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Single Preexposure to Fluphenazine Produces Persisting Behavioral Sensitization Accompanied by Tolerance to Fluphenazine-Induced Striatal Dopamine Overflow in Rats

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MEIL, W. AND R. E. SEE. *Single preexposure to fluphenazine produces persisting behavioral sensitization accompanied by tolerance to fluphenazine-induced striatal dopamine overflow in rats.* PHARMACOL BIOCHEM BEHAV **48**(3) 605–612, 1994.—Single, previous exposure to a neuroleptic has been shown to produce long-lasting changes in various measures of behavior and neurochemistry upon subsequent drug exposure. The present study examined the effects of a single preexposure to fluphenazine (0.3 or 1.0 mg/kg) or vehicle on the effects of subsequent fluphenazine administration 15 or 30 days later. Intracranial microdialysis was used to assess changes in striatal extracellular dopamine concentrations. Animals were tested for catalepsy response on a horizontal bar test while concurrently collecting dialysis samples. Previous fluphenazine exposure produced a profound tolerance to the effects of subsequent fluphenazine at day 15 or day 30 on increasing extracellular dopamine levels. In addition, animals that had received fluphenazine on the first trial showed significant sensitization to the cataleptic effects of fluphenazine at both time points. Pretreatment with vehicle did not result in tolerance to dopamine overflow and there was only minimal evidence of cataleptic sensitization to a subsequent fluphenazine challenge. Although the tolerance to dopamine overflow may only indirectly relate to behavioral sensitization, these results support the hypothesis that significant behavioral and neurochemical alterations persist for prolonged time periods following single neuroleptic exposure.

Fluphenazine Dopamine Sensitization Tolerance Catalepsy Microdialysis

WHILE neuroleptics clearly show therapeutic efficacy in the treatment of schizophrenia and other mental disorders, acute and chronic administration of these compounds can produce a variety of motor side effects (16). Some evidence suggests that dosing regimen can influence both the therapeutic efficacy and motor side effect profile of neuroleptics (13,25,41). Furthermore, the frequency of neuroleptic administration has been associated with the differential development of tolerance and sensitization as measured by behavioral and neurochemical indices. For example, daily injections of haloperidol produce tolerance to the initial increases in dopamine (DA) turnover elicited by the drug in the striatum and nucleus accumbens, whereas weekly administration produces sensitization to these effects in the striatum, posterior olfactory tubercle, and ventral tegmental area (18). The opposite trend has been found when examining certain behavioral endpoints, with daily administration of haloperidol producing tolerance and intermittent administration favoring sensitization to haloperidol-induced reduction of locomotor activity (15) and catalepsy (11,34). Additionally, it has been found that even a single pretreatment with a neuroleptic will produce time-dependent increases in catalepsy (9). This time-dependent sensitization to a neuroleptic is an example of behavioral sensitization, a phenomenon in which acute exposure to a stimulus results in a significant behavioral increase upon reexposure to a stimulus, an effect which is often augmented with time (9,29). Behavioral sensitization has been demonstrated to pharmacological challenges with a variety of compounds, including antidepressants (7), psychostimulants (6,29), opiates (26), and neuroleptics (5,9,10), as well as physical (8,9,37)

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and psychological (10) stressors. Thus, there is considerable evidence that acute exposure to a pharmacological challenge results in long-term behavioral and neurochemical changes.

One behavioral measure that is widely used to assess the effects of pharmacological challenge with neuroleptics in animals is catalepsy, which is a putative index of the extrapyramidal motor effects of neuroleptics. Although catalepsy is presumed to be due to the antidopaminergic action of neuroleptics, the neural basis of catalepsy remains controversial (31). The duration of catalepsy following acute administration of haloperidol and trifluoperidol has been correlated with overall decreases in whole tissue measures of striatal DA (21). However, increases in extracellular DA in the striatum following acute administration of haloperidol, sulpiride, and cis-flupenthixol were not correlated with the occurrence of catalepsy, suggesting that neuroleptic-induced catalepsy may be dissociated from presynaptic events (47).

While behavioral sensitization of catalepsy to neuroleptic administration is clearly a robust effect (9,11), it remains to be determined as to whether alterations in forebrain DA function are associated with neuroleptic-induced behavioral sensitization of catalepsy. Following a single pretreatment with haloperidol or saline, a subsequent haloperidol challenge 2 weeks later failed to elicit any differences between groups for changes in DA, 3,4-dihydroxyphenylacetic acid (DOPAC), or the DOPAC/DA ratio in the substantia nigra, striatum, nucleus accumbens, or frontal cortex (9). However, reduced levels of DA in the nucleus accumbens following a haloperidol challenge were found 2 weeks, but not 2 h after exposure to a novel stimulus (10). The present study applied microdialysis techniques to investigate whether a single neuroleptic pretreatment results in time- and dose-related alterations in extracellular DA that may be associated with behavioral sensitization of catalepsy. The high potency neuroleptic fluphenazine was chosen to examine neuroleptic-induced catalepsy in the present study. Fluphenazine is a mixed D_1/D_2 DA receptor antagonist, with slightly higher affinity for the D_1 receptor (23), and has previously been utilized to demonstrate sensitization of catalepsy (9).

