An isolated vascular tissue preparation showing a specific relaxant effect of dopamine

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Dopamine produces hypotension and dilates certain vascular beds in dogs, cats, rabbits and man, an action that is suggested to be mediated by stimulation of specific receptor sites (Goldberg, 1972). In rabbits, dopamine increases blood flow in the coeliac artery and produces hypotension which is inhibited by bulbocapnine (Kullman, Rissing & Wasserman, 1978; Tseng & Walaszek, 1970). We have studied the vascular relaxation effect of dopamine *in vitro*, using the splenic branch of the coeliac artery of the rabbit.

Spirally cut strips of the splenic artery were suspended under 1.5 g isometric tension, in organ baths containing Krebs solution maintained at 37°C, bubbled with 95% O_2/5% CO_2, and to which had been added indomethacin (2 μg/ml). After stabilisation for 2 h, tissues were incubated with phenoxybenzamine (5×10^{-6} M) for 30 min, and then thoroughly washed prior to contraction with $PGF_{2\alpha}$ (10^{-7} to 10^{-5} M) to increase tension by 1400 ± 300 mg. When the tension was steady, doses of agonists were added cumulatively, 5 min after the previous dose or when the relaxation reached a maximum. After each agonist dose–response curve, maximum relaxation was determined by addition of papaverine (10^{-4} M). Tissues were equilibrated with antagonists for 30 min at the basal tension of 1.5 g.

Dopamine (3×10^{-8} to 3×10^{-5} M) caused dose-related relaxations in all tissues, while isoprenaline (3×10^{-9} to 10^{-6} M) caused relaxations in only one out of six tissues. After incubation with propranolol (10^{-6} M) isoprenaline responses were markedly attenuated and the dose–response curve shifted to the right by at least 1000, whereas dopamine responses were unchanged. Propranolol (10^{-6} M) was included in the Krebs solution throughout all subsequent experiments.

After equilibration of the tissues with bulbocapnine (10^{-6} to 3×10^{-5} M), relaxations to dopamine were antagonised. Analysis by the method of Arunlakshana & Schild (1959) gave a slope of unity and a PA_2 value of approximately 6.2. Bulbocapnine had no marked effect on the dose-related relaxations produced by sodium fluoride (0.03 to 3 mg/ml), histamine (10^{-7} to 10^{-4} M), prostaglandin E_2 (0.1 to 30 ng/ml), papaverine (10^{-7} to 10^{-4} M) and erythrityl tetranitrate (0.01 to 1 μg/ml).

The phenylethylamines epinine, noradrenaline and adrenaline, and the semi-rigid analogue of dopamine, 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (6,7-ADTN) each caused dose-related relaxations which were antagonised by bulbocapnine (10^{-5} M). The order of agonist potency was:

Epinine = 6,7-ADTN > Dopamine > Adrenaline > Noradrenaline

1 : 3 : 8 : 15.

These experiments demonstrate a specific vascular relaxant effect of dopamine which is selectively antagonised by bulbocapnine.

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Comparison of plasma, erythrocyte and brain lithium concentrations in the guinea-pig and rat

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Lithium was first used clinically as an antimanic agent because of its reported sedative effect in guinea-pigs (Cade, 1949). Since, unlike in man and the rat, little subsequent work has been done in the original test animal (Smith, 1977), we initiated studies comparing lithium in the guinea-pig and rat.

Female rats (Wistar, 190–220 g) or guinea-pigs (Dunkin-Hartley, 380–420 g) were given oral LiCl either as a single dose (2 mmol/kg) or chronically for the maximum period which avoided intoxication at the high dose (10, 20 or 40 mmol/kg dry weight of diet for 18 d, 6 rats at each dosage; 1, 2 or 4

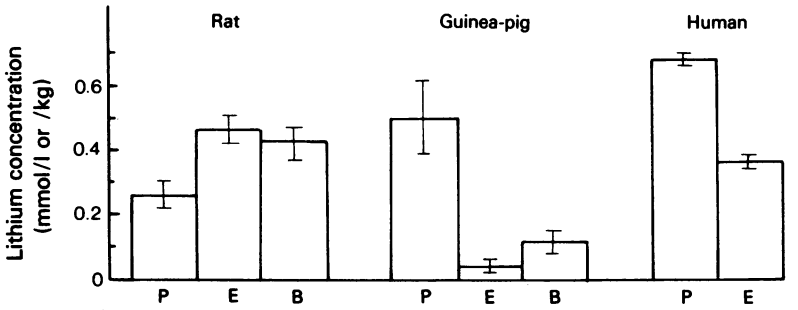

Figure 1 Interspecies variation in plasma (P), erythrocyte (E), and brain (B) lithium concentration after chronic dosage. Six rats received 1.43 mmol LiCl/kg daily for 18 d administered in the diet (dosage calculated on basis of mean daily dietary intake). Five guinea-pigs received 2.0 mmol LiCl/kg orally as a daily divided dose for 7 days. The human data have been obtained from 150 patients attending the Dundee lithium clinic who has been receiving a mean daily oral dose of Li_2CO_3 of 0.41 mmol/kg for a mean period of 3 years. The lithium concentrations are given as means ± s.e. mean.

mmol/kg in daily divided doses for 7 d, 5 guinea-pigs at each dosage). Groups of 3 rats or 4 guinea-pigs were killed at time intervals up to 16 h after acute dosage. Lithium was assayed by atomic absorption spectrophotometry and sodium and potassium by flame photometry (Coombs, Coombs & Mee, 1975).

After acute dosage guinea-pig plasma and erythrocyte lithium levels peaked at about 1.3 mM and 0.14 mM respectively within 1 h and declined to half-maximal levels by 8 hours. Brain levels reached a maximum within 2 h and remained at 0.2 mmol/kg. In rats maximal concentrations occurred at 8 h (plasma, 0.7 mM) and 12 h (erythrocytes, 0.6 mmol/l cells; brain, 0.4 mmol/kg).

After chronic treatment at the intermediate dose, guinea-pig erythrocyte and brain lithium levels were 10 and 20% of the plasma levels respectively, while in the rat they were 60 to 80% greater than the plasma levels (Figure 1). This trend was similar at the other doses. There was no significant interspecies difference in erythrocyte and plasma sodium/potassium concentrations. In neither species was sedation apparent, although polyuria occurred at the higher dose.

The erythrocyte/plasma lithium ratio in man of about 0.5 (Figure 1) is intermediate between that of the guinea-pig and rat. The guinea pig may therefore provide a useful model to study transmembrane lithium transport.

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A demonstration of the ability of apomorphine to act on dopamine receptors on nerve terminals in the nucleus accumbens to reduce locomotor hyperactivity

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Peripherally administered apomorphine has been shown to reduce locomotor activity in both animals and man. This effect has been attributed to an action on dopamine 'autoreceptors' whose stimulation leads to a decrease in the functional capacity of dopamine (see Di Chiara, Corsini, Mereu, Tissari & Gessa, 1978). Both behavioural and biochemical studies directed at the striatum have supported this hypothesis, and the present studies attempt to extend the concept of an action of apomorphine on nerve terminals to the nucleus accumbens.

Chronically indwelling cannulae for direct injections into the nucleus accumbens were implanted in the brains of male, Sprague–Dawley rats (weighing 300 ± 25 g at the time of operation) using standard