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Effects of some α-adrenoceptor antagonists on central cardio-decelerator mechanisms in the rabbit

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1 Bradycardia was evoked in rabbits anaesthetized with chloralose-urethane by electrical stimulation (200 or 300 μA, 1 ms, 60 s^{-1} for 9 s, repeated every 5 min) of a selected point in the caudal hypothalamus 1.5 mm from the midline dorsal to the mammillary bodies.

2 Phenoxybenzamine, prazosin and yohimbine solutions were infused intracerebroventricularly at a rate of 20 μl min^{-1}. Phenoxybenzamine did not cause any effects additional to those attributable to the solvent alone. Prazosin attenuated the evoked bradycardia at all doses (40 to 300 μg) and altered resting heart rate (HR) and arterial blood pressure (BP) after the higher doses. Yohimbine (200 + 300 μg) attenuated the bradycardia with negligible effects on HR and BP.

3 Prazosin and yohimbine were given intravenously. Both caused dose-related attenuation of evoked bradycardia but prazosin also lowered BP sufficiently for this action alone to account for almost all the loss of the bradycardia. The weaker hypotensive action of yohimbine was insufficient to account for the attenuation, a conclusion confirmed in animals whose BP was maintained constant by noradrenaline infusion after cervical spinal transection. In this preparation yohimbine caused dose-related attenuation of the bradycardia.

4 The experiments have shown that yohimbine and probably prazosin also, can prevent hypothalamic stimulation from evoking bradycardia. The results suggest the presence of an α-adrenergic pathway from this region of the hypothalamus which projects caudally to increase the gain of the cardio-decelerator baroreceptor reflex in the rabbit.

Introduction

Powell *et al.* (1972) observed that cardio-deceleration obtained during dorsal or posterior hypothalamic stimulation in the unanaesthetized rabbit is attenuated after subcutaneous administration of the α-adrenoceptor antagonist phentolamine. Because stimulation simultaneously evoked arterial pressor responses, which were also attenuated by the phentolamine, these authors concluded that the bradycardia was mainly a baroreflex response to the rise in arterial blood pressure. Evans (1978) showed that the cardio-deceleration evoked by stimulation of the posterior hypothalamus in the anaesthetized rabbit was sometimes too great to be accounted for by a baroreceptor reflex activated during the accompanying rise in arterial blood pressure, and there is evidence that a pathway from this part of the rabbit hypothalamus acts on the baroreceptor reflex so as to increase the gain of the cardio-inhibitory mechanism (Buss & Evans, 1984).

Manchanda *et al.* (1977) have found that phenoxybenzamine abolished some cardiovascular responses associated with stimulation of the hypothalamic 'defence area' in dog and cat, following either intravenous administration or topical injection into the hypothalamus. Destruction of central adrenergic systems by 6-hydroxydopamine results in profound changes in baroreflex control in the rabbit (Korner *et al.*, 1979; Head & Korner, 1980), yet the baroreceptor cardio-decelerator reflex is not itself attenuated by α-adrenoceptor antagonists (Evans *et al.*, 1983). There is evidence that various α-adrenoceptor antagonists, given intravenously, can prevent hypothalamic stimulation from evoking large reductions in heart rate in the anaesthetized rabbit (Evans, 1980; Evans *et al.*, 1983) but the evidence for a central blockade of the hypothalamic projection has been blurred by the peripheral changes, brought about by these drugs, upon resting arterial blood pressure and on the pressor

responses that usually accompany stimulation of the posterior hypothalamus.

The present experiments, during which the drugs were administered either into the cerebral ventricles, or given intravenously to animals whose spinal cords had been divided to eliminate changes in blood pressure, were carried out to provide more direct evidence for a central α-adrenergic link between the posterior hypothalamus and the baroreceptor reflex.

