for 60 min at a rate of 0.1 μg/min, this being supplemented by a single additional injection sufficient to bring the total i.v. dose administered to 3.0 μg/kg. At this dose level, clonidine always reduced the local vasoconstriction induced by lumbar sympathetic stimulation; the reflex pressor response to afferent femoral stimulation was also clearly decreased. In contrast, spontaneous and evoked sympathetic activity remained almost unchanged and in several instances the drug exerted clear-cut haemodynamic effects when sympathetic activity was entirely unaffected. It is concluded that clonidine can affect the circulation by an action independent of any depressant effect on sympathetic discharge.

We are grateful to the Wellcome Trust for financial assistance. P.P-N is a British Council Technical Assistance Training Study Fellow.

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The cardiovascular effects of clonidine in rabbits after cervical spinal cord transection

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The hypotension and bradycardia produced by clonidine appear to be mediated by a central action of the drug, causing a reduction in peripheral sympathetic discharges (Schmitt, Schmitt, Boissier, Giudicelli & Fichelle, 1968) and facilitation of vagally mediated cardiodepressor reflexes (Kobinger & Walland, 1972). We have investigated the contributions of increased vagal tone and sympathetic withdrawal to the action of clonidine following spinal cord transection under pentobarbitone anaesthesia at the level of the sixth cervical vertebra. Transection at this level leaves vagal outflow and spinal reflex activity intact, but interrupts bulbospinal pathways modulating sympathetic outflow. Clonidine (30 or 100 μg/kg) was administered into the marginal ear vein of conscious rabbits before, 1 h, 24 h and 7 days after transection. Mean arterial pressure (MAP) was recorded directly from the central artery of the ear.

Before transection, the MAP and heart rate were 79.5 ± 2.6 mmHg and 207.0 ± 10.2 beats/min (mean ± s.e. mean, $n = 8$). Clonidine (30 μg/kg) caused an initial pressor response ($+16.8 \pm 2.3$ mmHg) lasting less than a minute. This was followed by prolonged hypotension. MAP fell to 66.1 ± 3.0 mmHg at 10 min and returned to control after 40 minutes. Bradycardia (-102.5 ± 8.7 beats/min) accompanied the pressor effect and lasted 30 minutes.

One hour after spinal transection, the MAP had fallen to 47.6 ± 5.0 mmHg, due to loss of sympathetic tone, since there was no significant change in heart rate. Clonidine caused a significantly greater pressor effect ($+26.3 \pm 3.2$ mmHg) which persisted for 5 min and the fall in MAP was completely abolished. Bradycardia still occurred but was less (-63.1 ± 16.0 beats/min). Twenty-four hours after transection, the MAP was not significantly different from pre-operative control. At both 24 h and 7 days the pressor action of clonidine (30 μg/kg) was increased ($+33.5 \pm 2.1$ and 26.3 ± 4.4 mmHg respectively) and lasted for 20 minutes. Bradycardia was present but MAP did not fall.

Similar results were obtained in a further group of rabbits after clonidine 100 μg/kg. Once again at no time after transection was a hypotensive effect of the drug observed. Intracisternal injection of clonidine (1 μg/kg) reduced MAP by 38.0 mmHg in intact pentobarbitone anaesthetized rabbits. In animals examined 7 days after transection, intracisternal clonidine had no hypotensive effect.

These results confirm that the principal site of hypotensive action of clonidine is in the central nervous system. Hypotension results from withdrawal of sympathetic tone rather than vagal facilitation as in transected rabbits vagally mediated bradycardia still occurred but blood pressure did not fall. Heart rate changes result predominantly from vagal mechanisms, although sympathetic withdrawal may contribute. The potentiation and prolongation of the pressor effect may represent the effect on peripheral α-adrenoceptors unopposed by a central hypotensive action.

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Pressor responses to noradrenaline administered into the third cerebral ventricle of anaesthetized and conscious cats

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Administration of noradrenaline into a lateral cerebral ventricle has been reported to cause falls in blood pressure in both anaesthetized (Nashold, Mannarino & Wunderlich, 1962) and conscious (Day & Roach, 1974) cats. However, pressor responses have been observed after noradrenaline administration into the third ventricle (Phillippu, Przuntek, Heyd & Burger, 1971) and after the administration of low doses of noradrenaline into the lateral ventricles of anaesthetized cats (Gagnon & Melville, 1966).

In the present study we have infused noradrenaline into the third ventricle of both anaesthetized and conscious cats and have recorded the effects on blood pressure and heart rate. Blood pressure was recorded from a femoral artery in anaesthetized (chloralose 70 mg/kg i.v.) animals and from an indwelling carotid catheter in conscious animals. Heart rate was obtained from the blood pressure pulse. In both series of experiments cannulae were inserted stereotaxically into the third ventricle.

The administration of noradrenaline (15 and 30 μg) into the third ventricle of 12 anaesthetized cats produced mean (± s.e. mean) pressor responses of 56.0 ± 13.4 and 80.3 ± 12.4 mmHg systolic and 42.0 ± 11.8 and 56.9 ± 9.0 mmHg diastolic, respectively, with a variable effect on heart rate. The duration of the pressor response was usually 10 to 20 minutes. In seven experiments spinal section at C-2 was performed and in five of these the response to noradrenaline was significantly ($P < 0.05$) reduced, whilst in the remaining two a potentiation was seen. In 6 cats bilateral adrenalectomy significantly ($P < 0.05$) reduced the pressor response to noradrenaline administered into the third ventricle whilst in three other cats the response was potentiated. Responses to systemic noradrenaline (0.25 to 1 μg/kg i.v.) were not affected by either adrenalectomy or spinal section.

In conscious cats lower doses of noradrenaline (1.65 to 10 μg) produced pressor responses when infused into the third ventricle. These responses were usually associated with tachycardia, and both pressor and heart rate responses were markedly reduced after hexamethonium (1 to 10 mg/kg i.v.) indicating that they were of central origin. Propranolol (0.5 to 1 mg) infused into the third ventricle of 4 cats reduced by approximately 60% the pressor response and tachycardia to noradrenaline administered by the same route. Phentolamine (0.5 mg) infused into the third ventricle of 3 cats reduced the noradrenaline pressor response by approximately 45%.

The results suggest that noradrenaline administered into the third cerebral ventricle of cats can produce a centrally-mediated pressor response which is apparently the result of stimulation of both α and β adrenoceptors and which in some cats is partly due to central activation of the adrenal medulla.

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