Neuronally-induced vasodilator response in the splanchnic region of the chloralosed cat

During the course of studies involving stimulation of the periarterial mesenteric nerves and the recording of vascular changes in the splanchnic region of the choralosed cat, the administration of guanethidine was observed to abolish the neuronally mediated vasoconstriction and, in some cats, to reverse the response producing vasodilatation. The present study involved an investigation of this vasodilator response. Ross (1973) reported a similar effect in the cat after bretylium.

Seventeen cats of either sex, 2·2–3·0 kg, were anaesthetized with chloralose, 80–100 mg kg^{-1} intraperitoneally. Systemic blood pressure was recorded from a carotid artery and heart rate was monitored. A femoral vein was cannulated for the intravenous injection of drugs. The method of continuous and simultaneous measurement of blood flow, perfusion pressure and vascular conductance in the autoperfused splanchnic region has been described previously (Gardiner, Hamilton & Parkes, 1971). Blood flow was measured by an electromagnetic flowmeter, using an extra-corporeal flow probe, interposed in the superior mesenteric artery. Perfusion pressure was measured distal to the flow probe. Vascular conductance was obtained by electronic division of flow by perfusion pressure and provides a continuous record of vascular changes irrespective of changes in perfusion pressure.

The bundle of sympathetic nerves enveloping the superior mesenteric artery was dissected from the vessel, ligated and divided. The distal end of the nerve, laid over bi-polar electrodes, was stimulated at 10–20 V, with pulses of 1 ms duration, at varying frequency (0·5–20 Hz), for periods of 5 s–5 min.

Heparin (5 mg kg^{-1}), dissolved in saline (0·9% w/v NaCl,) was injected intravenously immediately the cannulations were completed. Arterial injections were made via a side branch in the perfusion circuit, in a volume of 0·1 or 0·2 ml, and washed into the blood-stream with 0·1 ml saline.

Some cats were pre-treated with reserpine, 3 mg kg^{-1} intraperitoneally, injected in divided doses 24 and 18 h before the experiment.

Drugs used were atropine sulphate (BDH), cyproheptadine (MSD), dipyridamole (Boehringer–Ingelheim), guanethidine sulphate (CIBA), haloperidol (Searle), mepyramine maleate (May & Baker), noradrenaline bitartrate (Koch–Light), phenoxybenzamine hydrochloride (SKF), propranolol (ICI) and reserpine (Koch–Light). Drugs were dissolved in saline, unless otherwise stated below and doses are expressed in terms of the base. Dipyridamole and reserpine were dissolved by the addition of acetic acid and haloperidol by the addition of dilute citric acid.

Intra-arterial injection of vasodilators in the splanchnic region of the cat produced a dose-dependent increase of vascular conductance with a concomitant increase of blood flow and decrease of perfusion pressure, whereas vasoconstrictors produced the converse effect. Neuronally-induced vasodilatation and vasoconstriction occurred if the direction of changes in blood flow, perfusion pressure and vascular conductance were the same as those produced by vasodilator and vasoconstrictor drugs respectively. Resting levels (mean $\pm$ s.e.m.) of mean blood pressure, perfusion pressure, heart rate, superior mesenteric artery blood flow and splanchnic region vascular conductance, from 8 cats, were respectively, 120 $\pm$ 14 mm Hg, 110$\pm$ 10 mm Hg, 230 $\pm$ 13 beats min^{-1}, 25·2 $\pm$ 2 ml min^{-1} and 0·24 $\pm$ 0·02 ml min^{-1} mm^{-1} Hg.

Post-ganglionic stimulation of the sympathetic innervation of the splanchnic region elicited vasoconstriction in this vascular bed; the decrease in conductance was frequency-dependent for a constant duration (5 s) of stimulation (Table 1). As the period of stimulation was prolonged the maximum decrease in conductance was not maintained, some degree of recovery to the pre-stimulation level occurring. Cessation

Table 1. *Effect of peri-arterial mesenteric nerve stimulation on the vascular conductance of the splanchnic region of the chloralosed cat, before and after guanethidine.* (See text for stimulation parameters).

Hz	% Change in conductance (mean ± s.e.m.) Before guanethidine (5 cats)	Hz	% Change in conductance (mean ± s.e.m.) After guanethidine (5 cats)
0·5	− 6·2 ± 3·8	5	1·5 ± 1·5
1·0	−22·6 ± 3·9	10	23·9 ± 4·9
2·0	−33·6 ± 4·6	20	40·9 ± 4·8
5·0	−53·7 ± 4·9	50	39·7 ± 6·3
10·0	−62·7 ± 6·3		
20·0	−70·7 ± 5·8		

of stimulation was marked by an increase in conductance above its pre-stimulation level before the resting level was re-attained. Guanethidine, 2-4 mg intra-arterially, abolished neuronally-mediated vasoconstriction but that produced by injected noradrenaline persisted. In the presence of guanethidine neuronal stimulation in 9 of 12 cats produced frequency-dependent vasodilatation; in 2 animals no change in vascular conductance was recorded whilst in another a small vasoconstrictor response persisted despite increasing the dose of guanethidine. Table 1 shows the reversal by guanethidine of neuronally-mediated vasoconstriction to vasodilatation in 5 cats.

