Br. J. Pharmac. (1983), **80**, 573–580

Effects of apamin on α-adrenoceptor-mediated changes in plasma potassium in guinea-pigs

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1 An intravenous K^+-sensitive electrode has been used to monitor plasma $[K^+]$ changes induced by adrenaline (1.4–6.8 $\mu g\,kg^{-1}$) and amidephrine (14–340 $\mu g\,kg^{-1}$) in anaesthetized guinea-pigs.

2 A biphasic response consisting of an initial increase in $[K^+]$ followed, within 1 min, by a fall below baseline was observed with both agonists.

3 Apamin (0.4–40 $\mu g\,kg^{-1}$) reduced the hyperkalaemic phase of the response to amidephrine in a dose-related, non-competitive manner. The response to adrenaline was also reduced but to a lesser extent.

4 Apamin caused little or no reduction of the hypokalaemic phase of the response to either agonist.

Introduction

Intravenous injection of adrenaline in most mammals, including man, causes a transient rise in plasma K^+ concentration which is often followed by a fall below the resting value. (D'Silva, 1933; 1934; Brewer, Larson & Schroeder, 1939; O'Brien, Murphy & Meek, 1953; Ellis & Beckett, 1963; Tsujimoto, Tanino, Kaniike, Seto & Kurogochi, 1965; Castro-Tavares, 1971; Todd & Vick, 1971). The major source of the additional K^+ during the hyperkalaemic phase is the liver (D'Silva, 1936; Ellis & Beckett, 1963; Vick, Todd & Luedke, 1972). The mechanism of the K^+-loss from the liver is most likely to be an increase in the K^+-permeability of the parenchymal cell membrane (Haylett & Jenkinson, 1972a) subsequent to a receptor-initiated increase in cytosolic Ca^{2+} (Haylett, 1976; Weiss & Putney, 1978; Egashira, 1980). The hyperkalaemic response can be elicited by either α-adrenoceptor activation alone, or more markedly, by simulataneous α- and β-adrenoceptor stimulation (Todd & Vick, 1971; Castro-Tavares, 1975a, see also Jenkinson & Koller, 1977).

The subsequent hypokalaemic phase of the response to adrenaline has been shown to be due to K^+-uptake by both liver and skeletal muscle (Vick *et al.*, 1972). Although the K^+-uptake by skeletal muscle is now generally accepted to be a consequence of a β-adrenoceptor initiated increase in the rate of Na^+/K^+ transport (Clausen & Flatman, 1977; 1980), K^+-uptake by the liver is a complex phenomenon which is not fully understood but has generally been believed to take place via β-adrenoceptors (see Vick *et al.*, 1972; Castro-Tavares, 1975b; 1976; Jauchem & Vick, 1979).

The K^+-releasing effect of adrenoceptor agonists on liver can be shown readily *in vitro* using either perfused liver (Craig, 1958), liver slices, (Haylett & Jenkinson, 1972 a,b) or isolated hepatocytes (Burgess, Claret & Jenkinson, 1981). It has been found recently than apamin, a neurotoxic polypeptide isolated from bee venom (Habermann & Reiz, 1965), inhibits the Ca^{2+}-activated increase in K^+ permeability in guinea-pig hepatocytes (Banks, Brown, Burgess, Burnstock, Claret, Cocks & Jenkinson, 1979; Burgess *et al*, 1981). Apamin might, therefore, be expected to reduce the hyperkalaemia elicited by the α-adrenoceptor *in vivo* and the aim of the present work was to test this. The experiments were performed with anaesthetized guinea-pigs using a K^+-sensitive electrode to obtain a continuous measure of the venous plasma K^+ concentration.

A preliminary report of this study was presented to the British Pharmacological Society (Coats, Cocks & Jenkinson, 1982).

