subgroups, paired animals received raphe stimulation or sham treatment (Collard & Roberts, 1974).

Results are expressed as the difference between unstimulated and stimulated animals (Table 1). This difference does not appear to reflect drug induced changes in 5-hydroxyindole levels of unstimulated animals. Only the combination of Li^+ and chlorimipramine significantly altered changes in 5-HT levels, but Li^+ abolished the effect of chlorimipramine on 5-HIAA.

The reduction of 5-HIAA by chlorimipramine alone may indicate that the 5-HIAA produced by raphe stimulation arises predominantly from the metabolism of extraneuronally released 5-HT. Chlorimipramine by inhibiting uptake would deny released 5-HT access to intraneuronal monoamine oxidase and reduce the production of 5-HIAA.

Preliminary studies have indicated that Li^+ does not antagonize the inhibition of uptake by chlor imipramine. The lack of effect of chlorimipramine on the increase in 5-HIAA concentration in the Li^+ group suggests therefore that the 5-HIAA is produced primarily from 5-HT which remains intracellular. Since stored 5-HT is believed to be protected from deamination, the results may imply that Li^+ inhibits the extraneuronal release of 5-HT by promoting the release of 5-HT into the cytoplasm.

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The individual and combined effects of hypothermia and reserpine pretreatment on the rate and tension responses to isoprenaline and salbutamol in guinea-pig atria

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The dose-response curves for the positive inotropic and chronotropic effects on the heart of sympathomimetic amines have been shown to be displaced to the left by hypothermia, indicating supersensitivity (Trendelenburg, 1968; Reinhardt, Wagner & Schumann, 1972). Reserpine pretreatment has also been shown to produce supersensitivity of the rate (Taylor, Westfall & Fleming, 1974), and tension (McNeill & Shulze, 1972) responses, together with an increase in the maximum responses of the partial agonist salbutamol (Broadley & Lumley, 1975). We were therefore interested to determine the individual and combined effects of hypothermia and reserpine pretreatment upon the rate and tension dose response curves to isoprenaline and salbutamol, and whether the maximum response to the latter was also enhanced by hypothermia.

Separated left and right guinea-pig atria were suspended in Krebs bicarbonate solution (50 ml) initially at 38°C, and gassed with CO_2:O_2 (5%:95%). The left atrium was paced electrically at 2 Hz and isometric tension recorded on a Devices M19 polygraph for the inotropic responses. Chronotropic responses were obtained by means of a ratemeter triggered by the isometric tension signal of the spontaneous right atrium. An initial cumulative dose-response curve to isoprenaline was obtained at 38°; 30°; or 25°C. A third curve to salbutamol at the same temperature was compared with the second isoprenaline curve corrected for loss in sensitivity, from control experiments. Increase rate and increase tension responses were plotted as a percentage of the isoprenaline maximum response. Results are expressed as ng/50 ml to produce 50% of the maximal response.

The rate dose response curve to isoprenaline (60.2 ± 7.6) at 38°C lay to the left of the tension curve (354.4 ± 86.4). On cooling the preparation to 30°C both rate and tension curves were displaced to the left, tension to a greater extent, and the curves became virtually superimposable (Rate 23.57 ± 4.9; Tension 26.0 ± 2.5). Cooling to 25°C resulted in a further shift, and the tension curve now lay to the left of rate (Rate 8.75 ± 2.2; Tension 6.1 ± 1.7). The salbutamol curves were similarly displaced to the left by cooling, and their maxima were progressively raised from 61.2 ± 6.5 and 21.6 ± 11.3 at 38°C, to 75.2 ± 12.0 and 56.0 ± 15.6 at 30°C, and to 86.6 ± 7.1 and $66.3\% \pm 17.8$ at 25° for rate and tension respectively.

In atria from guinea-pigs pretreated with reserpine (5 mg/kg i.p. at 72 h and 3 mg/kg i.p. at 48 and 24 h before sacrifice) supersensitivity was demonstrated at 38°C by a shift of the dose response curves to isoprenaline to the left. Tension was potentiated more than rate as shown by their respective ED_{50} values of 46.2 ± 7.1 and 18.8 ± 3.3. At 30°C, reserpine-induced supersensitivity occurred in excess of that already

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