DRUG-INDUCED SELF-BITING IN RODENTS: IMPLICATIONS FOR THE LESCH-NYHAN SYNDROME

by

Kathyrne Jean Mueller

A Dissertation Submitted to the Faculty of the

DEPARTMENT OF PSYCHOLOGY

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

THE UNIVERSITY OF ARIZONA

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MUELLER, KATHYRNE JEAN

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The University of Arizona PH.D. 1980

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As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Kathyrne Jean Mueller

entitled Drug-induced Self-biting in Rodents: Implications for the Lesch-Nyhan Syndrome

and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor or Philosophy.

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Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Sigmund Hunis	April 4, 1980
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ACKNOWLEDGMENTS

The author thanks Karen Hoyt, Hugh Petit, and Tom Foster who assisted with data collection during this research. Thanks are also due to Drs. Sigmund Hsiao, Robert Lansing, Peter Pickens, Mac E. Hadley, and Neil Bartlett for critical readings of this manuscript.

The clonidine used in this research was kindly supplied by Dr. Stanley B. Garbus, Associate Director of Clinical Research, Boehringer Ingelheim, Ltd; 6-thioguanosine was provided by L. H. Kedda of the National Cancer Institute. Mice were generously donated by Dr. George T. Bowden of the Arizona Health Sciences Center. This research was partially supported by a grant from the University of Arizona Graduate Student Development Fund.

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ABSTRACT

Self-mutilation is a serious clinical problem. In humans self-mutilation is a characteristic of the Lesch-Nyhan syndrome and the de Lange syndrome. Several common drugs have been reported to produce self-biting in animals. The purpose of this project is to begin to determine whether drug-induced self-biting in animals shares behavioral or biochemical characteristics with self-biting in the Lesch-Nyhan syndrome. Availability of such an animal model would greatly facilitate development of rational therapies and elucidation of neurochemical mechanisms.

The Lesch-Nyhan syndrome is the result of a genetic defect in purine metabolism. Purines may function as neural transmitters or purines may be released along with classical neurotransmitters, or purines may modulate neural transmission. This research is based on the assumption that the self-mutilation which accompanies the Lesch-Nyhan syndrome is the result of a) decreased availability of purinergic neuroregulators b) increased amounts of hypoxanthine in the central nervous system c) a combination of the above.

The behavioral characteristics of three types of drug-induced self-biting (caffeine, clonidine, and pemoline) were examined. Then various purines were administered in an attempt to modify drug-induced self-biting. Pemoline was administered orally to rats in doses of 140 and 220 mg/kg. Self-biting of the medial digits and dorsomedial aspect of the foreleg was commonly observed and appeared to result from intense grooming of these areas. The severity of self-biting was dose-related

and self-biting was somewhat environmentally modifiable. The animals' behavior was characterized by poor response to sensorimotor stimuli and by highly repetitive behaviors. Caffeine was administered orally to rats for 14 days (185 mg/kg/day). There was a low incidence (less than 7%) of mild self-biting of the dorsomedial aspect of the forefoot. In all other respects the animals' behavior was normal. Clonidine (40 mg/kg) was administered to mice and produced self-biting of the medial digits of the foreleg in 30% of mice placed in a glass beaker. Mice placed in a wire enclosure with biting objects never exhibited self-biting. The animals' behavior was characterized by generalized biting.

No evidence was obtained that purines are directly involved in the etiology of drug-induced self-biting. Treatment of neonatal rats with a purinergic enzyme inhibitor did not render them more susceptible to pemoline-induced self-biting as adults. Adenosine had no effect on clonidine-induced self-biting. Contrary to expectations, hypoxanthine, a purine found in very high quantities in the central nervous system of Lesch-Nyhan patients, reduced the severity of pemoline-induced self-biting in rats. Behavior was also normalized to some degree by hypoxanthine. This phenomenon may be due to the benzodiazepinergic actions of hypoxanthine.

These three types of drug-induced self-biting were discussed in relation to self-biting exhibited by animals under other circumstances and in relation to self-biting exhibited by humans. In general, self-biting in animals and humans appears to be similar. In particular, the pemoline-treated rat appears to be a good model for the de Lange syndrome and the pemoline- and hypoxanthine-treated rat appears to be a

good model for the Lesch-Nyhan syndrome. A hypothesis was advanced that several distinctly different types of self-biting exist, one of which can be described (for both animals and humans) as exaggerated displacement grooming. The latter is associated with stimulants and/or with stress and becomes more severe as behavior becomes more stereotyped.

INTRODUCTION

Self-mutilation is a serious clinical problem which is sometimes associated with physiological syndromes. Several common drugs have been reported to produce self-biting in animals; in humans self-biting is a characteristic of the Lesch-Nyhan syndrome and the de Lange syndrome. The purpose of this project is to begin to determine whether drug-induced self-biting in animals shares behavioral or biochemical characteristics with self-biting in the Lesch-Nyhan syndrome. If so, drug-induced self-biting in animals may be a useful model for the Lesch-Nyhan syndrome. Availability of such a model would greatly facilitate development of rational therapies and elucidation of neurochemical mechanisms for this disturbing behavior.

Investigations into the cellular or biochemical bases of complex behavior have been only marginally successful. Classical theories of the physical bases of behavior have heavily relied upon the functions of various parts of the brain ("centers") and thus have been inadequate to explain events occurring on a cellular level. Although at one time knowledge of the neural circuits involved would have been sufficient explanation, recent reports of neuromodulators (e.g. prostaglandins, steroids, and peptides), of increasing numbers of putative neural transmitters, and of nonfunctional synaptic contacts have underlined the simplicity of this view. Thus the tremendous complexity of the mammalian brain has hampered progress in the description at a cellular or biochemical level of such complex behaviors as sleep, learning, and

and motivation. Given the fairly primitive nature of current understanding of the operation of the brain, a more productive approach would seem to be the investigation of a behavior of which crucial cellular counterparts are already known. The behavioral symptoms of the Lesch-Nyhan syndrome are among the few examples of stereotyped human behavior directly associated with a known biochemical event (Nyhan 1976).

The Lesch-Nyhan syndrome is associated with a near complete loss of activity of the enzyme hypoxanthine/guanine phosphoribosyltransferase (HGPRT), one of several important enzymes in purine salvage pathways. The syndrome is inherited and found only in males (X-linked). The most striking behavioral symptoms are motor disorders and self-mutilation. Although metabolic symptoms can be easily controlled, to date reliable normalization of behavior has not been obtained with either biochemical or behavioral therapy.

The Biochemical Deficit

Purines are ubiquitous cellular components. Various purine derivatives function as coenzymes (e.g. coenzyme A), as high energy intermediates (e.g. ATP), as second messengers (e.g. cAMP), and as DNA constituents (nucleic acids).

Nucleotides, like other cellular components, are constantly degraded and resynthesized. A schematic of purine biosynthesis, degradation, and two of the major salvage pathways is shown in Figure 1. salvage pathways convert the products of purine degradation into usable substrates. Adenine, guanine, and hypoxanthine must eventually have the ribose-5-phosphate group replaced before they can be utilized in the

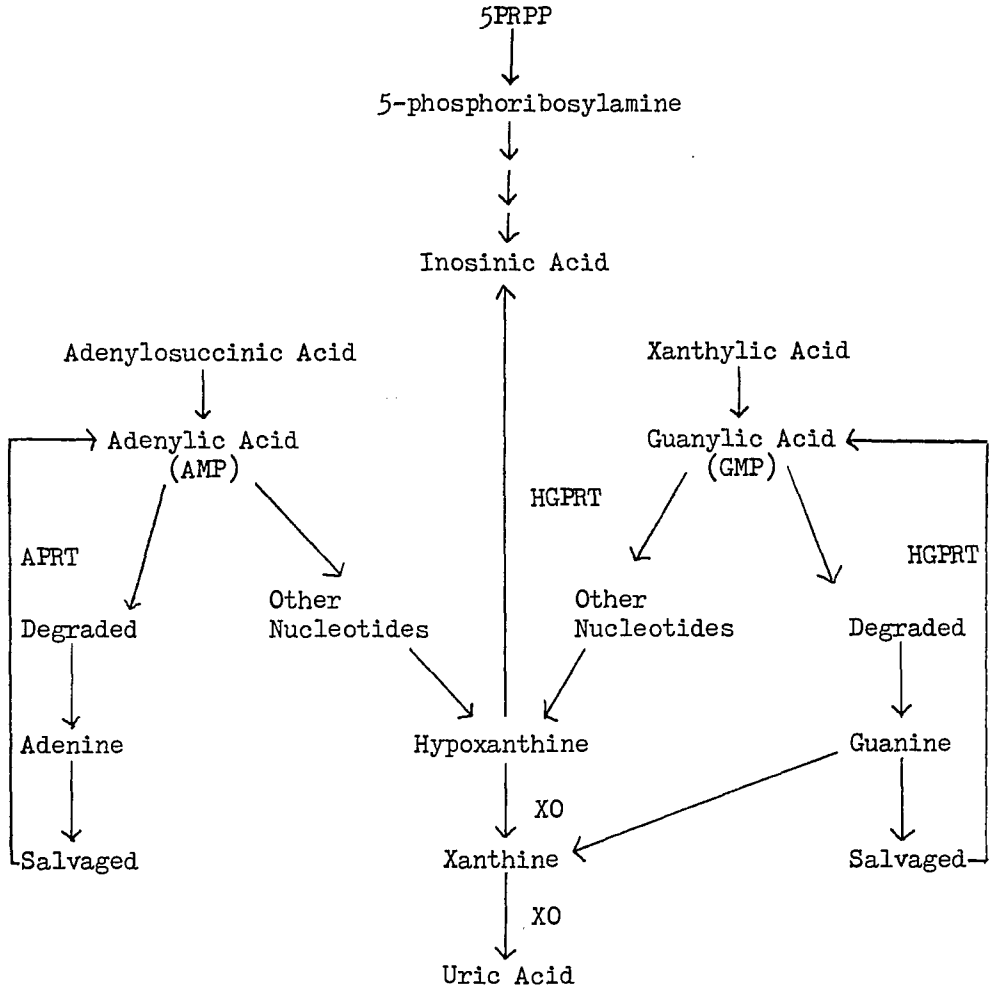

Figure 1. A schematic of purine biosynthesis and degradation.

