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Evidence for the release of hippocampal 5-hydroxytryptamine by α-methyltryptamine

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Previous studies have indicated that in the rat the initial behavioural response produced by α-methyltryptamine (10 mg/kg) involves stimulation of 5-hydroxytryptamine (5-HT) receptors following a pre-synaptic action of α-methyltryptamine on 5-HT neurones (Marsden, 1978). In the present study an *in vivo* electrochemical technique for measuring 5-HT release in the unanaesthetised rat (Conti, Strope, Adams & Marsden, 1978; Marsden, Conti, Strope, Curzon & Adams, 1979) has been used to show whether or not the pre-synaptic action of α-methyltryptamine causes an increase in extra-neuronal 5-HT.

The electrochemical activities (oxidation potentials) of 5-HT, tryptamine, α-methyltryptamine and L-tryptophan were determined in 10 ml 1×10^{-3} M solutions of each prepared in 0.1 M phosphate buffer pH 7.4 using linear sweep voltammetry (CV-1A, Bioanalytical Systems-Anachem Ltd). with semi-micro carbon paste working, silver-silver chloride reference and stainless steel auxiliary electrodes. The potential sweep was from 0.0 to 1.2 V at 100 mV/sec. 5-HT was oxidised at about +0.4 V while α-methyltryptamine, tryptamine and L-tryptophan were oxidised at potentials between +0.75 and +0.85 V.

Release of 5HT was monitored in male Wistar rats (240–280 g) using micrographite electrochemical electrodes implanted into the dorsal hippocampus (Conti, *et al.*, 1978). Linear sweep voltammetry (0.0 − +1.0 V at 50 mV/sec) and chronoamperometry (fixed potential +0.6 V applied for 1 sec every 10 min) were used to measure the current changes. Rats injected with saline showed no clear oxidation peaks following a linear potential sweep. However, 45 min after giving α-methyltryptamine (10 mg/kg) there were two peaks clearly visible, one between +0.35 − +0.5 V and the other between +0.75 − +0.85 V. The peak at the higher potential first appeared 10–15 min and the lower peak 30–45 min after injection. The appearance of the peak at the lower potential coincided with the onset of the initial behavioural response. The occurrence of the two peaks suggested that α-methyltryptamine increased the extra-neuronal 5-HT concentration (peak at +0.4 V) following its accumulation in the brain (peak at +0.8 V). If this were so, depletion of brain 5-HT prior to α-methyltryptamine administration would be predicted to prevent the increase in detectable 5-HT and thus the peak at +0.4 V but not to affect the peak at the higher potential. Pretreatment with p-chlorophenylalanine (PCPA, 200 mg/kg i.p.) 24 h before prevented the initial behavioural response produced by α-methyltryptamine and the appearance of the oxidation peak at +0.4 V. There was however also a small reduction in the peak at the higher potential indicating either that PCPA reduced the uptake of α-methyltryptamine into the brain or that α-methyltryptamine released something oxidisable at +0.8 V (e.g. tryptamine). The marked peak at +0.4 V after α-methyltryptamine injection does not simply reflect MAO inhibition as whole brain 5-HT, measured fluorometrically, was only increased by 19% ($n = 6$) 45 min after 10 mg/kg injection. Furthermore, other MAO inhibitors do not produce the same initial behavioural response.

The results support findings relating the initial behavioural response induced by α-methyltryptamine to a pre-synaptic effect on 5-HT neurones leading to increased 5-HT in the synaptic cleft. This may be caused either by release of 5HT or by blockade of 5-HT re-uptake (Horn, 1973) combined with some inhibition of MAO.

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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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