Propranolol interferes with inhibitory behaviour in rats

Although there have been clinical reports that propranolol is associated with psychotic depression in patients receiving the drug for cardiac conditions (Waal, 1967) and that it is as effective as chlordiazepoxide in reducing anxiety in psychiatric out-patients (Wheatley, 1969), Laverty & Taylor (1968) did not find behavioural effects of propranolol in rats and no subsequent reports of behavioural effects of the drug in animals have appeared. However, we have found that propranolol disrupts the performance of rats on a DRL-20 operant conditioning schedule, a task requiring the inhibition for 20 s of a previously learned response in order to receive reinforcement.

Twenty male hooded rats, maintained at 80% of their free feeding body weight by food deprivation, were trained to press the bar in a Skinner Box for food reinforcement. Seven daily 45 min sessions in which each bar press was reinforced, were followed by 15 daily 45 min sessions of DRL-20 on which only responses at least 20 s apart were reinforced. Five min before each DRL-20 session, 5 rats were given a 5 mg/kg intraperitoneal injection of propranolol dissolved in 0·9% saline, 5 rats received 12·5 mg/kg of the drug, 5 rats had saline, and 5 rats had no injection.

A two way analysis of variance of the per cent reinforced responses on the DRL sessions showed a significant difference between the control groups and the two drug groups [$F(2,17) = 3{\cdot}99$; P 0·05]. Fig. 1 shows that less than 10% of the responses of the two drug groups were reinforced on most of the 15 days of DRL, while the two control groups rapidly improved to 30% reinforced responses.

Pellegrino (1968) found that ablation of the baso-lateral amygdala of rats disrupted the performance of a DRL-20 task in much the same way as propranolol did in the present study. Horovitz (1966) suggested that the amygdala is the site of action of antidepressant drugs and therefore that the amygdala is implicated in depression psychoses. Schallek & Kuehn (1965) concluded that the amygdala may be involved in the production of anxiety. Thus the effects of propranolol reported by Waal (1967) on depression, by Wheatley (1969) on anxiety, and by our experiments on the performance of a task requiring inhibition of a previously learned response, all parallel suggested functions of the amygdala.

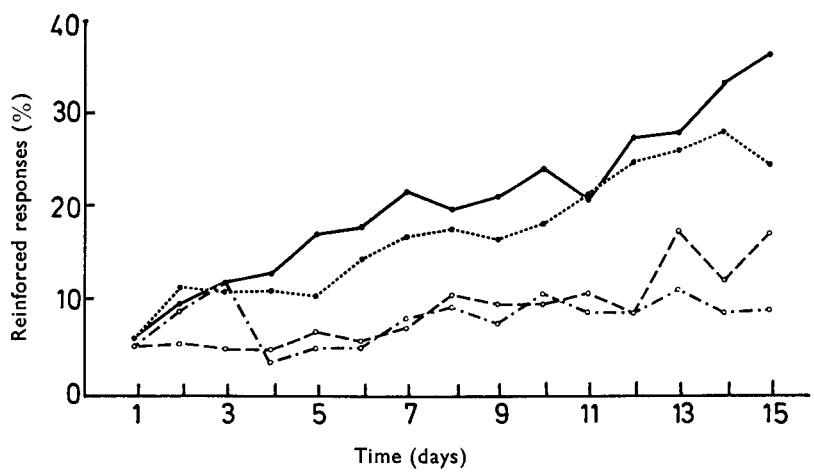

FIG. 1. Mean number of correctly inhibited responses expressed as % of total responses for each group of 5 rats on each of the 15 daily 45 min DRL-20 sessions. ●—● Normal. ●... ● Saline. ○— —○ Propranolol 5 mg/kg. ○—·—○ Propranolol 12·5 mg/kg.

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Influences of cholinergic mechanisms on the function and turnover of brain dopamine

Anticholinergic drugs have long been used in the treatment of both spontaneous and drug-induced parkinsonism. The dopamine receptor stimulating drug apomorphine has also been reported to have a beneficial effect on Parkinson's disease, though weaker than L-dopa (Cotzias, Papavasiliou & others, 1970). Furthermore, hallucinations can be evoked both by blockade of central acetylcholine receptors and by stimulation of central catecholamine receptors. In the present investigation we have compared the effects of anticholinergics and of apomorphine on the function and turnover of dopamine in the rat corpus striatum both after and without treatment with the neuroleptic drug haloperidol.

The following drugs were used: DL-α-methyltyrosine methylester HCl (H 44/68; *Hässle, Mölndal), haloperidol (*Leo, Hälsingborg), *N*-ethyl-2-pyrrolidylmethyl-cyclopentyl-phenyl-glycolate HCl plus *N*-ethyl-3-piperidyl-cyclopentyl-phenyl-glycolate HCl (70 + 30% = Ditran; *Lakeside, Milwaukee), trihexyphenidyl HCl (*Kabi, Stockholm), (±)-hyoscyamine sulphate (atropine; Sigma, St. Louis), (−)-hyoscine hydrobromide (scopolamine; Merck, Darmstadt), *N*-methylscopolamine nitrate (Pharmacia, Uppsala), apomorphine HCl (Sandoz, Basle). The doses given refer to the salts.

The corpus striatum of adult hooded rats (150–300 g) was removed on one side by suction during diethylether anaesthesia. All brains were examined after the experiment and only animals with correct lesions were considered. The drugs tested were given 2–5 h after the operation. As previously described (Andén, Dahlström & others, 1966), haloperidol (1 mg/kg, i.p.) produced a longlasting and marked turning of the head and the tail to the unoperated side. When the haloperidol-induced asymmetry was well established after about 2 h, hyoscine (20 mg/kg, i.p.) was administered to 16 rats. It caused a clearcut and long lasting change in the position in 13 of these rats: their position became almost symmetrical in 5 min and they could turn to the operated side. A larger dose of hyoscine did not modify this response. In the remaining 3 rats, no obvious change was observed. Hyoscine (20–100 mg/kg, i.p.) given alone did not cause any observable asymmetry in unilaterally treated rats. In contrast, apomorphine (1 mg/kg, i.p.) did not change the haloperidol-induced asymmetry but evoked by itself a strong turning of the head and the tail to the operated side for about 1½ h (Andén, Rubenson & others, 1967).