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Pharmacologic Control of Pemoline Induced Self-Injurious Behavior in Rats

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MUELLER, K. AND W. L. NYHAN. *Pharmacologic control of pemoline induced self-injurious behavior in rats.* PHARMAC. BIOCHEM. BEHAV. 16(6) 957–963, 1982.—Administration of oral pemoline produces long lasting amphetamine-type stereotyped behavior and persistent self-biting behavior in rats. The effects of haloperidol, pimozide, diazepam, and serotonin depletion by pretreatment with p-chlorophenylalanine (PCPA) or chronic pretreatment with p-chloroamphetamine (PCA) on abnormal behavior produced by pemoline were studied. Diazepam consistently increased the duration of stereotyped behavior. It also reduced licking/biting and self-biting but the latter effects were not consistent. Pretreatment with PCA had negligible effects on stereotyped behavior. Pretreatment with PCPA dramatically increased locomotion and rearing without affecting the other components of stereotypy—stereotyped head movements, licking/biting, and self-biting. Haloperidol (0.2 and 0.3 mg/kg) produced a dose related normalization of pemoline induced behaviors, including elimination of self-biting. Pimozide (0.5, 0.8 and 1.3 mg/kg) had little or no effect on behaviors such as locomotions, rears, licking/biting, or stereotyped head movements but eliminated self-biting at 1.3 mg/kg. These data suggest that pemoline, like amphetamine, produces stereotyped behavior through central dopaminergic mechanisms. Dopaminergic mechanisms also appear to be involved in pemoline induced self-biting. Pemoline is apparently pharmacologically and behaviorally very similar to amphetamine. Pemoline may provide a useful animal model for syndromes characterized by self-injurious behavior and other repetitive behaviors.

Pemoline Benzodiazepines Diazepam p-Chloroamphetamine p-Chlorophenylalanine Haloperidol Pimozide Self-biting

PEMOLINE (2-imino-5-phenyl-4-oxazolidinone) is a long acting central stimulant which produces amphetamine-like behavioral effects in rats. Because pemoline also reliably produces self-biting behavior in rats it may provide a useful model for severe self-injurious behavior in humans, particularly in those cases associated with physiological disorders such as the Lesch-Nyhan syndrome, the deLange syndrome, and Tourette's syndrome. We therefore investigated the pharmacological control of pemoline induced self-biting, beginning with three systems which have been implicated in self-injurious behavior in humans, serotonin, benzodiazepines, and dopamine.

Self-injurious behavior occurs with some frequency in the Lesch-Nyhan syndrome [19], the deLange syndrome [23], and occasionally in Tourette's syndrome [6]. Each of these syndromes is also accompanied by motor disorders. Cerebral palsy accompanies the Lesch-Nyhan syndrome, hyperactivity and stereotyped behavior accompany the deLange syndrome, and tics and other repetitive behaviors are defining characteristics of Tourette's syndrome.

Serotonergic mechanisms have been implicated in each of these syndromes. Excretion of serotonin metabolites is abnormal in the Lesch-Nyhan syndrome [27] and administration of 5-hydroxytryptophan improves behavior at least temporarily [16,20]. Whole blood serotonin levels are depressed in the deLange syndrome [10] and the ratio of serotonin to dopamine metabolites is altered in the cerebrospinal fluid of Tourette's patients [3].

There is reason to believe that benzodiazepines may be involved in behavioral abnormalities of Lesch-Nyhan patients, since high levels of inosine and hypoxanthine are found in their cerebrospinal fluid [26]. Both of these purines bind to brain benzodiazepine receptors [24], although whether they exert behavioral effects similar to diazepam is unclear [5,25]. Most Lesch-Nyhan patients are maintained on Valium®.

Compulsive behaviors exhibited by deLange and Tourette's patients are suggestive of stereotyped behaviors seen after amphetamine overdose. Thus, neuroleptics with dopamine receptor blocking activity would seem to be a logical therapeutic choice. Thus haloperidol effectively improves behavior in many Tourette's patients [15] and droperidol has recently been reported to improve self-injurious behavior in a heterogenous group of mentally handicapped patients [2]. Central dopaminergic dysfunction has recently been suggested in the Lesch-Nyhan syndrome [13].

