

# Effects of Fluphenazine Decanoate (A Long-Acting Phenothiazine) on Serum Prolactin and Amphetamine-Induced Behavioural Changes

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MERALI, Z. AND G. TOTH. *Effects of fluphenazine decanoate (a long-acting phenothiazine) on serum prolactin and amphetamine-induced behavioural changes.* PHARMAC. BIOCHEM. BEHAV. 17(1) 25-30, 1982.—A single injection of fluphenazine decanoate (FD) antagonized effects of acute d-amphetamine (2.5 mg/kg) for a variable period of time (4 to 28 days), depending upon the dosage of the neuroleptic used (2.5 or 5.0 mg/kg) and the behavioural parameter(s) monitored. Locomotion and rearing were antagonized for a longer duration than was sniffing. Normal locomotor response to amphetamine was attained 12 and 28 days following the administration of 2.5 and 5.0 mg/kg FD, respectively. However, the 2.5 mg/kg FD group displayed significantly more locomotor activity on days 20 and 24 post-treatment. A similar supersensitive response was not demonstrable with the higher dose of FD (5.0 mg/kg), or with the other behavioural measures. The prompt and pronounced elevation of serum prolactin returned to within the normal range by days 4 and 14, following administration of 2.5 and 5.0 mg/kg FD, respectively. These results indicate that the behavioural paradigm is more sensitive in monitoring the effects of FD and could serve as a useful model in investigating the dose- and time-related effects of other long-acting neuroleptics.

Fluphenazine decanoate      Prolactin      Antagonism of amphetamine-induced behavioural changes  
Supersensitivity

CONSIDERABLE body of evidence supports the contention that schizophrenia might be associated with abnormally sensitive dopamine synapses and that neuroleptics are effective by virtue of their ability to block dopamine receptors [7, 27, 29]. It is presumed that whereas nigrostriatal blockade causes the extrapyramidal reactions, the mesolimbic blockade may be related to the antipsychotic activity of the neuroleptics [30]. Furthermore, it is believed neuroleptics disinhibit prolactin release from the anterior pituitary by blocking the dopamine receptors functionally influenced by the activity of the tuberoinfundibular tract [15,17]. Thus neuroleptic-induced changes in serum prolactin may serve as a convenient index of dopamine blockade in this, and possibly the other dopaminergic systems.

Amphetamine elicits a behavioural syndrome characterized by purposeless and repetitive movements which in the rodents take the form of stereotyped locomotion, sniffing, rearing and biting. According to current views, these stereotyped behaviours result from stimulation of dopamine receptors of the nigrostriatal and the mesolimbic systems [10, 19, 20].

It is hypothesized that administration of fluphenazine decanoate should antagonize behavioural effects of acute amphetamine, and that as the effects of this long-acting neuroleptic diminish with time, a concurrent reinstatement of amphetamine effects should be observed.

The objectives of the present investigation were to study the time-course and dose-effect of fluphenazine decanoate on (1) the tuberoinfundibular-pituitary dopamine system (as reflected by changes in serum prolactin) and (2) the nigrostriatal and/or mesolimbic dopamine systems (as reflected by antagonism of amphetamine-induced behavioural changes).

## METHOD

### *Animals*

Male Sprague-Dawley rats (St. Constant, Quebec) were housed individually with free access to food (Master Laboratory Chow) and water. The environment was maintained at 24°C, 60% relative humidity and with 12 hr of light (6 a.m. to 6 p.m.). Each animal was handled daily for a week prior to

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initiation of the experiment. At the time of the first injection, the animals weighed  $224 \pm 11$  g.

### *Behavioural Testing*

This portion of the study constituted of two experiments in which the antagonistic effects of two doses of fluphenazine decanoate (2.5 mg/kg and 5.0 mg/kg) upon behavioural changes induced by d-amphetamine (2.5 mg/kg), were monitored.