The increase in conductance reached its peak 20–30 s after stimulation commenced and irrespective of the duration of stimulation recovered to its pre-stimulation level in a further 30–40 s. This neuronally-induced vasodilatation, after adrenergic neuron blockade, was not reduced by propranolol, 500 μg (3 cats), atropine, 200 μg (3 cats), mepyramine, 200 μg (2 cats), haloperidol, 1 mg (2 cats) or cyproheptadine, 600 μg (1 cat). The doses of these antagonists were greater than those required to reduce, respectively, the vasodilator responses to intra-arterially injected isoprenaline, acetylcholine, histamine, dopamine and 5-HT in the splanchnic region. The antagonists did not affect resting conductance.

Dipyridamole, 1 mg kg^{-1} intravenously (2 cats), did not affect the increase in conductance occurring during neuronal stimulation. Simultaneous blockade of α- and β-adrenoceptors by large intra-arterial doses of phenoxybenzamine and propranolol failed to modify the vasodilator response; the response persisted in 3 animals pretreated with reserpine and after bilateral ligation of the adrenal glands in two further animals.

The neuronally-induced increase in vascular conductance in the splanchnic region of the chloralosed cat, in the presence of guanethidine, is a similar response to the increase in superior mesenteric artery flow of the cat, reported by Ross (1973), following infusion of bretylium. However, although the time (about 30 s) required to attain the maximum increase in conductance was similar in this study and in that of Ross, the duration of response differed in the two studies; this difference may be related to the anaesthetics employed—pentobarbitone by Ross and chloralose in the present study. In support of the evidence provided by Ross (1973) that the vasodilatation did not involve noradrenergic neurons, the response persisted after pre-treatment with reserpine and therefore does not depend on an intact noradrenergic innervation. In addition the possibility that the neurotransmitter mediating the response was dopamine, histamine or 5-HT was negated by the failure of the appropriate antagonists to abolish the increase in conductance. As also found by Ross (1973) the response persisted after atropine and is therefore not mediated by acetylcholine.

Previously (Hamilton, 1972), dipyridamole was shown to potentiate the vasodilator action to AMP in the splanchnic region of the chloralosed cat. However, in the present experiments, it did not affect the neuronally mediated vasodilatation suggesting that any transmitter involved was unlikely to be of a purinergic nature.

Although in the present work changes of intestinal motility were not recorded, Ross (1973) found that no significant changes of motility occurred concomitant with the vasodilator response. This evidence is supported by the present findings that simultaneous α- and β-adrenoceptor blockade failed to modify the effect. The possibility that adrenaline released from the adrenal medulla mediated this response was excluded by its persistence after propranolol and bilateral adrenal gland injection.

The present findings have confirmed those of Ross (1973) and extended them to exclude certain other transmitters from mediating the vasodilator response that occurs in the splanchnic region of the chloralosed cat in the presence of guanethidine. It remains likely that, as Ross (1973) suggested, stimulation of nerve fibres in the myenteric plexus of the intestinal wall is responsible for the increase in vascular conductance.

Pharmacology Department,
Roche Products Limited,
Welwyn Garden City,
Hertfordshire, U.K.

T. C. HAMILTON

March 4, 1975

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Effects of psychotropic drugs on prostaglandin biosynthesis *in vitro*

It has recently been shown that various local anaesthetics inhibit prostaglandin biosynthesis (Kunze, Bohn & Vogt, 1974a). Chlorpromazine, a psychotropic drug with local anaesthetic properties (Jarvik, 1970), was one of the most potent inhibitors. Because of these findings we thought it of interest to see, whether inhibition of prostaglandin biosynthesis is a general property of psychotropic drugs. We have studied reserpine, chlorpromazine, diazepam and meprobamate, as representatives of the major and minor tranquillizers. Those were kindly supplied by Ciba-Geigy (Basel, Switzerland), Bayer (Leverkusen, Germany), Hoffmann-La Roche (Basel, Switzerland) and H. Mack (Illertissen, Germany), respectively.

According to a general assumption, prostaglandin biosynthesis occurs in two main steps: a phospholipase A catalysed release of precursor acids, and their conversion into prostaglandins (Kunze & Vogt, 1971). Therefore, the effects of the drugs on endogenous prostaglandin formation were compared with their effects on phospholipase A and prostaglandin synthetase activities. Endogenous prostaglandin formation