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COMMUNICATIONS

Effect of clonidine on cardiac acceleration in pithed rats

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Scriabine, Stavorski & others (1970), reported clonidine to antagonize cardiac acceleration induced by low frequency electrical stimulation of the right cardiac sympathetic nerve fibres of dogs. Clonidine has also been shown to inhibit cardiac acceleration caused by low frequency electrical stimulation of peripheral sympathetic nerve fibres in pithed rats (Armstrong & Boura, 1973). Antonaccio & Robson (1973) examined the effects of clonidine in dogs and concluded that the inhibition of cardiac acceleration was the result of increased vagal activity. Scriabine & Stavorski (1973) however concluded that clonidine-induced antagonism of cardiac acceleration could not be explained by enhancement of vagal activity alone since clonidine was effective after bilateral vagotomy.

The effect of clonidine on cardiac acceleration was examined in pithed rats and the influence of phentolamine and desipramine on its action was studied.

Male rats, 250–300 g, were bilaterally adrenalectomized and then pithed during a brief period of halothane anaesthesia. The animals were subsequently artificially respired (50 strokes min^{-1}, 1 ml per 100 g). Blood pressure was recorded with a Hewlett Packard 1280 c pressure transducer from the left common carotid artery and displayed on an Hewlett Packard 7700 recorder. Heart rate was recorded using the pressure wave to trigger a ratemeter. The left femoral vein was cannulated to facilitate intravenous administration of drugs.

The pithing rod was used to stimulate sympathetic cardiac nerves, C_7–T_1 (Gillespie, Maclaren & Pollock, 1970). Tubocurarine (1 mg kg^{-1}, i.v.) was injected before stimulation commenced. The stimulus parameters were 10 V, 0·5 ms for 30 s at frequencies of 0·5 to 6Hz.

The effects of clonidine on the positive chronotropic effects produced either by selective stimulation of the sympathetic cardiac nerves or intravenous injections of noradrenaline were examined. Drugs were injected into the femoral vein, the series of nerve stimulations or noradrenaline injections being applied before and 5 min after each dose of test drug. Saline (0·9% w/v NaCl solution) was injected into further animals for control purposes.

Clonidine (30 μg kg^{-1}, i.v.) produced a pressor response in pithed rats, little change in heart rate and a significant ($P<0·05$) reduction in the tachycardia produced by sympathetic nerve stimulation (Fig. 1a). Pretreatment with phentolamine mesylate (1 mg kg^{-1}, i.v.) prevented both the pressor effect and inhibition of cardiac acceleration produced by clonidine (Fig. 1b). Phentolamine itself caused a significant ($P<0·05$) increase in the cardiac acceleration produced by sympathetic nerve stimulation. Desipramine (30 μg kg^{-1}, i.v.) increased the cardiac acceleration produced by sympathetic nerve stimulation (Fig. 1c) but failed to prevent the cardiac inhibitory effects of clonidine. In a control experiment there was no significant difference ($P>0·05$) between three consecutive response curves to electrical stimulation, (Fig. 1d).

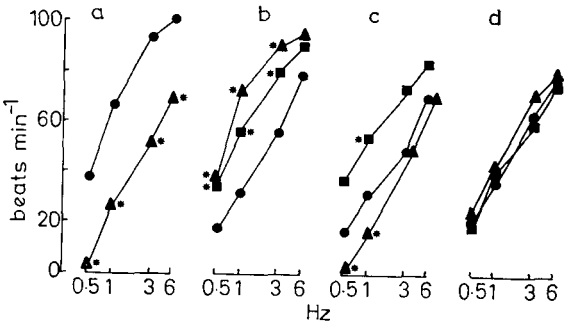

FIG. 1. Dose response curves for the positive chronotropic effects of cardiac nerve stimulation: a–Before (●-●) and after 30 μg kg^{-1} (i.v.) (▲-▲) clonidine. b–Before (●-●) and after 1 mg kg^{-1} (i.v.) (■-■) phentolamine mesylate and after a subsequent injection of clonidine, 30 μg kg^{-1} (i.v.) (▲-▲). c–Before (●-●) and after 30 μg kg^{-1} (i.v.) (■-■) desipramine and after a subsequent injection of clonidine, 30 μg kg^{-1} (i.v.) (▲-▲). d–Before (●-●) and after 1 ml kg^{-1} (i.v.) (■-■) saline and after a second injection of saline, 1 ml kg^{-1} (i.v.) (▲-▲). The results are the mean of a minimum of 5 experiments ± s.e.m. Asterisks indicate a mean response differing significantly ($P < 0·05$) from initial values, using a t test for paired data. Ordinate—Increase in heart rate (beats min^{-1}). Abscissa—Stimulation frequency (Hz).