Methods

Animals

Male guinea-pigs (Hartley, 330–460 g) were anaesthetized with pentobarbitone (25–30 $mg\,kg^{-1}$), sup-

plemented for surgery with fentanyl (0.1 mg kg^{-1}) and droperidol (10 mg kg^{-1}), all intraperitoneally. The left carotid artery was cannulated for the recording of carotid pressure (Bell & Howell pressure transducer type 0002-1-134175). The K^+-sensitive electrode was then inserted into the right jugular vein and positioned (in the best experiments) with its end in the vena cava above the entry point of the hepatic vein. Sometimes, however, the electrode entered, and remained in, the heart. The final electrode position was always checked *post mortem*. The indifferent electrode was inserted under the skin of the chest.

A tracheal cannula was inserted for artificial ventilation (if this had not been required previously) and surgical anaesthesia was maintained by further injections of pentobarbitone (i.p.) as required. The animal's body temperature was maintained at 37.5 to 38.5°C by means of a heated table.

Drugs were given at 7-8 min intervals in 0.05 to 0.2 ml volumes made up in saline (145 mM NaCl, 4 mM KCl) and washed in with 0.25 ml of saline via a cannula in the left jugular vein. Drug dosages are given as $\mu g\ kg^{-1}$ of the salt.

K^+-sensitive electrodes

These were constructed by forming a polyvinylchloride (PVC) membrane containing valinomycin on the end of a 15 cm length of narrow PVC tubing (0.96 mm o.d., 0.58 mm i.d.). The end of the tubing was dipped into a tetrahydrofuran solution containing PVC, valinomycin and the other ingredients described by Hill, Gettes, Lynch & Herbet (1978) or, for earlier experiments, by Band, Kratochvil & Treasure (1977). Because of capillary action the mixture fills a few mm of the tubing which was then tapped on a tissue to leave only 1 mm of mixture in the tube. The other end was clamped and the tube gently squeezed so that as the mixture dried (i.e. as the tetrahydrofuran evaporated) a thin membrane was left at the very end of the tubing. When the membrane was almost dry (1-2 min) the clamp was removed and the electrode left for 15-20 min before being filled with 4.6 mM KCl, 153 mM NaCl.

The indifferent electrode consisted of a butterfly cannula filled with the same salt solution as the K^+-sensitive electrode. Both electrodes were connected by agar/saline-filled PVC tubing to reference electrodes (Ag/AgCl pellets on Ag wire, Clark Electromedical). The potential difference between the electrodes was measured by means of an operational amplifier (Analog AD515K) feeding to a chart recorder (Lectromed MX216).

The sensitivity of the electrode was checked before and after each experiment by applying 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. K^+-sensitive electrodes made by this method normally had a resistance of 10-50 MΩ.

Materials

The following materials were used: pentobarbitone sodium (Sagatal, May & Baker), fentanyl citrate (Sublimaze, Janssen), droperidol (dehydrobenzperidol, Droleptan, Janssen), (±)-amidephrine mesylate (Mead & Johnson), (−)-adrenaline bitartrate (B.D.H.), 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).

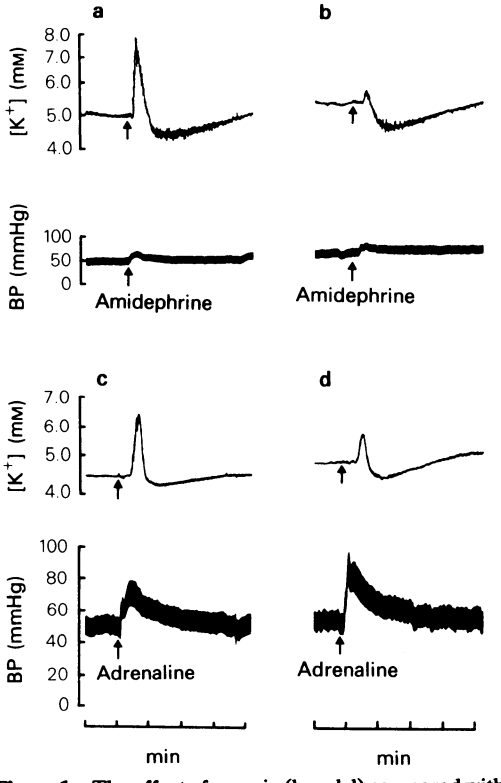

Figure 1 The effect of apamin (b and d) compared with controls (a and c) on the response of the arterial blood pressure (lower traces) and plasma [K^+] (upper traces) to amidephrine (68 $\mu g\ kg^{-1}$) and adrenaline (3.4 $\mu g\ kg^{-1}$).

