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Pemoline-Induced Self-Biting in Rats and Self-Mutilation in the deLange Syndrome[1]

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MUELLER, K. AND S. HSIAO. *Pemoline-induced self-biting in rats and self-mutilation in the deLange syndrome.* PHARMAC. BIOCHEM. BEHAV. 13(5) 627–631, 1980.—Self-mutilation in humans occasionally accompanies physiological disorders such as the deLange syndrome. If pemoline-induced self-biting is behaviorally similar to self-mutilation in the deLange syndrome, similar neurochemical mechanisms may be involved in both. Oral administration of 140 and 220 mg/kg pemoline reliably induced persistent self-biting in rats. This behavior was indistinguishable from stereotyped grooming and its most common target was the medial digits of the foreleg. Pemoline-induced self-biting was accompanied by hyperactivity, stereotyped behavior, abnormal social behavior, abnormal sensorimotor behavior, and unresponsiveness or avoidance of moderate levels of sensory stimuli. Several of these behaviors have also been reported in deLange patients.

deLange syndrome Pemoline Grooming Self-mutilation Stereotyped behavior

AN animal model for self-mutilation in humans would facilitate the study of neurochemical mechanisms and would suggest appropriate treatments for this disturbing behavior. A useful animal model would share both behavioral and biochemical aspects with self-mutilation in humans. This report is concerned with the behavioral aspects of self-biting induced in rats by pemoline and the similarities to the behavioral characteristics of the deLange syndrome.

Self-mutilation occurs in about 10% of the severely retarded population [2], but occurs at a much higher frequency in certain syndromes, one of which is the deLange syndrome. These patients exhibit mental and physical retardation, a distinctive facial appearance, and deformities of hands, feet, and upper limbs. These physiological abnormalities are often accompanied by distinct behavioral symptoms. Hyperactivity and self-mutilation are obvious [2, 6, 15] but more subtle abnormalities have also been reported. These include stereotyped behavior and abnormal social behavior [7].

Interest in the use of animal models for the study of self-mutilation has become evident only recently. Jones and Barraclough [8] have reviewed reports of self-mutilation in animals in relation to self-mutilation in humans and Jones *et al.* [9] have compared the circumstances surrounding self-injury in humans with those surrounding self-mutilation in animals.

Several drugs (caffeine, theophylline, clonidine, and pemoline) have been reported to induce self-biting in rodents [1, 5, 10, 13] but the behavioral characteristics which accompany self-biting have received little attention. Pemoline was employed in this study because of the reliability of the phenomenon and the low ratio of effective dose to lethal dose. A behavior test was devised in an attempt to characterize self-biting induced by pemoline and to determine circumstances which might reduce the severity of self-biting.

METHOD

Subjects

Male albino rats bred from Holtzman stock were housed individually in standard wire mesh cages. Water was always available; food was available ad lib except as noted below. Body weights of the 28 rats ranged from 280 to 393 g at the time of testing. The animals were maintained on an artificial 12-hr light/dark cycle.

Procedure

The week prior to testing the animals were habituated to consuming a graham cracker slurry (presented on a spoon) and peach flavored yogurt (available in a beaker in the cage). Pemoline is virtually insoluble and does not form uniform suspensions suitable for intragastric administration. Therefore, to insure accuracy of the dose administered, pemoline was given orally by addition to yogurt, a highly preferred food for rats.

After 18 hr of food deprivation 12 rats were fed 140 mg/kg pemoline (Sigma) and 12 rats were fed 220 mg/kg. Pemoline was always administered at the beginning of the dark cycle. Immediately after consumption of the drugged yogurt the animals were transferred to individual polyethylene nesting boxes (44 by 24 by 21 cm) with wood shavings for bedding.

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TABLE 1
LATENCY AND SEVERITY OF PEMOLINE-INDUCED SELF-BITING IN RATS

Dose	Latency*	Severity†
220 mg/kg	18 (3–48)	183 (84–200)
140 mg/kg	22.5 (7–58)	34 (0–198)

*The median (hours) and range are shown.
†Severity scores range from 0 (no self-biting) to 200 (maximal self-biting). The median and range are shown.