Methods

The experiments were performed on New Zealand Red and N.Z. White rabbits of either sex, weighing 1.9–3.8 kg. They were anaesthetized by intravenous administration of a solution containing urethane (ethyl carbamate, 25 g 100 ml^{-1}) and α-chloralose (1.5 g 100 ml^{-1}), the initial doses falling in the ranges: urethane 1.08–1.17 g kg^{-1}; α-chloralose 65–70 mg kg^{-1}. small supplementary doses were given from time to time as required. After tracheotomy and catheterization of the femoral artery and vein in one hindlimb, the animal's head was placed in a headholder (Evans & Pepler, 1972) and adjusted to the co-ordinates of Sawyer *et al.* (1954) for stereotaxic placement of the stimulating electrode.

In some experiments the spinal cord was divided in the mid-cervical region. Although this generally spared enough of the phrenic 'outflow to maintain some diaphragmatic movement, the animals were artificially ventilated as soon as the cord had been divided. At the same time a slow intravenous infusion of noradrenaline tartrate (40 μg ml^{-1} in saline) was given at a rate sufficient to prevent mean arterial blood pressure from falling below about 50 mm Hg. Later in the experiment the infusion rate was increased, to maintain mean arterial blood pressure in the range 70–90 mm Hg.

The femoral arterial catheter was connected to a Bell & Howell type 4-327-L221 pressure transducer, the amplified output of which was taken in parallel to: (a) a chart recorder to obtain a trace of pulsatile arterial blood pressure, (b) another channel of the recorder to register mean arterial blood pressure, electronically damped, $\tau = 0.5$ s, (c) a digital voltmeter (via electronic smoothing, $\tau = 20$ s) that printed mean pressure every 1.0 min. Heart rate was derived electronically from the systolic pulsations and was recorded: (a) on the chart recorder as the analogue output of a beat-to-beat heart rate meter (Toner & Stephens, 1975), (b) as the average rate per min by counting total beats during 60 s and printing the count every 1.0 min in parallel with the mean arterial blood pressure. End-tidal CO_2 was maintained, by artificial ventilation if necessary, in the range: 3.8–5.5%. Rectal temperature was maintained between 38.5 and 39.0°C.

The brainstem was stimulated through a monopolar stainless steel electrode, 0.3 mm diameter and with the tip bared of insulation for approximately 0.2 mm. This cathodal electrode was lowered into the brainstem under stereotaxic control, through a burr hole in the skull, 3.5 to 4 mm caudal to bregma and 1.5 mm from the midline and responses sought at depths between the H-1 and H-4 co-ordinates (from the stereotaxic maps of Fifková & Maršala, 1967). The anode was a platinum plate on nearby tissue. Electrode depth was adjusted in 0.25 mm steps to obtain maximum cardio-deceleration during a 9 s train of constant-current stimulation (usually 200 or 300 μA, 1 ms pulse duration, 60 s^{-1}, repeated every 5 min).

In some experiments the effects of multiple drug doses were investigated. An initial intravenous administration was followed by supplementary doses every 15 min, allowing triplicate replication of the responses at 5 min intervals at each dose value. The supplementary doses were calculated to raise the dose values in steps that were usually 1: 3: 10, with the assumption that each dose accumulated fully with the preceeding ones during the time of the investigation.

To administer drugs into the cerebral ventricular system, a stainless steel cannula (0.3 mm o.d.) was inserted stereotaxically through a burr hole in the skull. It was angled 20° from the stereotaxic vertical and passed through the skull 2.5 mm anterior to bregma and usually 2.5 mm from the midline. It was advanced until the lateral ventricle was entered, 6.2–7.5 mm below skull surface near the AP0 plane. The cannula was connected by fine polythene tubing (total deadspace 10 μl) to an 'Agla' micrometer syringe. Drug or control solutions were infused at a rate of 20 μl min^{-1}.

In some experiments mass activity in afferent fibres from baroreceptors was recorded from the peripheral end of a divided aortic nerve. The raw electroneurogram was photographed from an oscilloscope screen together with the rectified and partly smoothed ($\tau = 5$ ms) response and the arterial pressure waveform from one carotid artery. Averaged records of the rectified electroneurogram were accumulated with a Biomac signal averager and copied on an X-Y plotter.