Results

The normal plasma K^+-concentration was found to be 4.4 ± 0.2 mM (mean ± s.e.mean, $n = 24$). This is close to the value of 4.9 ± 0.1 ($n = 149$) reported by Burns & Lannoy (1966).

Two adrenoceptor agonists were used throughout: adrenaline and amidephrine. The latter is relatively selective for the α_1-receptor subtype (Butler & Jenkinson, 1978; McGrath, 1982; Docherty, 1983). Figure 1 (left) illustrates the response to each agent with the electrode positioned in the suprahepatic

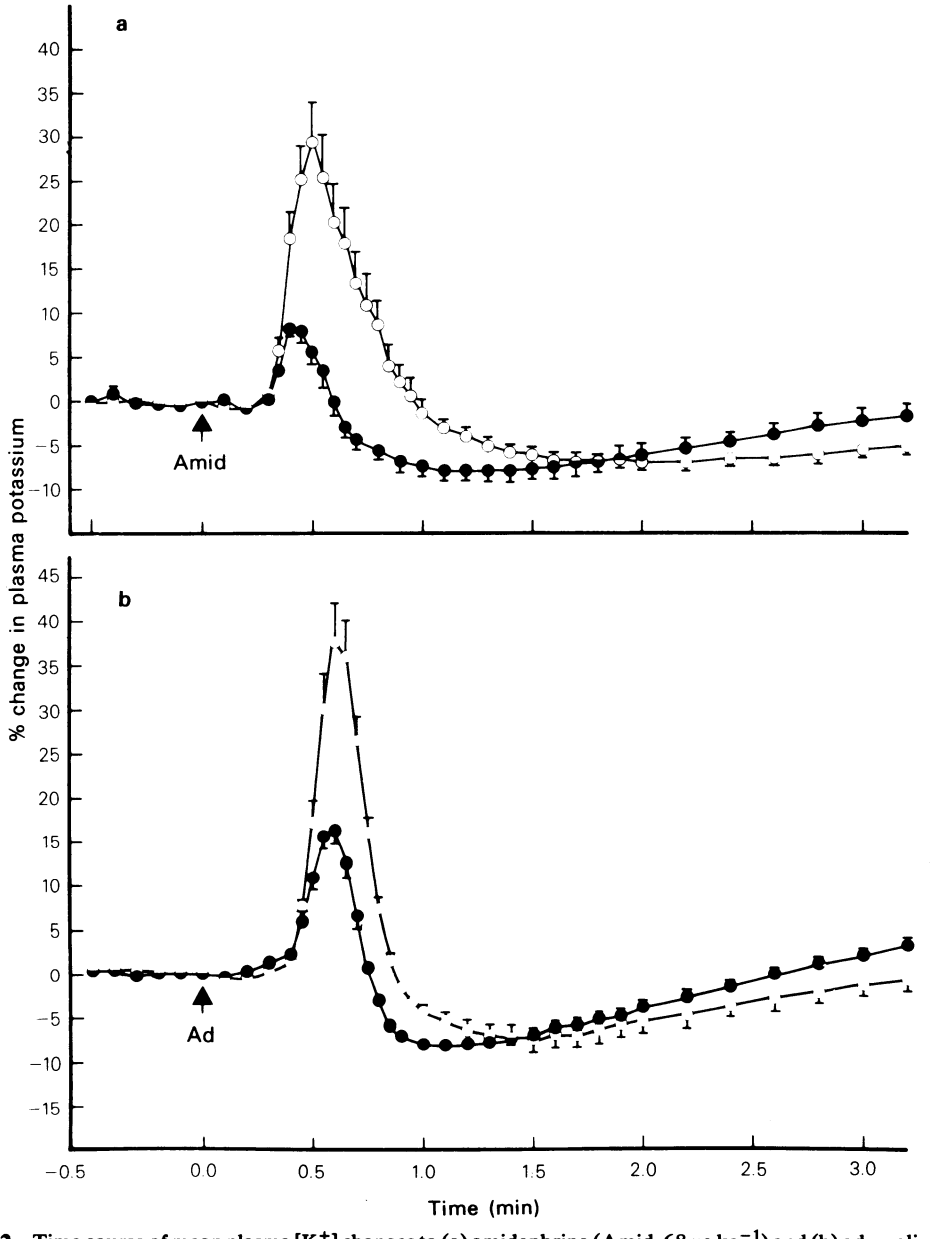

Figure 2 Time course of mean plasma $[K^+]$ changes to (a) amidephrine (Amid, 68 μg kg^{-1}) and (b) adrenaline (Ad, 3.4 μg kg^{-1}) before (○) and after (●) apamin. The values plotted are the K^+ concentrations expressed as the % change from the value at the moment of drug injection (at arrow). In (a) $n = 10$ and in (b) $n = 5$. (All responses taken from a single guinea-pig in each case). Bars indicate s.e.mean.

inferior vena cava. Both agonists caused biphasic changes in K^+-concentration. A rapid hyperkalaemic phase reaching a maximum 30–35 s after drug injection was followed by a fall below the baseline level, reaching a minimum at 1–2 min and returning to the baseline by about 4 min. (When the electrode was positioned in the heart the peak increase in plasma $[K^+]$ for a given dose of α-agonist was only about half that recorded when the electrode was in the vena cava. The peak of the response was also less well defined with a slightly longer delay after drug injection. These differences are probably due to the K^+-rich blood from the liver becoming more diluted before reaching the electrode). When the liver was releasing or taking up K^+ the $[K^+]$ recorded by the K^+-sensitive electrode in the vena cava was often seen to fluctuate in time with respiration: the excursions being in opposite directions during hyper- and

