Time-course analysis of the cardiovascular effects of clonidine resulting from the activation of cardiac pre- and vascular postsynaptic α-adrenoceptors in the pithed rat

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Clonidine administered intravenously to pithed rats produces hypertension and a reduction in the cardiac acceleration evoked by electrical stimulation of the thoracic sympathetic outflow (Armstrong & Boura, 1973). Whilst the vascular action of clonidine is attributed to an activation of α-adrenoceptors present in the arterial vascular wall, the effect on the cardiac pacemaker is believed to be due to clonidine stimulating α-adrenoceptors located on noradrenergic neuronal endings which results in a reduced release of noradrenaline (Langer, 1977).

In pithed male Charles River rats given i.v. atropine sulphate (1.0/mg kg) and (+)-tubocurarine (5.0 mg/kg) a sustained tachycardia of about 90–110 bts/min was evoked by continuously stimulating the thoracic spinal cord (0.3–0.7 Hz, 0.5 ms, 60–70 V). The changes in carotid diastrolic blood pressure (BP) and heart rate (HR) produced by 1.0 and 5.0 μg/kg clonidine as well as the time (t) at which they occurred were read from the traces and the rate constants of onset and decay of these two effects were then determined using a biexponential equation (Gibaldi & Perrier, 1975): $\Delta BP\ (\Delta HR) = -A \exp(-\alpha t) + B \exp(-\beta t)$. The ratios $0.693\alpha^{-1}$ and $0.693\beta^{-1}$ respectively give the half lives of the appearance and disappearance of BP and HR responses. The times (t_{max}) at which the BP (ΔBP_{max}) and HR (ΔHR_{max}) reached their peaks were obtained from the original data.

The continuous electrical stimulation of the thoracic spinal cord produced a tachycardia which remained constant for at least 60 minutes. The hypertension and the fall in the heart rate produced by clonidine were well described by the exponential function utilized for the analysis of the data. The peak changes in heart rate (−28.4 ± 1.9 and −57.2 ± 5.2 bts/min after 1.0 and 5.0 μg/kg clonidine, respectively) occurred within 120 and 150 s after the clonidine injections, whereas the hypertension reached its maximum in approximately 10 seconds. Therefore, the rate constant of the onset (α) of the vascular effect of clonidine was 8–9 times greater than that of the fall in heart rate. Similarly, the cardiac effects of clonidine recovered to control levels much later than the vascular effects. The times required for a 50% recuperation of the peak changes in heart rate ($t_{\frac{1}{2}\beta}$) were 406 and 835 s after 1.0 and 5.0 μg/kg clonidine respectively, whilst the $t_{\frac{1}{2}\beta}$ values for the clonidine pressor responses were 58 and 88 seconds.

These results indicate that in the pithed rat with an experimentally induced sympathetic tachycardia clonidine in small doses was able to mediate sustained decreases in heart rate via activating presynaptic α-adrenoceptors. The kinetic profile of this clonidine effect is entirely different from that characterizing the hypertensive response implying that the general classical analysis using only the peak changes in diastolic carotid blood pressure and heart rate (Drew, 1976) is unsuitable to evaluate the relative potencies of clonidine and other similar compounds as agonists of cardiac pre- and vascular postsynaptic α-adrenoceptors.

Finally, the complete time-course analysis of the cardiovascular effects of clonidine may underline a structural difference between the cardiac pre- and the vascular postsynaptic α-adrenoceptors; it would also provide a better methodology to evaluate the relative potencies of compounds possessing pre- and postsynaptic α-adrenoceptors stimulant properties.

References

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The effects of prazosin on the clonidine induced hypotension and bradycardia in rats and sedation in chicks

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Clonidine produces centrally mediated hypotension, bradycardia and sedation which are inhibited by various α-adrenoceptor antagonists (Delbarre & Schmitt, 1971; Schmitt, Schmitt & Fénard, 1973). Whilst these cardiovascular effects of clonidine are attributed to an activation of central postsynaptic α-adrenoceptors (Haeusler, 1974), the clonidine sedation has been postulated to result from an action on presynaptic α-adrenoceptors or at least receptors resembling peripheral presynaptic α-adrenoceptors