induced by the hypothermia but, at 25°C was minimal and no longer significant.

The dose response curves to salbutamol at each temperature were displaced to the left by reserpinization and their maxima were also raised. In contrast to isoprenaline, reserpine was still apparently able to produce supersensitivity to salbutamol at 25°C, by increasing its maximum response from 73.8 ± 10.8 and 55.7 ± 20.1 at 38°C to 93.9 ± 13.8 and $77.3\% \pm 12.8$ at 25°C for rate and tension respectively.

This study demonstrates a supersensitivity of the rate and tension responses to isoprenaline and the partial agonist salbutamol by both hypothermia and reserpinization, with a trend towards full agonist activity of the latter.

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Peripheral vascular effects of clonidine independent of a reduction in sympathetic activity

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Clonidine is a powerful drug and can produce a wide range of effects depending on the dose and route of administration. For example, when the drug is given to animals parenterally in large doses, or is administered locally into the cisterna magna, the lateral cerebral ventricle or the vertebral artery, a variety of central nervous system effects can be produced. Because of this, the assumption that the hypotensive effect of clonidine results only from a central action underlies a great many statements made during the past few years (Schmitt, Schmitt, Boissier & Giudicelli, 1967; Klupp, Knappen, Otsuka, Streller & Teichmann, 1970).

When clonidine is administered orally to cats in daily doses similar to those used clinically, it reduces both the magnitude and the duration of vasoconstrictor and vasodilator responses elicited either by the electrical stimulation of the lumbar sympathetic chain, or by the close-arterial administration of vasoconstrictor and vasodilator drugs. It appears, therefore, that, with doses below 10 μg/kg, the hypotensive action of the drug is the result of a vascular smooth muscle change and not of a central nervous system effect (Zaimis, 1969; Larbi, 1970; Zaimis, 1974). The present findings lend further support to clonidine having a direct action on vascular smooth muscle.

Eight cats were anaesthetized with a mixture of chloralose and pentobarbitone sodium, atropinized and artificially ventilated after the administration of gallamine triethiodide. The arterial blood pressure, electrocardiogram and left femoral blood flow of each animal were recorded on a Grass P7 polygraph. The third thoracic ramus communicans was exposed where it enters the stellate ganglion, cut distally and dissected into small filaments until impulse activity from a single fibre or from a few fibres only could be recorded. The central stump of the cut right femoral nerve was stimulated and cardiovascular responses as well as changes in sympathetic discharge were measured. Changes in sympathetic discharge were also induced by increasing or decreasing blood pressure in the carotid sinuses. For inducing blood flow changes at various frequencies of stimulation an electrode was placed on the left lumbar sympathetic trunk and the nerve ligated centrally to the electrode.

After a number of control measurements of baseline activity and evoked responses, clonidine was infused

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.

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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.