Hypoxanthine/guanine phosphoribosyltransferase (HGPRT) converts guanine and hypoxanthine into usable substrates. In its absence large amounts of uric acid accumulate peripherally and large amounts of hypoxanthine accumulate in the central nervous system. Xanthine oxidase (XO) is not present in the central nervous system. Adenine is salvaged by a separate enzyme, adenine phophoribosyltransferase (APRT).

cell. This is accomplished by HGPRT. The Lesch-Nyhan syndrome is associated with a near complete loss of HGPRT activity, often less than .004% of normal (Kelley 1968).

The first consequence of the functional absence of this enzyme is severe gout. Large quantities of xanthine and hypoxanthine, which would regularly be salvaged, are now converted to uric acid. Uric acid is fairly insoluble, and large amounts precipitate in joints, kidney, and urine. This aspect of the disease can be effectively controlled with allopurinol, which increases the amounts of xanthine and hypoxanthine excreted directly before conversion to uric acid. Uric acid, however, is not produced in the brain, nor does it cross the blood-brain barrier. Thus, large amounts of hypoxanthine accumulate in the brain and cerebrospinal fluid.

Purine biosynthesis is regulated in such a way that a deficit in guanine derivatives (because of inadequate salvage) also may slow the synthesis of adenine derivatives. Thus the second implication of the functional absence of HGPRT is increased dependence upon the purine biosynthetic pathway for adequate quantities of both adenine and guanine derivatives. Very high levels of HGPRT in the normal brain suggest that the brain is unusually dependent upon salvage pathways for its purines (Gutensohn and Guroff 1972).

Behavior and the Lesch-Nyhan Syndrome

The most striking behavioral feature of the Lesch-Nyhan syndrome is severe self-mutilation. This behavior usually begins with the eruption of teeth, although delayed self-mutilation has been reported.

Early self-mutilation appears to involve the lips and fingers but occasionally the tongue may also be damaged (Kelley and Wyngaarden 1972). Extraction of teeth has sometimes been employed to prevent complete amputation of fingers. As the patient becomes older, additional forms of self-mutilation may appear such as head-banging or entanglement in restraints (Nyhan 1974).

Self-mutilation in the Lesch-Nyhan syndrome seems to be distinct from self-mutilation accompanying other syndromes. Serious tissue damage is generally rare in other cases, but commonplace in this syndrome (Nyhan 1976). Second, punishment applied in a strict behavior modification paradigm has successfully eliminated self-mutilation occurring in other syndromes, but worsens self-mutilation in the Lesch-Nyhan syndrome (Anderson, Dancis, Alpert, and Herrmann 1977).

The most successful therapy for these behavioral disorders has been the placement of restraints on the elbows to prevent bringing the hand to the mouth. Patients whose restraints are removed have been reported to become agitated, to beg for replacement of restraints, and to attempt to control biting by sitting on their hands (Nyhan 1976).

To date, there is no other reliable treatment for the self-mutilation which accompanies the Lesch-Nyhan syndrome. Inconsistent results have been obtained with adenine treatment and 5-hydroxytryptophan treatment (Schulman et al. 1971; Mizuno and Yugari 1974; Anderson, Hermann, and Dancis 1976; Frith et al. 1976). Some success has been obtained with extinction and positive reinforcement for the absence of biting (Anderson et al. 1977), but the possibility of serious injury

during behavior modification would seem to render this approach of questionable value. Long-term results of extinction have not been reported.

No obvious neurological or sensory abnormalities accompany this syndrome (Crussi, Robertson, and Hiscox 1969; Kelley and Wyngaarden 1972). Both elevated and lowered plasma dopamine-beta-hydroxylase activity have been reported (Rockson et al. 1974; Lake and Ziegler 1977).

Choreoathetoid cerebral palsy is also a consistent symptom of the Lesch-Nyhan syndrome (Nyhan 1974). Increases in muscle tone and abnormal movements may begin by 8 months of age (Nyhan 1976). Most patients cannot sit unassisted and none have stood or walked unassisted. Deep tendon reflexes are enhanced and sudden extensor spasms are common. (Nyhan 1974).

The intelligence of Lesch-Nyhan patients is controversial. Early reports consistently indicated severe retardation (Nyhan 1974) but retardation may have been secondary to the poor physical condition which often resulted from delayed diagnosis. Many patients currently under investigation have received allopurinol and institutional care since soon after birth and are considered to be bright or of average intelligence. All patients learn to talk. They are described as having particularly warm personalities and are often favorite patients in the wards (Nyhan 1976).

Paradoxically, however, these patients are also described as aggressive. They may bite others and they vomit on their caretakers with uncanny frequency. Spastic movements often strike another person. Toys may be thrown at relatives; older patients may become verbally aggressive. Such behavior is often accompanied by apologies (Nyhan 1974).

Biochemistry of Behavior

The role of purines in behavior is not well understood, however, several possibilities exist. In addition to their classic intracellular roles, purines have recently been suggested to play a role in neural transmission. Purines may actually function as neural transmitters, purines may be released along with classical transmitters, or purines may modulate neural transmission. In this dissertation, the term neuromodulator will refer to those compounds which "amplify or dampen" local neural activity rather than directly participating in cell to cell comminication. The term neuroregulator will include both neurotransmitters and neuromodulators (Barchas et al. 1978).

The first cohesive evidence that purines might be neural transmitters was obtained during studies of the innervation of the gut, but the concept has since been extended to other areas of the nervous system including the central nervous system. Stimulation of many central neurons causes release of adenine derivatives (McIlwain 1974; Schubert et al. 1976; Rose and Schubert 1977). ATP, which has been most often suggested to be the transmitter, shares certain structural features with other putative transmitters (Boyd 1973).

An alternative to the role of purines as classical neurotransmitters is the possibility that purines may be released along with established transmitters as additional transmitters (Burnstock 1976b). Some evidence for this hypothesis has been obtained in the cholinergic septal system (Rose and Schubert 1977). Presumably the purines would initiate long-term changes in the post synaptic neuron or participate in the feedback regulation of the established transmitter.

Whether or not purines actually act as neurotransmitters, much evidence suggests that purines modulate neural activity. Adenosine and adenine derivatives decrease the excitability of many cortical neurons (Phillis and Kostopoulos 1975). Caffeine and theophylline block these effects (Phillis, Kostopoulos, and Limacher 1975). Large amounts of phenoxybenzamine also block purinergic receptors in some tissues (Burnstock 1976a). Intraperitoneal and intraventricularly administered adenosine has sedative effects in dogs and mice (Haulica et al. 1973; Maitre et al. 1974). Interestingly, about half of the diagnosed Lesch-Nyhan patients experience seizures (Krooth, May, and Stern 1977).

Purines may also modulate neural activity in less conventional ways. Coenzyme A (a substituted purine) may be a feedback inhibitor of acetylcholine release and this inhibition is also antagonized by theophylline (Cook, Hamilton, and Okwausaba 1978). Catecholamines have recently been shown to form complexes with purine derivatives in solution at pH 7 (Granot and Fiat 1977). Guanine derivatives have been implicated in the regulation of adrenergic receptors, and noradrenaline release may also be modified in a negative feedback fashion by purines (Enero and Saidman 1977). Since purines are released by neural tissue and affect neural activity in various ways, they are likely to also play a role in behavior.

This research is based on the assumption that the self-biting which accompanies the Lesch-Nyhan syndrome is the result of a) decreased availability of purine neuroregulators because of the absence of salvage pathways, b) increased amounts of hypoxanthine in the brain and cerebrospinal fluid which may act as purinergic blockers, c) both a) and c).

If lowered levels of purinergic neuroregulators in the central nervous system are responsible for the behavioral disorders of the Lesch-Nyhan syndrome, administration of purinergic receptor blockers should also induce similar behavioral disorders. In support of this hypothesis, administration of caffeine (Boyd et al. 1965; Peters 1966, 1967) or theophylline (Morgan, Schneiderman, and Nyhan 1970; Sakata and Fuchimoto 1973) induce self-mutilation in rats and rabbits. However, these compounds have several different actions, any one of which could be responsible for the induction of self-biting.

Both caffeine and theophylline may release norepinephrine in the central nervous system (Berkowitz, Tarver, and Spector 1970). This action, however, may be consistent with the hypothesis of purinergic regulation of norepinephrine release. As purinergic blockers, methylxanthines might eliminate the feedback inhibition normally provided by purines, and therefore indirectly lead to increased release of norepinephrine. So the precise nature of theophylline- and caffeine-induced self-mutilation is unclear.

