Cardiovascular responses to centrally administered adrenaline in spontaneous hypertensive rats

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The involvement of central noradrenergic neurones in the control of blood pressure is well established and both clonidine and α-methyldopa are thought to exert their action via these neurones (Finch, 1974; Finch & Haeusler, 1973). The exact role of specific central adrenergic neurones, which have only recently been demonstrated in the rat brain (Hökfelt, Fuxe, Goldstein & Johansson, 1973) in areas known to be involved in the control of blood pressure, however, remains unclear.

Preliminary studies, in various species, have shown that intracerebroventricular (i.c.v.) injections of adrenaline exert a variable effect on blood pressure (Toda, Matsuda & Shimamoto, 1969; Day & Roach, 1974). Intracerebral injections of adrenaline into various regions of the brain also induce centrally mediated changes in blood pressure (Struyker Boudier & Bekers, 1975). The present study sets out to characterize the cardiovascular activity of icv administered adrenaline in spontaneous hypertensive rats.

In conscious spontaneous hypertensive rats, prepared for direct recording of blood pressure by the method of Popovic & Popovic (1960), adrenaline (1–20 μg ICV) in 10 μl of 0.01 N HCl caused a dose-related fall in blood pressure and heart rate, while i.c.v. injections of vehicle were without effect. Pretreatment with phentolamine (100 μg i.c.v.) did not significantly antagonize the hypotension or bradycardia induced by adrenaline (10 μg i.c.v.), while pretreatment with (±)-propranolol (100 μg i.c.v.) completely abolished the bradycardia and reversed the hypotensive effects of adrenaline (10 μg i.c.v.) resulting in an increase in blood pressure. Moreover, the hypotension and bradycardia induced by adrenaline (10 μg i.c.v.) was only slightly reduced by pretreatment with (+)-propranolol (100 μg i.c.v.), while pretreatment with the active isomer (−)-propranolol (100 μg i.c.v.) abolished the bradycardia and reversed the hypotension. Similar antagonism of adrenaline (10 μg i.c.v.) induced responses was obtained after pretreatment with sotalol (100 μg i.c.v.) and with the selective β_1-antagonist metoprolol (100 μg i.c.v.).

These results indicate that i.c.v. administered adrenaline is capable of consistently inducing hypotension and bradycardia in conscious spontaneous hypertensive rats and that, in this hypertensive model at least, these effects are probably mediated by central β-adrenoceptors rather than central α-adrenoceptors.

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Selective blockade of presynaptic tryptamine receptors by (−)-cocaine and (+)-cocaine

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5-Hydroxytryptamine (5-HT) stimulates the rabbit isolated heart by releasing noradrenaline from the terminal sympathetic nerves (Fozard & Mwaluko, 1976). Transmitter release results from activation of specific receptor sites which in terms of potencies of selective agonists are closely similar to the receptors on the cholinergic nerves of the guinea-pig ileum (Fozard & Mobarok Ali, 1976) originally designated 'M' because of their sensitivity to blockade by morphine (Gaddum & Picarelli, 1957). However, morphine is not a selective antagonist of 5-HT on rabbit heart, and therefore a search was instituted for a more selective antagonist and to determine if the responses to 5-HT on both noradrenergic and cholinergic neurones might be similarly affected.

Rabbit hearts were perfused at constant pressure with Tyrode solution containing atropine (0.5 μg/ml) at 37°C. Right atrial and ventricular tensions and cardiac rate were recorded as previously described (Fozard & Muscholl, 1971). Drugs were given by bolus injection or incorporated into the perfusion fluid. Segments of guinea-pig ileum were set up in Tyrode solution containing methysergide (1 μg/ml).

On the heart, (−)-cocaine antagonized chronotropic responses to bolus injections of 5-HT (0.5–32 μg) over the range 0.5–8 μg/ml. At 0.5 and 2 μg/ml, the curves were shifted to the right in a parallel fashion and there was no depression of the maximum response. At 8 μg/ml the maximum response to 5-HT was markedly depressed. (−)-Cocaine (0.5 μg/ml) had no effect on responses to 1,1-dimethyl-4′-phenylpiperazinium iodide (DMPP; 5–160 μg/ml) although 8 μg/ml caused marked inhibition with depression of the maximum response. (−)-Cocaine (0.5 μg/ml) significantly enhanced responses to noradrenaline (0.01–2.56 μg). pA_2 values for the antagonism of 5-HT and DMPP by (−)-cocaine were 6.24 ± 0.08, $n=4$ and 4.95 ± 0.09, $n=3$ respectively. (+)-Cocaine, which does not block noradrenaline uptake, was a more potent antagonist of 5-HT than (−)-cocaine. The pA_2 values for the antagonism of 5-HT and DMPP by (+)-cocaine were 6.90 ± 0.07, $n=3$ and 5.02 ± 0.003, $n=3$ respectively. Lignocaine proved to be only a weak antagonist of 5-HT ($pA_2 = 3.87 \pm 0.09$, $n=3$) and showed no selectivity (pA_2 lignocaine against DMPP $= 4.16 \pm 0.09$, $n=3$). On the ileum treated with methysergide (−)-cocaine antagonized responses to 5-HT over the concentration range 0.5–8 μg/ml. The pA_2 value for the antagonism of 5-HT by (−)-cocaine was 6.00 ± 0.14, $n=5$.

Local anaesthetic properties seem unlikely to explain the 5-HT blocking actions of the cocaine isomers since lignocaine lacked potency and specificity as an antagonist of 5-HT. Similarly, the effects cannot be referred to events at the noradrenaline uptake pathway of the terminal fibres since both the (+)- and the (−)-isomers were effective and there was antagonism of 5-HT at cholinergic nerve endings. The data can be interpreted in terms of an interaction of the cocaine isomers with 5-HT at pre-synaptic tryptamine receptors. Should this be correct then the data provide support for the suggestion that neuronal receptors of the heart and ileum for 5-HT are similar (Fozard & Mobarok Ali, 1976).

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A benzotriazinium salt as a potential antiarrhythmic agent

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Four series of substituted benzotriazinium iodides have recently been synthesized (Stevens & Stevens, 1970). These compounds have many pharmacological properties similar to those of quinidine, notably the effects on cardiac tissue. We have investigated 2-n-propyl-4-p-tolylamino-1,2,3-benzotriazinium iodide (TnPBI) in view of its potential antiarrhythmic properties.

Guinea-pig isolated atrial pairs were mounted on a Sylgard 182 resin base in a channel cut from a perspex block and perfused at 32°C with oxygenated Locke solution of the following composition (mM) NaCl 154, KCl 5.6, $CaCl_2$ 2.16, glucose 5.5, $NaHCO_3$ 2.4. Cells were impaled with glass microelectrodes filled with 3M KCl, and the action potentials were amplified by a Grass P16 DC preamplifier and displayed on an Advance OS 4000 digital storage oscilloscope. Stored action potentials were then drawn out on a pen recorder via an Advance OS 4001 analogue output unit. The atria were stimulated at a frequency of approximately 10% above their spontaneous frequency by means of bipolar platinum electrodes in contact with the surface of the left atrium.

TnPBI increased the duration of the action potential (APD), decreased the maximum rate of depolarization (MRD) and decreased conduction velocity. These effects were dose related between 1×10^{-6} M and 1×10^{-5} M. TnPBI did not significantly alter the resting membrane potential but the size of the overshoot and consequently of the action potential were reduced. With one exception, these effects are similar to those produced by quinidine: the exception is the prolongation of the APD. The work of Vaughan Williams (1958) on