METHOD

Subjects and Drug Administration

Female, Sprague-Dawley rats (weight 240–300 g) were group housed (two per cage) and maintained on a 12 h light : dark cycle with continuous access to food and water. All animals were extensively handled prior to testing. Injections were intraperitoneally (IP) administered and consisted of fluphenazine hydrochloride (Sigma Chemical) dissolved in saline or saline alone. Fluphenazine was given in a high dose (1.0 mg/kg) or low dose (0.3 mg/kg) and all injections, including saline alone, were administered in a volume of 1.0 ml/kg body weight. Animals were tested after initial injection of fluphenazine or vehicle (day 1) and then tested with a subsequent injection after an appropriate interval (day 15 or day 30 following the first injection).

Intracranial Microdialysis

Rats were anesthetized with Equithesin (0.3 ml/100 g) and mounted in a stereotaxic apparatus. Bilateral guide cannulae (20 gauge, stainless steel) were implanted into the striatum (from bregma: A +0.0, L −3.4, V −5.0) according to the atlas of Paxinos and Watson (36). The cannulae were secured in place with dental cement anchored with stainless steel screws. Obturators were placed in the guide cannulae and the animals allowed to recover for 1 week prior to testing. Dialysis probes were constructed with dialysis tubing based on previously described methods (28,39). The probes were approximately 250 μm in diameter at the tip, and the dialysis membrane (nominal molecular weight cut off of 6000) was glued to a 25 gauge cannula. Dialysis membrane (3 mm) was exposed at the tip of the probe which extended 3 mm beyond the guide cannula. In vitro recovery of DA at 37°C consistently ranged from 10–15% for these probes. Probes were unilaterally inserted into a flexible connector which allowed optimal placement and fixation onto the chronic guide cannula. Animals were equally divided so that half were initially probed in the right striatum and half in the left striatum. The probes were left in place overnight prior to beginning sample collection. The next day, perfusion of the dialysis probes began 60–80 min prior to collecting baseline samples. Probes were perfused (2 μl/min) with a syringe pump containing dialysis buffer (in mM: NaCl, 147; $CaCl_2$, 1.8; KCl, 5; $MgCl_2$, 1.2; pH 7.4). Perfusate samples were collected in microcentrifuge tubes containing 20 ml of the mobile phase (0.1 M citric acid, 0.75 mM Na_2HPO_4, 1.2 mM heptane sulphonic acid, 0.1 mM ethylenediamine-tetraacetic acid, 14% methanol, pH 4.2) which contained 2 pmol dihydroxybenzylamine as the internal standard. Three consecutive samples collected at 20 min intervals for 1 h provided a baseline prior to drug administration. Samples were collected at 20 min intervals for 4 h after injection and once again at 5 h. Each sample was injected by an autosampler into a high performance liquid chromatography (HPLC) system. Separation of DA was accomplished on a reversed phase column (C-18; 25 cm) and a coulometric electrochemical detection system (Model 5100A, ESA Inc.) for detecting analytes (guard electrode = +0.4 V, oxidation electrode = +0.35 V, and reduction electrode = −0.25 V). At the end of all testing, rats were sacrificed with an overdose of Equithesin and brain tissue fixed with a 10% formalin solution. Coronal sections of tissue were cut on a microtome (75 μm), stained with cresyl violet, and dialysis probe sites visually inspected.

Assessment of Catalepsy

Following injection of fluphenazine or vehicle, duration of catalepsy was assessed for 5 h at 30 min intervals. The duration of catalepsy was measured by gently placing the rat's forepaws on a horizontal metal bar (situated 7.5 cm from the bottom of the dialysis chamber) and recording the time until the rat removed one paw from the bar. At each time point, a single measure of catalepsy was taken. Catalepsy lasting longer than 180 s was recorded as 180 s and the animal was removed fom the bar. The dialysis swivel apparatus was carefully balanced to minimize any effect of extra weight during catalepsy measures.