Pemoline (Genovese, Napoli, and Bolego-Zonta 1969) and clonidine (Razzak et al. 1973, 1977; Razzak, Fujiwara, and Ueki 1975) also induce self-mutilation in rodents. The mechanism of the pemoline-induced self-biting has not been investigated, but clonidine may induce self-biting via adrenergic pathways.

The behavioral aspects of chemically-induced self-mutilation have received little attention. Repeated administration of theophylline is necessary to produce self-mutilation (Morgan et al. 1970; Sakata and Fuchimoto 1973). Eventually the rats bite their paws, especially

forepaws, and the base of the tail. These behaviors, however, are preceded by other stereotyped behaviors including biting and killing (Sakata and Fuchimoto 1973). Theophylline occassionally induces biting of the thorax (Morgan et al. 1970). Repeated administration of caffeine is also necessary to induce a high percentage of rats that self-bite. Biting is most often directed toward the hind legs and base of the tail (Peters 1967).

A single treatment of clonidine has been reported to induce self-biting in mice housed in the absence of other objects to bite. Self-biting never occurred when the mice were observed in groups (Razzak et al. 1975). A single treatment of pemoline causes biting of paws, tail, and abdomen (Genovese et al. 1969).

Although many experiments could be done to clarify the mechanisms of chemically-induced self-mutilation, the purpose of this research is to determine whether drug-induced self-biting can be considered animal models for the self-mutilation occurring in the Lesch-Nyhan syndrome. A more satisfactory procedure for developing an animal model would be to manipulate HGPRT activity in the rat brain. However, the likelihood of specifically lowering brain HGPRT activity to .004% (the level of activity found in Lesch-Nyhan patients which exhibit self-biting) is very low. A more indirect procedure using chemically-induced self-mutilation has therefore been adopted.

This research is based on the assumption that self-mutilation accompanying the Lesch-Nyhan syndrome is the result of a) a decrease in the availability of certain purines leading to an inadequate quantity of purinergic neuroregulators, b) high levels of brain hypoxanthine, c) or

to a combination of a) and b). Two main strategies are employed: first, to provide a behavioral analysis of drug-induced self-biting and its stimulus control, so that these parameters can be compared to those exhibited by Lesch-Nyhan patients; second, to determine whether drug-induced self-biting can be modified by administration of purine derivatives or HGPRT inhibitors. If the behavioral characterization and the stimulus control of self-biting are similar to those in the Lesch-Nyhan syndrome, and if chemically-induced self-biting can be modified with purines, drug-induced self-mutilation can be considered a model system for the self-mutilation accompanying the Lesch-Nyhan syndrome. Availability of an animal model would greatly facilitate development of reliable and rational treatments for self-biting in the Lesch-Nyhan syndrome and would also provide a useful system for studying the cellular basis of this behavior.

EXPERIMENT 1:

BEHAVIORAL ASPECTS OF DRUG-INDUCED SELF-BITING IN RODENTS

Pemoline and caffeine were administered to rats and clonidine was administered to mice to induce self-biting. In each case an attempt was made to either delay the appearance of self-biting or to decrease the severity of self-biting by a simple environmental manipulation. When self-biting occurred the animals' response to a variety of stimuli was observed; that is, each animal was given a similar "behavior test".

Pemoline-induced 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 except as noted below. Body weights of the 28 rats ranged from 280 to 393 grams at the time of testing. The animals were maintained on an artificial 12-hour 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 siutable 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 hours 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. Two hours later the bedding was removed from half of the nesting boxes. Thus, four groups of six animals each were formed: high dose/no bedding, high dose/bedding, low dose no/bedding, low dose/bedding. The presence or absence of bedding was a simple environmental manipulation designed to alter the frequency and or severity of self-biting. An additional four animals were treated in the same manner with the exception that the yogurt was undrugged and bedding was always present in the nesting box.

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 hours after drug administration) in the following manner. The behavior of each animal was recorded for 5 minutes (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 a euthanasia solution. Because the animals often did not drink during the

first 36 hours after testing, all animals were administered 5 ml of tap water intragastrically at 13 hours after drug administration. Food and bedding were returned to all rats after the final observation period (58 hours after drug administration).

Behavior Test. The behavior test was administered in two parts separated by 2 hours. In part one, the animals were first observed undisturbed for 6 minutes and the time spent self-biting was recorded. These periods of undisturbed observations 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 animals' ability to orient to a mild tactile stimulus. Several objects (a food pellet, several food chips, shredded paper towels, a pencil with an erasor, 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 animals' response to this highly preferred food was recorded. After 90 seconds the spoon was withdrawn and the animal was placed in an open field (71 by 52 by 22 cm) divided into 12 areas. For 4 minutes 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 animals' ability to cling to the wire and climb to the top of the cage was recorded.

This "clinging" test is a simple measure of motor control. After a 3-minute baseline period an undrugged rat was placed in the nesting box for 3 minutes. (The same undrugged rat was used throughout testing.) The occurrence of sniffing, following, mutual grooming, or other social behaviors was recorded. Another 3-minute baseline period was followed by 3 minutes of loud auditory stimulation; the animals' cage was repeatedly struck with a metal coffee can. Five minutes later bedding, if present, was removed. If bedding was absent, it was added at this time. Two hours later part two of the behavior test was administered.

Part two began with a 5-minute baseline period. This was followed by removal or addition of bedding such that the animal was again maintained in the same manner as in the beginning of the behavior test. These bedding manipulations were intended to provide a diversion for the animal and were hoped to alter the time spent self-biting. Xylocaine lotion (a topical anesthetic) was applied to areas of the rats' body that had been bit and the animal was observed for 3 minutes. The animal was then briefly immersed in warm water and returned to the nesting box for 3 minutes of observation. Wetting the fur of undrugged rats reliably induces grooming. Thus, if pemoline-induced self-biting is related to grooming, the increased frequency of grooming behavior should be accompanied by increased self-biting.

Results

Preliminary Observations. All animals consumed the yogurt within 5 minutes; the beakers were usually licked clean. Within 10 minutes after ingestion of the drugged yogurt the animals appeared hyperactive

with respect to the controls. By the first observation period (2 hours after drug administration) drugged animals were exhibiting highly repetitive behaviors, referred to collectively as stereotypies. One rat, for example, was observed to stand on its hind legs and sniff the top of the nesting box continuously for 10 minutes. A common stereotopy was sitting on the haunches and chewing or manipulating bits of nesting material held near the mouth with the front feet. Another common stereotopy was intense sniffing of a particular area of the box 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 were virtually never observed to groom their bodies (side, flank, abdomen, or tail) but undrugged rats groomed both 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.

By the end of the 58 hours 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

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

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

Latencies to self-biting were highly variable. Latencies to behaviors resembling self-biting ranged from 2 to 32.5 hours (140 mg/kg) and 3 to 28 hours (220 mg/kg) after drug administration. The dose of pemoline and the environmental manipulations (presence or absence of bedding) both significantly affected these latencies (Kruskal Wallis ANOVA, $p < .05$). The shortest latency was exhibited by the low dose/bedding group followed by the high dose/no bedding group. The low dose/no bedding group exhibited the longest latencies.

Latencies to physical evidence of self-biting ranged from 7 to 46 hours (140 mg/kg) and 3.5 to 48 hours (220 mg/kg) after drug administration. However, there were no significant differences in latencies between groups (Kruskal Wallis ANOVA, $p > .05$).

To further determine whether the severity of self-biting was significantly affected by the dose of pemoline or the environmental manipulations, severity of self-biting was operationally defined as the sum of the percent of times spent self-biting in the opening baseline periods of part one and part two of the behavior test. The severity of self-biting was significantly affected by both environment (presence or absence of bedding) and dose (Kruskal Wallis ANOVA, $p < .001$). The most severe self-biting was exhibited by the high dose/bedding group followed

by the high dose/no bedding group. Self-biting was least severe in the low dose/no bedding group. The severity of self-biting, as defined above, was only moderately correlated with latency to behaviors resembling self-biting (Spearman's $r = .181$) or with the latency to physical evidence of self-biting (Spearman's $r = .414$, $p < .05$). Latencies to physical evidence of self-biting and estimates of severity of self-biting are summarized in Table 1.

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

Behavior Test. Characteristic responses to part one of 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 jumped and ran from 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. The most common response, if any, was to push the objects 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, $p < .001$). Thus locomotion decreased as a function of dose. When the proportion of time spent self-biting

Table 1

Median latency and severity of self-biting by pemoline-treated rats

Environment		Dose 220 mg/kg	140 mg/kg
Bedding	Latency[a]	19 (3- 48)[b]	18 (7-58)
	Severity[c]	200 (110-200)	95 (0-198)
No Bedding	Latency	7 (3- 28)	27 (7-58)
	Severity	175 (84-198)	14 (0-150)

[a]A latency of 58 indicates the absence of self-biting

[b]The range of scores is shown in parentheses.

[c]Severity scores range from 0 (no self-biting) to 200 (maximum self-biting).

Table 2

Behavioral characteristics of pemoline-induced self-biting

Dose	Behavior Test Part 1						
	Orientation	Biting Objects	Graham Cracker	Open Field	Clinging	Social Behavior	Auditory Stimulation
220 mg/kg	NR 5[a] A 6 R 0	NR 0 A 11 R 0	NR 3 A 2 R 6	LC 3[b] **	NR 10 R 1	NR 5 A 6 R * 0	*
140 mg/kg	NR 6 A 1 R 3	NR 3 A 3 R 4	NR 1 A 1 R 8	LC 21 *	NR 5 R 5	NR 5 A 2 R * 3	*
con-trol	NR 0 A 0 R 4	NR 0 A 0 R 4	NR 0 A 0 R 4	LC 50	NR 0 R 4	NR 0 A 0 R 4	

[a]The number of rats exhibiting the indicated behaviors is shown. R: appropriate response (see text); NR: no observable response; A: avoidance (the animal turns away from the stimulus or pushes the stimulus away).