### *Apparatus*

The experimental chambers for behavioural observation were identical to the rats home cage (clear polycarbonate;  $43 \times 23 \times 15$  cm) except for the following modifications: the cage was elevated by 4 cm from the counter, by spacers placed at each corner. The floor was marked off into six equal sections and had seven holes (2.5 cm diameter). Three of the holes were centered along the median, 10.75 cm apart, and the remaining four were placed 15 cm from each corner (5.75 cm from the side wall). An inverted cage of the same dimensions but with a metal grid floor, served as a lid that allowed adequate ventilation and room for rearing.

### *Procedure*

Twelve rats received fluphenazine decanoate (5.0 mg/kg; IM) whereas the control group (12 rats) were given an equal volume (0.1 ml/100 g) of the vehicle (sesame oil). During alternate observation sessions, only half of the animals (6 controls and 6 neuroleptic-treated) were distributed into individual experimental chambers, according to the Latin square design. Thus each animal was subjected to these experimental conditions only once every 7 to 8 days (to minimize effects of repetitive exposure to d-amphetamine). Each of the two pairs of raters (one to observe, one to record) were assigned 3 control and 3 fluphenazine-treated rats for behavioural rating. The raters were blind to the drug history of the subjects under observation. Each rat was observed consecutively for 1 min duration, every 6 min, for the entire observation session. The behavioural parameters being monitored were operationally defined as follows:

(1) Sniffing: nose and whiskers moving (score of 1, for every 10 seconds of continuous sniffing).

(2) Poking: rat's nose visibly protruding through one of the holes on the floor (score=number of pokes during observation).

(3) Rearing: standing on hindlegs, with forelimbs off the floor (score=number of rears during observation).

(4) Locomotion: hindlegs crossing into another section of the floor (score=number of sections crossed during observation).

(5) Gnawing: rats biting on anything in the cage (score=number of gnaws during observation).

Once in their experimental chambers, the rats were allowed 0.5 hr of acclimatization period. Following which all rats received a saline (placebo) injection and were observed and rated for the subsequent 0.5 hr period. Immediately following this all rats were injected with d-amphetamine (2.5 mg/kg; IP) and the behaviours rated for 2.5 hr, as described above.

The above experiment was repeated with a smaller dose of fluphenazine decanoate (2.5 mg/kg). The procedure remained identical to that described in the above experiment except for the following modifications: the duration of the

experiment was reduced to 28 days and each post-amphetamine observation period extended to 3 hr.

### *Prolactin Studies*

In addition to behavioural studies, separate experiments were performed to assess the effects of two doses of fluphenazine decanoate (2.5 and 5.0 mg/kg) on serum prolactin levels.

### *Procedure*

Forty-eight rats were injected with fluphenazine decanoate (5.0 mg/kg; IM) and 18 control rats with an equal volume (0.1 ml/100 g) of the vehicle (sesame oil). Six hours after the first injection (day 0), groups of control (n=6) and fluphenazine treated (n=6) rats were decapitated. Trunk blood was collected and serum separated out, and stored frozen until subsequent analysis. Serum samples from groups of 6 neuroleptic-treated rats were similarly obtained on days 1, 4, 7, 14, 21, 28 and 35 following the administration of fluphenazine decanoate. Sera from 2 additional groups of control animals were obtained about mid-way through (day 21, n=6) and at the end of the experiment (day 35, n=6).

The above procedure was repeated on additional 66 rats, using a different dose of fluphenazine decanoate (2.5 mg/kg).

### *Prolactin Assay*

Prolactin levels were determined in the serum samples in duplicate by a double antibody radioimmunoassay method, using reagents kindly supplied by Dr. A. F. Parlow, through the NIAMDD Rat Pituitary Hormone Distribution Program. The levels were expressed as ng/ml of NIAMDD rat-PRL-PR-1. The intra-assay variability was 5% and the inter-assay variability was 12%. All of the samples for a given comparison were analyzed in the same batch.