Statistics

For dialysis data, basal levels of DA were compared using between groups analysis of variance (ANOVA) (dose × administration interval × collection time) and post hoc comparisons for individual group comparisons. The average of the three basal samples was taken as 100% and postinjection samples were analyzed as percent of baseline using mixed model factorial ANOVA (dose × administration interval × collection time). Simple effects between treatment groups at each dose and administration interval were made using a repeated measures ANOVA and post hoc comparisons for individual group comparisons (Tukey's test). Significant differences were defined at $p < 0.05$ and $p < 0.01$. The Kruskal–Wallis test was used for catalepsy data. This nonparametric test was cho-

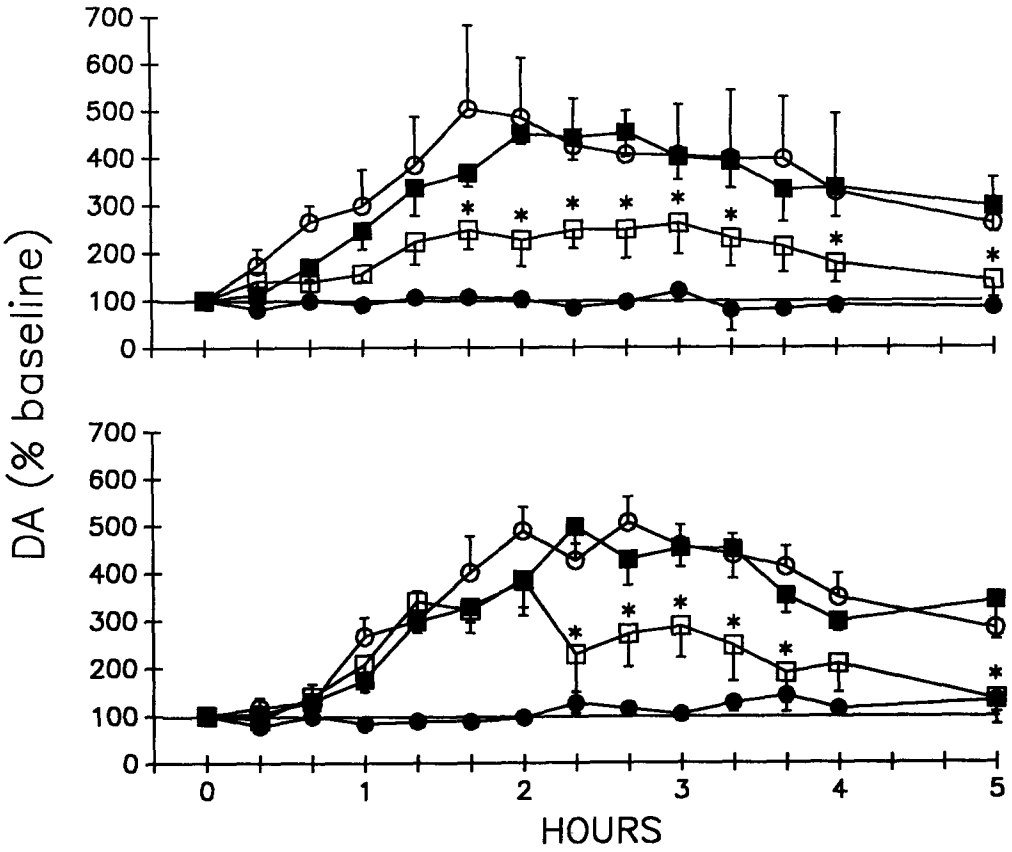

FIG. 1. Changes in striatal extracellular DA levels as a percent of baseline (time 0) over time following IP injection of low dose fluphenazine (0.3 mg/kg) for 15 day between injections interval (top) and 30 day between injections interval (bottom). Groups (n = 5-6) shown are: saline on day 1 (●); first exposure to fluphenazine on day 15 or day 30 (○); first exposure to fluphenazine on day 1 (■); second exposure to fluphenazine on day 15 or day 30 (□). Significant differences are noted for comparison of first injection of fluphenazine on day 1 and the second injection of fluphenazine on day 15 or day 30 (*$p < 0.05$; Tukey's test).

sen because a 180 s time limit was used for catalepsy measures and, therefore, catalepsy scores were not normally distributed. If the H value was associated with $p < 0.05$, specific comparisons were made with the Mann-Whitney U-test for individual comparisons. To minimize the number of between-group comparisons, only catalepsy scores up to 180 min after drug administration were analyzed. Catalepsy scores beyond this point typically exceeded the 180 s time limit for measurement of catalepsy in all fluphenazine injection conditions. Criterion for statistically significant differences was set at $p < 0.05$ and $p < 0.01$.

