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Neurochemical effects of fluphenazine decanoate in socially-reared and isolated young rats

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We have previously reported the neurochemical effects of the long-acting thioxanthene neuroleptic, α-flupenthixol decanoate (α-FPD) in socially-reared and isolated rats (Morinan & Leonard, 1978). In this study we found that α-FPD caused a decrease in γ-amino-n-butyric acid (GABA) and an increase in noradrenaline (NA) concentrations in the amygdala, while in the striatum there was a significant drug-environment interaction for GABA.

Fluphenazine decanoate (FZD) is a phenothiazine neuroleptic that has been shown to be active for up to one month (Ray-Johnson: personal communication; Voith, 1977). The present study was designed to investigate the effects of a single dose of FZD on the steady state concentrations of the catecholamines and GABA in the nigro-neostriatal and mesolimbic systems of differentially-housed rats; rats were housed together (SOC) and separately (ISOL).

Two days after weaning, male Wistar rats (60–70 g) were randomly assigned to one of four treatment groups. On the second day, half of the animals from both housing conditions (SOC-FZD and ISOL-FZD) were given a subcutaneous (s.c.) injection of FZD (25 mg/kg). The other two groups (SOC-CON and ISOL-CON) received 1.0 ml/kg (s.c.) of sesame oil. At the end of the three week isolation period, the concentration of GABA, NA and dopamine (DA) was determined in the midbrain, corpus striatum, hippocampus and amygdala.

FZD caused a significant decrease in the concentration of DA ($F = 7.81$, d.f. = 1, 28, $P < 0.01$) and NA ($F = 6.50$, $P < 0.025$) in the striatum of both isolated and grouped rats (Table 1). In the amygdala, FZD and isolation ($F = 12.68$ and 11.45 respectively) resulted in a decrease ($P < 0.01$) in DA concentrations (Table 1). No significant changes in the concentration of GABA was found in any of the four brain regions.

Table 1 Significant changes in catecholamine concentrations of rats housed together (SOC) or separately (ISOL)

	DA		*NA*
	Striatum	*Amygdala*	*Striatum*
SOC–CON	3.14 ± 0.14	0.48 ± 0.02	0.93 ± 0.05
SOC–FZD	2.60 ± 0.20	0.45 ± 0.01	0.80 ± 0.05
ISOL–CON	2.94 ± 0.30	0.46 ± 0.01	0.92 ± 0.08
ISOL–FZD	2.30 ± 0.21	0.37 ± 0.01	0.77 ± 0.05

FZD, fluphenazine; con, control.
Values are the means (μg/g wet weight of tissue) ± s.e. mean of 8 determinations.
* Data analyzed by 2 × 2 Analysis of Variance: Fixed Effects ($P < 0.05$).

The neurochemical change caused by an altered social environment, namely the decrease in amygdaloid DA in isolated rats, has been noted in an earlier study (Morinan & Leonard, 1976). FZD in common with α-FPD affected steady state neurotransmitter concentrations in the striatum and amygdala only. However, whereas α-FPD was selective for NA and GABA, FZD affected the concentrations of the catecholamines. Although these two neuroleptics have similar clinical potencies, the results presented here suggest that they may have different actions on central neurotransmitters.

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Modulation of picrotoxin-induced forepaw myoclonus in the rat by benzodiazepines

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Unilateral injection of GABA antagonists into the anterior caudate nucleus of rats produces sustained rhythmic jerking of the contralateral forelimb (Marsden, Meldrum, Pycock & Tarsy, 1975). Since benzodiazepeines appear to facilitate GABA dependent processes in the brain (Waddington, 1978) we have investigated their ability to inhibit contralateral forepaw myoclonus induced by unilateral injection of picrotoxin in the anterior caudate of rat.

Myoclonus following intrastriatal injection of picrotoxin (1 μg in 2 μl 0.9% saline) commenced between 2 and 15 min later (mean 7.6 ± 0.3; $n = 154$) and lasted approximately 45–140 min (mean 76.8 ± 4.8; $n = 59$). The intensity of myoclonus, assessed on a 0–4 scale, was 2.7 ± 0.9 ($n = 123$) 10 min following onset of myoclonus. Modulation of picrotoxin-induced myoclonus was assessed by time of onset, duration and intensity following intrastriatal administration of benzo-diazepines 30 min prior to picrotoxin administration or 10 min following the onset of myoclonus.

Clonazepam (1–8 μg in 1–8 μl vehicle) delayed the onset of myoclonus (time of onset 18.5 ± 4.0 min; $n = 8$; $P < 0.01$) and reduced the intensity of myoclonus (score 1.4 ± 0.4; $n = 10$; $P < 0.05$) at doses of 4 μg and above when administered 30 min prior to picrotoxin. The duration of myoclonus was unchanged. When clonazepam (4 μg and above) was administered 10 min after onset of myoclonus both the intensity of myoclonus (score 1.1 ± 0.4; $n = 9$; $P < 0.01$) and the duration of myoclonus (32.3 min ± 14.0; $n = 9$; $P < 0.05$) were reduced.

Diazepam (5–50 μg in 1–10 μl vehicle) when administered 30 min prior to picrotoxin delayed the onset of myoclonus (time of onset 14.5 ± 2.1; $n = 5$; $P < 0.01$) at doses of 25 μg and above. The intensity and duration of myoclonus was unaffected. Diazepam (5–50 μg in 1–10 μl vehicle) administered after the onset of myoclonus was only effective in reducing the duration (23.7 ± 12.3 min; $n = 6$; $P < 0.05$) and the intensity (score 1.0 ± 0.5; $n = 6$; $P < 0.05$) of myoclonus at the highest dose (50 μg).

Chlordiazepoxide and flurazepam were much less effective in blocking picrotoxin-induced myoclonus. Flurazepam (50–500 μg in 1–2 μl saline) administered prior to picrotoxin administration delayed the onset of myoclonus (time of onset at 15.8 ± 3.3 min; $n = 4$; $P < 0.05$) but only reduced the duration (5.0 ± 5.0 min $n = 6$) and intensity (score 0.3 ± 0.3; $n = 6$) of myoclonus at 400 μg. Flurazepam administered after the onset of myoclonus only reduced the intensity of myoclonus (score 1.9 ± 0.3; $n = 10$; $P < 0.05$) at doses of 200 μg and above while the duration of myoclonus was only reduced at 400 μg (18.3 ± 6.7 min; $n = 11$; $P < 0.05$). Chlordiazepoxide (50–400 μg in 1–2 μl saline) produced similar results when administered after the onset of myoclonus. Doses of 200 μg were required to reduce the onset of myoclonus (time of onset 12.4 ± 2.3 min; $n = 5$; $P < 0.05$) when administered prior to picrotoxin and no changes were observed in the intensity and duration of the myoclonus.

The potency of benzodiazepines in this behavioural model reflects their activity at benzodiazepine receptors and may be of use for detecting agents modifying GABA action and of potential use in the treatment of human myoclonic disorders.

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