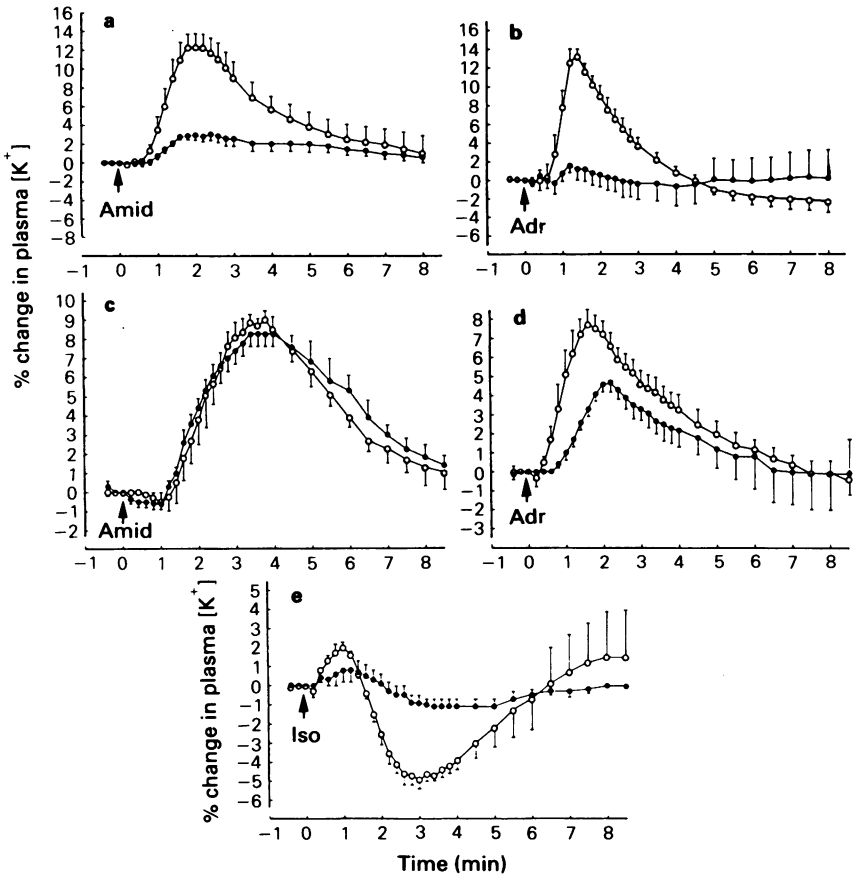

Figure 7 The effect of phentolamine (10 mg kg^{-1}; a and b) and propranolol (0.3 mg kg^{-1}; c, d and e) on responses to amidephrine (Amid, 68 μg kg^{-1}; a and c), adrenaline (Adr, 6.7 μg kg^{-1}; b and d) and isoprenaline (Iso, 1.6 μg kg^{-1}; e) in the rabbit. Data were treated as in Figure 6. Points are means of at least 4 responses from 2 experiments; vertical lines indicate s.e.mean.