The self-injurious behavior produced in rats by pemoline has been described previously [17]. Self-biting most frequently occurs on the medial digits of the forelimbs or the dorsomedial aspect of the forefoot. Less frequently self-biting occurs on the thorax or abdomen, and very rarely, self-biting occurs on the hindlimb or tail. Occasionally, tissue damage secondary to repetitive behaviors other than self-biting also occurs. Self-biting is accompanied by other stereotyped behaviors, such as stereotyped head movements (SHM) and persistent licking/biting of the cage. The animals

exhibit impaired open field behavior, impaired responsiveness to sensory stimuli, and impaired social behavior.

In contrast to amphetamine, which exerts effects on several neurotransmitter systems, pemoline is thought to release almost exclusively central dopamine [7]. With the exceptions of the presence of self-biting and the absence of such behaviors as backwards locomotion and circling, pemoline induced stereotyped behavior is virtually indistinguishable from amphetamine induced stereotyped behavior. With these observations in mind, we wondered whether pemoline induced self-biting is also under dopaminergic control, or whether it represents a pharmacological effect of very high doses of pemoline on non-dopaminergic receptor populations.

We found that haloperidol was extremely effective in normalizing pemoline induced behaviors; pimozide eliminated self-biting but at fairly high doses. Diazepam consistently increased the duration of pemoline stereotypy. p-Chlorophenylalanine (PCPA) dramatically increased locomotions without affecting the other components of stereotypy; p-chloroamphetamine (PCA) had little effect on pemoline stereotypy.

METHOD

Subjects

Male Long Evans hooded rats (Simonsen, Gilroy, CA) weighing from 200 to 330 g were used. The animals were maintained on a 12 hour light/dark cycle in individual nesting boxes (54×23×20 cm). Water (in an automatic delivery system) and food were available ad lib.

Drugs

Pemoline (Sigma) was administered orally to all animals at a dose of 230 mg/kg as described previously [17]. PCA (Sigma) was injected intraperitoneally (IP) at 5 mg/kg for three days, with the last injection 44 hours before pemoline administration. PCPA (Sigma) was injected IP (in arachis oil) 44 hours before pemoline administration. Diazepam (Hoffman LaRoche) was suspended in gum arabic and injected IP at 5 mg/kg. Haloperidol (McNeil) was dissolved in warm lactic acid, diluted with normal saline, and administered IP (0.2 or 0.3 mg/kg). Pimozide (Janssen) was suspended in gum arabic and administered IP (0.5, 0.8, or 1.3 mg/kg). Animals not injected with diazepam, haloperidol, or pimozide were injected with gum arabic.

Data Collection

The animals were observed in the home cages for 3 minutes every 3 hours for 36 hours (because of the long duration of action of pemoline, behavioral changes occurred very slowly). Behaviors were recorded in the following manner:

Locomotion. The animal's cage was divided longitudinally into three areas and the number of times a line was crossed with all four feet was recorded.

Rearing. A rear was defined as raising the forefeet at least three inches off the floor for at least one second. The subsequent rear was not recorded unless the animal's feet had returned to the floor for at least one second. The number of rears during the three minute period was recorded.

Licking/biting. Licking or biting of the cage wall, floor, or the metal ring surrounding the automatic watering system aperture were rated on a scale from 0 (none) to 3 (occupying the entire three minute period). Fractional values were occasionally recorded.

Stereotyped head movements (SHM). Repetitive head movements were rated on a scale from 0 (none) to 3 (rapid and intense). Fractional values were occasionally recorded.

Occurrence of grooming, eating, drinking, and resting was also noted. At the conclusion of each observation period, the animals were examined for tissue damage; animals which exhibited severe SB such as amputation of digits or extensive involvement of the thorax were sacrificed with an overdose of barbitureates. Otherwise the animals were returned to the rack for completion of the experiment.

Experiment 1

Twenty-four rats were pretreated with PCA as described above. These rats and 24 others were administered oral pemoline. One half of the animals in each group (PCA and no PCA) were injected with diazepam immediately after pemoline administration and every five hours thereafter for a total of four injections. The remaining animals were injected with gum arabic. Thus the experiment was a 2×2 factorial design with the two factors being PCA and diazepam.

Experiment 2

Twenty-four rats were pretreated with PCPA as described above. These rats and 24 others were administered oral pemoline. One half of the animals in each group (PCPA and no PCPA) were injected with diazepam (5 mg/kg) immediately after pemoline administration and every five hours thereafter for a total of four injections. The remaining animals were injected with gum arabic. Thus the experiment was a 2×2 factorial design.