An additional group of four animals were treated in the same manner with the exception that the yogurt was undrugged.

The animals were examined for signs of self-biting at various times (2, 4, 7, 10, 13, 22, 26, 31, 34, 46, 50, 55, and 58 hr after drug administration) in the following manner. The behavior of each animal was recorded for 5 min (during the dark cycle a red light was illuminated to facilitate observation). After all animals had been observed each rat was examined for hair removal, irritated or lacerated tissue, or other physical evidence of self-biting. If the rat was observed to bite any area of the body and if physical evidence of self-biting was observed, the animal was subjected to a behavior test as described below.

If self-biting continued to the point of amputation of digits or extensive involvement of the thorax the animal was injected with an overdose of anesthetic solution. Because the animals often did not drink during the first 36 hr after treatment, all animals were administered 5 ml of tap water intragastrically at 13 hr after drug administration.

Behavior Test

The animal was first observed undisturbed for 6 min and the time spent self-biting was recorded. (These periods of undisturbed observation are referred to below as 'baseline' periods.) Next the animal was gently prodded on the flank and head with a Q-tip. This portion of the behavior test is referred to as 'orientation' since it tests the animal's ability to orient to a mild tactile stimulus. Several objects (rat chow, shredded paper towels, a pencil with an eraser, and a small wire grid) were then placed in the nesting box directly in front of the rat. Each object, or set of objects, was removed before the next was placed in the box. Exploration or biting of the objects was recorded. This portion of the behavior test is referred to as 'biting objects.' A spoon containing a graham cracker slurry was placed in front of the rat and the animal's response to this highly preferred food was recorded. After 90 sec the spoon was withdrawn and the animal was placed in an open field (71×52×22 cm) divided into 12 areas. For 4 min the number of lines crossed and the time spent self-biting were recorded. Open fields are commonly used to infer activity levels in a mildly stressful situation. Upon removal from the open field the animal was placed on the side of a wire mesh cage suspended in the air. The animal's ability to cling to the wire and climb to the top of the cage was recorded. This 'clinging' test is a simple measure of sensorimotor competence [14]. After a 3-min baseline period an undrugged rat was placed in the nesting box for 3 min. (The same undrugged rat was used throughout testing.) The occurrence of sniffing, following, mutual grooming, and other social behaviors was recorded. Another 3-min baseline period was followed by 3 min of loud auditory stimulation; the animal's cage was repeatedly struck with a metal coffee can.

The remainder of the behavior test was performed 2 hr later. It consisted of a 5 min baseline, application of xylocaine, a topical anesthetic, on the affected areas, and immersion in water. Wetting the fur of undrugged rats reliably induces grooming. Thus if pemoline-induced self-biting is related to exaggerated grooming, the increased frequency of grooming behavior should be accompanied by an increased frequency of self-biting.

RESULTS

Preliminary Observations

All animals consumed the yogurt within 4 min; the beakers were usually licked clean. Within 10 min after ingestion of the drugged yogurt the animals appeared hyperactive with respect to the controls. By the first observation period (2 hr after drug administration) drugged animals were exhibiting highly repetitive behaviors, referred to collectively as stereotypes. One rat was observed to stand on its hind legs and sniff the top of the nesting box continuously for 10 min. A common stereotypy was sitting on the haunches and chewing or manipulating bits of nesting material held near the mouth with the forefeet. Another common stereotypy was intense sniffing of a particular area of the body accompanied by repetitive movements of the front feet and lateral movements of the head. Locomotion was rare except that drugged rats often leaped from the nesting box and ran as soon as the lid was removed. Rarely, highly stereotyped behavior was punctuated by wild leaping and running about the nesting box. Backwards locomotion was also occasionally observed. None of these behaviors was exhibited by the control animals. Drugged rats groomed their forefeet but were virtually never observed to groom their bodies (side, flank, abdomen, or tail) but undrugged rats groomed forefeet, face, and body frequently. Drugged rats were never observed to sleep until the second day after drug administration although control rats often slept during observation periods. Most drugged rats did not eat or drink until the second day of testing.

