The technique may also be combined with behavioural activity recording using ultrasonic transducers as described by Hill & Miller (1973).

The implantation of the connector, cannula and screws was performed under halothane anaesthesia. Rats prepared by this method have shown no abnormal behaviour and have provided satisfactory EEG recordings over several months.

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A centrally-acting antihypertensive agent R28935, a pimozide analogue, not acting via α-adrenergic neurones

L. FINCH

School of Studies in Pharmacology, University of Bradford, Bradford 7, W. Yorks., U.K.

Clonidine and α-methyldopa (Schmitt, Schmitt & Fenard, 1973; Finch, 1974; Finch & Haeusler, 1973a; Van Zwieten, 1975) are known to exert their antihypertensive action via stimulation of central α-adrenoceptors. However, the role of dopaminergic neurones in the central regulation of blood pressure remains unclear, since the potent dopamine agonist apomorphine lowers blood pressure with an accompanying bradycardia in both the anaesthetized cat and rat (Barnett & Fiore, 1971; Finch & Haeusler, 1973b), whilst dopamine administered intraventricularly in the conscious cat has been reported to exert a hypertensive action (Day & Roach, 1974).

Erythro-1-{1-[2-(1,4-benzodioxan-2-yl)-2-OH-ET]-4-piperidyl}-2-benzimidazolinone (R.28935), structurally related to the neuroleptic pimozide (Wellens, Van Neuten & Janssen, 1975) when administered intraventricularly (i.c.v.) lowered blood pressure in conscious renal hypertensive cats for a period of 5 h without altering the resting heart rate. Pretreatment with α-adrenoceptor blocking agents phentolamine (200 μg, i.c.v.) or tolazoline (200 μg, i.c.v.) failed to modify the hypotensive action of R.28935 (25 μg, i.c.v.). Similar pretreatments with tolazoline and phentolamine completely abolished the hypotensive effects of α-methyldopa (1 mg, i.c.v.) or clonidine (20 μg, i.c.v.) respectively.

Peripheral administration of haloperidol (1-5 mg/kg i.p.) and pimozide (1-2 mg/kg i.p. or 100-200 μg, i.c.v.) produced a dose-dependent fall in blood pressure and associated bradycardia which was also accompanied by stereotyped behaviour. However, administration of R.28935 (0.05-0.1 mg/kg i.p.) produced a dose-dependent fall in blood pressure without any accompanying bradycardia and no behavioural changes were detected.

In the Krebs-perfused mesenteric artery preparation, R.28935, in doses of 0.1-5 mg, did not exert any vasoconstrictor action whilst clonidine (0.1-1 mg) exhibited a dose-dependent vasoconstrictor effect. Infusions of R.28935 (0.1-10 mg) exhibited a dose-dependent vasoconstrictor actions of noradrenaline, 5-hydroxytryptamine or ATP. The vasoconstrictor action of clonidine was completely abolished by infusions of phentolamine (0.5 mg/l).

From the results it is concluded that R.28935 is a novel centrally-acting antihypertensive agent not acting via central α-adrenoceptors and is devoid of peripheral sympathomimetic properties. Similar observations have been reported in studies using the anaesthetized cat, dog and rabbit ear artery preparations (Van Zwieten, 1975; Wellens, Van Neuten & Janssen, 1975).

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Evaluation of narcotic and narcotic antagonist analgesic drugs in the dog dental pulp stimulation test

A.S. MARRIOTT, M. SKINGLE & M.B. TYERS

Pharmacology Department, Allen & Hanburys Research Ltd., Ware, Hertfordshire SG12 0DJ

In antinociceptive tests based on electrical stimulation of the dental pulp it is difficult to identify the response to electrical stimulation and to quantify the degree to which this response is changed by drugs. In the present work a procedure in the conscious dog is described in which the effects of drugs and placebo were measured in terms of changes in the stimulus threshold for eliciting a minimal response to dental pulp stimulation. Using this procedure reproduceable, dose-dependent increases in stimulation threshold can be obtained with narcotic and narcotic antagonist analgesic drugs.

Adult, male beagle dogs were trained to sit in well ventilated individual boxes (32 x 23 x 28 in high). The boxes were illuminated inside and were fitted with a clear plate glass door for observation of the dogs. Following a training period, which ranged from 1-4 weeks, stainless steel stimulation electrodes were implanted in an upper canine tooth under pentobarbitone anaesthesia, using an operative technique similar to that described by Neat & Peacock (1971). Leads from the electrodes were passed subcutaneously to an external connector located on the back of the neck. The dogs were ready for testing 7-10 days post-operatively.

All tests were carried out such that the operator did not know whether a dog had received a drug or placebo. Each dog received one placebo and one drug trial each week. Drugs were administered either orally in gelatin capsules or subcutaneously. Groups of at least five dogs were used for each dose-level. Electrical stimulation thresholds (0.5-15 V) to cause a characteristic, minimal response (i.e. licking, chewing, head movement, etc.) were determined for each dog prior to, and then at 30 min intervals up to 3 h after drug administration. Stimulus trains were delivered from a Devices isolated stimulator using square wave pulses of 5 ms pulse width, 10 Hz frequency and 10 s train duration; at least 30 s was allowed between trains of impulses during threshold determinations. The resistances of the tooth pulp electrodes (4-30 k) were monitored continuously on an oscilloscope as a check for open circuits.

The mean change (± s.e.) in stimulation threshold during placebo trials was $-0.14 \pm 0.41\%$ ($n = 20$). Maximum drug-induced changes in stimulation thresholds ranged from +35 to +40%. Statistically significant ($P = 0.05$), dose-dependent increases in stimulation thresholds were obtained with subcutaneous doses (mg/kg) of pentazocine (0.25-2) and nalorphine (0.1-1) and with oral doses (mg/kg) or morphine (0.25-3) and codeine (2-5). The potencies of these analgesic drugs were therefore similar to those found clinically. Results obtained with aspirin (100 mg/kg orally) were inconsistent. The following non-analgesic drugs (mg/kg orally) were inactive: atropine (1.0), mepyramine (0.5), phentolamine (1.0) and propranolol (1.0).

In our experience, dental pulp stimulation in the beagle dog provides an accurate and reproduceable model for the evaluation of the antinociceptive activities of narcotic and narcotic antagonist analgesic drugs.

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