The following drugs were administered: phenoxybenzamine hydrochloride (S.K. & F.), prepared as a stock solution of 50 mg ml^{-1} in the acidified ethanol-glycol solvent suggested by the suppliers, was diluted in saline to 1 mg ml (pH: 2.2–3.0) before use. Prazosin HCl (Pfizer) was dissolved with a few drops of lactic acid in distilled water to 1 or 2 mg ml^{-1} (pH: 2.3–2.5). It was diluted further, if required, with saline (pH: 2.5–2.8). Yohimbine HCl (Sigma), either 1 or 2 mg ml^{-1} in saline (pH: 5.1–6.6) was sometimes diluted further with saline for administration. The saline was not buffered, being composed of (mM):

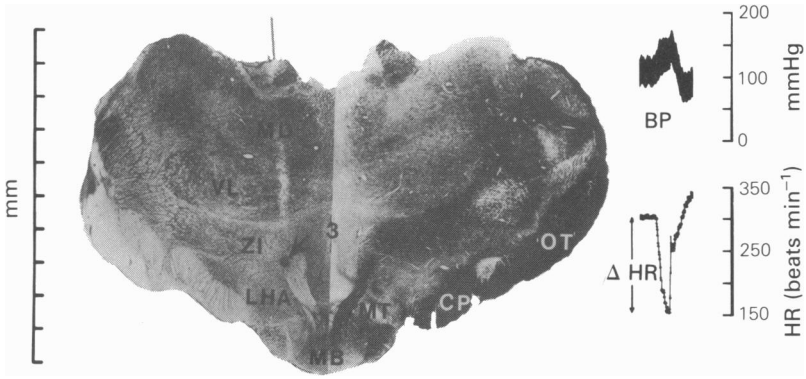

Figure 1 Transverse section of the brain of a 2.4 kg rabbit, at the level of the mammillo-thalamic tract. The left half shows a 50 μm frozen section stained with cresyl fast violet to show cell groups. The right half is an adjacent section stained with luxol fast blue to show myelinated fibre tracts. A 'prussian blue' spot (arrowed) in the left half marks the location of the stimulating cathode, on the border between zona incerta and lateral hypothalamic area, near the course of the mammillo-thalamic tract. Stimulation at this locus evoked pressor responses with strong bradycardia, typical examples being shown to the right of the section.
Abbreviations: CP cerebral peduncle, LHA lateral hypothalamic area, MB mammillary bodies, MD medio-dorsal nucleus, MT mammillothalamic tract, OT optic tract, VL ventro-lateral nucleus, ZI zona incerta, 3 third ventricle.

NaCl 144, KCl 3.7 and $CaCl_2$ 3.2. When it was used as a vehicle control for intracerebroventricular (i.c.v.) administration it was acidified with either NaH_2PO_4, lactic acid or HCl to a pH approximately equal to that of the drug solution. Vagally mediated baroreflex cardio-inhibition was assessed by intravenous injection of phenylephrine.

Statistical analysis of the results included the comparison of means by Student's *t* test, calculation of linear regression lines with analysis of variance (Anovar programme) and calculation of 95% confidence limits.

Results

Resting values

Mean arterial blood pressure (BP) in the anaesthetized animals whose spinal cords were intact averaged 101 ± 2 mm Hg (mean ± s.e.mean) during the 0.5 h before drug administration. During the same period the resting heart rate (HR) averaged 293 ± 6 beats min^{-1} ($n = 28$). Brainstem stimulation, for 9 s every 5 min, evoked changes in heart rate (ΔHR) which were usually reproducible during the control period to within ± 12% of the mean change in any one animal, but the absolute magnitude of ΔHR varied from one animal to another within the range: − 30 to − 184 beats min^{-1}. For this reason, when assessing the effects of drug administration on this response, ΔHR was normalized as a percentage of the mean ΔHR measured during the 0.5 h control period. Figure 1 illustrates the location of the stimulated region, together with examples of recorded responses from one typical experiment.