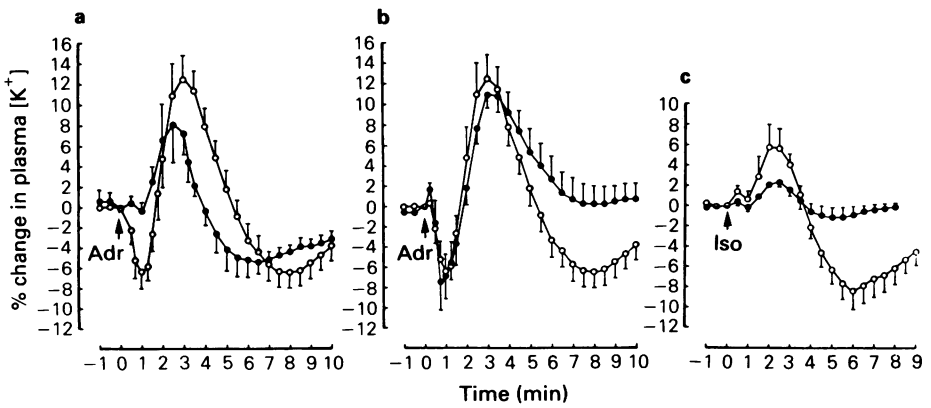

Figure 8 The effect of phentolamine (1 mg kg^{-1}) on the response to adrenaline (Adr; 1.3 μg kg^{-1}) (a) and the effect of propranolol (0.3 mg kg^{-1}) on the response to adrenaline (1.3 μg kg^{-1}) (b) and isoprenaline (Iso; 0.4 μg kg^{-1}) (c) in the rat. Data were treated as in Figure 6. Points are means of at least 4 responses from 2 experiments in each case; vertical lines indicate s.e.mean.

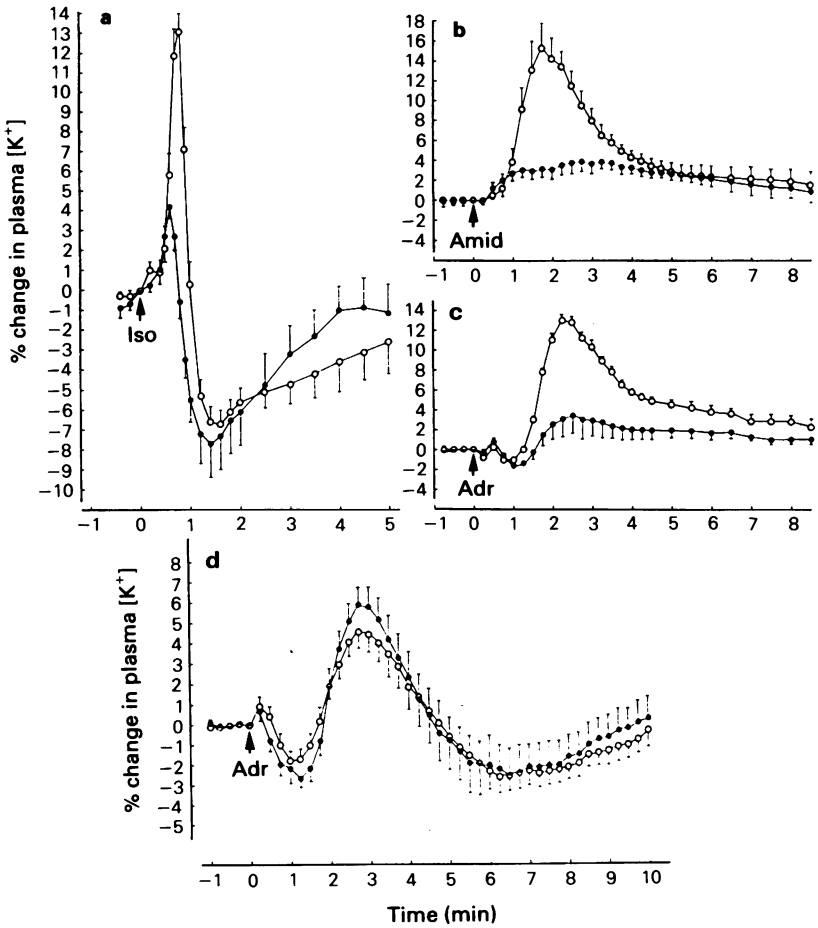

Figure 9 The effect of apamin (40 $\mu g\,kg^{-1}$) on the time course of meaned plasma [K^+] changes to (a) isoprenaline (Iso; 0.8 $\mu g\,kg^{-1}$) in the guinea-pig (b) amidephrine (Amid; 68 $\mu g\,kg^{-1}$) and (c) adrenaline (Adr; 13.3 $\mu g\,kg^{-1}$) in the rabbit, and (d) adrenaline (1.4 $\mu g\,kg^{-1}$) in the rat. Data were treated as in Figure 6. Points are means of at least 4 responses from 2 experiments; vertical lines indicate s.e.mean.