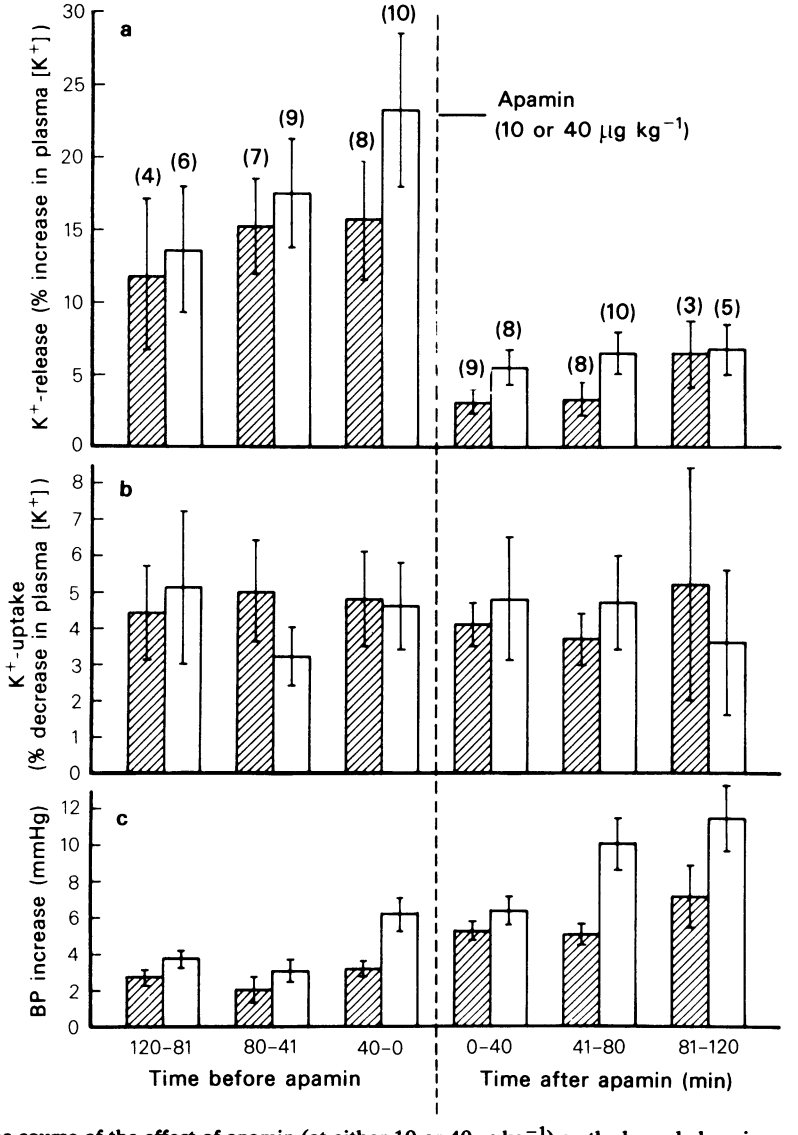

Figure 3 Time course of the effect of apamin (at either 10 or 40 $\mu g\,kg^{-1}$) on the hyperkalaemic response (a), the hypokalaemic response (b) and the mean blood pressure increases (c) elicited by amidephrine 34 $\mu g\,kg^{-1}$ (hatched bars) and 68 $\mu g\,kg^{-1}$ (open bars). Responses were grouped for 40 min intervals before and after apamin and averaged. Vertical bars indicate s.e.mean for the no. of individual responses which is shown above each column. Results pooled from 6 experiments.

hypokalaemia. This can be seen as a thickening of the line in Figure 1 (a) and (b) and is probably a consequence of the mixing of blood from the liver and the general circulation: during inspiration flow in the inferior vena cava increases while hepatic venous outflow decreases, the reverse occuring during expiration (Moreno, Burchell, van der Woude & Burke, 1967).

When the K^+-sensitive electrode was located in the vena cava, proximal to the entry of the hepatic vein (see Methods), amidephrine at 34 $\mu g\,kg^{-1}$ increased the recorded plasma K^+ by 1.10 ± 0.12 mM ($n = 15$ experiments). During the subsequent hypokalaemic phase, plasma K^+ fell to 0.28 ± 0.04 mM ($n = 15$) below the control (i.e. pre-drug) level. The corresponding values with amidephrine at 68 $\mu g\,kg^{-1}$ were 1.59 ± 0.21 and 0.38 ± 0.04 mM ($n = 16$) respectively. With adrenaline at 3.4 $\mu g\,kg^{-1}$, corresponding values of 1.83 ± 0.37, and 0.32 ± 0.06 mM ($n = 9$) were observed. The hyperkalaemic response to adrenaline in guinea-pigs is thus comparable in magnitude to those reported by others using bolus injection (as in the present work) in cats (Ellis & Beckett, 1963) and dogs (O'Brien *et al.