Baroreceptor activity after administration of yohimbine

It has been shown that hypothalamically-evoked bradycardia (− ΔHR) was strongly attenuated after i.v. administration of yohimbine, and that this effect could not be due either to a vagolytic action of the drug or to central block of the baroreflex arc *per se* (Evans *et al.*, 1983). The possibility of a direct action of yohimbine on arterial baroreceptors was sought in 4 of the present experiments, in which afferent activity was recorded from one aortic nerve before and after administration of the drug in doses of 1 and 5 mg kg^{-1} i.v. Noradrenaline was infused after yohimbine administration to maintain BP near the control value.

Figure 2 illustrates the results from one such experiment. Even after the maximum dose of yohimbine (Figure 2c) the arterial baroreceptors appeared to be firing normally (lower trace) and there were no observable changes in the rectified electroneurogram recordings (middle trace in each set). In other similar experiments the rectified electroneurogram was averaged during 128 cardiac cycles and no essential changes could be discerned in the baroreceptor activity after yohimbine.

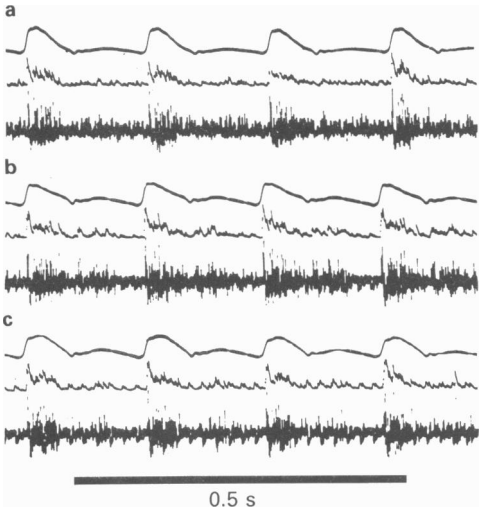

Figure 2 Traces to show activity in aortic nerve afferents before and after administration of yohimbine (i.v.): (a) control records; (b) recorded 10 min after giving yohimbine 1 mg kg^{-1}; (c) recorded 40 min after (b) and 20 min after raising yohimbine to 5 mg kg^{-1}. In each set, (a to c), the 3 traces show from above downwards: pressure in one common carotid artery, the rectified and partly smoothed electroneurogram, the mass electroneurogram recorded from the peripheral divided end of the right aortic nerve. In (b) and (c), noradrenaline was infused at a rate approximately sufficient to offset the vasodepressor action of yohimbine. The mean arterial blood pressures (mm Hg) were: (a) 73, (b) 84, (c) 71. The horizontal bar indicates time 0.5 s.

Effects of yohimbine i.v. on cardio-deceleration

The cardio-deceleration evoked by stimulation of the defined area in the hypothalamus was usually accompanied by an increase in arterial blood pressure. These pressor responses varied in magnitude in different experiments and in many cases could be expected to contribute to the overall cardio-deceleration through the action of the baroreflex.

The graph in Figure 3a illustrates that after i.v. administration of yohimbine the evoked cardio-deceleration is reduced in proportion to the log dose. In these animals the sympathetic efferent pathway was intact and there was a significant reduction in BP after administering yohimbine. Figure 3b shows results from experiments where yohimbine was injected into animals in which spinal cords had been divided at the cervical level and BP maintained near a normal value by i.v. infusion of noradrenaline. In these preparations there were no pressor responses during hypothalamic stimulation and it was possible to offset much of the vasodepressor action of yohimbine by increasing the rate of noradrenaline infusion. Comparison of Figure 3a and 3b shows that the hypothalamically-evoked bradycardia was attenuated by i.v. yohimbine in rabbits whose spinal cords were divided as well as in those with intact cords.

Effect of prazosin i.v. on cardio-deceleration

In 5 experiments prazosin HCl was given i.v. at an initial dose of 0.01 mg kg^{-1}, raised in 4 further steps to

