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BENZTROPINE-INDUCED PROLONGATION OF RESPONSES TO VASODILATOR NERVE STIMULATION IN THE CANINE PAW PAD

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After blockade of noradrenergic transmission with guanethidine in anaesthetized dogs, stimulation of the peripheral end of the cut tibial nerve (1 Hz, 10 pulses) produces a vasodilator response which is localized to the circulation of the paw pads. The time course of the response is considerably prolonged after systemic administration of the dopamine-uptake blocking drug, benztropine (1 mg/kg). This effect is not due to inhibition of Uptake$_1$, as benztropine, unlike desmethylimipramine, does not prolong responses to noradrenergic vasoconstrictor nerve stimulation. The results support previous evidence suggesting that the dilator response to tibial nerve stimulation involves neural release of dopamine.

Introduction In anaesthetized dogs pretreated with guanethidine so as to inactivate the noradrenergic vasoconstrictor nerves, electrical stimulation of specific descending autonomic pathways in the midbrain and hypothalamus causes active vasodilatation in the circulation of the paw pads. This response is prevented by section of the tibial nerve trunk, and can be mimicked by electrical stimulation of the peripheral stump of the cut nerve (Bell & Lang, 1974; 1979). Dilatation in response to either mode of stimulation is abolished after intra-arterial administration of the dopamine-receptor antagonist, ergometrine (Bell, Conway, Lang & Padanyi, 1975), suggesting that it may be due to neuronal release of dopamine. This proposal is supported by biochemical and histochemical demonstration of neurones in the sympathetic supply to the hind paw which contain large amounts of dopamine (Bell, Lang & Laska, 1978; Bell & McLachlan, 1982).

At noradrenergic autonomic neuroeffector junctions in the cardiovascular system, pharmacological inactivation of the axonal uptake process for noradrenaline (Uptake$_1$) prolongs responses to low-frequency nerve stimulation, without having consistent effects on response amplitude (Bell & Grabsch, 1976; Bell & Kushinsky, 1978). It might therefore be anticipated that responses to dopaminergic nerve stimulation would also be prolonged by inhibition of axonal reuptake of the transmitter. This study examines the effect on vasodilator responses to tibial nerve stimulation of the dopamine-uptake blocking drug, benztropine.

Methods Adult mongrel dogs (10–20 kg) were anaesthetized with α-chloralose (70 mg/kg i.v.) after thiopentone sodium induction and ventilated under positive-pressure. Systemic blood pressure and heart rate were monitored and mean flow through the left femoral artery was measured using an electromagnetic flowmeter (Devices). The left tibial nerve was exposed and divided above the ankle, and the distal stump was stimulated using a silver Dastré electrode with 10 s trains of 1 ms square wave pulses delivered from a Grass S48 stimulator at 1 Hz and supramaximal voltage. During each experiment, the animal was immobilized with pancuronium (0.1 mg/kg i.v.) so as to prevent somatic activation. Further details of the methodology have been published previously (Bell & Lang, 1979).

In experiments concerned with vasodilator responses to tibial stimulation, the animals were treated with guanethidine (5 mg/kg s.c.) 18 and 2 h before the experiment started. In experiments in which noradrenergic vasoconstrictor responses were studied, this pretreatment was omitted.

After reproducible control responses to nerve stimulation had been obtained, benztropine mesylate (1 mg/kg) or desmethylimipramine hydrochloride (DMI) (1 mg/kg) in 0.9% w/v NaCl solution was slowly injected intravenously. After at least 10 min further responses to nerve stimulation were elicited. The time courses of responses were assessed in terms of the time between initiation of the response and its recovery to 50% of the peak change.

Results Femoral flow responses to tibial nerve stimulation were studied in 8 animals pretreated with guanethidine (vasodilator responses) and in 6 animals not so pretreated (vasoconstrictor responses). In no case did nerve stimulation produce appreciable changes in heart rate or systemic blood pressure.