RESULTS

Extracellular DA Overflow

Basal levels of extracellular DA in the striatum did not differ between any of the treatment groups or administration intervals (overall mean ± SEM for basal DA = 97 ± 13 fmol/sample). No significant changes from baseline in DA overflow were observed following vehicle injection at any time point. Following a pretreatment injection of fluphenazine, animals showed significant increases in extracellular striatal DA overflow from baseline. Sixty minutes after injection, DA levels remained elevated over the next 4 h, except for the low dose fluphenazine which returned to near baseline after 4 h, $F(12, 456) = 35.8\ p < 0.01$. Dose-dependent increases in extracellular DA levels were observed following fluphenazine injection, $F(4, 38) = 8.38$, $p < 0.01$, with animals receiving the larger dose of fluphenazine (1.0 mk/kg) showing greater elevations in extracellular DA levels (maximal increases above 700% of baseline) than animals receiving the lower dose of fluphenazine (0.3 mg/kg) (maximal increases above 400% of baseline).

Figure 1 presents alterations in extracellular DA levels, expressed as the percent of baseline for the low dose of fluphenazine (0.3 mg/kg). For the day 1 to 15 interval (Fig. 1, top), significant differences were seen between the first and second administration of fluphenazine, $F(1, 9) = 8.40$, $p < 0.05$. Post hoc comparisons (Tukey's test) showed a significant decrease in DA overflow for the day 15 treatment at several time points beginning 100 min after injection. For the 1 to 30 day interval (Fig. 1, bottom), significant differences were also found between the first and second administration of fluphenazine, $F(1, 9) = 27.4$, $p < 0.01$, and specific comparisons between the first and second fluphenazine injection were significant at several time points beginning 140 min after injection.

Figure 2 shows changes in extracellular DA from baseline for the high dose of fluphenazine (1.0 mg/kg). Comparison of the day 1 to day 15 injections showed significant differences

