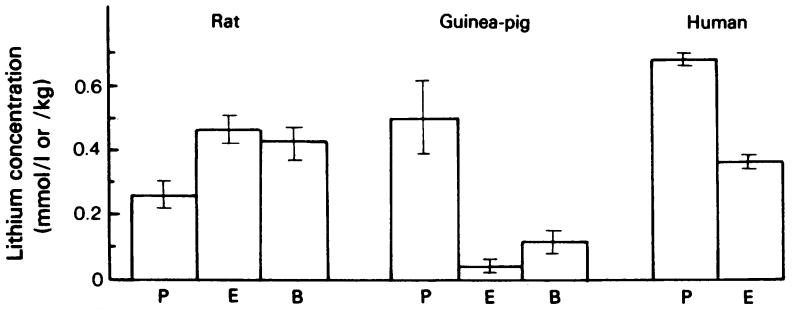

Figure 1 Interspecies variation in plasma (P), erythrocyte (E), and brain (B) lithium concentration after chronic dosage. Six rats received 1.43 mmol LiCl/kg daily for 18 d administered in the diet (dosage calculated on basis of mean daily dietary intake). Five guinea-pigs received 2.0 mmol LiCl/kg orally 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

stereotaxic techniques. Animals were first used 14 days after surgery when they were manually restrained as 1 μl drug or solvent was delivered bilaterally to the centre of the nucleus accumbens (Ant. 9.4, Vert. 0.0, Lat. ±1.6; De Groot, 1959). Hyperactivity was assessed by placing animals in individual screened cages, measuring 25 × 15 cm and 15 cm high, and used in banks of 30 in a sound-proofed room maintained at 21 ± 2°C. Each cage was fitted with one photocell unit and the number of interruptions of the individual light beams was recorded electromechanically and noted for each 5 min period. Experiments were carried out between 08.00 and 18.00 hours.

Intra-accumbens (+)-amphetamine (1.25–25 μg) caused dose related hyperactivity which was prevented by pretreatment with α-methyl-paratyrosine (250 mg/kg i.p., see also Jackson, Andén & Dahlström, 1975). The amphetamine hyperactivity was also prevented, dose-dependently, by intra-accumbens apomorphine (1.56–6.25 μg given immediately after the amphetamine), although similar injections of apomorphine above (into the caudate-putamen) or below (into the tuberculum olfactorium) the nucleus accumbens were without effect. The abolition of the amphetamine hyperactivity (10 μg) caused by apomorphine (6.25 μg) was prevented by pretreatment with pimozide (0.0625 mg/kg i.p.) or haloperidol (0.00625 mg/kg i.p.), although these doses of neuroleptic did not modify the amphetamine response *per se*. Doses of pimozide (0.125–0.5 mg/kg i.p.) and haloperidol (0.0125–0.05 mg/kg i.p.) were required to reduce/abolish the amphetamine response. Pretreatments with aceperone (2.5 mg/kg i.p.), propranolol (5 mg/kg i.p.), atropine (5 mg/kg i.p.) and cyproheptadine (2.5 mg/kg i.p.) failed to modify the effects of amphetamine or apomorphine.

In a further series of experiments 6-hydroxydopamine (8 μg/4 μl) was injected bilaterally into the nucleus accumbens of rats pretreated for 4 h with tranylcypromine (5 mg/kg i.p.) and for 1 h with desmethylimipramine (25 mg/kg i.p.). After 14 days animals were either used in behavioural studies or sacrificed for biochemical assessment of the lesion. The 6-hydroxydopamine lesion depleted accumbens dopamine by approximately 80%. In these selectively denervated animals the response to intra-accumbens amphetamine was only slightly attenuated but the inhibitory effects of apomorphine were abolished. It is therefore suggested that dopamine receptors (sensitive to apomorphine and neuroleptic agents) located on dopamine nerve terminals the nucleus accumbens are able to prevent the locomotor hyperactivity caused by amphetamine injected into the same nucleus.

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Adenosine may mediate neuronal depressant effects of morphine

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Recent evidence suggests that theophylline, widely regarded as a relatively specific antagonist of adenosine, will block the inhibition of transmitter release produced not only by adenosine but also by morphine (Jhamandas, Sawynok & Sutak, 1978). It is therefore possible that morphine is acting indirectly by releasing adenosine. One of the properties of morphine receiving much attention is its ability to depress the firing of central neurones, and as adenosine shares this property we have investigated the possibility that a relationship may exist between these compounds.

Male rats were anaesthetised with urethane and the skull removed to allow access to the corpus striatum. All compounds were administered by microiontophoresis from 6- or 7-barrelled micropipettes, recording unit activity through one of the barrels or through a separate electrode glued alongside. Morphine sulphate was ejected from a 50 mM solution, adenosine hemisulphate 100 mM; naloxone HCl 50 mM; and aminophylline (theophylline ethylenediamine) was ejected from a 50 mM solution in distilled water, pH 9 (not adjusted). Aminophylline was ejected as an anion.

Morphine produced a rapid depression of firing of 19 of 21 striatal neurones tested, using ejecting currents of 60–160 nA. Adenosine and GABA also