[b]The mean number of lines crossed (LC) is shown.

*Self-biting is increased with respect to baseline; **self-biting is decreased.

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, $p < .001$). 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 a slight loss of motor control. All four control rats clung to the wire cage; they climbed to the top in a mean time of about 16 seconds. Only 5 of the 10 low-dose animals tested climbed to the top of the ca e; only 1 of the 12 high-dose animals reached the top (Fisher's exact test, $p < .05$). Some animals clung to the cage but did not climb; 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 rat, or pushed the rat away, or leaped away from the rat whenever they were approached. Although, two rats exhibited agonistic postures (rearing while baring teeth or boxing). There was a tendency, although not significant, 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 bedding manipulations at the end of part one of the behavior test did not appear to affect the percent of time spent self-biting. Similarly, 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 lengthly grooming, the drugged rats occasionally shook themselves but virtually never groomed. This manipulation was therefore unsuccessful in determining 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 hours. 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 areas of the body which were not always the most accessible areas.

The self-biting appeared to be grooming-related for two reasons. First, it was behaviorally indistinguishable from grooming, except that

the self-biting did not spread to other body areas in the same manner that grooming usually does. 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 front feet to the mouth and licking, nibbling, and manipulating the front feet -- especially the dorsal area and the medial didits. 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 (Fentress 1971). Self-biting of the thorax and abdomen was observed the least often. Hind feet and tail are groomed less frequently (except for grooming of the hind foot which accompanies scratching of the ear) 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. Even the simple environmental manipulation of placing the

animal in a nesting box with or without bedding affected both the latency and severity of self-biting.

Throughout the behavior test the drugged animals consistently failed to respond normally to sensory stimuli. Generally, 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 (Schallert and Wishaw 1978).

The animals also showed motor impairments. Many 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.

Because of the behavioral similarity of pemoline-induced self-biting to portions of the grooming sequence, the time engaged in stereotyped grooming, rather than the time spent self-biting, was recorded during the behavior test. Because most drugs have multiple behavioral effects the question arises as to whether stereotyped grooming is a "side effect" of high doses of pemoline or whether pemoline-induced self-biting is in fact highly exaggerated grooming. A similar problem surrounds interpretation of the observed sensorimotor deficits in pemoline-treated rats. The present data are insufficient to determine

whether these deficits are characteristic of self-biting per se or are due to some unrelated behavioral effect of the drug.

Pemoline-induced self-biting is probably due to formation of an active metabolite. Intracranial administration of pemoline does not induce self-biting (Genovese, Napoli, and Bolego-Zonta 1969) and subcutaneous or intraperitoneal administration during pilot work did not produce any discernable behavioral effects. Structurally, pemoline and amphetamine are related to phenylethylamine. There are also unpublished reports that amphetamine induces self-biting in rats.

Pemoline has been suggested by some to improve learning and memory in rats but these claims have been disputed (Soumireu-Mourat and Caido 1968; Eisenstein and D'Amato 1975). Most positive results seem to have been obtained with active avoidance tasks. For example, Plotnikoff (1966) 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 pemoline-treated rats in this experiment, however, suggests that "jumping out" is a high frequency behavior following pemoline administration regardless of whether learning contingencies are present.

Caffeine-induced Self-biting

Method

Subjects. The subjects were selected (as decribed below) from 49 male albino rats. The animals were derived from Holtzman stock and ranged in body weight from 258 to 472 grams at the beginning of testing. Food and water were available ad lib and the animals were maintained on

an artificial 12 hour light/dark cycle. The animals were habituated to consuming a graham cracker slurry from a spoon.

Procedure. Again the animals were maintained in different environmental conditions in an attempt to delay the appearance of or reduce the severity of self-biting. Twenty-seven rats were housed individually in standard wire mesh cages. The remainder were housed in groups of either 3 (6 groups) or 5 (2 groups) animals. Polyethylene nesting boxes housed the groups of 3 and a 20 gallon aquarium housed the groups of 5.

Before treatment began each animal was food deprived and placed in a polyethylene nesting box for the behavior test. The same procedure was repeated a second time at a later date for those rats which showed physical evidence of self-biting, for the control rats, and for 8 randomly chosen rats which did not exhibit physical evidence of self-biting (4 individually housed and 4 group housed).

Each day for 14 days the animals were given 185 mg/kg caffeine (in an approxiamte volume of 5 ml) intragastrically. Four individually housed and four group housed animals were intubated each day with tap water. Caffeine was always administered at the beginning of the dark cycle. The animals were carefully examined each day for physical evidence of self-biting.

The behavior test consisted of one part which began with a baseline period (6 minutes). Orientation, biting objects, the graham cracker slurry, the open field and clinging tests were performed in the same manner as described previously. The remainder of the test in the order given was social behavior (3 minutes), baseline (3 minutes), auditory

stimulation (3 minutes), baseline (3 minutes), xylocaine application (3 minutes), and immersion in water (3 minutes).

Results

One group-housed animal became excited during an intubation, exhibited convulsions, and died. The animal had gained weight steadily and appeared healthy prior to this episode. One individually housed animal exhibited a mild seizure followed by transient paralysis during an intubation. This animal also had gained weight steadily throughout the experiment. Although a slight loss of body weight was observed the day following the seizure the animal had completely recovered.

No other deaths occurred among the animals housed in groups. However, of the individually-housed animals, three died and two were excluded from further drug treatment because of dramatic loss of body weight. Interestingly, these five animals were among the oldest and heaviest used. Thus the experiment was completed with 8 control animals, 21 group-housed animals, and 22 individually housed animals.

Only three animals, all housed individually, exhibited physical evidence of self-biting after 14 days of drug treatment. Fur removal and swelling were observed on the dorsomedial aspect of the forefoot at latencies of 5, 7, and 10 days of drug administration. The behavior of these animals was indistinguishable from controls except for occasional periods of intense grooming of the front feet.

The behavior test did not differentiate between caffeine-treated or control animals. In addition, behavior was very similar for each rat during the first and second behavior test with the possible exception that many rats crossed fewer lines during the second open field test.

Discussion

Peters (1967) administered 185 mg/kg caffeine to 26 male rats housed individually and reported an "automutilation" rate of 31%. Of the 22 individually-housed animals that completed this experiment only 3 exhibited self-biting. There are no obvious reasons for the different rates of self-biting observed in the two studies.

Food deprivation dramatically increases the caffeine-induced rate of self-biting (Boyd et al. 1965; Peters 1966; Peters 1967) but mortality rates increase concurrently, complicating interpretation of possible behavioral effects of caffeine. In addition, food deprivation induces metabolic changes throughout the body; brain enzyme activities are altered, further complicating interpretation. Therefore food deprivation was not employed in the current study to increase the incidence of caffeine-induced self-biting.

The small number of animals which exhibited self-biting precludes firm conclusions about the behavioral characteristics of caffeine-induced self-biting. However, the phenomenon may be environmentally dependent since no self-biting was observed in the animals housed in groups. The group-housed animals in general seemed healthier than the individually-housed animals. Only one death and no incidences of precipitous weight loss occurred among group-housed animals while five such incidents occurred among individually-housed animals. In addition, the younger and lighter animals seemed to tolerate the caffeine administration much more easily than the older and heavier animals. Immediately after intubation the older animals became lethargic but the younger animals showed no obvious behavioral changes. The younger

animals also tended to gain weight far more steadily than the older animals during chronic caffeine treatment.

The apparent lack of behavioral effects of chronic administration of large doses of caffeine was surprising. Caffeine has been reported to facilitate aggressive behavior (Peters 1967) but there was no indication of aggressive behavior in the current study. Fighting or agonistic postures were never observed during the social behavior portion of the behavior test nor during observations of the group-housed animals. Although all animals, including water-intubated animals, struggled during the intubations the caffeine-treated animals were always easy to handle.

Peters (1967) administered caffeine to rats for up to 40 days. He described stereotyped behaviors such as backward locomotion and tail chasing (the latter seemed to be associated with self-biting of the tail and hind feet) although he did not note how many days of drug administration preceded these behaviors. The necessity of administering caffeine for long periods of time to induce a reasonable proportion of animals that exhibit self-biting renders this technique somewhat impractical for developing an animal model.

Clonidine-induced Self-biting

Method

Subjects. The subjects were 36 male albino mice (Swiss). They were housed in groups ranging from 5 to 15 in polyethylene nesting boxes or in a 20 gallon aquarium. Food and water were available ad lib except that the mice were food deprived for 12 hours prior to testing. They

were maintained on a 12 hour light/dark cycle; testing usually occurred during the light cycle.

Procedure. Before testing the mice were habituated to consuming a graham cracker slurry. All mice were observed after intraperitoneal administration of 40 mg/kg clonidine. Fifteen of the animals were placed in a 4-liter glass beaker immediately after drug administration and 15 were observed in a wire mesh enclosure of the same dimensions as the beaker. Food pellets and bedding were also provided for this latter group. These two groups were intended to determine the extent of environmental modifiability of clonidine-induced self-biting. This manipulation compares with the bedding/no bedding manipulation in pemoline-induced self-biting and with the group housing vs individual housing in caffeine-induced self-biting.