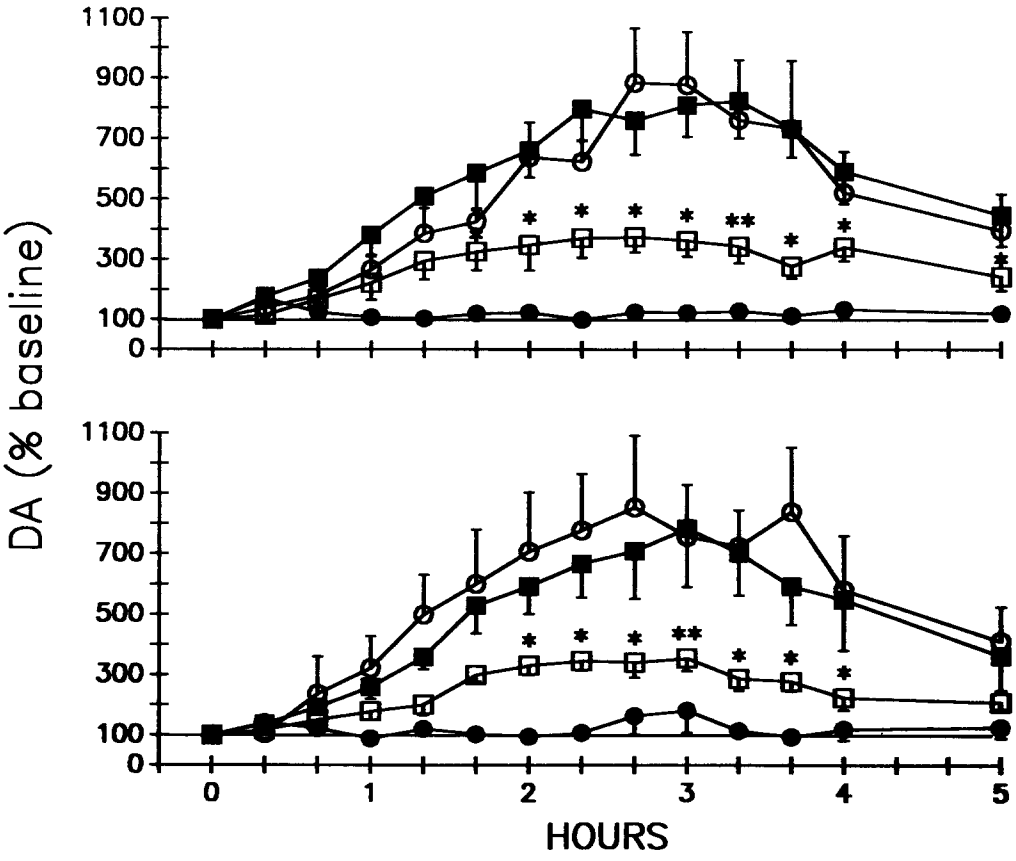

FIG. 2. Changes in striatal extracellular DA levels as a percent of baseline (time 0) over time following IP injection of high dose fluphenazine (1.0 mg/kg) for 15 day between injections interval (top) and 30 day between injections interval (bottom). Groups (n = 5–7) shown are: saline on day 1 (●); first exposure to fluphenazine on day 15 or day 30 (○); first exposure to fluphenazine on day 1 (■); second exposure to fluphenazine on day 15 or day 30 (□). Significant differences are noted for comparison of first injection of fluphenazine on day 1 and the second injection of fluphenazine on day 15 or day 30 (*$p < 0.05$; **$p < 0.01$; Tukey's test).

between the first and second administration of fluphenazine, $F(1, 9) = 17.6, p < 0.01$, (Fig. 2, top). Post hoc comparisons were significant at several time points beginning 100 min after injection. Significant differences in extracellular DA overflow were also observed between the first and second administration of fluphenazine for the day 1 to day 30 interval, $F(1, 11) = 13.4, p < 0.01$ (Fig. 2, bottom), with significant decreases for the day 30 treatment at several time points beginning at 120 min following injection.

Striatal DA overflow did not differ in animals pretreated with either dose of fluphenazine and animals challenged with that same dose but pretreated with vehicle 15 or 30 days earlier. Fluphenazine-induced tolerance of extracellular striatal DA overflow did not differ between the 15 and 30 day administration intervals and for the dose × time interval interaction.

Catalepsy

Robust and persisting catalepsy was produced with both doses of fluphenazine. Significant catalepsy was seen up to 5 h after each fluphenazine injection. In contrast, animals receiving saline showed no indication of cataleptic behavior at any time (data not shown in figures). Figure 3 shows catalepsy scores for the low dose of fluphenazine (0.3 mg/kg). For the 1 to 15 day interval (Fig. 3, top), significant differences were seen between groups at the following time points: 60 min ($H = 8.63, p < 0.05$), 90 min ($H = 7.88, p < 0.05$), 120 min ($H = 10.65, p < 0.01$), and 150 min ($H = 7.90, p < 0.05$). Mann-Whitney U-tests of day 1 fluphenazine injection and day 15 fluphenazine injection indicated significant differences between groups (Fig. 3, top). In addition, specific comparison of animals receiving their first fluphenazine injection on day 1 vs. those receiving fluphenazine the first time on day 15 showed a significant difference at 120 min and 150 min ($p < 0.05$). For the 1 to 30 day interval (Fig. 3, bottom), significant differences were seen between groups at 60 min ($H = 7.30, p < 0.05$), 90 min ($H = 7.74, p < 0.01$). Mann-Whitney U-tests again indicated significant differences between day 1 and day 15 fluphenazine injections (Fig. 3, bottom). Variability (SEM) in catalepsy measures for the treatment groups at 120 min after administration ranged from 12–25 s.

Figure 4 shows catalepsy scores for the high dose of fluphenazine (1.0 mg/kg). For the 1 to 15 day interval, significant differences were seen between groups at the 30 min time point ($H = 6.14, p < 0.05$), with a significant difference seen between day 1 and day 15 fluphenazine injections (Fig. 4, top). For the 1 to 30 day interval, significant differences were