Experiment 3

Three experiments were performed. In the first experiment animals received 0.2 mg/kg haloperidol, 0.5 mg/kg pimozide, or gum arabic immediately after pemoline administration, and at 5, 10, and 15 hours after pemoline administration. There were 12 animals in each group for a total of 36 animals. In the second experiment animals received 0.3 mg/kg haloperidol, 0.8 mg/kg pimozide, or gum arabic 1 hour before pemoline administration, and at 5, 10, and 15 hours after pemoline administration. Again, a total of 36 animals was tested. In the third experiment animals were administered 1.3 mg/kg pimozide or gum arabic 1 hour before pemoline administration and 5, 10, and 15 hours after pemoline administration. There were 13 animals in each group for a total of 26 animals. In addition, five animals were treated in the same manner but were undrugged. These animals were injected with gum arabic at times coinciding with the pimozide injections.

RESULTS

Undrugged animals slept during most observation periods. During active observation periods the most frequent activity was grooming, followed by rearing and locomotion. Undrugged animals never exhibited more than 5 locomotion counts or 6 rearing counts in the home cage during a single observation.

An example of the type of data yielded by our collection system is shown in Fig. 1. The sequence of behavioral changes exhibited by this rat is characteristic of pemoline. Locomotions and rears generally occur only at the beginning and end of the 36 hour testing period. SHM become rapidly

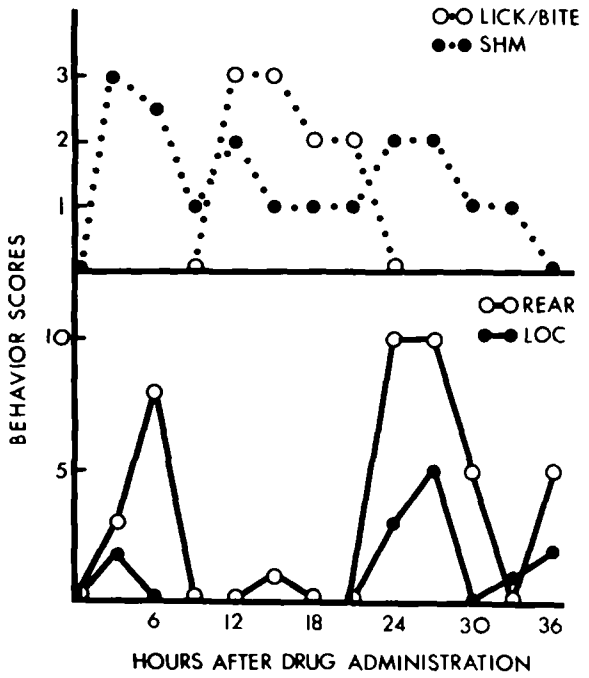

FIG. 1. Behavior of an individual animal after administration of oral pemoline (at 0 hours).

TABLE 1

INCIDENCE AND LATENCY (MDN AND RANGE) TO SELF-BITING

Group	Incidence*	Latency (hr)
No PCPA-No Diazepam	5/12	27 (6–27)
No PCPA-Diazepam	2/12	33
PCPA-No Diazepam	7/12	18 (9–27)
PCPA-Diazepam	7/12	12 (6–18)
No PCA-No Diazepam	8/12	18 (9–33)
No PCA-Diazepam	7/12	27 (12–33)
PCA-No Diazepam	7/12	18 (12–27)
PCA-Diazepam	4/12	21 (12–24)
Control	5/12	9 (3–18)
Haloperidol 0.2 mg/kg	0/12	—
Pimozide 0.5 mg/kg	5/12	9 (6–36)
Control	6/12	13.5 (3–27)
Haloperidol 0.3 mg/kg	1/12	12
Pimozide 0.8 mg/kg	5/12	12 (6–21)
Control	6/13	10.5 (6–21)
Pimozide	0/13	—

*The number of animals exhibiting self-biting is shown in the numerator; the number of animals tested is shown in the denominator.

apparent, but decrease as the animals spend more time licking/biting (the biting behavior often differs from that seen in an undrugged rat only in its duration). As licking/biting decrease, SHM increase, then decrease as locomotions and rears reappear. Pemoline treated rats were virtually never observed grooming, sleeping, eating, or drinking during the first 24 hours of testing.