The behavior test described below was administered to 6 saline-injected mice, to all mice that exhibited self-biting, and to 4 mice that were clonidine-treated but did not exhibit self-biting during 35 minutes of observation. The animals were terminated by cervical dislocation when testing was completed.

Behavior Test. The clinging portion of the behavior test was administered first. It was identical to that described above except that a 13-cm wire mesh cube was used. A baseline period (5 minutes) was followed by orientation, presentation of the graham cracker slurry, and biting objects. The open field measured 35 by 19 by 11 cm and, like the rat open field, was divided into 12 areas. The remainder of the behavior test in the order presented was baseline (4 minutes), social behavior (4 minutes), baseline (4 minutes), auditory stimulation (the

beaker was tapped with a pencil for 3 minutes), baseline (4 minutes), and immersion in warm water (4 minutes).

Results

Preliminary Observations. Within 60 seconds after injection all animals exhibited a noticeable impairment of motor control. Within 5 minutes the animals exhibited a severe tremor which became more pronounced during locomotion or head movements. Piloerection and exophthalmos were also observed. Several animals vocalized for no apparent reason during undisturbed observation periods.

About 10 minutes after injection many animals began to bite the floor or walls of the beaker. Those animals which were observed in the wire mesh environment bit at the wire or food pellets, often vigorously. The mice sometimes struck rapidly, scattering bedding. They sometimes maintained their grip on the food pellet, with the head and anterior portion of the body pressed to the floor. The animals which were observed in the beakers leaped up at the walls; those which were observed in the wire mesh environment climbed the wire up to the top of the cage and sometimes remained moving about the wire for 2 minutes or more. Another common behavior resembled aborted grooming of the snout. The front feet would simultaneously move toward the snout and often jerked up and down just below the mouth. However, more complete grooming was never observed after clonidine treatment. Activity seemed to decrease by about 15 minutes after injection and by 30 minutes after injection most mice assumed a crouching position. Of the mice observed in the beaker, five (30%) exhibited self-biting of the medial digits of the

forefeet with a mean latency of 13 minutes. No mouse in the wire mesh enclosure exhibited self-biting. One mouse died during observation and several exhibited mild convulsions.

Behavior Test. The behavioral characteristics of clonidine-induced self-biting are summarized in Table 3. The ability to cling to and climb the wire grid ("clinging" test) did not differentiate between control and drugged animals or between drugged animals that did or did not exhibit self-biting. Many of the drugged mice leaped forward in response to the tactile stimulation of the Q-tip ("orientation" test). Most drugged mice and all undrugged mice consumed the graham cracker slurry. Although the control mice explored the biting objects they seldom bit any of them. However, virtually every drugged mouse bit each biting object, sometimes repeatedly. The mean number of lines crossed in the open field were 41.2, 11.6, and 9.8, respectively, for the saline-treated, drugged mice that did not self-bite, and drugged mice that exhibited self-biting. This tendency toward decreased locomotion in the open field by drugged animals was not significant (ANOVA, $F = 2.9$, $p > .05$), however. The drugged mice often bit the mouse introduced into their enclosure during the social behavior test. Little behavior was exhibited by the drugged mice during the remainder of the behavior test, although several drugged mice groomed the snout after immersion in water.

Several of the mice that exhibited self-biting amputated one or more digits. However, relatively small proportions of time were spent self-biting during the behavior test. During the first baseline the proportion of time spent self-biting ranged from 0 to 60%. In the open

Table 3

Behavioral characteristics of clonidine-induced self-biting

Group	Behavior Test							
	Clinging	Orientation	Graham Cracker	Biting Objects	Open Field	Social Behavior	Auditory Stimulation	Wetting Fur
Clonidine Self-biters	NR 3[a] R 2	NR 0 A 4 R 1	Bite Spoon 1 R 4	Rep. Bit. 3 NR 2	LC 10[b] SB 20[c]	Bite 1 SB 2 R 1 NR 3	SB 3	SB 0
Clonidine Non self-biters	NR 0 R 6	NR 1 A 3 R 2	Bite Spoon 3 R 2 A 2	Rep. Bit. 3 NR 0 R 3	LC 11 SB 0	Bite 3 SB 0 R 2 NR 1	SB 0	SB 0
Saline Control	NR 2 R 2	NR 2 A 0 R 2	Bite Spoon 0 R 4	Rep. Bit. 0 NR 0 R 4	LC 41 SB 0	Bite 0 SB 0 R 3 NR 1	SB 0	SB 0

[a]The number of mice exhibiting the indicated behaviors is shown. R: appropriate response (see text); NR: no observable response; A: avoidance (the animal turns away from the stimulus or pushes the stimulus away); Rep. Bit.: repetitive biting.

[b]The mean number of lines crossed (LC) is shown.

[c]The percent (median) of time spent self-biting (SB) is shown.

field the proportion of time self-biting ranged from 0 to 31% and by the final baseline only one mouse exhibited self-biting (12%). Thus the time spent self-biting seemed to decrease as a function of time. This, in combination with the low rate of self-biting, obscured any possible usefulness of the various manipulations in the behavior test for reducing self-biting.

Discussion

The most striking finding of this experiment is the degree of environmental modifiability of clonidine-induced self-biting in mice. When the mice were observed in a glass beaker in the absence of objects to bite, 30% exhibited self-biting. But when various biting objects were provided no self-biting occurred. This finding is in agreement with that of Razzak et al. (1975).

The effects of clonidine on activity in mice have been investigated by others who reported that low doses decreased activity but high doses increased activity (Maj et al. 1972; Razzak et al. 1973). In this experiment an additional variable, environment, also affected activity. Many animals that were observed in the beaker crouched in the same position during the major portion of observation. But mice observed in the wire enclosure often dug in the bedding, repeatedly inserted the nose through the wire, and climbed the wire. However, in both groups activity decreased as a function of time.

Clonidine has been described by Morpurgo (1968) as inducing aggressive behavior in mice, even though he noted that species-specific fighting postures are not displayed by clonidine-treated mice. The

behavioral effects of clonidine, however, seem better described as generalized biting rather than aggression. The mice bit anything introduced into their enclosure.

Although clonidine-induced self-biting was intimately related to biting in general, again only particular areas of the body were bit. If the clonidine-treated mouse self-bites solely because nothing else is available to bite, why should self-biting be restricted to medial digits of the forefeet? The lateral digit, the dorsal aspect of the forefoot, the foreleg, or the tail are all equally accessible targets but were not bit. Razzak et al. (1975) included a photograph of the foreleg of a clonidine-treated mouse which had amputated three digits; the lateral digit was unharmed. The specificity of the self-biting, and the observation of behaviors similar to aborted grooming suggest that clonidine-induced self-biting may also be related to grooming.

EXPERIMENT 2:

PURINERGIC ASPECTS OF DRUG-INDUCED SELF-BITING IN RODENTS

Determination of the biochemical, pharmacological, and cellular mechanisms of drug-induced self-biting would require a complex series of experiments. The purpose of this experiment is not to elucidate mechanisms but to determine whether purines might be involved in drug-induced self-biting. If purines can either decrease or increase self-biting induced by these drugs, drug-induced self-biting may be useful in developing an animal model of the Lesch-Nyhan syndrome.

In this experiment self-biting was induced in rats with 140 mg/kg pemoline and hypoxanthine was administered at various times in an attempt to increase self-biting. Self-biting was induced in mice with 40 mg/kg clonidine and adenosine was concurrently administered. Behavior tests were administered to determine whether these purines had affected self-biting. Caffeine was not used in this experiment because of the low rate of self-biting obtained with this drug.

Pemoline and Hypoxanthine

Method

Male albino rats ranging in body weight from 264 to 575 grams were maintained as described previously. Under nembutal anesthesia cannulae were stereotaxically inserted into the lateral ventricle of the brain. The cannulae were flushed daily with 5 to 10 µl of artificial

cerebrospinal fluid and were sealed when not in use. After completion of the experiment the animals were injected with a euthanasia solution. The brains were removed, fixed in 30% formalin, and sectioned in the sagital plane. Data are included only from those animals (18) of which histological examination showed that the cannula was properly placed.

Three days after surgery all animals were drugged and observed as previously described. At 0, 2, 4, and 7 hours after drug administration 8 animals were administered 10 µl of artificial cerebrospinal fluid intraventricularly at a rate of 2 µl/minute. In the same manner and at the same times 10 animals were administered 10 µl of a saturated hypoxanthine solution (3 mg/ml of artificial cerebrospinal fluid). When physical evidence of self-biting was observed, the behavior test was administered. It consisted of baseline (5 minutes), orientation, biting objects (pencil and wire grid), graham cracker slurry, open field (4 minutes), clinging, baseline (4 minutes), social behavior (4 minutes), baseline (4 minutes), auditory stimulation (3 minutes), baseline (3 minutes), and immersion in water (4 minutes).

Results

Of the 8 control rats (artificial cerebrospinal fluid) 4 exhibited self-biting; of the 10 experimental rats 5 exhibited self-biting. One of the experimental rats which exhibited physical evidence of self-biting recovered from the behavioral effects of the drug before testing could be initiated. The data below (with the exception of latencies) refer to the four animals of each group that completed the behavior

test. All data in this portion of the experiment were analyzed with the Kruskal Wallis analysis of variance.