## RESULTS

### *Behavioural Experiments*

The raw data of the individual behaviours were pooled over 0.5 hr intervals, and subjected to analysis of variance with repeated measures. Post-hoc comparisons between the control and neuroleptic-treated groups were done using the Tukey test [12].

To test the effects of amphetamine, behavioural recording during placebo period (where all animals received a saline injection) were conducted prior to every amphetamine session. Globally, these experiments revealed that as compared to saline (placebo) injection, d-amphetamine treatment markedly stimulated the locomotor, rearing and sniffing activity, but failed to significantly stimulate the poking and grooming behaviours. The latter two behaviours were thus excluded from subsequent statistical analyses. The locomotor, rearing and sniffing responses to amphetamine alone (controls) did not vary over successive trials and the respective scores were therefore combined over days to yield averaged single profiles for the individual behavioural parameters.

In Fig. 1, the average locomotor activity of the control group is represented as a single profile, as there was no statistically significant difference in this response over days. However, the locomotor response of the neuroleptic-treated rats was significantly lower than that of controls on test days 4, 7, 11, 14, 18, 21 and 28, at the 0.5 hr bins indicated on the

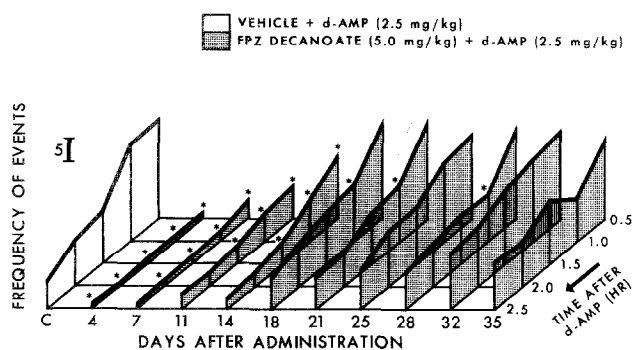


FIG. 1. Time-course of fluphenazine-decanoate (5.0 mg/kg) effect on d-amphetamine-induced locomotor activity. Tridimensional figure: On the ordinate: frequency of the quantified activity; on the horizontal abscissa: days following the administration of fluphenazine decanoate; on the oblique abscissa: time after d-amphetamine administration. The cumulative profile of vehicle-treated controls did not vary across days and is represented by the unshaded area on the extreme left and profiles of fluphenazine decanoate-treated groups are represented by the subsequent shaded areas.  $n=6$  for each test session. \*Significantly different with respect to controls at  $p<0.05$ .

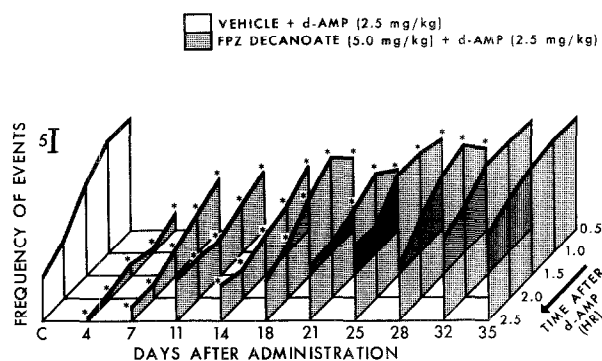


FIG. 2. Time-course of fluphenazine decanoate (5.0 mg/kg) effect on d-amphetamine-induced rearing. \*Significantly different with respect to controls at  $p<0.05$ . For further information see legend to Fig. 1.

