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Rapid communication

EMERGENCE OF APOMORPHINE-INDUCED 'VACUOUS CHEWING' DURING 6 MONTHS CONTINUOUS TREATMENT WITH FLUPHENAZINE DECANOATE

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The treatment of animals with neuroleptic drugs for periods of a few results in the induction of dopamine (DA) receptor supersensitivity that is reflected, on drug withdrawal, by enhanced behavioural responses to DA agonist drugs (Muller and Seeman, 1978). Such phenomena have been considered to exemplify the pathophysiology of tardive dyskinesia (Baldessarini and Tarsy, 1980) despite the requirement for neuroleptic withdrawal and DA agonist challenge in animals for their manifestation. We describe here the emergence of apomorphine-induced 'vacuous chewing' *during* 6 months treatment with the depot neuroleptic fluphenazine decanoate while other DA-mediated behaviours are enduringly antagonised.

Adult male Sprague-Dawley rats of 500—600 g were given 0.2 ml of fluphenazine decanoate (FPZ-D, 25 mg/ml) or placebo oil vehicle by i.m. injection into alternate rear leg muscles at 2—3 week intervals. They were subjected to direct visual observation and ratings of stereotyped behaviour over 15—50 min after challenge with the DA agonist apomorphine (APOM, 0.15 mg/kg s.c.) by an observer unaware of the animals' drug history (Waddington and Gamble, 1980). Observations were made on separate groups at 7 days after either a single depot FPZ-D injection or the final depot FPZ-D injection completing 6 months of repeated treatment.

At 7 days following a single FPZ-D injection the stereotypy response to 0.15 mg/kg APOM was completely abolished; a similar effect was seen at 7 days following the FPZ-D injection completing the 6 months treatment regimen (table 1). In the single FPZ-D injection group this APOM challenge induced the occasional incidence of non-stereotyped perioral behaviour. These animals appeared to manifest 'chewing' movements that were not directed towards physical material, distinct from APOM-induced gnawing, and these were, therefore, termed 'vacuous chewing'. While there was no significant difference between the incidence of this APOM-provoked syndrome in single FPZ-D- and placebo-treated animals, following 6 months of repeated FPZ-D or placebo injections APOM induced

TABLE 1

Stereotypy scores (means ± S.E.M.) and incidence of 'vacuous chewing' induced by APOM after 1 week or 6 months treatment with fluphenazine decanoate (FPZ-D) or placebo.

Behaviour	Treatment period	
	1 week	6 months
Stereotypy		
Placebo	4.0 ± 0.0	3.5 ± 0.4
FPZ-D	0.0 ± 0.0 [1]	0.4 ± 0.2 [1]
Chewing		
Placebo	0/8	1/8
FPZ-D	3/8	7/10 [2]

[1] Significant antagonism, $P < 0.001$ (Mann-Whitney U test).
[2] Significantly increased incidence, $P < 0.025$ (Fisher test).

the syndrome in 70% of depot neuroleptic animals in comparison with only 12.5% of those receiving depot placebo (table 1).

In this study stereotypy responses to 0.15 mg/kg APOM were enduringly antagonised during 6 months treatment with FPZ-D. However, after 6 months, but not 1 week, of depot neuroleptic treatment a very high incidence of APOM-induced 'vacuous chewing' was evident despite continuing antagonism of APOM stereotypy. This suggests that stereotypy and 'vacuous chewing' have distinct substrates and that these are differentially influenced by prolonged neuroleptic treatment. Though the requirement for APOM provocation confounds the relevance of these findings for current theories on the pathophysiology of tardive dyskinesia, the present results suggest that some DA-dependent behaviours may be enduringly antagonised during 6 months of depot phenothiazine treatment while other perioral responses can be contemporaneously enhanced. The functional heterogeneity and differential adaptive capacity of distinct DA-ergic substrates (Kebabian and Calne, 1979; Waddington et al., 1979) during prolonged phenothiazine treatment is indicated.

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