Latencies to physical evidence of self-biting ranged from 6.4 to 34 hours (experimental) and 4.5 to 23.5 hours (control). There were no significant differences in latencies between the two groups.

The behavioral effects of hypoxanthine are summarized in Table 4. In every baseline period of the behavior test the hypoxanthine-treated rats exhibited significantly less self-biting than controls. Each hypoxanthine rat consumed the graham cracker slurry; none of the control animals ingested the slurry. Each hypoxanthine-treated rat clung to the vertical wire grid and three climbed to the top; control rats did not cling to the wire. During the social behavior portion of the test no hypoxanthine-treated rat exhibited self-biting but 3 of the 4 control rats self-bit from 19 to 100% of the 4-minute observation period. The hypoxanthine-treated rats exhibited significantly less self-biting after immersion in water and three exhibited some grooming. The hypoxanthine-treated rats tended to cross more lines and self-bite less often in the open field but these differences were not significant. The response of all animals to the biting objects and tactile stimulus of the Q-tip (orientation test) were similar.

Discussion

Although the incidence of self-biting was not affected by the administration of hypoxanthine, the severity of self-biting was markedly reduced by hypoxanthine. Equally important, behavior was normalized to some degree; there were signs of improved responsiveness to sensory

Table 4

Effects of hypoxanthine on pemoline-induced self-biting by rats

Group	First Baseline	Orientation	Biting Objects	Graham Cracker	Open Field	Clinging	Second Baseline
		Behavior Test					
Hypoxanthine	SB 10[a]	R 2[b] NR 1 A 3	R 2 NR 0 A 2	R 4 NR 0 A 0	LC 33[c] SB 6	R 0 NR 4	SB 12
Control	SB 88	R 1 NR 1 A 2	R 1 NR 1 A 2	R 0 NR 4 A 0	LC 18 SB 6	R 3 NR 1	SB 82

Table 4--Continued

Effects of hypoxanthine on pemoline-induced self-biting by rats

Group	Behavior Test									
	Social Behavior		Third Baseline		Auditory Stimulation		Fourth Baseline		Wetting Fur	
Hypoxanthine	SB	0	SB	7	SB	0	SB	8	SB	6
	R	1							R	3
	NR	0							NR	4
	A	3								
Control	SB	21	SB	88	SB	18	SB	100	SB	87
	R	0							R	1
	A	3							NR	3

[a]The percent (median) of time spent self-biting (SB) is shown.

[b]The number of rats exhibiting the indicated behaviors is shown. R: appropriate response (see text); NR: no observable response; A: avoidance (the animal turns away from the stimulus or pushes the stimulus away).

[c]The mean number of lines crossed (LC) is shown.

stimuli (ingestion of the graham cracker slurry and clinging to the wire grid). For one animal the duration of self-biting was so brief that a behavior test could not be administered.

The amount of hypoxanthine actually administered during this experiment is unclear. Hypoxanthine is poorly soluble so that far less than 3 mg/ml was probably administered. The major degradative enzyme for hypoxanthine, xanthine oxidase, is not found in the central nervous system; therefore, hypoxanthine levels probably remained quite high throughout the first day of testing.

Because Lesch-Nyhan patients exhibit high hypoxanthine levels in cerebrospinal fluid, the original hypothesis of this experiment was that hypoxanthine might increase the incidence and or severity of pemoline-induced self-biting. There are at least two possible ways to explain the observation that hypoxanthine reduces pemoline-induced self-biting. One possibility is that pemoline-induced self-biting is a poor animal model of the Lesch-Nyhan syndrome. Another possibility is that self-biting in Lesch-Nyhan patients would be much more severe if hypoxanthine levels were reduced. In support of the second possibility, there is evidence that hypoxanthine acts as a benzodiazepine agonist; there is also one report that in some respects the Lesch-Nyhan patients' behavior is what one would expect following benzodiazepine treatment.

The endogenous ligand of the benzodiazepine receptor has not been identified but there are several reports that hypoxanthine and inosine are both benzodiazepine agonists (Skolnick et al. 1978; Asano and Spector 1979). Although the affinities of these compounds for the benzodiazepine receptor are relatively low, the high levels of hypoxanthine

present in the central nervous system of Lesch-Nyhan patients are probably sufficient to produce clinical results. A well known behavioral effect of benzodiazepines is the disinhibition of punished responding (Cook and Davidson 1973; Lippa et al. 1978). The so called conflict-punishment paradigm involves pairing a reinforcement (usually food or water made available to a suitably deprived rat) with a punishing stimulus (usually an electric shock). The undrugged rat discontinues responding when the reinforcement is paired with punishment. But when benzodiazepines are given responding continues in spite of concurrent punishment. The affinity of different benzodiazepines for the receptor is highly correlated with their effectiveness in the conflict-punishment paradigm (Lippa et al. 1978).

Anderson et al. (1979) trained Lesch-Nyhan patients to press a bar for a small monetary reinforcement. Eventually delivery of the reinforcement was accompanied by an electric shock to the hand. Like the benzodiazepine-treated rat, the Lesch-Nyhan patients continued to respond in spite of the concurrent punishment. If endogenous hypoxanthine is providing anxiolytic effects in Lesch-Nyhan patients, developing an animal model for this syndrome would become much more complex.

Clonidine and Adenosine

Method

Fifteen male Swiss mice were maintained as described previously. The animals were injected with 40 mg/kg clonidine followed by 50 mg/kg adenosine and were observed in a glass beaker as described previously. When self-biting was exhibited the behavior test described above was

administered. Six mice which had not exhibited self-biting by 35 minutes after the injection were also administered the behavior test.

Results

Three of the 15 mice exhibited self-biting of the medial digits of the foreleg at a mean latency of 16 minutes. In general, the behavior of these mice was similar to the behavior of clonidine-treated mice described earlier.

When those mice which exhibited self-biting in this experiment are compared to those mice which exhibited self-biting in Experiment 1, few differences emerge. None of the 3 adenosine-treated mice consumed the graham cracker slurry; 4 of the 5 clonidine-only mice consumed the slurry. Adenosine-treated mice crossed significantly more lines in the open field (ANOVA, $F = 17.02$, $p < .01$) than clonidine-only mice. There were no other apparent effects of the adensoine. In this experiment there were also no apparent differences in the behavior of mice which exhibited self-biting and those which did not.

Discussion

Adenosine has been reported to have sedative effects in rats, dogs, and mice and to protect against audiogenic seizures in mice (Haulica et al. 1973; Maitre et al. 1974). ATP or adenosine are candidates for purinergic neural transmission and there is some evidence that Lesch-Nyhan patients are deficient in adenosine-related compounds. For example, fibroblasts from Lesch-Nyhan patients which are grown in culture require exogenous adenine for growth (Felix and DeMars 1969). Activity of the enzyme adeninephosphoribosyltransferase is increased in

Lesch-Nyhan patients (Nyhan 1973). For these reasons, the hypothesis of this experiment was that adenosine would reduce clonidine-induced self-biting in mice. Except for a slight increase in open field activity, there was no evidence of normalization of behavior by adenosine.

EXPERIMENT 3:

HGPRT INHIBITORS AND PEMOLINE-INDUCED SELF-BITING

The development of the mammalian brain is incompletely understood but is thought to depend upon successful completion of a series of precisely timed events. Interruption of this series may lead to permanent disorders. However, in some cases, such as hypothyroidism or phenylketonuria, early treatment prevents permanent damage. The Lesch-Nyhan syndrome may also be a disorder of development.

Brain HGPRT activity increases dramatically from day 0 to day 20 in the rat (Gutensohn and Guroff 1972) and during the early postnatal period in humans (Adams et al. 1971). In all other tissues examined HGPRT activity is stable during development. Some consequence of the absence of HGPRT activity may interfere with proper brain development. If this is true, an animal model of the Lesch-Nyhan syndrome would require manipulation of the developing nervous system.

The purpose of this experiment was to decrease HGPRT activity by administering an HGPRT inhibitor to rat pups. Because HGPRT activity is virtually undetectable in Lesch-Nyhan patients who exhibit self-biting, spontaneous self-biting in these pups was not expected. Rather the hypothesis was that the treated pups would be more susceptible to pemoline-induced self-biting as adults.

Method

Albino rats from Holtzman stock were mated at the University of Arizona animal laboratories. Pregnant females were housed individually in nesting boxes and were examined daily for delivery. The first day that pups were found was designated day 0. On days 2, 5, and 10 pups were anesthetized on ice and injected with a 6-thioguanosine solution (30 mg/ml of artificial cerebrospinal fluid) or with artificial cerebrospinal fluid. On the dorsal aspect of the head a 27 guage needle was inserted to just beneath the skull and 10 µl were slowly administered. Pups were warmed before being returned to the litter.

Pups were weaned at 21 days and housed in groups of from 6 to 10. At approximately 4 months of age 6 control males and 12 experimental males were randomly selected for testing. The animals were drugged with pemoline (140 mg/kg) and were observed and tested as described previously.

Results

Of the 6 control rats tested 4 exhibited self-biting; of the 12 experimental rats tested 8 exhibited self-biting. Latencies to physical evicence of self-biting ranged from 7 to 14 and 3.5 to 24 hours after drug administration for controls and experimentals, respectively. There were no apparent differences in the behavior of the two groups.