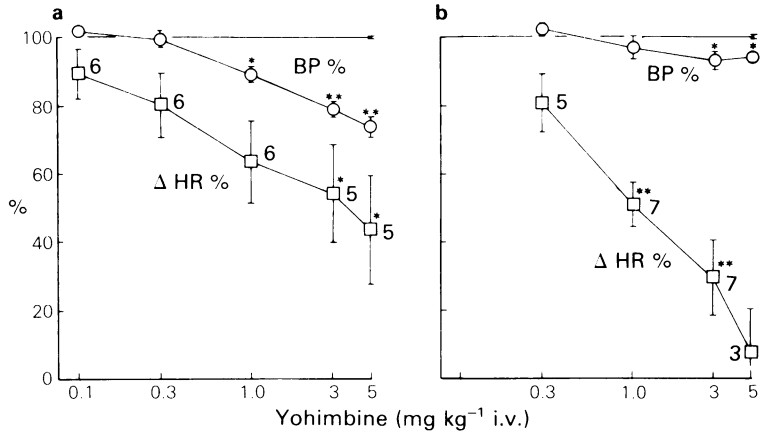

Figure 3 Changes in resting mean arterial blood pressure (○, BP%) and hypothalamically-evoked cardio-deceleration (□, ΔHR%) after cumulative i.v. doses of yohimbine. All values are expressed as percentages of the mean control values before drug administration (ordinate scale). Doses shown on a log scale (abscissa scale). Each point is the mean, of triply replicated averages per animal, from 3–7 animals as indicated next to the ΔHR% symbols. Vertical lines indicate ± 1 standard error. Points significantly different from the mean control are marked *(*P*: 1 to 5%) or **(*P*: 0.1 to 1%). (a) Experiments on animals with intact spinal cords, in which BP fell after yohimbine; (b) results from rabbits with cervical cord transection, in which noradrenaline was infused i.v. to maintain BP and partly offset the depressor effect of yohimbine.

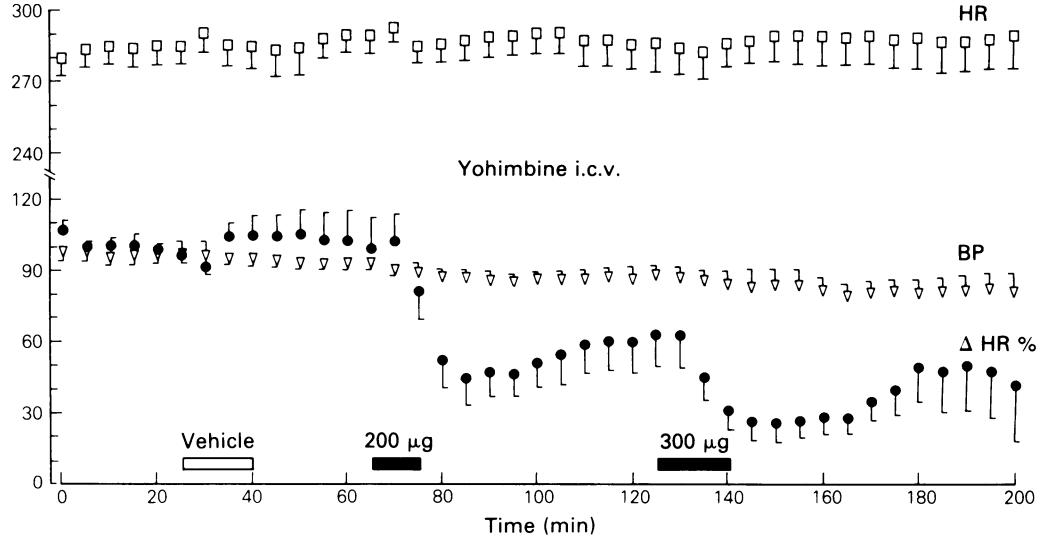

Figure 4 Changes in resting heart rate (□, plotted as beats min^{-1}), resting blood pressure (▽, plotted as mm Hg) and hypothalamically-evoked cardio-deceleration (●, plotted as a percentage of the mean control response) after infusion of yohimbine into a lateral cerebral ventricle; (■) indicate periods of infusion: 200 μg in 200 μl during 10 min, followed 1 h later by an additional 300 μg in 300 μl during 15 min. The vehicle control (□) was an infusion of 300 μl saline at the same pH for 15 min. Each point is the mean from 6 animals, the vertical bars indicating 1 standard error.