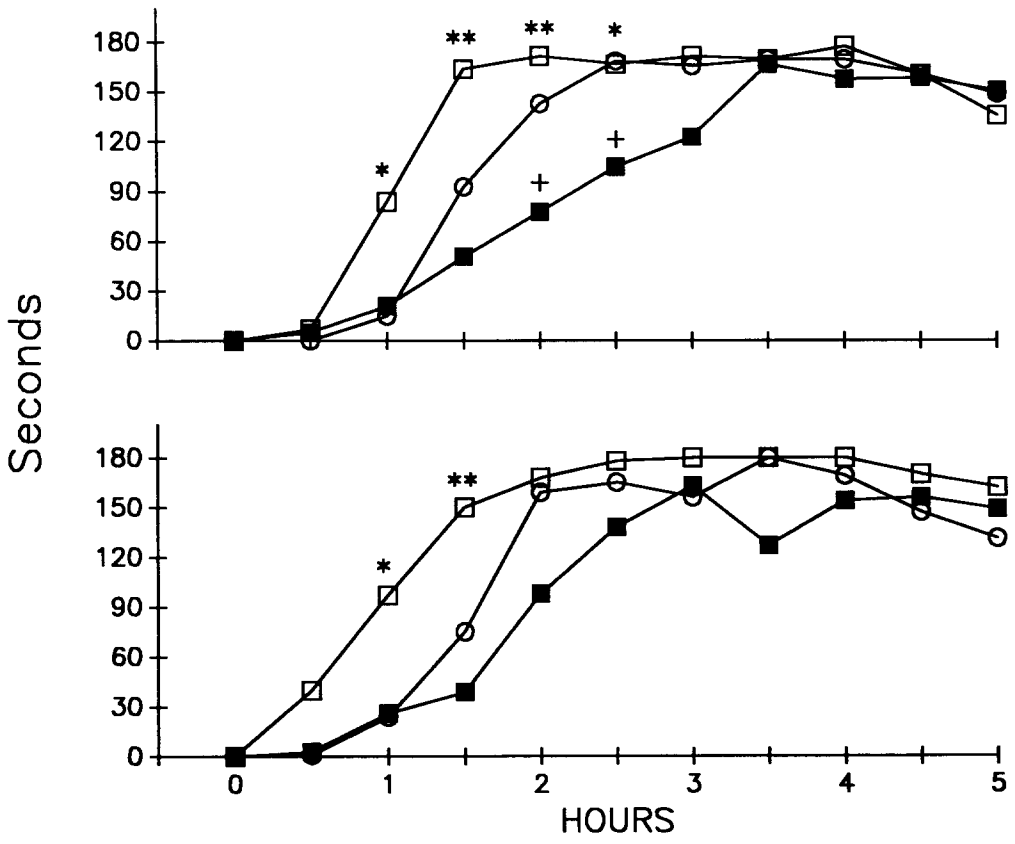

FIG. 3. Time course for catalepsy following IP injection of low dose fluphenazine (0.3 mg/kg) for 15 day between injections interval (top) and 30 day between injections interval (bottom). Groups (n = 5–8) shown are: first exposure to fluphenazine on day 15 or day 30 (○); first exposure to fluphenazine on day 1 (■); second exposure to fluphenazine on day 15 or day 30 (□). Significant differences are noted for comparison of first injection of fluphenazine on day 1 and the second injection of fluphenazine on day 15 or day 30 (*p < 0.05; Mann-Whitney U-test) and for comparison of first exposure to fluphenazine on day 1 and first exposure to fluphenazine on day 15 (^+p < 0.05; Mann-Whitney U-test). Animals receiving saline showed no indication of catalepsy at any time (data not shown).

seen between groups at 30 min (H = 8.24, p < 0.05) and 60 min (H = 9.65, p < 0.01), with a significant difference seen between day 1 and day 30 fluphenazine injections (Fig. 4, bottom). Variability (SEM) in catalepsy measures for the treatment groups at 120 min after administration ranged from 4–23 s.

DISCUSSION

The findings of this study support previous evidence suggesting that single exposure to a neuroleptic can result in long-term behavioral and neurochemical changes. Following a single pretreatment injection of fluphenazine, a subsequent fluphenazine challenge 15 or 30 days later resulted in behavioral sensitization of catalepsy and tolerance to the elevated DA overflow elicited by fluphenazine in the striatum. Neither cataleptic sensitization or tolerance of extracellular DA overflow were found to be time dependent, although there was a trend toward increased catalepsy at the 30 day injection time.

The present results are consistent with those of Antelman et al. (9) who found sensitization of catalepsy following a single pretreatment with a neuroleptic. Additionally, the onset and duration of catalepsy to fluphenazine previously observed were comparable to those seen in this study. However, Antelman et al. failed to observe alterations in striatal DA and the DOPAC/DA ratio 1 h after administration of a haloperidol dose associated with behavioral sensitization. This discrepancy with the present findings may be explained by differences in methodology and experimental design. While whole tissue sample assays of DA and DOPAC/DA ratio provide a measure of total DA and DA turnover, microdialysis techniques more accurately reflect extracellular DA activity (12). Based on evidence that behavioral sensitization of locomotor activity to psychostimulants can be associated with an augmentation of DA release (2,3,38), neuroleptic-induced behavioral sensitization may also be related to alterations in extracellular DA overflow. Another possible explanation for the previous inability to detect alterations in dopaminergic activity accompanying cataleptic sensitization is the evaluation of a single early time point (1 h). In the present study using microdialysis, attenuation of extracellular striatal DA overflow to a fluphenazine challenge was not observed until after the 1 h collection time (see Figs. 1 and 2).