Discussion

In cell culture systems 6-thioguanosine produces an 85% inhibition of HGPRT; it is a fairly specific enzyme inhibitor (Lau and Henderson 1972). To date, however, HGPRT inhibitors have not been

administered in vivo. Since brains were not assayed for HGPRT activity in this experiment, one cannot be certain that HGPRT levels were, in fact, reduced by this manipulation. The possibility that certain neurochemical interventions during development may predispose an animal to self-biting as an adult warrants further consideration.

GENERAL DISCUSSION

Possible mechanisms by which purines might affect behavior were discussed in the introduction. However, these experiments provided no direct evidence for the involvement of purines in the etiology of drug-induced self-biting in animals. Evidence was obtained that hypoxanthine, a purine which is present in high concentrations in the central nervous system of Lesch-Nyhan patients, reduced pemoline-induced self-biting. The possibility has been discussed that hypoxanthine acts as a benzodiazepinergic agent to normalize behavior somewhat in both the pemoline-treated rat and the Lesch-Nyhan patient.

The three drugs employed to induce self-biting in these experiments were characterized by very different behavioral repertoires. Pemoline seemed to produce the most abnormal behavior; highly repetitive behaviors and abnormal sensorimotor behaviors were observed. Clonidine produced motor disturbances (tremor) and generalized biting behavior. Caffeine produced few apparent behavioral effects. These differences in behavioral repertoires provide readily testable hypotheses about the behavioral characteristics of self-biting in humans.

Self-biting examined by these experiments will be compared to self-biting observed in other circumstances in both animals and humans, especially the Lesch-Nyhan syndrome. A hypothesis will be advanced that several behaviorally distinct (and perhaps neurochemically distinct) types of self-biting exist, one of which can be described as exaggerated displacement grooming.

Self-biting in Animals

Although self-biting is not a common behavior, neither is it extremely rare. Self-biting has been observed in many species under diverse conditions, although this behavior has usually been described only in passing. Harlow (1962) observed self-mutilation by adult monkeys which had been raised in partial isolation. The animals were described as "grasping and tearing at their legs with ... fury...". Unfortunately, this account does not describe the form of this behavior or under what circumstances this behavior most frequently occurred.

Tinklepaugh (1928) described self-biting of the hind feet by a male monkey. Initially this behavior was exhibited after reunion with a favorite female. The behavior was similar in form to that which had been observed during play. Severe self-biting involving the hips, scrotum, and tail was exhibited during one episode when the monkey was separated from his favorite female; his removal had precipitated a series of violent threat displays between two rival females. Following this episode the monkey bit his legs when "greatly excited". Eventually, this behavior became ritualized so that the biting produced no noticeable tissue damage.

A similar case was described by Allyn et al. (1976). A male monkey exhibited self-biting which was often accompanied by species characteristic threat displays. Self-grooming also increased in frequency prior to self-biting episodes. The behavior was highly ritualized so that tissue damage rarely occurred. This monkey self-bit the hands and feet, usually during agonistic encounters with the handler

or during confinement in a small cage. Head-banging has also been reported in monkeys (Mason and Sponholz 1963).

Many cases of self-biting have been reported among zoo animals. (Meyer-Holzapfel 1968). Amputation of limbs or tails has been reported in opossums, leopards, and monkeys. For example, a martin was observed to chase its tail "playfully". Eventually the tail became covered with small bite wounds and all fur was removed. The majority of these descriptions are not accompanied by further details such as the precise area of the body bit, the form of the behavior, and the circumstances under which the behavior increases in frequency. However, the author does note that monkeys with prehensile tails do not bite the tail.

Interestingly, zoo animals also exhibit highly stereotyped motor behavior. One stereotopy described by Meyer-Holzapfel (1968), "weaving", resembles a stereotopy exhibited by pemoline-treated rats. The animal swings the head rhythmically, usually from side to side, and at the same time alternately lifts and replaces the front paws. The author interprets this behavior as abbreviated pacing; the animal takes fewer and fewer steps before turning until it remains in the same spot lifting its feet and swaying its head.

A popular explanation for all the above behaviors would be that the animals were bored; that sensory stimulation has been severely reduced by the artificial nature of the surroundings, and that self-biting restores a certain critical level of sensory stimulation. If this hypothesis were true, one would expect the most frequent targets of self-biting to be those areas of the body with the most sensory innervation. That is, self-biting (or perhaps severe scratching) of the digits

of the forelegs and of the oral area would be expected. Self-biting of the tail or legs would not be predicted by this hypothesis.

Multiple dorsal rhizotomy induces self-biting of involved dermatomes in rats (Basbaum 1974; Duckrow and Taub 1977). Common popular explanations for this phenomenon emphasize the loss of sensibility of the affected area. That is, grooming may become intensified because of the loss of sensory feedback, or the animal removes the affected area as if it were a foreign object. Self-biting following this procedure, however, does not appear to be related to grooming. As discussed earlier, grooming begins with medial digits but following multiple dorsal rhizotomy lateral digits are commonly bit before medial digits. Further, grooming and self-biting are behaviorally distinct (Duckrow and Taub 1977). Instead, self-biting following this procedure appears to be due to abnormal sensory input rather than due to the loss of sensory input. Lesions of certain hyperactive central sensory areas reduce self-biting following multiple dorsal rhizotomy, although sensibility is hardly restored. Subsedative doses of diphenylhydantoin, which is reported to stabilize hyperactive neurons, also reduce self-biting (Duckrow and Taub 1977).

Self-biting in Humans

The cognitive capacities of humans allow self-injury by more sophisticated methods than self-biting (such as head-banging, wrist-cutting, etc.) and this phenomenon renders study much more difficult. Self-mutilation of some form occurs in about 10% of the severely

retarded population (Bryson et al. 1971). To limit the scope of this discussion, only those instances which involve self-biting will be included.

Interestingly, Nyhan (1973) and others (Bryson et al. 1971) have observed that in most cases, self-mutilation involves banging some part of the body so that callus, swelling, and hypertrophy of injured tissue are common. In contrast, self-biting involves immediate tissue damage, direct loss of tissue, and is much more rare.

Self-biting in the Lesch-Nyhan syndrome has been introduced and only a few characteristics will be mentioned here. Although the behavior is environmentally modifiable, it is not modifiable by punishment (Anderson et al. 1977); characteristic targets are lips and digits; many patients exhibit "favorite" fingers for self-biting (Nyhan 1973, 1976).

Self-biting and other forms of self-mutilation are also observed in the de Lange syndrome (Bryson et al. 1971; Shear et al. 1971; Johnson et al. 1976). Like the Lesch-Nyhan patient direct loss of tissue is common, but unlike the Lesch-Nyhan patient this behavior is easily reduced with punishment (Shear et al. 1971). These patients are severely retarded, exhibit highly stereotyped behavior, and avoid physical contact and social interactions (Johnson et al. 1976).

Similarities between Human and Animal Self-biting

At first glance, these various descriptions of self-biting appear to have little in common. Drug-induced self-biting seems to be related to grooming; self-biting in monkeys and other animals appears to involve isolation or social stress; self-mutilation in humans is

bewildering in its complexity. However, several of these apparent dissimilarities may disappear if one considers grooming in the ethologist's terminology as "displacement" activity.

Grooming is a "maintenance" activity, that is, it serves to clean the body, remove parasites, and, in some conditions, it also serves to maintain body temperature (Jolles, Romper-Barendregt, and Gispen 1979). However, grooming also occurs in situations in which cleaning of the body would seem innappropriate. When placed in a novel environment, mice exhibit many brief episodes of facial grooming; if the enclosure is small, very vigorous grooming occurs. Mice also groom after "freezing" in response to a stressful stimulus (Fentress 1971). Novelty reliably induces grooming in rats as well as mice (Jolles et al. 1979). Grooming also occurs during agonistic encounters, such as after an upright posture directed toward another rat, after aggressive grooming of a conspecific, and after retreat from an agonistic encounter (Grant 1963). Recall that one male monkey increased self-grooming during episodes of self-biting. The authors interpreted this behavior as displacement grooming. Grooming during these apparently innappropriate activities is referred to as displacement grooming. Displacement grooming appears to be more rapid than maintenance grooming and often involves only facial grooming (Grant 1963; Fentress 1971).

Displacement grooming in general seems to occur in the presence of potentially stressful stimuli (Jolles et al. 1979). Delius (1967) hypothesized that much displacement activity is similar to a homeostatic process to de-arouse the organism. This hypothesis received little attention until recently, when several reports appeared that ACTH induces

grooming in rats (Gispen, Wiegant, Greven, and de Wied 1975; Cools, Wiegant, and Gispen 1978; Jolles et al. 1979). Jolles et al. (1979) have also suggested that grooming serves to de-arouse the organism following ACTH administration. Grooming following pemoline, clonidine, and caffeine administration may be viewed in a similar vein.

That is, as stimulants, these drugs arouse the animal and should increase displacement grooming. In some animals, grooming may increase to such an extent that irritation of tissue occurs. In further support of this hypothesis, recall that all caffeine-induced self-biting was exhibited by animals housed individually. Rats are social animals, and individual housing is likely to represent a stressor. (Recall also that the individually-housed animals were generally less healthy than the group-housed animals.) This additional stressor may have been sufficient to produce exaggerated grooming, or self-biting.

This hypothesis is supported by recent suggestions that stimulants in general provide useful models for "endogenous" stress (Post 1975). Antelman et al. (1980) note that behavioral, pharmacological, biochemical, and electrophysiological responses to stress are similar to those accompanying amphetamine administration. For example, a stressor can sensitize an animal to the effects of amphetamine. Many stimulants (caffeine, theophylline, amphetamine, cocaine, pemoline) seem to induce hyperactivity followed by stereotyped behaviors as the dose increases.