By the end of the 58 hr of observation 10 of 12 rats and 12 of 12 rats receiving 140 and 220 mg/kg, respectively, exhibited physical evidence of self-biting. The most frequently bitten areas of the body were the medial digits and the dorsomedial aspect of the forefeet. Lateral digits of the forefeet were never bitten. Occasionally the involved area extended up the medial surface of the foreleg and less often the skin of the throat and thorax was bitten. Amputation of digits was

TABLE 2

BEHAVIORAL CHARACTERISTICS OF PEMOLINE-INDUCED SELF-BITING BY RATS

Group	First baseline	Orientation	Biting objects	Graham cracker	Open field	Clinging	Social behavior	Auditory stimulation
140/mg/kg	SB‡-28	R-2* NR-7 A-1	R-5 NR-2 A-3	R-8 NR-1 A-1	LC†-21 SB-2	Climb-3 Cling-3 Fall-4	R-3 NR-3 A-2 Box-2 SB-1	SB-8
220 mg/kg	SB-98	R-0 NR-5 A-6	R-1 NR-4 A-7	R-5 NR-1 A-5	LC-3 SB-100	Climb-1 Cling-2 Fall-8	R-0 NR-4 A-6 Box-1	SB-83
Control	SB-0	R-4 NR-0 A-0	R-4 NR-0 A-0	R-4 NR-0 A-0	LC-50	Climb-4 Cling-0 Fall-0	R-4 NR-0 A-0 Box-0	SB-0

*The number of animals exhibiting the indicated response is shown. R—the appropriate response is exhibited (see text), NR—no response; A—the animal avoids the stimulus by turning away, running away, or pushing it away.

†The mean number of lines crossed (LC) is shown.

‡The percent of time (median) spent self-biting (SB) is shown.

relatively common, but only the skin of the foreleg and thorax was bitten; i.e., muscle and bone of the foreleg or thorax were never damaged.

Behaviorally, the self-biting was indistinguishable from grooming of the forefeet (or thorax). The two rats which did not show physical evidence of self-biting exhibited behaviors resembling severe fragmented grooming.

Latencies to self-biting were highly variable (see Table 1). There were no significant differences between the latencies of the high and low dose animals (Kruskal Wallis ANOVA, $p<0.05$). To estimate the severity of self-biting, the percent of time spent self-biting in the opening baseline was added to the percent of time spent self-biting during the baseline which began the second portion of the behavior test (after the 2 hr interval). These severity scores are shown in Table 1. Self-biting was more severe in the group which received the high dose (Kruskal Wallis ANOVA, $H=10.26$, $p<0.001$). Thus, the severity, but not the latency of self-biting was dose-related.

The severity and latency of self-biting were only moderately correlated (Spearman's $r=4.4$, $p<0.05$). That is, some rats which began self-biting the second day after drug administration exhibited very persistent and severe self-biting. The control animals never exhibited any sign of self-biting.

One rat was found dead 13 hours after drug administration (220 mg/kg). Three other rats from this group were overdosed with anesthetic before completion of testing because of the severity of the self-biting.

Behavior Test

Characteristic responses to the behavior test are shown in Table 2. Each of the four undrugged rats tested oriented to the tactile stimulus of the Q-tip ('orientation' test). However, rats which exhibited self-biting either did not respond to the tactile stimulus (characteristic of 140 mg/kg) or actively avoided the tactile stimulus (characteristic of 220 mg/kg). All control rats explored the biting objects and occasionally manipulated and/or bit them. No experimental rat manipulated or bit the objects although some sniffed the objects. The most common response was to push the object aside with the foreleg and re-engage in stereotyped behavior. All control rats consumed the graham cracker slurry but there was an increasing tendency for drugged rats to ignore the food or to push it away.

