Inhibitory effect of clonidine on a peripheral adrenergic synapse

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Clonidine is a potent hypotensive agent and is known to possess powerful central nervous system effects (Schmitt, Schmitt, Boissier & Giudicelli, 1967). Its peripheral actions have generally been regarded to be too insignificant to contribute to its hypotensive effect (Kobinger, 1975). Investigations of its action upon the release of noradrenaline (NA) in peripheral adrenergically innervated tissues have led to conflicting conclusions (Werner, Starke & Schümann, 1972; Stjärne, 1975). In the present study an attempt has been made to analyse the peripheral effects of clonidine at concentrations comparable to those observed in human plasma during antihypertensive therapy (Dollery, Davies, Draffan, Dargie, Dean, Reid, Clare & Murray, 1976) on a suitable adrenergically innervated *in vitro* preparation. The rat isolated anococcygeus (Gillespie, 1972) was used because of its ability to give reproducible mechanical responses to both long and short trains of electrical pulses.

Isolated anococcygii from male rats were set up in 10 ml organ baths between parallel platinum electrodes in Krebs–Henseleit at 37°C and contractions were recorded isometrically. For electrical field stimulation, pulses of 1 ms duration at 12 V were used.

Clonidine had a profound inhibitory effect on adrenergic motor transmission evoked by short trains (< 10 pulses). Its effect declined as the train-length was increased (% inhibition at 10 Hz: 91.9 ± 5.3 with 2 pulses; 1.5 ± 3.0 with 40 pulses). Another factor which determined the intensity of inhibition was the frequency of pulses in each train; inhibition was more marked at lower frequencies (% inhibition of 5-pulse trains: 96.8 ± 1.9 at 1 Hz; 63.7 ± 6.8 at 40 Hz).

The threshold concentration of clonidine for inhibition was around 10^{-10}M and maximum inhibition was achieved by concentrations of 10^{-9}M–10^{-8}M.

NA-evoked contractions were not inhibited by clonidine, indicating that clonidine has a presynaptic site mediating its inhibitory effect on adrenergic transmission. Unlike clonidine, neither NA (10^{-9} M – 10^{-6} M), nor phenylephrine (10^{-9} M – 10^{-7} M), appeared to reduce the twitch-height. The indirect sympathomimetic tyramine (10^{-7} M – 10^{-5} M) induced contraction of the smooth muscle, but did not inhibit the transmission. Inhibition due to clonidine was unaffected by the concurrent presence of tyramine (10^{-5} M) or NA (10^{-6} M) in the bath. The inhibitory effect of clonidine persisted unimpaired after blockade of neuronal uptake of NA by cocaine (10^{-6} M) or by desmethylimipramine (3×10^{-8} M – 3×10^{-7} M), and exogenous NA still lacked an inhibitory effect.

These results suggest that clonidine in low concentrations is an effective adrenergic neurone blocking agent; train-length and the frequency of stimulation are the critical factors, in that order, limiting its effectiveness. The mechanism of its inhibitory action involves presynaptic sites upon which NA, exogenous or endogenous, and phenylephrine have little or no effect.

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