Self-biting (SB) appeared throughout the 36 hours (see Table 1) but was most often seen from 12 to 15 hours after drug administration. SB ranged in severity from fur removal, usually on the dorsomedial aspect of the forefoot, to amputation of digits. There was no obvious difference in the severity of SB or in the amount of time engaged in SB among the various groups.

Home cage behaviors such as locomotions, rears, SHM, and licking/biting were virtually identical for rats which exhibited SB and for those which did not. Therefore, to avoid statistical problems generated by the euthanasia of self-biters before completion of the 36 hour test, behaviors of animals not exhibiting SB are shown in subsequent figures. Behavior scores have been added each four observation periods, thus the maximum possible score for SHM and licking/biting is 12. Unless otherwise noted medians are reported throughout as they are more conservative with respect to differences between groups since distributions of locomotions and rears tended to be positively skewed. However, analysis of variance (ANOVA) was used to evaluate differences between groups (with respect to locomotions and rears) as this procedure is robust with respect to degree of normality of distributions involved.

As indicated in Fig. 2, PCA had no significant effect on locomotions, rears, SHM, or licking/biting in the home cage. PCPA also had no effect on SHM or licking/biting, but dramatically increased locomotion counts at 24, ANOVA, $F(1,23)=13.31$, $p<0.005$, and 36 hours $F(1,23)=22.30$, $p<0.001$. Rearing counts were also dramatically increased by PCPA at both 24, $F(1,23)=5.84$, $p<0.025$, and 36 hours, $F(1,23)=21.56$, $p<0.001$.

Diazepam slightly reduced locomotions at 24 hours, but this effect was significant only in the PCA experiment, $F(1,23)=8.94$, $p<0.01$. Diazepam had no consistent effect on rears. SHM were prolonged by diazepam. Diazepam significantly increased SHM at 24 hours in the PCPA experiment, and significantly increased SHM at 24 hours in the PCPA experiment, and significantly increased SHM at 36 hours in both experiments, (Kruskal-Wallis, $p<0.05$). In the PCA experiment diazepam reduced licking/biting at 12 and 24 hours, although the effect was only significant at 12 hours, (Kruskal-Wallis, $p<0.05$). In both experiments one of the diazepam groups exhibited higher licking/biting at 36 hours, but this effect was significant only in the PCPA experiment. Thus diazepam consistently increased the duration of SHM, and had less consistent effects on licking/biting.

The effects of pimozide and haloperidol on the incidence and latency to self-biting are shown in Table 1. Haloperidol virtually eliminated SB at both 0.2, ($\chi^2=6.93$, $p<0.05$), and 0.3 mg/kg, ($\chi^2=5.25$). One haloperidol treated rat exhibited a small superficial puncture wound on the ventral surface of the neck. We believe that this wound was unrelated to administration of pemoline since we occasionally observe similar wounds on undrugged animals. The appearance of the wound was unlike any we have observed during pemoline induced SB. Further the animal in question exhibited minimal stereotypy throughout the 36 hour test. Pimozide reduced self-biting only at the highest dose tested, 1.3 mg/kg, ($\chi^2=5.90$, $p<0.025$).

Home cage behaviors of animals not exhibiting SB are shown in Fig. 3. Note that control data (pemoline plus gum