*, 1953; Tsujimoto *et al.*, 1965). Large doses of adrenaline and amidephrine were avoided because of the potential problems of desensitization and possible harmful effects on the animal: the maximal response to each agent has not been determined therefore.

Figure 1 (right) shows the effects of apamin (40 $\mu g\,kg^{-1}$ i.v.) on the response to amidephrine and adrenaline (upper and lower, respectively). It can be seen that the hyperkalaemic phase of the response was considerably reduced by apamin. In contrast, the hypokalaemic response was little affected. The increased pressor response to adrenaline seen after apamin was a common, though not invariable finding (see later). Although the background $[K^+]$ values are greater after apamin in the experiment in Figure 1, this was not a consistent finding; in 8 experiments the mean baseline plasma $[K^+]$ was 4.7 ± 0.2 before apamin (40 $\mu g\,kg^{-1}$) and 4.1 ± 0.4 (s.e.mean) after apamin.

The effect of apamin on the response to both agonists is further depicted in Figure 2. This shows the time course of the averaged responses to amidephrine and adrenaline both before and after apamin. Figures 3 and 4 illustrate the time course of the effects of apamin on the responses to amidephrine and adrenaline respectively. In each case in the upper section the individual hyperkalaemic responses to repeated doses of agonist have been grouped into 40 min intervals and averaged, before and after the administration of apamin. Since there was no significant difference between the degree of block of the hyperkalaemic response to amidephrine produced by apamin at 10 and 40 $\mu g\,kg^{-1}$, the results with both