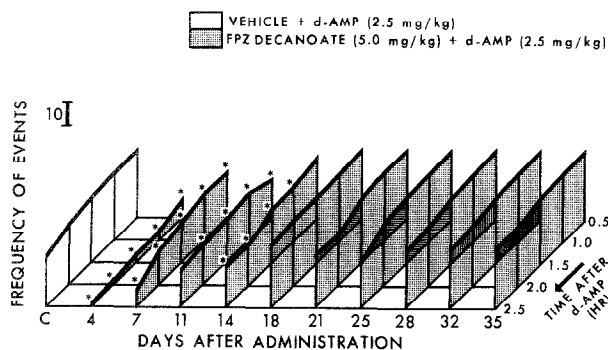


FIG. 3. Time-course of fluphenazine decanoate (5.0 mg/kg) effect on d-amphetamine-induced sniffing activity. \*Significantly different with respect to controls at  $p<0.05$ . For further information see legend to Fig. 1.

graph. Although initially the amphetamine-induced locomotor activity remained blunted at every 0.5 hr test interval, with the progression of days significant blockade was only demonstrable during the first and/or second post-amphetamine 0.5 hr bins. Similarly, the frequency of amphetamine-induced rearing was markedly suppressed for up to 28 days following the administration of fluphenazine decanoate (see Fig. 2). With the progression of days, as in the case of locomotor activity, the neuroleptic suppression of rearing was consistently demonstrable mainly at the initial two 0.5 hr bins of the amphetamine test. Amphetamine-induced sniffing was also suppressed by pre-treatment with fluphenazine decanoate (see Fig. 3). However, this suppression (in contrast to that of locomotion and rearing) was present for a shorter duration (14 days). With the lower dose of

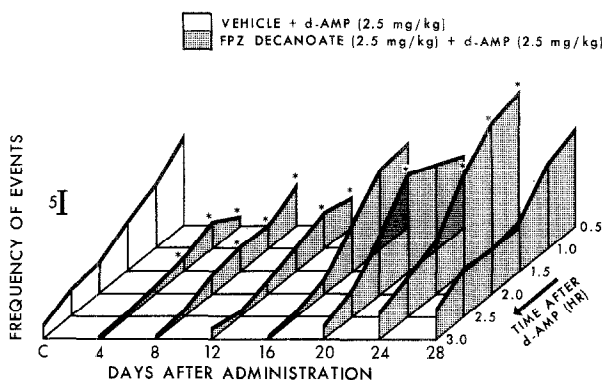


FIG. 4. Time-course of fluphenazine decanoate (2.5 mg/kg) effect on d-amphetamine-induced locomotor activity. \*Significantly different with respect to controls at  $p<0.05$ . For further information see legend to Fig. 1.

fluphenazine decanoate (2.5 mg/kg), a similar overall pattern in the blockade of amphetamine-induced locomotor activity (Fig. 4), rearing frequency and sniffing, could be seen. However, these effects were less pronounced and of a shorter duration than those resulting from the higher dose of fluphenazine decanoate.

Amphetamine-induced locomotor activity was partially antagonized by fluphenazine decanoate (2.5 mg/kg) on days 4, 8 and 12. However, on days 20 and 24 following the administration of fluphenazine decanoate (2.5 mg/kg), the neuroleptic treated rats displayed significantly more locomotor activity in response to amphetamine, than the matched control animals (see Fig. 4). With rearing behaviour, a partial blockade could also be seen for the same duration (up to 12 days), following which a reinstatement and maintenance of normal responsiveness was apparent. As in the case with the larger dose, amphetamine-induced sniffing was antagonized for the shortest period. In this instance, antagonism of sniffing was demonstrable mainly on the first test day (day 4) and on the second half hour of the next test session (day 8).