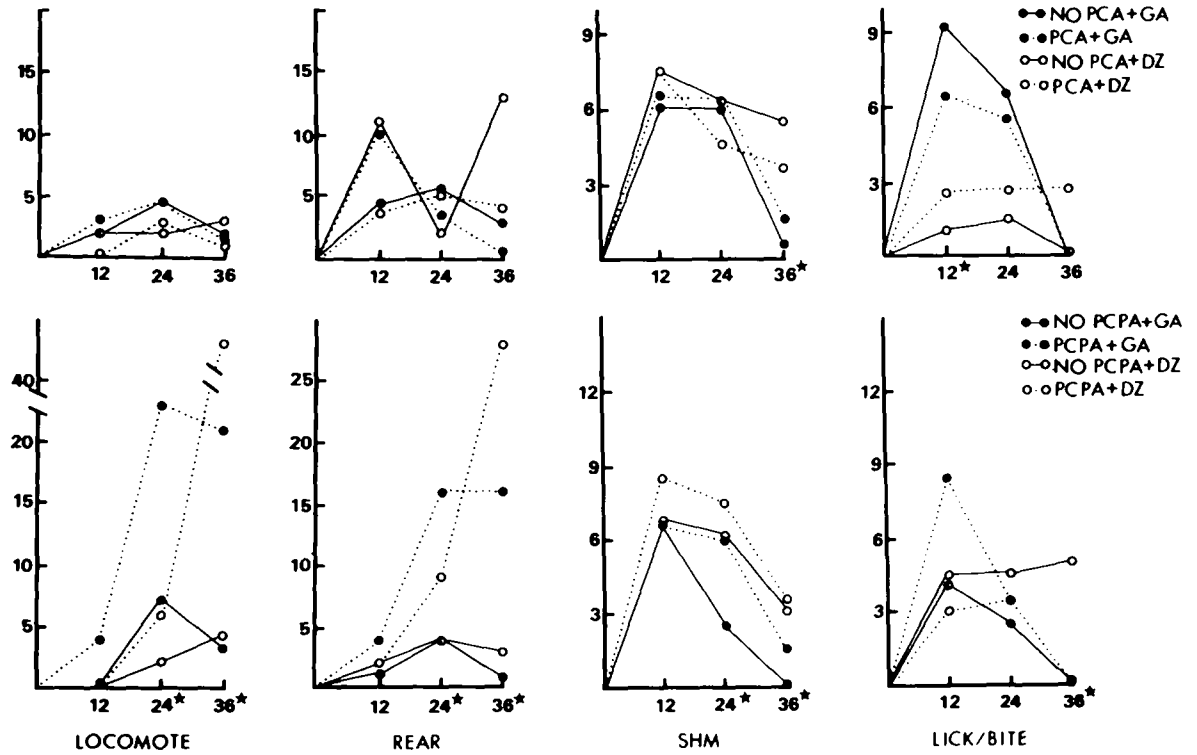

FIG. 2. Effects of PCA (upper), PCPA (lower), and diazepam (DZ) or vehicle (GA) on pemoline induced stereotyped behavior. * Indicates statistically significant ($p<0.05$) differences between groups.

arabic) were roughly similar in all three experiments. As shown in Fig. 3, haloperidol significantly increased locomotions, $F(2,22)=6.45$, $p<0.01$, and decreased licking/biting at 0.2 mg/kg, (Kruskal Wallis, $H=9.20$, $p<0.02$). At 0.3 mg/kg locomotions were increased, $F(2,21)=4.69$, $p<0.025$, (to a greater degree than at the lower dose) and licking/biting were reduced (to a greater degree than at the lower dose) at both 12 hours, ($H=14.10$, $p<0.001$), and 24 hours, ($H=11.36$, $p<0.01$). Thus the effects of haloperidol were dose related. These effects of haloperidol were apparent within the first 12 hours of observations; in fact, they were apparent within the first 3 hours (data not shown).

At 0.3 mg/kg haloperidol the animals were easily distinguishable from those receiving pemoline plus pimozide or pemoline plus gum arabic. Licking/biting and SHM were dramatically reduced; locomotions were apparent during the first 12 hours of testing; sleeping reappeared within 12 hours after drug administration (over half of the haloperidol rats slept through 3 of the 4 observations from 15 through 24 hours after drug administration while only 3 instances of sleeping were observed during the same time period for rats receiving pemoline alone); haloperidol treated rats exhibited grooming both during the early and late portions of testing while rats receiving pemoline plus gum arabic virtually never groomed. Thus haloperidol was extremely effective in normalizing behavior.

Pimozide had no significant effect on locomotions, rears, or SHM at any dose tested. At 1.3 mg/kg pimozide significantly reduced licking/biting at 24 hours after pemoline administration, ($H=4.74$, $p<0.05$). However, the magnitude of reduction was small with respect to that produced by haloperidol.

Of the various behaviors recorded, locomotions and licking/biting seemed to be the most useful for detecting changes in the pemoline response. The number of rears was always highly variable, perhaps because it reflected both rearing which accompanies usual exploratory behavior, and repetitive rearing which is occasionally a component of pemoline induced stereotyped behavior. SHM were not a sensitive measure of the pemoline response; that behavior suggested only a decrease in the duration of stereotypy in rats receiving 0.3 mg/kg haloperidol, ($H=11.98$, $p<0.01$).