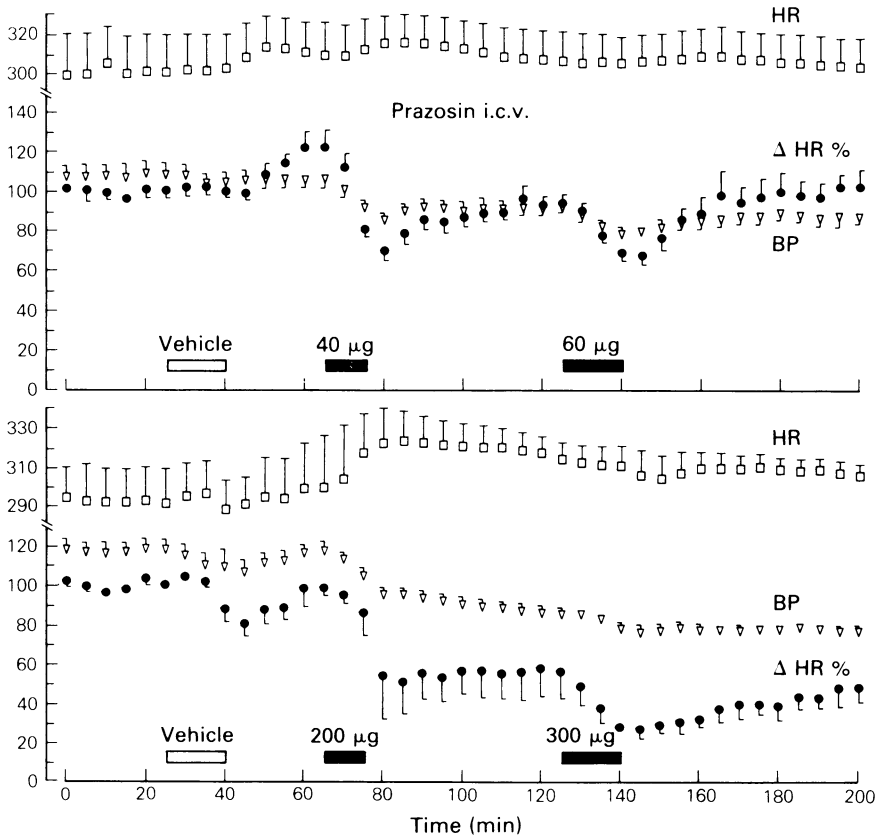

Figure 5 Graphs showing the same variables as in Figure 4, after i.c.v. infusion of prazosin. The upper half shows effects after 40 μg in 200 μl followed by an additional 60 μg in 300 μl, averaged from 5 animals. The lower half shows effects after 200 μg in 200 μl followed by 300 μg in 300 μl. Other details as in Figure 4.