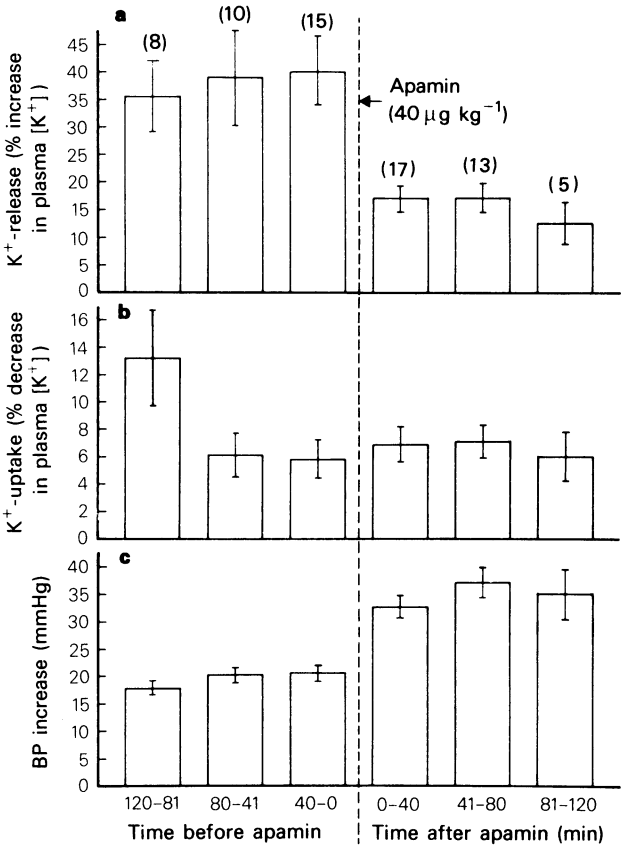

Figure 4 Time course of the effect of apamin (40 $\mu g\,kg^{-1}$) on hyperkalaemic response (a), hypokalaemic response (b) and pressor response (c) to adrenaline (3.4 $\mu g\,kg^{-1}$). Treatment of data as in Figure 3. Results from 5 experiments.

these doses have been combined in Figures 3 and 5. Apamin was tested at a single dose of 40 $\mu g\,kg^{-1}$ when adrenaline was the agonist. There are two important findings. Firstly, the control hyperkalaemic responses either remained constant or slowly increased before the injection of apamin and, secondly, the effect of apamin was rapid in onset and prolonged, wearing off only slightly, if at all, over two hours. This allowed the blocking action to be studied by comparing a series of responses obtained before and after a single dose of apamin in each animal (as in Figure 2). Only with the lowest dose of apamin used (0.4 $\mu g\,kg^{-1}$) was the block clearly transient, lasting for about 10 min. The middle and lower sections of Figures 3 and 4 show the effect of apamin on the hypokalaemic phase of the response and on the pressor responses (measured as the mean of the peak increases in the systolic and diastolic pressure) eli-