on the arterial blood pressure in the guinea-pig consisting of an initial rapid fall followed by a rise. It was found that apamin significantly reduced the depressor part of the response from 8.4 ± 1.8 mmHg to 2.2 ± 0.7 mmHg ($n = 4$) ($P < 0.05$, two-tailed Student's t test) while having no effect on the subsequent pressor response which was 15.6 ± 6.2 mmHg before apamin and 16.2 ± 5.9 mmHg after apamin, ($n = 4$).

Apamin (40 $\mu g\,kg^{-1}$) was tested against responses to amidephrine and adrenaline in the rabbit. The results are shown in Figure 9b and c. The hyperkalaemic response to amidephrine was reduced from a 15 ± 1% increase in plasma [K^+] to a 3.8 ± 0.1% increase ($n = 3$) giving a block of 75%, which is close to the value of 78.3% seen with the same dose of apamin against the plasma [K^+]-response to amidephrine in the guinea-pig (Coats, 1983). With adrenaline, as in the guinea-pig, the block was slightly less. In 2 experiments, the response was reduced from 12.1% (individual values 10.3 and 13.9) to 4.1% (2.9 and 5.3) giving a block of 66%.

Apamin was also tested against the adrenaline-induced changes in plasma [K^+] in the rat. Unlike the other two species, it was found that apamin had no effect on any of the three phases of the response (Figure 9d). Apamin did, however, have some effect on the adrenaline-induced blood pressure changes in the rat. The response to adrenaline normally consisted of an initial increase in blood pressure followed by a fall below the baseline level. The control values for these were +12.0 ± 1.6 mmHg and −28.0 ± 2.9 mmHg ($n = 5$). After apamin (40 $\mu g\,kg^{-1}$) the pressor response was doubled to 24.0 ± 4.0 mmHg and the

depressor responses were halved to 12.5 ± 4.4 mmHg (n = 5).

Discussion

In the guinea-pig, all the adrenoceptor agonists tested produced biphasic changes in plasma [K^+]. The responses to adrenaline and amidephrine have been discussed previously (Coats, 1983). Briefly, it appears that in the guinea-pig α-adrenoceptor stimulation can produce first hyperkalaemia and then hypokalaemia.

The biphasic response elicited by the β-adrenoceptor agonist isoprenaline was unexpected since in most species β-adrenoceptor agonists generally produce only K^+-uptake (see Introduction for refs.). It should, however, be mentioned that β-adrenoceptor-mediated release of K^+ from the liver is not exclusive to the guinea-pig, since some workers using the dog have found that there are two populations of animal; those which respond to β-agonists with K^+-release and those which show K^+-uptake only (Castro-Tavares, 1975). Also, *in vitro*, some batches of guinea-pig hepatocytes showed K^+-release in response to β-agonists and glucagon (Cocks *et al.*, 1984). Why this should be seen only occasionally *in vitro* while being almost invariable *in vivo* requires further study. Nevertheless, it appears that in the guinea-pig both K^+-release and uptake can be elicited by either α- or β-adrenoceptor stimulation.

In the rabbit the results were different. α-Adrenoceptor agonists caused only K^+-release which was blocked by phentolamine while β-adrenoceptor stimulation produced K^+-uptake after a relatively modest release. Thus, in this species, K^+-release is predominantly mediated by α-adrenoceptors and K^+-uptake by β-adrenoceptors. These findings are similar to the results of others in the dog (Todd & Vick, 1971; Castro-Tavares, 1976) in terms of the adrenoceptors responsible for these changes. However, the magnitude and time course of the hyper- and hypokalaemic responses to adrenaline seen by workers using drug injection rather than infusion in dogs (O'Brien *et al.*, 1954; Tsujimoto *et al.*, 1965; Lim *et al.*, 1982) were more similar to the responses in the guinea-pig than to those in the rabbit.