DISCUSSION

Pemoline reliably induces SB behavior that is dose dependent [17]. If serotonin is involved in this abnormal behavior, serotonin depletion by PCA or PCPA would result in either altered rates of SB, or differences in the severity of SB. Neither of these results was obtained consistently in the current experiment. Benzodiazepines also had no clear effect on SB behavior, although the duration of stereotypy was consistently increased by diazepam. On the other hand, haloperidol, a presumed dopamine receptor blocker, was extremely effective in preventing SB and normalizing behavior. Pimozide also eliminated SB, although at fairly high doses. Thus pemoline induced SB appears to be primarily a dopaminergic phenomenon.

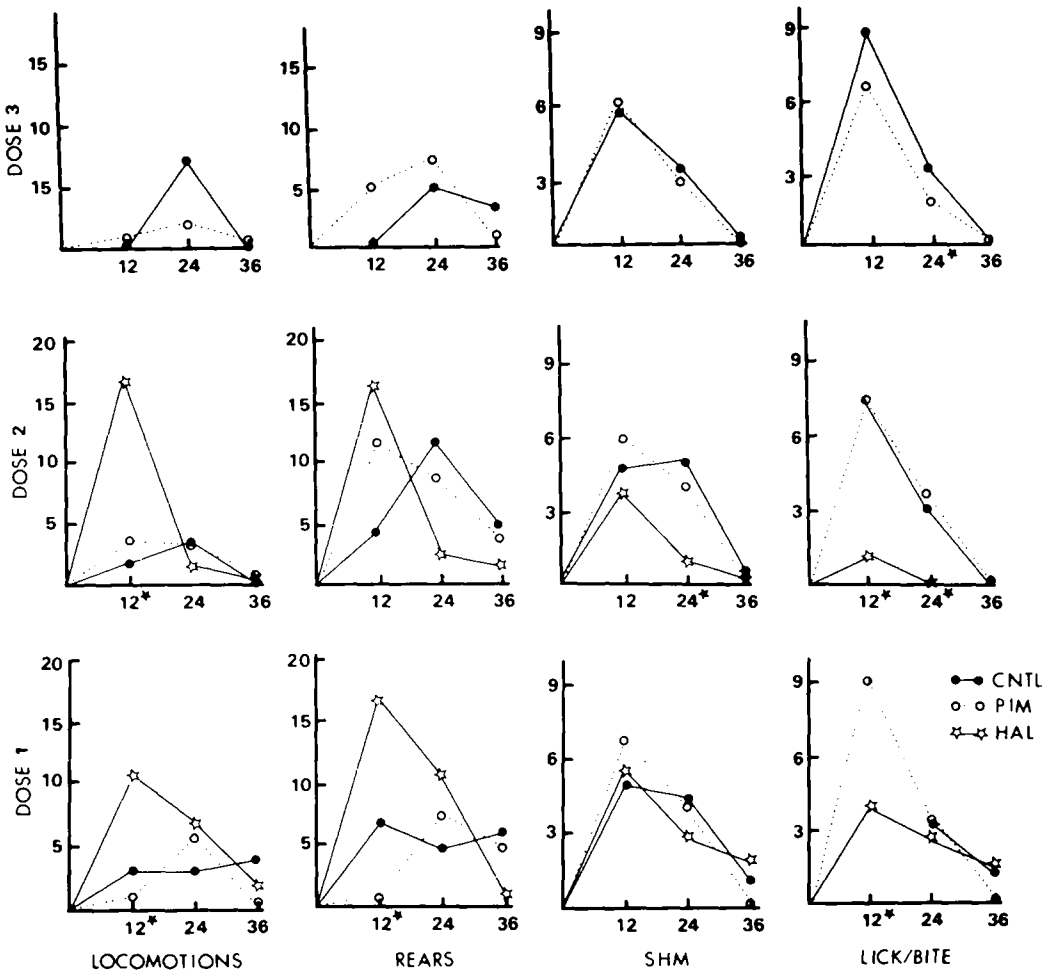

FIG. 3. Effects of pimozide (PZ) and haloperidol (HAL) on pemoline induced locomotions (far left), rears (left), SHM (right), and licking/biting (far right). Dose 1 (lower) is 0.2 mg/kg haloperidol and 0.5 mg/kg pimozide; dose 2 (center) is 0.3 mg/kg haloperidol and 0.8 mg/kg pimozide; dose 3 (upper) is 1.3 mg/kg pimozide. Control (CNTL) animals received pemoline and gum arabic. * Indicates statistically significant ($p<0.05$) differences between groups.