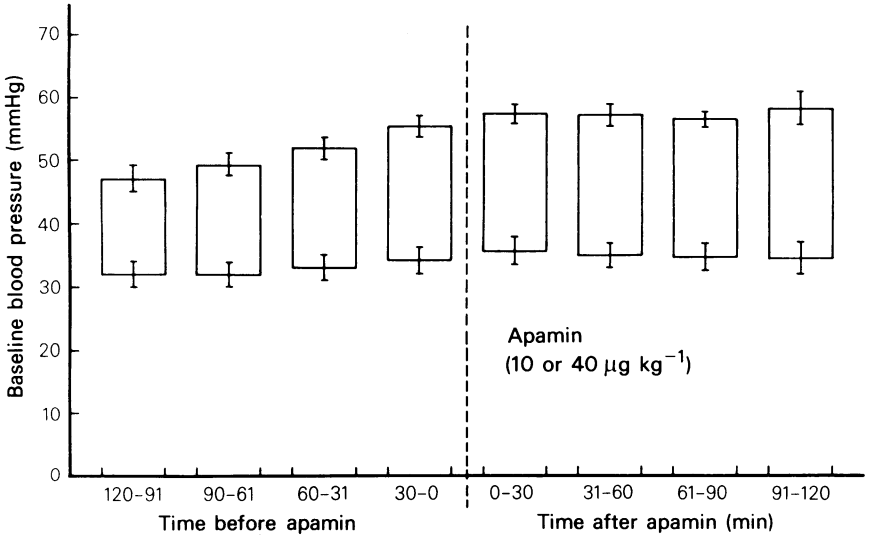

Figure 5 Time course of the effect of apamin on mean blood pressure. The upper and lower limit of each rectangle represent systolic and diastolic pressure (with s.e.mean, $n = 12$ experiments) respectively. Treatment of data as in Figure 3, except that 30 min periods were used. Apamin (10 or 40 $\mu g\,kg^{-1}$) was given at zero time (dashed line).

cited by each agonist. The apparent fall in the hypokalaemic response to adrenaline 80 min before apamin in Figure 4 is not statistically significant and is probably a consequence of the initial hypokalaemic responses in a single animal being unusually large. There was a significant ($P < 0.05$, two tailed Student's $t$test) increase of 54% in the adrenaline-induced pressor response after apamin (comparing the last dose before apamin with the first after). The pressor response to amidephrine may also have risen, though more experiments would be needed to settle the point. Although the mean blood pressure was higher after apamin this may merely have been because it was in any case increasing slowly with time, as shown in Figure 5. (This Figure was constructed by taking the blood pressure just before each response to either amidephrine or adrenaline and grouping these into 30 min intervals before and after apamin (10 or 40 $\mu g\,kg^{-1}$). The mean blood pressure (systolic and diastolic) for each 30 min period of each experiment was then taken and the mean of these values used for each time interval).

The effects of four doses of apamin on part of the dose-response curve to amidephrine are illustrated in Figure 6. Since the size of the control responses varied considerably from one animal to another (particularly when the siting of the K^+-sensitive electrode differed) the results have been normalized so that all the values could be combined. This normalization has been performed by expressing each response observed in a given experiment as a percentage of the mean response to 68 $\mu g\,kg^{-1}$ amidephrine before apamin. (Although this dose is not maximal, higher doses gave rather inconsistent responses, possibly due to desensitization, and were therefore avoided.) Figure 6 suggests that apamin is acting as a non-competitive blocking agent since the response is 'scaled down' rather than the curve being shifted to the right in a parallel manner as would be expected with a competitive antagonist. This is in keeping with the results obtained with isolated hepatocytes (Cook, Haylett & Strong, 1983). Because of the non-competitive nature of the block, the effect of apamin is best expressed in terms of percentage inhibition rather than as a dose ratio. The mean percentage inhibitions (average for the two doses of amidephrine in each experiment) obtained with 0.4, 2, 10 and 40 $\mu g\,kg^{-1}$ apamin were: 35.6 ± 6.2 ($n = 3$), 63.2 (mean of 59.0 and 67.4), 73.0 (mean of 71.8 and 74.2) and 78.3 ± 1.7 ($n = 3$) respectively. This suggests that the maximal block may be less than 100% although further experiments are needed to confirm this.

As illustrated by Figures 1, 2 and 4, apamin was also effective against adrenaline-induced hyperkalaemia although the degree of block was less than with amidephrine. The response to 3.4 $\mu g\,kg^{-1}$ adrenaline was reduced by $58.4 \pm 1.7\%$ ($n = 5$) by 40 $\mu g\,kg^{-1}$ apamin as compared to $78.3 \pm 1.7\%$ when the agonist was amidephrine. This difference was significant ($P < 0.001$, two tailed Student's $t$test).