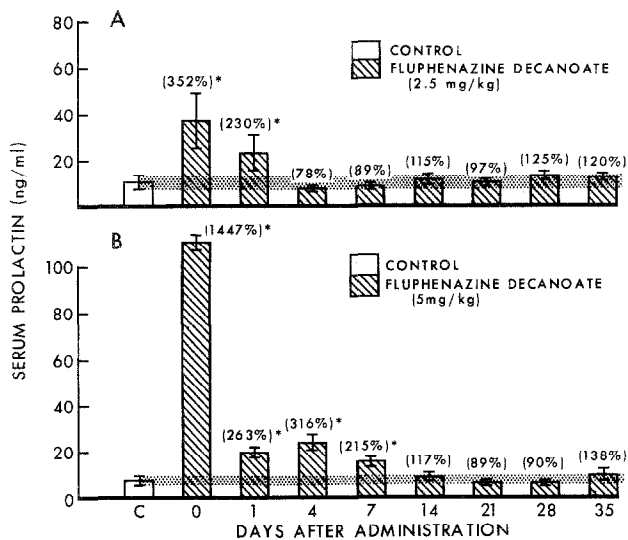


FIG. 5. Time-course of fluphenazine decanoate (A, 2.5 mg/kg and B, 5.0 mg/kg) on prolactin disinhibition. Each column represents the mean prolactin level  $\pm$  S.E.M. of 6 animals per group. Open column represents vehicle controls and the hatched bars the neuroleptic-treated groups, at various days following the treatment. Value as a percent of control is given in parentheses. \*Significantly different from vehicle controls, at  $p < 0.05$ .

### Prolactin Studies

There was no statistically significant difference in the prolactin levels of 3 control groups ( $n=6$ ) sacrificed on days 0, 21 and 35. As can be seen in Fig. 5, administration of fluphenazine decanoate (5.0 mg/kg) resulted in a pronounced elevation of prolactin (1447% of control) within 6 hours of the injection (day 0). The prolactin level remained significantly elevated, albeit by a smaller magnitude, on sampling days 1, 4 and 7 (see Fig. 5B). By day 14, prolactin level had returned to within the normal range and remained there for the duration of the experiment. With the lower dose of fluphenazine decanoate (2.5 mg/kg), prolactin concentration increased significantly (by 352%) within 6 hours of administration (day 0) (see Fig. 5A). However, this elevation was of a much smaller magnitude than that following the larger dose of the neuroleptic, and was detectable only up to day 1 of sampling. By day 4, serum prolactin had dropped to within the normal range, and remained relatively unaltered for the duration of the experiment.

### DISCUSSION

The present results demonstrate that a single injection of fluphenazine decanoate can antagonize behavioural effects of acute d-amphetamine (2.5 mg/kg) for a variable period of time (4 to 28 days), depending upon the dosage of the neuroleptic used (2.5 or 5.0 mg/kg) and the behavioural parameter(s) monitored. Globally, the magnitude of behavioural antagonism and its time course were greater with the higher dose of the neuroleptic.

At the level of individual behavioural components, there seemed to be a differential antagonistic effect engendered by this neuroleptic: locomotion and rearing behaviours were an-

tagonized for a much longer duration than was the sniffing response. This differential antagonistic effect may be related to the involvement of distinct neurochemical and/or neuroanatomical mechanisms in the mediation of d-amphetamine-induced behavioural changes. Indeed in addition to enhancing the release and inhibiting the reuptake of dopamine, d-amphetamine is also known to influence, for example, noradrenergic and serotonergic neurotransmission [25]. Furthermore, in recent years it has become evident that whereas locomotion seems to depend on stimulation of dopaminergic mechanisms in the mesolimbic system, the licking, sniffing and gnawing behaviours arise from the striatum [2, 6, 10, 11, 19, 24]. It is thus tempting to suggest that at the doses employed in this experiment, fluphenazine may be exerting a preferential effect on limbic over striatal dopaminergic neurotransmission. Alternatively, it is thus also possible that the sniffing behaviour may depend more on the stimulation of the dopamine receptors relatively insensitive to fluphenazine effects. Indeed, Ljungberg and Ungerstedt [14] found that neuroleptic drugs differ widely in their ability to antagonize gnawing as compared to locomotion, and tentatively explained this finding, by the existence of two different dopamine receptors [5, 14].