It is interesting that in both guinea-pigs and rabbits, amidephrine was relatively more active on K^+-release than on blood pressure, as compared with adrenaline. One possible factor is that amidephrine is broken down less rapidly in the liver than adrenaline and since the K^+-release is a slower effect than the pressor response there is relatively more amidephrine still present to produce it. Also, since K^+-release occurs in the liver, which rapidly inactivates adrenaline, the concentration of adrenaline at the liver cell receptors may be less than that in the general circulation. Another factor could be that part of the adrenaline-induced pressor response is mediated via α_2-adrenoceptors whereas the effect on K^+-release and the responses to amidephrine are solely due to α_1-adrenoceptor activation.

In the rat, triphasic changes in plasma [K^+] were observed in response to adrenaline (Figure 1). The first phase of this response was K^+-uptake which was fairly similar in both magnitude and time course to the K^+-uptake seen in the guinea-pig. A net uptake of K^+ by rat hepatocytes *in vitro* has been shown in response to α-adrenoceptor agonists and other agents which elevate cytosolic [Ca^{2+}] (Burgess *et al.*, 1981; 1983; Capiod *et al.*, 1982). These agents cause K^+-uptake by increasing the rate of action of the Na^+/K^+-pump. The time course of the effect on the pump is compatible with the α-adrenoceptor-mediated K^+-uptake seen in the rat *in vivo*, being maximal at 30 s and returning to normal within 3–5 min. The finding that the α-adrenoceptor agonists amidephrine and methoxamine were ineffective in the rat is in keeping with the results of others that amidephrine is inactive in rat liver *in vitro* (El-Rafai *et al.*, 1979) although the reason for this is not known.

The second, slower K^+-uptake seen in the rat in response to adrenaline was shown to be β-adrenoceptor mediated since it was seen with isoprenaline but not phenylephrine and was blocked by propranolol. The adrenaline-induced K^+-release in the rat is more difficult to classify since neither phentolamine nor propranolol blocked it to any great extent and both isoprenaline and oxymetazoline were able to elicit it. It is possible, therefore, that this response can be elicited by either α- or β-adrenoceptor stimulation. These results are in keeping with the findings of Jacob & Diem (1975) who observed that perfusion of rat liver with adrenaline caused K^+-uptake for the first 2 min followed by a release which was maximal 5 min from the start of the infusion. Also in agreement with the results presented here, these workers found that the initial K^+-uptake was blocked by phentolamine (0.1 mM) but not by the β-adrenoceptor antagonist RO 3-4784 (0.1 mM). Both agents reduced the K^+-release to some extent although the effect was more marked with the β-adrenoceptor antagonist. More recent work (Becker & Jacob, 1982), has shown that phenylephrine causes a marked uptake of K^+ followed by a small release. Thus, the rat and the guinea-pig both show an adrenaline-induced K^+-release which can be mediated through either α- or β-adrenoceptor stimulation. However, the mechanisms of these two responses must differ since the response in the guinea-pig was blocked by apamin while that in the rat was not. It is believed that apamin acts by blocking Ca^{2+}-activated K^+-channels rather than acting at the pharmacological receptors that initiate the increase in K^+-permeability (Banks *et al.*, 1979; Burgess *et al.*, 1981).

The observation that in the guinea-pig apamin blocked the isoprenaline-induced K^+-release as well as that mediated by α-adrenoceptor agonists is in keeping with this suggestion. The finding that apamin had no effect on the adrenaline-induced K^+-release in the rat corroborates the suggestion that rat liver lacks the Ca^{2+}-activated K^+-channel at which apamin acts (Banks *et al.*, 1979; Burgess *et al.*, 1981). The mechanism by which adrenoceptor stimulation leads to K^+-release in this species requires further investigation.

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