Nonpharmacological stressors, such as acute foot shock, have been found to induce sensitization of locomotor activity in a fashion similar to amphetamine, cocaine, and morphine

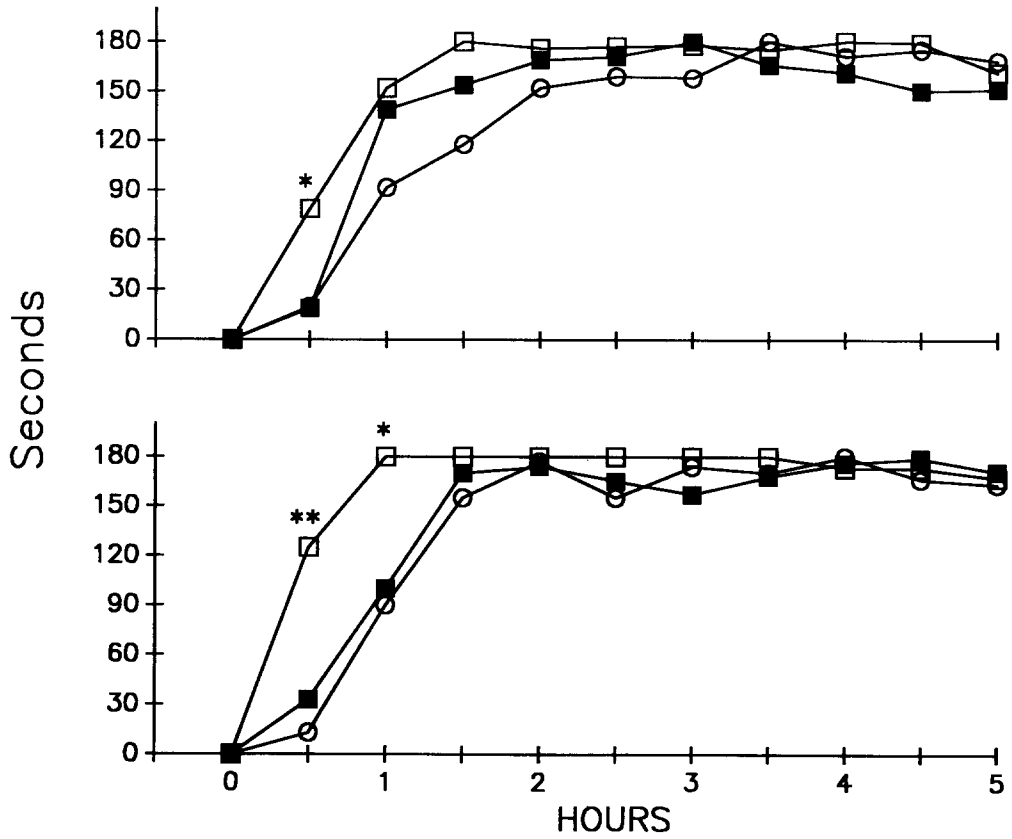

FIG. 4. Time course for catalepsy following IP injection of high dose fluphenazine (1.0 mg/kg) for 15 day between injections interval (top) and 30 day between injections interval (bottom). Groups (n = 5–8) shown are: first exposure to fluphenazine on day 15 or day 30 (○); first exposure to fluphenazine on day 1 (■); second exposure to fluphenazine on day 15 or day 30 (□). Significant differences are noted for comparison of first injection of fluphenazine on day 1 and the second injection of fluphenazine on day 15 or day 30 (*$p < 0.05$; Mann-Whitney U-test). Animals receiving saline showed no indication of catalepsy at any time (data not shown).

(6,8,27,33). Such stressors have also been shown to augment DA levels in a manner similar to psychostimulants (1,19). Additionally, pretreatment injections of saline have been found to increase catalepsy to a subsequent neuroleptic challenge (9). Preexposure to a novel stimulus has also been shown to elevate corticosterone levels and both enhance catalepsy and decrease DA levels in the nucleus accumbens with subsequent neuroleptic challenge (10). Because acute stress induces behavioral augmentation to both psychostimulants and neuroleptics, which presumably have opposite pharmacological effects, it has been suggested that the sensitizing effect of a drug may not be the direct result of its pharmacological actions, but rather to nonspecific stress-inducing effects resulting from its novelty (4,10). For the most part, vehicle injection in the present study failed to alter catalepsy and extracellular DA overflow in the striatum to subsequent vehicle or fluphenazine administration. The one exception was measurement of catalepsy with the low dose of fluphenazine at the day 1 to day 15 interval, where the vehicle pretreatment group showed some evidence of sensitization when administered fluphenazine on the second test (day 15). The lack of robust sensitization to the injection procedure is not entirely surprising, considering animals were handled regularly to decrease the stress of handling during catalepsy measures and facilitate implantation of the dialysis probes. Because it has been demonstrated that some minimal threshold of stress is necessary to induce behavioral sensitization (10), the handling of animals in this study may have decreased the amount of stress induced by initial vehicle injections. Previous work in our laboratory has indicated no significant effects of saline vehicle injection on extracellular DA levels (42), further supporting the idea that a single saline vehicle injection may be below the threshold required to induce DA mediated sensitization to stressors in regularly handled animals.