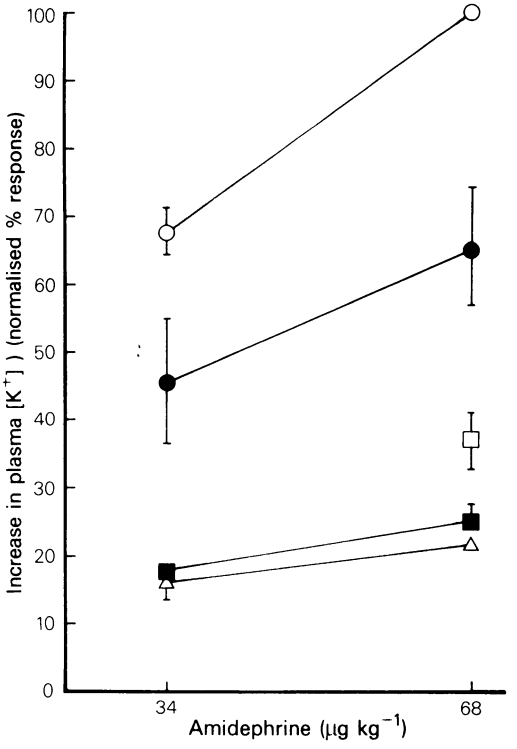

Figure 6 Effect of apamin on part of the dose-response curve to amidephrine, (○) = control, ($n = 7$) (●), (□), (■) and (△) represent responses obtained after apamin 0.4 ($n = 3$), 2 ($n = 2$), 10 ($n = 2$), and 40 ($n = 3$) $\mu g\,kg^{-1}$ respectively. Responses have been normalized (see text). Vertical bars represent s.e.mean or range when $n = 2$.

Discussion

Both adrenaline and amidephrine caused a transient increase, followed by a fall, in the concentration of K^+ in the plasma of guinea-pigs, as previously described for adrenaline in other mammals (see introduction). The presence of a hypokalaemic phase of the response with amidephrine is noteworthy since K^+-uptake has generally been considered to be via β-adrenoceptor stimulation. The first main finding of the present work is that apamin selectively inhibited the initial, hyperkalaemic, phase of the response. The block was rapid in onset and long lasting (Figures 3 and 4) except with the lowest dose tested ($0.4\,\mu g\,kg^{-1}$). The inhibition was also non-competitive in character (Figure 6) which is in keeping with the suggestion that apamin works by blocking (or preventing the opening of) the Ca^{2+}-activated K^+ channels, rather than acting at the receptor site (Banks *et al.*, 1979; Burgess *et al.*, 1981).

The second main finding is that apamin did not reduce the hypokalaemic phase of the response to either amidephrine or adrenaline. The mechanism of the hypokalaemic response is uncertain. There is good evidence that potassium uptake by skeletal muscle contributes to adrenaline hypokalaemia and that this uptake is mediated by β-adrenoceptors. However, amidephrine is, at most, only a weak partial agonist at β-adrenoceptors (Buchthal & Jenkinson, 1970). Another possibility is that K^+-uptake by skeletal muscle and/or liver is triggered by the high plasma $[K^+]$ during the hyperkalaemic phase of the response. However, the finding that apamin has little effect on the hypokalaemic portion of the response while greatly reducing the K^+-release suggests that this mechanism of K^+-uptake can only be of limited significance. It therefore seems possible that the amidephrine-induced hypokalaemia is at least in part due to an α_1-adrenoceptor induced K^+-uptake, perhaps by the liver. Recent work with isolated liver cells of the rat has shown that α_1-adrenoceptor agonists, and other agents which elevate cytosolic Ca^{2+}, increase the Na^+/K^+-pump rate which results in a net uptake of K^+ (Capiod, Berthon, Poggioli, Burgess & Claret, 1982; Berthon, Burgess, Capiod, Claret & Poggioli, 1983). The time course and magnitude of this effect are comparable to the hypokalaemia found *in vivo* (see Figure 2) being maximal at 30 s and returning to baseline within 3 to 5 min. However, the operation of this mechanism in guinea-pig hepatocytes remains to be confirmed by more direct methods.

There were two incidental findings. Firstly, a dose of apamin which reduced the response to amidephrine by $78.2 \pm 1.7\%$ inhibited the adrenaline response by only $58.4 \pm 1.7\%$. This may mean that a part of the response to adrenaline occurs by an apamin-insensitive mechanism, though higher doses of apamin would have to be tested to confirm this. Secondly, apamin markedly, though rather variably, increased the pressor response to adrenaline. Both these findings merit further study.

The author is an M.R.C. Scholar. I would like to thank Professor D.H. Jenkinson for many valuable discussions and I am most grateful to Dr T.M. Cocks for help with early experiments.

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(Received June 6, 1983.)