The rats' behavior in the open field was also dose related. The control, low dose, and high dose animals crossed a mean of 49.5, 21.2, and 2.8 lines, respectively, (ANOVA, $p<0.001$). Thus locomotion decreased as a function of dose. When the proportion of time spent self-biting in the open field is compared to the proportion of time self-biting in the opening baseline, significant differences are also found (Fisher's exact test, $p<0.001$). The low-dose rats self-bit less often (by about 22%) but the high-dose rats self-bit more often (by about 19%). The large proportion of time spent self-biting by the high-dose rats (about 87%) is consistent with the small number of lines crossed by that group.

As measured by the 'clinging' test, the drugged rats exhibited sensorimotor incompetence. All four control rats clung to the wire cage; they climbed to the top in a mean time of about 16 sec. Only 5 of the 10 low-dose animals tested climbed to the top of the cage; only 1 of the 12 high-dose animals reached the top (Fisher's exact test, $p<0.05$). Some animals clung to the cage but did not climb to the top; some did not cling and fell off repeatedly.

The rats which exhibited self-biting did not exhibit normal social behavior. Few low-dose animals approached the undrugged rat which had been placed in the cage, although several exhibited exploratory sniffing when they were approached by the rat. The high-dose rats generally did not engage in any social behavior. These rats either continued highly stereotyped behaviors while being explored by the

undrugged rat, or pushed the rat away, or leaped away from the rat whenever they were approached. Although, some rats exhibited agonistic postures (rearing while baring teeth or boxing). There was a tendency for animals to spend a smaller proportion of time self-biting during the social behavior test than during the following baseline.

The loud auditory stimulation decreased self-biting in both groups. The proportion of time spent self-biting was compared to the mean proportion of time spent self-biting in the baseline periods immediately preceding and following the auditory stimulation. Fifteen of the 21 rats exhibited decreased self-biting (by about 20%) while only 1 rat exhibited increased self-biting.

The application of xylocaine and the immersion in water did not consistently affect the amount of time spent self-biting. Although wetting the fur of the four control rats always produced lengthy grooming, the drugged rats occasionally shook themselves but virtually never groomed. From this manipulation we could not tell whether pemoline-induced self-biting is grooming related.

DISCUSSION

Oral administration of pemoline in doses far below the oral LD_{50} (500 mg/kg) reliably induced self-biting in rats. The effects of the drug were dose-related and lasted for over 48 hr. The self-biting appeared to be intimately related to the appearance of stereotypies involving primarily the snout, mouth, and forefeet.

The self-biting was not simply a result of increased biting behavior in general. The drugged animals never bit any of the objects placed before them in their cage; nor did they bite a conspecific. Further, self-biting was restricted to particular body areas which were not always the most accessible areas.

The self-biting appeared to be the result of exaggerated fragmented grooming responses for two reasons. First it was behaviorally indistinguishable from certain components of grooming, with the exception that the components were not intermingled as they are in normal grooming. Self-biting of the digits and forefeet appeared to be the result of exaggeration of the licking, nibbling, and manipulative component of facial grooming. Self-biting of the thorax also was indistinguishable from repetitive grooming of the thorax and included both the combing, and biting, nibbling, and licking components.

Second, grooming often occurs in a fixed sequence which parallels the frequency with which the body areas were involved in self-biting. For example, in the control animals grooming after wetting of the fur virtually always began with bringing the forefeet to the mouth and licking, nibbling, and manipulating the forefeet—especially the dorsal area and the medial digits. This was followed by rapid stroking of the snout and face. The dorsal aspect of the foreleg and the medial digits were the most frequently observed targets of self-biting. Grooming generally next spreads to the foreleg and the animal's side. At this point the sequence may begin again, or grooming may spread to the flank or to the thorax,, abdomen, and genital area. A similar sequence has been described for the mouse [4]. Self-biting of the thorax and abdomen was observed the least often. Hind feet and tail are groomed less frequently and generally at the end of the grooming sequence. Self-biting of the hind foot and tail were not observed in this experiment, although during pilot work one rat exhibited mild self-biting of the tail. Thus, those areas of the body which are groomed early in the sequence were self-bit the most often; those areas which are groomed late in the sequence were self-bit the least often.