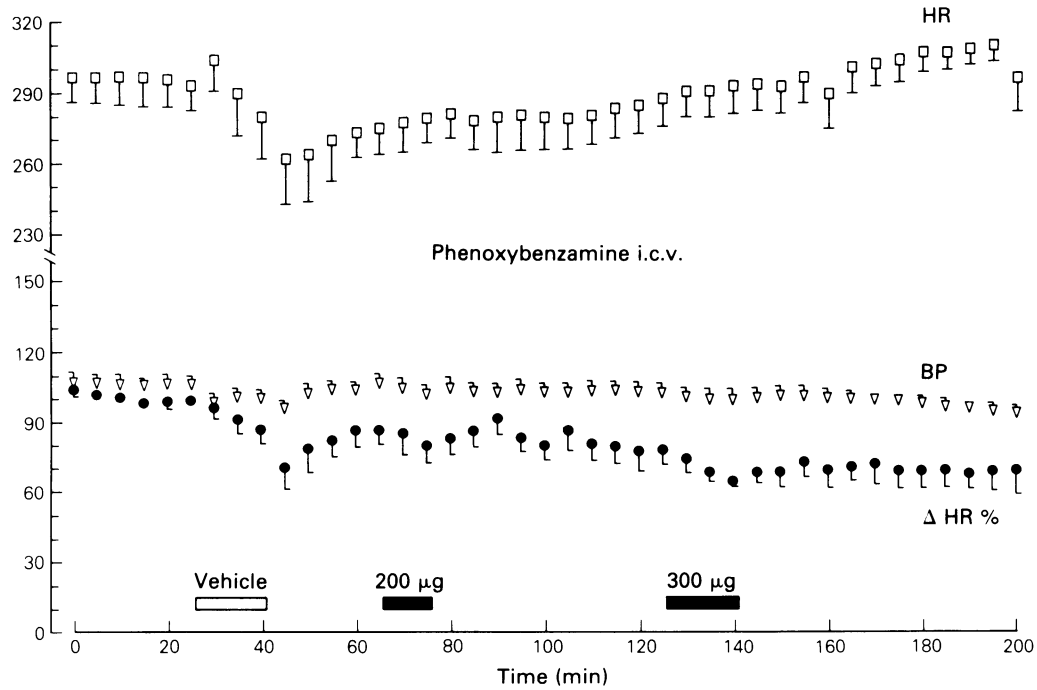

Figure 6 Graphs showing the same variables as in Figure 4, after i.c.v. infusion of phenoxybenzamine. Black rectangles indicate 200 μg in 200 μl, followed by an additional 300 μg in 300 μl. Other details as in Figure 4.

a total of 1 mg kg^{-1}. Cardio-deceleration, BP and HR were measured after each dose. There were dose-related reductions in BP and − ΔHR. After 1 mgkg^{-1} BP had fallen from a mean of 99 to 59 mm Hg, a percentage fall of 40 ± 2%. The corresponding percentage change in − ΔHR was a fall of 58 ± 9%. Pressor responses were also attenuated. The powerful peripheral α_1-blocking action of prazosin precluded the use of a noradrenaline infusion to maintain a near-normal BP.

Effects following intra-ventricular administration of α-adrenoceptor antagonists

Yohimbine, prazosin and phenoxybenzamine were administered via a cannula into one lateral ventricle. Preliminary experiments showed that small volumes of concentrated drug solutions were less effective than slow infusion of a larger volume of greater dilution. All drugs were therefore given in a volume of 200 μl in 10 min, followed 1 h later by a second infusion of 300 μl in 15 min. Responses continued to be recorded for at least 1 h after completion of the second infusion. As all three drugs were in acid solutions, a vehicle control of 300 μl at an equivalent pH was infused in 15 min, beginning 40 min before the first drug administration.

Yohimbine strongly attenuated the cardio-deceleration evoked by hypothalamic stimulation. Figure 4 shows results averaged from 6 experiments. The first infusion of 200 μg reduced − ΔHR to less than half its amplitude 20 min after the start of infusion. A slow partial recovery occurred until the second infusion of 300 μg reduced − ΔHR to 25% of its control amplitude. The vehicle control (NaH_2PO_4, pH 4.9–6.2) caused no significant reduction in − ΔHR. Neither the vehicle nor the yohimbine had any consistent effect on resting HR or BP. The pressor responses evoked during stimulation were not altered.

Prazosin was about as potent as yohimbine in attenuating − ΔHR (Figure 5, bottom) and even doses of 40 and 60 μg caused some transient attenuation (Figure 5, top). All doses of prazosin were followed by falls in BP and increases in resting HR.

The phenoxybenzamine required excess HCl to keep it in solution. The strongly acid vehicle control (lactic acid or HCl, pH 2.2–2.75) itself caused changes in − ΔHR and resting HR. Subsequent administration of phenoxybenzamine, 200 μg followed by 300 μg, produced only minor attenuation of − ΔHR with no consistent changes in resting HR or BP (Figure 6).