Although serotonin has been implicated in the three syndromes mentioned earlier, one must keep in mind the difficulty of inferring brain serotonin levels from peripheral fluids, or even from cerebrospinal fluid [9]. And further a role of hindbrain, rather than forebrain serotonin has not been excluded. Both PCA and PCPA dramatically and selectively reduce forebrain serotonin but by different mechanisms; PCA is a selective neurotoxin [12] and PCPA inhibits serotonin synthesis [11]. Although we were unable to alter the incidence or severity of SB produced by pemoline with either of these drugs, serotonin depletion had dramatic effects on other behaviors.

PCPA increased both spontaneous [8] and amphetamine induced activity [14]. In the current experiment PCPA dramatically increased both locomotions and rears (regardless of the presence of diazepam) in pemoline treated rats without affecting the other components of stereotyped behavior such as SHM or licking/biting. Thus although serotonin depletion was not verified by biochemical analysis in this study, the behaviors observed suggest that serotonin depletion was in fact achieved but did not affect SB behavior.

Diazepam has been previously reported to increase the duration of stereotyped behavior induced by amphetamine [1] and we found that diazepam had similar effects when given with pemoline. There were indications that diazepam might also reduce locomotions, licking/biting and SB, but the latter findings were inconsistent.

Pemoline induced self-biting was eliminated by two widely used dopamine antagonists, haloperidol and pimozide. Other components of stereotyped behavior were reduced in a dose related fashion by haloperidol; the effect of haloperidol in these experiments seemed to be to produce behaviors which would be apparent following a much lower dose of pemoline. That is, stereotyped behaviors were reduced and hyperactivity was revealed. Pimozide was relatively ineffective in reducing SHM and licking/biting or in increasing locomotions.

Thus dopaminergic mechanisms are at least in part re-

sponsible for pemoline induced self-biting. But the ability of pimozide to selectively reduce SB suggests that the mechanisms of SB are not entirely identical to the mechanisms of stereotyped behavior in general. This hypothesis is supported by the observation that of the many central stimulants which produce stereotypy reports of SB produced by these agents have been rare and anecdotal (cf. [22]). In spite of the uncanny similarity between pemoline and amphetamine produced stereotypy, we have been unable to consistently produce SB with acute amphetamine.

Various classification systems for dopamine receptors have been proposed, but they do not immediately explain the ability of pimozide to selectively reduce pemoline induced SB. For example Puech, Simon, and Boissier [21] suggested that pimozide is a selective presynaptic antagonist. There seems to be general agreement that whatever the proper receptor classification, haloperidol is a relatively nonselective antagonist [4,21]. Further, pimozide is known to be less effective than haloperidol in reducing stereotypy.

Given the multiple injection schedule employed and the relatively long half-life of haloperidol and pimozide, levels of these drugs probably accumulated throughout the first 18 hours of the experiment. The rapid (within three hours) effect of haloperidol suggests that an accumulation of drug is not essential for its ability to normalize pemoline induced abnormal behavior. On the other hand, pimozide should have accumulated to high levels, particularly during the first 24 hours of the experiment. Thus the actual dose required to reduce pemoline induced SB by pimozide may be greater than 1.3 mg/kg.

The ability of dopamine blockers to eliminate pemoline induced SB may have implications for the self-injurious behavior which accompanies the Lesch-Nyhan syndrome, deLange syndrome, and Tourette's syndrome. Tourette's syndrome is generally thought to be related in part to a central dopaminergic dysfunction [3] and droperidol (which is closely related to haloperidol) has been reported to improve self-injurious behavior in a heterogenous group of mentally handicapped patients including deLange patients [2]. Pemoline appears to provide a uniquely appropriate model for the deLange and Tourette's syndrome, in which both self-injurious behaviors and other repetitive behaviors are seen. The recent report of dopamine deficiency in the basal ganglia of Lesch-Nyhan brains examined post mortem [13] may be suggestive of dopamine receptor supersensitivity. Thus very high doses of a dopaminemimetic such as pemoline may also provide a useful model system for the Lesch-Nyhan syndrome. Further, a recent case report of a pemoline overdose suggests that its behavioral effects are similar in both rats and humans. Hyperactivity, repetitive tongue protrustion, and stereotyped movements of fingers and hands were observed [18]. We have observed repetitive tongue protrusion in some Lesch-Nyhan patients.

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