Although the self-biting was very persistent, it was also somewhat environmentally modifiable. Several of the manipulations in the behavior test were successful in reducing the amount of time spent self-biting.

Throughout the behavior test the drugged animals consistently failed to respond normally to sensory stimuli. Many of the low-dose animals failed to respond at all. The high-dose animals appeared to avoid sensory stimulation by running in the opposite direction or by pushing the object away. They did not orient well to tactile or food stimuli and did not respond to the biting objects. Nor did they respond to a strong stimulus to groom—wetting of the fur. These phenomena may be similar to sensory neglect or sensory rejection which accompany certain lesions of the lateral hypothalamus [14].

There were also indications of sensorimotor incompetence. Many animals did not cling to a vertical surface or climb to the top of a wire mesh cage. One animal continued to self-bite while held by the tail in an inverted position. These observations may indicate failure to respond to equilibratory stimuli and further support the hypothesis that pemoline treated animals are unresponsive to many sensory stimuli.

Comparing self-biting by animals to self-mutilation by humans is complicated by the cognitive capacities of humans. The latter can inflict self-injury not only by biting, picking, scratching, or banging, but also by the use of tools. In spite of these difficulties, there are obvious similarities between pemoline-induced self-biting in rats and self-mutilation by deLange patients.

DeLange patients, like pemoline-treated rats are hyperactive [6] and exhibit highly repetitive, or stereotyped, behaviors [2,7]. Further, several of the published descriptions of self-mutilative episodes by deLange patients are very suggestive of human counterparts of grooming.

For example, Bryson *et al.* [2] described a patient who licked the hand and rubbed the cheek with the back of the hand for hours at a time, resulting in secondary infection and chronic saliva dermatitis. These authors also described other cases of self-mutilation by picking at the eyes, hands, and feet. Another case particularly suggestive of exaggerated grooming was described by Shear *et al.* [15]. This patient would pick at the cheek with one hand and stroke the hair with the other. When the elbows were immobilized to prevent these activities, severe lip-biting began. These authors also described other cases of self-mutilation by picking and scratching. At this point one should note that combing the fur combined with licking and nibbling occurs in the grooming repertoire of cats, rats, and primates but picking and scratching become increasingly important components of grooming in primates.

Self-mutilation by deLange patients is environmentally modifiable; it has been suppressed by punishment [15]. Social behavior is also abnormal in deLange patients. Rather than orienting to another person, most deLange patients turn away. Avoidance of physical contact is also common [7].

In summary, deLange patients and pemoline-treated rats both exhibit the following behavioral characteristics: stereotyped behavior, hyperactivity, abnormal social behavior, avoidance of physical contact, and self-biting (or self-mutilation) in a manner suggestive of grooming. These behavioral similarities may indicate neurochemical similarities;

that is, pemoline may provide a useful animal model for the deLange syndrome.

We believe that these similarities between pemoline-induced self-biting in rats and self-mutilation in the deLange syndrome indicate that further study of the possible human counterparts of grooming is warranted. Further, they indicate the usefulness of precise behavioral descriptions, which are often not included in published reports of self-mutilation in humans or animals. Self-biting induced by other drugs is accompanied by distinctively different behavioral characteristics [11], just as self-mutilation which accompanies other syndromes in humans is likely to be somewhat different from that found in the deLange syndrome.

Finally we note in passing that some controversial claims have been made concerning the effects of pemoline on learning and memory in rats [3,16]. Most positive results seem to have been obtained with active avoidance tasks. For example, Plotnikoff [12] reported that pemoline improved learning and memory in the 'jump out' test; animals were trained to jump out of an apparatus to avoid an electric shock. The behavior of rats in this experiment, however, suggests that active avoidance behaviors of all types, including 'jumping out', are high frequency behaviors following pemoline administration regardless of whether learning contingencies are present.

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