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Some observations on the behavioural responses to metoclopramide in the pig and the guinea pig

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Paradoxical responses to neuroleptic drugs are frequently observed in the pig (Marsboom & Symoens, 1968). In our studies on the use of such drugs in the pig we have often seen repetitive oral behaviour as an unwanted side effect. Fry & Sharman (1976) described the stereotyped snout-rubbing that can occur in some pigs following an intravenous injection of metoclopramide, a drug that shows several similarities with neuroleptic drugs when tested in the rat. This behavioural response in the pig was almost identical with the behaviour of pigs from the same herd that had been treated with apomorphine (0.5–1.0 mg/kg, i.v.). Metoclopramide causes an increase in the concentration of homovanillic acid (HVA), a metabolite of dopamine, in the brains of rats and mice and also produces catalepsy in these species (Ahtee, 1975; Ahtee & Buncombe, 1974; Costall & Naylor, 1973).

Following the administration of metoclopramide (5 mg/kg, i.p.) to pigs there were increases in the concentration of HVA and of 3,4-dihdroxyphenylacetic acid (DOPAC) in the striatum.

In the guinea pig, metoclopramide has been reported to have little or no effect on drug-induced dyskinesias or stereotypies with doses up to 32 mg/kg i.p. (Costall & Naylor, 1976). In our experiments with guinea pigs, metoclopramide was injected subcutaneously at the back of the neck. With doses of 25–100 mg/kg no catalepsy was observed. Doses of 75 mg/kg and above caused a stereotyped nose-rubbing with infrequent gnawing after about 15 minutes. This behaviour resembled that seen after apomorphine (1 mg/kg, s.c.) but the nose-rubbing was the most prominent behavioural response with metoclopramide, whereas gnawing characterized the response to apomorphine. The behavioural response to apomorphine (1 mg/kg s.c.) could be suppressed by metoclopramide in a dose of 25 mg/kg s.c. Metoclopramide (100 mg/kg, s.c.) caused an increase in the concentration of HVA in the striatum, the largest increase being observed in the medial part of this tissue. The stereotyped response to metoclopramide in the guinea pig has some pharmacological characteristics similar to those of the dyskinesias that can be induced by the intra-striatal injection of dopamine (Costall & Naylor, 1975).

Recent evidence has suggested that blockade of the dopamine receptors on cells in the striatum is not necessary for the activation of dopamine-containing neurons following the administration of neuroleptic drugs (Garcia-Munoz, Nicolaou, Tulloch, Wright & Arbuthnott, 1977; Di Chiara, Porceddu, Fratta & Gessa, 1977). The paradoxical behavioural response seen after metoclopramide is similar to that which ensues from drug treatments that are thought to bring about the activation of dopamine receptors in the brain. Such behaviour could thus be a result of the activation of dopaminergic neurons either without the blockade of post-synaptic dopamine receptors subserving behaviour, or overcoming the blockade.

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The behavioural effects of (+)-amphetamine and apomorphine in the marmoset

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In primates, administration of amphetamine (Randrup & Munkvad, 1972) or apomorphine (Shintomi & Yamamura, 1975) may cause stereotyped hand and head movements. These effects may be compared to the effect of amphetamine (Schiørring, 1971) or apomorphine (Ernst, 1967) in rodents in which increased locomotion and stereotyped sniffing, licking and gnawing may be seen.

Intramuscular doses of (+)-amphetamine sulphate (0.125–8.0 mg/kg) and apomorphine (0.063–1.0 mg/kg) were administered in a sequence of increasing doses to a group of 8 marmosets (*Callithrix jacchus*). The behaviour of each animal was observed for one min periods at selected time intervals during the following 6 h and again after 22 hours. Behaviour was classified each second into one of four categories:

1. *Checking* (head movements only).
2. *Activity* (behaviour involving part of the body, excluding head only, but including eating, drinking, grooming, manipulation of objects, gnawing, and behaviours of unknown function).
3. *Movement* (displacement of the whole body).
4. *Inactivity* (no observable behaviour).

(+)-Amphetamine had behavioural effects for a period of at least 6 hours. These consisted of a dose-dependent increase in checking ($P < 0.001$ 2-tailed matched pairs t test), with a concomitant decrease in activity ($P < 0.001$) and inactivity scores ($P < 0.001$). There was no change in the amount of movement. Checking decreased at higher doses (4 mg and 8 mg/kg) after ~1.5 h when the onset of severe stereotypy occurred.

Apomorphine administration elicited a biphasic response. The initial response consisted of an increase in movement ($P < 0.01$) and in checking ($P < 0.001$) with associated decreases in activity ($P < 0.01$) and inactivity scores ($P < 0.05$) which lasted for ~0.5–1 hour. The later phase (1–5 h) was characterized by an increase in inactivity ($P < 0.01$) and a decrease in activity scores ($P < 0.001$) but no significant change in checking or movement. Injection of apomorphine usually resulted in vomiting after 2–4 min, and at the highest dose (1 mg/kg) extremely vigorous, self-destructive running and jumping interspersed with episodes during which the animals were prostrate and dyskinetic.

Thus (+)-amphetamine and apomorphine may be contrasted not only in the duration of their effect but also in the nature of the behavioural response, amphetamine inducing mainly checking, and apomorphine mainly affecting the degree of locomotion. At high doses amphetamine induced small stereotypic movements whereas high doses of apomorphine resulted in dyskinesia. The greater behavioural repertoire of the marmoset over rodents may be of use in differentiating the mechanism of these and related drugs.

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