Discussion

It is known that electrical stimulation in the brainstem of the anaesthetized rabbit can cause cardio-deceleration (Evans, 1976; Sampson *et al.*, 1977; Gellman *et al.*, 1981). Stimulation in the zona incerta and lateral hypothalamic area close to the mammillothalamic tract evokes bradycardia by a mechanism in which a projection from the stimulated area appears to raise the gain of the cardio-inhibitory limb of the baroreceptor reflex (Evans, 1978; Buss & Evans, 1984). There have been indications that this increase in gain could be blocked by some α-adrenoceptor antagonists which did not block the baroreceptor reflex itself (Powell *et al.*, 1972; Evans, 1980; Evans *et al.*, 1983). However, interpretation of this effect after i.v. administration of these drugs has always been complicated by their peripheral vasodepressor action. The intensity of the cardio-decelerator response is approximately proportional to the value of the mean arterial blood pressure above a threshold value (Buss & Evans, 1984) and, in addition, pressor responses that usually accompany the cardio-deceleration presumably add to the overall bradycardia. Evans *et al.* (1983) lowered blood pressure by haemorrhage to obtain control values of $-\Delta HR:BP$, with which to compare the drug effects, but haemorrhage was an imperfect control because it allowed the pressor responses to remain more-or-less unchanged, compared to the reduced responses recorded after many α-adrenoceptor antagonists.

It is believed that the present experiments have removed these uncertainties and substantiate the view that there is a facilitatory α-adrenergic link between the cardio-inhibitory zone in the rabbit hypothalamus and the baroreceptor reflex pathway in the caudal brainstem. The experiments have shown that some α-adrenoceptor antagonists attenuate the cardio-decelerator response after intracerebroventricular (i.c.v.) infusion, without causing changes in resting blood pressure and heart rate sufficient to affect the decelerator response. It has also been shown that when it is possible to maintain a near-constant, and approximately normal blood pressure, by i.v. infusion of noradrenaline in spinally transected rabbits (in which all cardiac chronotropic control is vagal and in which stimulation evokes no pressor responses) then α-adrenoceptor antagonists still attenuate the decelerator response. In fact, the attenuation after most doses of yohimbine was greater in the spinally transected normotensive animals than in those with intact cords. This probably reflects the continued presence of pressor responses in the latter group, responses that probably evoked small additional baroreflex decelerations, which are not attenuated by yohimbine.

One or two observations deserve comment. Yohimbine and prazosin appeared to be approximately equipotent, on a weight basis, in attenuating the cardio-decelerator response when given i.c.v. This makes it difficult to decide whether the receptors involved in the adrenergic link are of the α_1- or α_2-type, since yohimbine is generally regarded as a preferential α_2-antagonist (Weitzell *et al.*, 1979) while prazosin appears to be a potent and selective α_1-blocker (Cambridge *et al.*, 1977). Surprisingly large amounts of drugs had to be infused i.c.v. in order to obtain definite effects. The distance between the ventricular walls and the receptor sites is unknown, but the slow onset of effects suggest that diffusion times were of the order of minutes. The slow rates of infusion would have allowed much material to pass into the cerebral circulation without reaching the receptors. For these reasons the concentration of the antagonists would have been very much lower at the receptors than in the ventricular c.s.f. Further experiments will be required before one can speculate usefully on the significance of these observations.

Yohimbine is, to date, the only adrenoceptor blocker tested to have produced incontrovertible attenuation of the hypothalamic cardio-decelerator response after both i.v. and i.c.v. administration. In the experiments of Evans *et al.* (1983), phentolamine reduced deceleration and blood pressure in equal proportions after i.v. administration, so a central action could not be demonstrated for this route of administration, but it did appear to attenuate the deceleration selectively when given i.c.v. Prazosin behaved similarly in the present experiments. It appears to be able to penetrate the brain after i.v. administration (Roach *et al.*, 1978), but intracerebral concentrations are low (Pfizer Ltd, personal communication). The depressor action seen after administration of large i.c.v. doses may however have been a peripheral effect, since prazosin readily enters the systemic circulation after i.c.v. administration (Roach *et al.*, 1978). This depressor effect would have diminished the cardio-decelerator response. Phenoxybenzamine given i.v. appeared to show a strong central blocking action in the experiments of Evans *et al.* (1983) but failed to produce a significant block of decelerator responses when infused i.c.v. in the present experiments, even 1 h after completing the second infusion. The strongly acid nature of the phenoxybenzamine solutions may possibly have masked or interfered with its effects when given i.c.v. in the present experiments.

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