The normal locomotor response to amphetamine was attained after 12 and 28 days following the administration of 2.5 mg/kg and 5.0 mg/kg fluphenazine decanoate, respectively. However, following the apparent reinstatement of normal locomotor response, the 2.5 mg/kg fluphenazine group displayed significantly more locomotor activity on days 20 and 24 post-treatment. This reversal in activity lends further credence to the hypothesis that dopamine receptors become supersensitive during withdrawal from chronic exposure to receptor blocking agents [9, 13, 28, 31]. It is of interest to note that a similar supersensitive response was not demonstrable with the higher dose of fluphenazine decanoate (5.0 mg/kg). This could possibly be attributed to the experimental span and testing intervals, which may not have coincided with the supersensitive state, or perhaps this response may have reversed before effective levels of fluphenazine were gone [33]. Choi and Roth [4] using neurochemical techniques detected supersensitivity resulting from fluphenazine decanoate treatment at 14 and 21 but not at 27 days post-injection. Burt, Creese and Snyder [3] have provided evidence of increased striatal dopamine receptor binding at 5 and 12 days but not at 17 days after discontinuation of daily neuroleptic treatment. Voith [32], using a relatively large dose of fluphenazine decanoate (12.5 mg/kg) reported a supersensitive state lasting less than two weeks. In the present study, supersensitivity was noted at 20 and 24 days (post injection). However, due to the testing intervals employed, it remains possible that the supersensitive state may have extended anywhere from a few days to a few weeks. The mechanism(s) underlying the induction and disappearance of supersensitivity remain obscure [3, 4, 9, 13, 23, 26, 28, 31, 32].

In contrast to the locomotor activity, supersensitive response was not reflected in rearing and sniffing behaviours. These results also indicate that the monitoring of discrete behavioural components might be more informative than single stereotypy scores obtained from the constellation of behavioural repertoires.

Administration of fluphenazine decanoate resulted in a prompt and pronounced elevation of serum prolactin level, already demonstrable at the time of the first sampling (6 hr post injection). This is concordant with the clinical observa-

tion of Nasrallah *et al.* [22] who reported that plasma prolactin concentration of patients increased (2–16 fold) between 3 and 6 hr after the injection of fluphenazine decanoate. These observations are also consistent with the kinetics of fluphenazine after fluphenazine decanoate administration and may have considerable significance for the use of fluphenazine decanoate in acute conditions [8].

In rats administered 2.5 and 5.0 mg/kg dose of fluphenazine decanoate, prolactin levels were within the normal range by days 4 and 14, respectively. In male schizophrenic subjects being treated with fluphenazine decanoate, the prolactin levels remained elevated for up to 4 weeks [18]. Furthermore, in the behavioural experiments reported here, effects of fluphenazine decanoate (5 mg/kg) could also be detected for up to 28 days. Normally, prolactin released from the pituitary is pulsatile and it remains possible that the change in prolactin profile (as reflected by the number and/or the magnitude of prolactin peaks) may have revealed a different time-course. However, it is also possible that the continuous interruption of the pituitary dopamine receptors may have rendered them "supersensitive" to dopamine, the physiological prolactin inhibitory factor. Recently, Annunziato *et al.* [1] reported that serum prolactin levels, 24 hr after the last neuroleptic (short-acting) injection, were significantly lower in the

repeat-treated group than in the acute treated rats. This can be interpreted as an enhanced sensitivity of pituitary dopamine receptors or alternatively, the consequence of an increased turnover of tuberohypophyseal dopamine neurons which follows prolonged elevation of circulating prolactin levels [1,21].

In conclusion, these data indicate that fluphenazine decanoate effects are reflected by changes in serum prolactin as well as by antagonism of amphetamine-induced behavioural changes. The time course of fluphenazine decanoate effect on the nigrostriatal and/or mesolimbic dopamine system(s) (as reflected by antagonism of amphetamine-induced behavioural changes) is longer than that on the tuberoinfundibular-pituitary system (as reflected by circulating prolactin levels). Thus the behavioural paradigm reported here seems more sensitive in detecting the effects of relatively low levels of fluphenazine decanoate, and suggests that this could serve as a useful model in investigating the dose- and time-related effects of other long-acting neuroleptics.

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