Clonidine (30 μg kg^{-1}, i.v.) had no effect on the tachycardia produced by noradrenaline (Fig. 2a). Phentolamine (1 mg kg^{-1}, i.v.) reduced the tachycardia produced by noradrenaline (Fig. 2b), but the reduction was not statistically significant ($P>0·05$). Desipramine (30 μg kg^{-1}, i.v.) produced a significant ($P<0·05$) increase in the tachycardia produced by

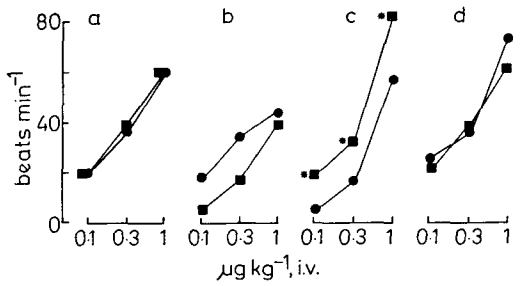

FIG. 2. Dose response curves for the positive chronotropic effect of cardiac nerve stimulation: a–Before (●-●) and after 30 μg kg^{-1} (i.v.) (■-■) clonidine. b–Before (●-●) and after 1 mg kg^{-1} (■-■) phentolamine mesylate. c–Before (●-●) and after 30 μg kg^{-1} (i.v.) (■-■) desipramine. d–Before (●-●) and after 1 ml kg^{-1} (i.v.) (■-■) saline. The results are the mean of a minimum of 5 experiments ± s.e.m. Asterisks indicate a mean response differing significantly ($P < 0.05$) from initial values, using a *t*-test for paired data. Ordinate—Increase in heart rate (beats min^{-1}). Abscissa —Noradrenaline bitartrate (μg kg^{-1}, i.v.).

noradrenaline (Fig. 2c). In a control experiment there was no statistically significant ($P>0.05$) difference between two consecutive dose response curves to noradrenaline, (2d).

The above study indicates that clonidine has a significant inhibitory effect on peripheral sympathetic cardiac nerves in pithed rats. The inhibitory effect is mediated via α-receptors since the effect was antagonized be pretreatment with phentolamine. Furthermore the α-receptors involved appear to be presynaptic (Starke & Altmann, 1973) since clonidine had no inhibitory effect on increases in heart rate produced by intravenous administration of noradrenaline.

The cardiac acceleration produced by stimulation of sympathetic cardiac nerves was potentiated by phentolamine. This effect also appeared to be mediated presynaptically since phentolamine reduced the tachycardia produced by intravenous administration of noradrenaline.

The results with clonidine and phentolamine support the hypothesis that sympathetic nerve endings possess α-receptors which control the release of noradrenaline (Langer, 1974). Stimulation of these α-receptors decreases noradrenaline release. The feedback control of the amount of noradrenaline released by nerve stimulation is governed by the concentration of noradrenaline at the presynaptic α-receptor. By interrupting this feedback loop, α-receptor antagonists are able to enhance noradrenaline release in response to nerve stimulation.

The presynaptic α-receptor appears to be on the presynaptic membrane and not within the nerve terminal since desipramine had no effect on the cardiac inhibitory effects of clonidine. Although the dose of desipramine was low it produced a significant blockade of uptake as was evident by the potentiation of the responses to intravenously administered noradrenaline. Higher doses of desipramine were tried but the cardiac responses to electrical stimulation were markedly prolonged and frequently did not return to pre-stimulation values.

The results are in general agreement with those found by other workers (Armstrong & Boura, 1973; Scriabine & Stavorski, 1973; Scriabine & others 1970; Pacha, Salzmann & Scholtysik 1975) but are at variance with those of Antonaccio & Robson (1973) in that they support the hypothesis that sympathetic nerves are under functionally significant feedback control mediated by α-receptors.

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