The time course of vasodilator responses varied considerably between animals, with half-recovery times ranging from 24 to 75 s (mean 46 ± 5.9 s.e.mean). In all but two of these animals, administration of benztropine produced prolongation of responses (Figure 1). The mean half-recovery time after benztropine was 68 ± 11.1 s ($P < 0.05$, 2-tailed paired t test). The prolongation of neurogenic re-

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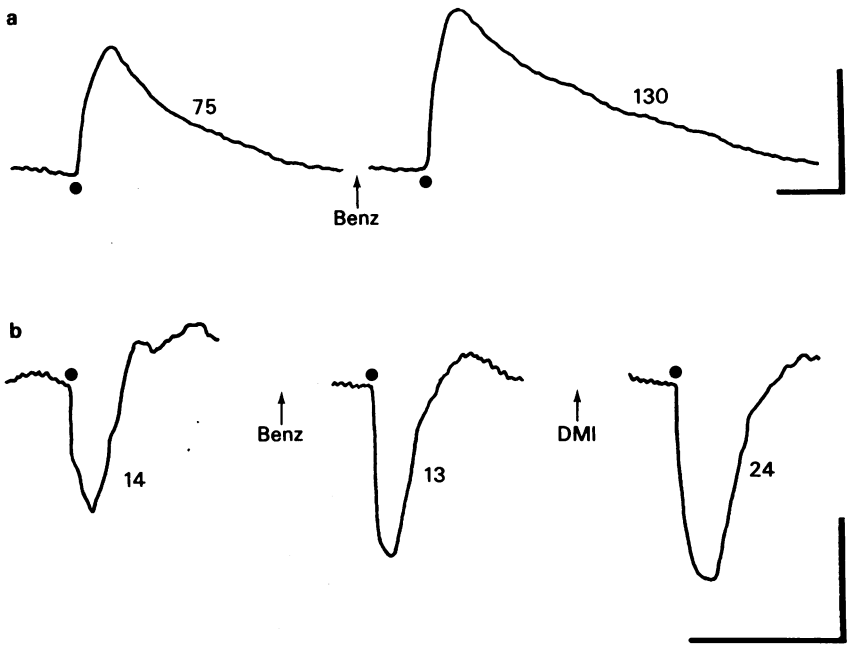

Figure 1 Blood flow responses of the dog hind paw to electrical stimulation of the distal end of the cut tibial nerve (1 Hz, 5 s, at the black dots). The values beside each response indicate the half-recovery time in seconds. (a) Vasodilator responses in a guanethidine-treated animal. After administration of benztropine 1 mg/kg i.v. (Benz) the response was considerably prolonged. (b) Vasoconstrictor responses in an untreated animal. Benztropine 1 mg/kg i.v. had no effect on the time course of the response, but subsequent administration of desmethylimipramine 1 mg/kg i.v. (DMI) caused prolongation. Calibrations for each panel: vertical, 10 ml/min; horizontal 1 min.

sponses was not accompanied by any prolongation of femoral dilator responses to intra-arterial injections of nitroglycerine (1–5 μg).

Vasoconstrictor responses were shorter in time course than were vasodilator responses, with a mean half-recovery time of 14 ± 1.2 s. In four animals studied, benztropine had no effect on the time course of vasoconstriction (mean 14 ± 1.5 s). Subsequent administration of DMI, by contrast, prolonged the recovery phase considerably in each of three experiments, and DMI alone caused similar prolongation in a further two experiments. The mean half-recovery time for responses in all five DMI-treated animals was 18 ± 1.5 s ($P < 0.05$).

Discussion Previous studies by other workers have shown that DMI is many times more potent as an inhibitor of Uptake$_1$ than as an inhibitor of the dopamine-uptake process. In contrast, benztropine has been found to be approximately equipotent in its effects on each process (Farnebo, Fuxe, Hamberger & Ljungdahl, 1970; Horn, Coyle & Snyder, 1971; Koe, 1976). In the present experiments, the dose of benztropine used appeared to be devoid of appreciable Uptake$_1$-blocking activity, as it had no effect on the timecourse of vasoconstrictor responses to noradrenergic nerve stimulation, while a similar dose of DMI caused considerable prolongation of these. The prolongation of vasodilator responses to nerve stimulation by benztropine is therefore compatible with an action on dopamine uptake, although some other nonspecific action cannot be absolutely excluded. This result supports earlier evidence to suggest that the autonomic nerve supply to the digital blood vessels contains neurones which liberate dopamine during activation at physiological frequencies.

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