Pharmacokinetic factors have been proposed as a possible explanation for behavioral sensitization but would appear to be unable to account for the prolonged behavioral augmentation observed at extended time points following a single pharmacological challenge (9). Recently, Cohen et al. (17) demonstrated that fluphenazine was not detectable in brain tissue 4 days after a single administration, while 5 days of daily administration marginally prolonged elimination. By comparison, haloperidol was found to persist in the brain beyond 21 days. These results suggest that fluphenazine was no longer present when sensitization was assessed at 15 and 30 days following a single pretreatment injection, and suggest

that both the behavioral sensitization and neurochemical tolerance we observed was not related to persisting levels of fluphenazine.

Although neuroleptic-induced behavioral sensitization of catalepsy has been clearly demonstrated (9), the synaptic mechanisms required for its expression remain unclear. Consistent with previous studies (20,47), we observed dose-related augmentation of extracellular DA levels in the striatum following acute neuroleptic administration. This increase in DA presumably results, in part, from the action of neuroleptics on DA autoreceptors which are thought to mediate DA release at the nerve terminal (45,46). Autoreceptor supersensitivity following subchronic (35) and chronic (40) neuroleptic administration is well documented. The possibility of persisting tolerance to a single neuroleptic treatment has also been examined. It has been found that rapid tolerance to augmented DA release developed following a single injection with haloperidol (20). However, this effect was not evident when a 24 h time interval separated the two injections. One recent study found that 10 days of repeated fluphenazine administration produced significant autoreceptor supersensitivity in the striatum that was absent when fluphenazine was acutely administered (14). Our observation of profound tolerance of DA overflow to a second fluphenazine administration 15 and 30 days following an initial pretreatment suggests the existence of two possible tolerance mechanisms: an early tolerance possibly mediated by a transient feedback effect and a second tolerance phenomenon that may be associated with behavioral sensitization or other persisting neuroleptic induced changes.

Several studies have indicated that some forms of behavioral sensitization to psychostimulants are related to alterations in DA release (2,3,28,38), while other studies have found that increases in extracellular DA are not necessary for the development of locomotor sensitization (22,43). Although the long-lasting tolerance to fluphenazine-induced DA overflow produced by a single preexposure may be due to altered autoreceptor sensitivity, our findings do not imply that the phenomenon of behavioral sensitization is solely due to presynaptic mechanisms. In the present study, catalepsy and extracellular DA levels did not follow a clearly related temporal pattern (e.g., catalepsy persisted while extracellular DA levels fell significantly after 5 h). This lack of correlation is consistent with previous research suggesting a dissociation between catalepsy and extracellular DA activity (47). While our results do suggest alterations in extracellular DA accompany behavioral sensitization to neuroleptics, because of the apparent disassociation between the persistence of catalepsy and extracellular DA concentrations it remains unclear how these changes relate to cataleptic sensitization. In addition, while other studies have found cataleptic sensitization to neuroleptic exposure increases with time (9,10), we found no time-dependent alterations in extracellular DA overflow and catalepsy response when comparing the 15 and 30 day administration intervals.

In addition to DA release, a number of other factors may play a role in mediating neuroleptic-induced behavioral sensitization of catalepsy. Both D_1 and D_2 DA receptor subtypes appear to be important in the expression of catalepsy (32,44). However, catalepsy does not appear to be altered following an upregulation of postsynaptic DA receptors (24). One recent report (30) suggests behavioral sensitization may involve intracellular mechanisms based on the finding that inhibitors of protein synthesis block the initiation and expression of sensitization to cocaine and amphetamine in a manner independent of dopaminergic and glutamatergic function. Therefore, behavioral sensitization may involve both synaptic and intracellular mechanisms in a manner similar to long-term potentiation, a well-characterized adaptive phenomenon in which a single stimulus leads to prolonged neural changes.

The present results have demonstrated that a single fluphenazine administration produces long-lasting effects on motor function and striatal DA activity. These findings are consistent with previous literature suggesting that even limited neuroleptic exposure has a profound effect upon the extent to which neurochemical and behavioral measures show tolerance or become sensitized. Consequently, a better understanding of how the dosing regimen of neuroleptics differentially alters DA function and DA-mediated behaviors may serve to increase the psychotherapeutic effects of these compounds while minimizing their motor side effect liability.

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