Biting is an important component of grooming in rodents but scratching and picking become more important in primates. Thus, self-biting, self-scratching, and self-picking may be the human equivalents of displacement grooming. Biting of finernails and lips, bringing the

hand to the head to scratch the face or to manipulate the hair, have long been associated with stress. Many authors have noted the similarities between displacement grooming in animals and human behavior during stress. Fentress (1971) states "One cannot escape the impression that the animal is agitated to do something, and not having any obvious course of direct action, grooms. (It is rather like watching people fidget in a dentist's office.)" Descriptions of self-mutilation in the de Lange syndrome are reminiscent of repetitive grooming: picking at the eyes, rubbing the hand against the cheek to the point of drawing blood, picking the cheek with one hand while stroking the hair with the other (Shear et al. 1971).

Displacement activity occurs during potentially stressful circumstances. Self-biting in monkeys also occurred during stress: during confinement, during agonistic encounters, or following separation from a mate. Jones et al. (1979) have attempted to compare self-mutilation exhibited by humans with self-biting exhibited by monkeys. They concluded that "self-cutting" is similar in form to self-biting in animals (with an added cognitive aspect), occurs during states of agitation, and appears to reduce agitation.

As mentioned earlier, all drugs which produce self-biting are stimulants. Interestingly, many de Lange patients are hyperactive (Greenberg and Coleman 1973). The behavior of the de Lange patient is in this and other ways very similar to that of the pemoline-treated rat. Both are hyperactive, both display highly repetitive behaviors, both self-bite (or self-mutilate in other ways) in a manner which is often

similar to grooming, both exhibit poor social behavior and aversion to physical contact.

The behavior of the Lesch-Nyhan patient is in some ways similar to the behavior of the pemoline- and hypoxanthine-treated rat. Behavior is more normal than above, but self-biting occurs in association with grooming: digits in the rat and lips and digits in the human. Behavior is unaffected by punishment, presumably because of the benzodiazepinergic actions of hypoxanthine. Clonidine-induced self-biting appears to be a poor model of self-biting in humans. There are few, if any, reports of self-biting in humans associated with a generalized increase in oral behaviors.

Conclusions

There appear to be at least three distinct types of self-mutilation: self-mutilation due to hyperactivity in central sensory areas (e.g. multiple dorsal rhizotomy), self-mutilation which rarely results in direct tissue damage (e.g. head-banging), and self-mutilation which readily damages tissue and resembles grooming. A low incidence of self-mutilation of the latter type would be expected during prolonged stress or during administration of stimulants. A high incidence would be expected when stereotyped behaviors also develop. Benzodiazepines, which are thought to have specific anxiolytic effects, would be ineffective in treating the first type of self-mutilation, but should reduce the third type.

Self-mutilation in animals and humans appears to be similar in many ways. In particular, pemoline-induced self-biting is similar to

self-mutilation in the de Lange syndrome. Pemoline-induced self-biting and concurrent benzodiazepine treatment may be similar to the Lesch-Nyhan syndrome, but further precise behavioral descriptions of the latter are necessary before firm conclusions can be drawn. Clonidine-induced self-biting appears to be a poor model for human self-biting. Caffeine-induced self-biting is a poor model for practical reasons.

This dissertation provided no evidence for the direct involvement of purines in the etiology of drug-induced self-biting. It suggests instead that self-biting is associated with a generalized change in the balance of brain neurotransmitter systems similar to those produced during stress and stereotyped activity. Similarly, the Lesch-Nyhan syndrome is unlikely to be associated with a deficit in a single neurotransmitter system (e.g. purinergic neurotransmission). Rather the HGPRT defect is likely to affect neurotransmitter systems in a more generalized fashion.

REFERENCES

Adams, A., Anderson, J. M., Nicol, A. D., and Harkness, R. A. The development of hypoxanthine/guanine phosphoribosyltransferase activity in man. Biochemistry Journal. 1971, 125, 36.

Allyn, G., Demul, A., and Begue, I. Self-fighting syndrome in macaques: I. A representative case study. Primates. 1976, 17, 1-22.

Anderson, L., Dancis, J., Alpert, M., and Herrmann, L. Punishment learning and self-mutilation in Lesch-Nyhan disease. Nature. 1977, 265, 461-463.

Anderson, L. T., David, K., Bonnet, K., and Dancis, J. Passive avoidance learning in Lesch-Nyhan disease: Effect of 1-desamino-8-arginine vasopressin. Life Sciences. 1979, 24, 905-910.

Anderson, L. T., Hermann, L., and Dancis, J. The effect of 1-5-hydroxytryptophan on self-mutilation in Lesch-Nyhan disease: A negative report. Neuropadiatrie. 1976, 7, 439-442.

Antelman, S. M., Eichler, A. J., Black, C. A., and Kocan, D. Interchangeability of stress and amphetamine in sensitization. Science. 1980, 207, 329-331.

Asano, T., and Spector, S. Identification of inosine and hypoxanthine as endogenous ligands for the brain benzodiazepine binding sites. Proceedings of the National Academy of Sciences, USA. 1979, 76, 977-981.

Barchas, J. D., Akil, H., Elliot, G. R., Holman, R. B., and Watson, S. J. Behavioral neurochemistry: Neuroregulators and behavioral states. Science. 1978, 200, 964-973.

Basbaum, A. I. Effects of central lesions on disorders produced by multiple dorsal rhizotomy in rats. Experimental Neurology. 1974, 42, 490-501.

Berkowitz, B. A., Tarver, J. H., and Spector, S. Release of norepinephrine in the central nervous system by theophylline and caffeine. European Journal of Pharmacology. 1970, 10, 64-71.

Boyd, E. M., Dolman, M., Knight, L. M., and Sheppard, E. P. The chronic oral toxicity of caffeine. Canadian Journal of Physiology and Pharmacology. 1965, 43, 955-1005.

Boyd, H. ATP as a nerve transmitter substance. Journal of Theoretical Biology. 1973, 42, 49-53.

Bryson, Y., Sakati, N., Nyhan, W. L., and Fish, C. H. Self-mutilative behavior in the Cornelia de Lange syndrome. American Journal of Mental Deficiency. 1971, 76, 319-324.

Burnstock, G. Purinergic receptors. Journal of Theoretical Biology. 1976a, 62, 491-248.

Burnstock, G. Do some nerve cells release more than one transmitter? Neuroscience. 1976b, 1, 239-248.

Burnstock, G. Purine nucleotides and nucleosides as neurotransmitters or neuromodulators in the central nervous system. In E. Usdin, D. Hamburg, and J. D. Barchas (Eds.), Neuroregulators and hypotheses of Psychiatric Disorders. Oxford: Oxford University Press, 1976c.

Cook, L., and Davidson, A. B. Effects of behaviorally active drugs in a conflict-punishment procedure in rats. In S. Garattine, E. Mussin, and L. O. Randally (Eds.), The Benzodiazepines. New York: Raven, 1973.

Cook, M. A., Hamilton, J. T., and Okwausaba, F. K. Coenzyme A is a purine nucleotide modulator of acetylcholine output. Nature. 1978, 271, 768-771.

Cools, A. R., Wiegant, V. M., and Gispen, W. H. Distinct dopaminergic systems in ACTH-induced grooming. European Journal of Pharmacology. 1978, 50, 265-268.

Crussi, F. G., Robertson, D. M., and Hiscox, J. L. The pathological condition of the Lesch-Nyhan syndrome. American Journal of diseases of Childhood. 1969, 118, 501-506.

Delius, J. D. Displacement activities and arousal. Nature. 1967, 214, 1259-1260.

Duckrow, R. B., and Taub, A. The effect of diphenylhydantoin on self-mutilation in rats produced by unilateral multiple dorsal rhizotomy. Experimental Neurology. 1977, 54, 33-41.

Eisenstein, N., and D'Amato, M. R. Effects of magnesium pemoline on a delayed match-to-sample task in monkeys. Behavioral Biology. 1975, 15, 245-250.

Enero, M. A., and Saidman, B. Q. Possible feedback inhibition of noradrenaline release by purine compounds. Naunyn-Schmiedeberg's Archives of Pharmacology. 1977, 297, 39-46.

Felix, J. S., and DeMars, R. Purine requirement of cells cultured from humans affected with Lesch-Nyhan symdrome (hypoxanthine-guanine phosphoribosyltransferase deficiency). Proceedings of the National Academy of Sciences, USA. 1969, 62, 536-543.

Fentress, J. C. Development and patterning of movement sequences in inbred mice. Biology Colloquium. 1971, 32, 83-131.

Frith, C. D., Johnstone, E. C., Joseph, M. H., Powell, R. J., and Watts, R. W. E. Double-blind clinical trial of 5-hydroxytryptophan in a case of Lesch-Nyhan syndrome. Journal of Neurology, Neurosurgery, and Psychiatry. 1976, 39, 656-662.

Genovese, E., Napoli, P. A., and Bolego-Zonta, N. Selfaggressiveness: A new type of behavioral change induced by pemoline. Life Sciences. 1969, 8, 513-514.

Gispen, W. H., Wiegant, V. M., Greven, H. M., and deWied, D. The induction of excessive grooming in the rat by intraventricular application of peptides derived from ACTH: Structure activity studies. Life Sciences. 1975, 17, 645-652.

Granot, J., and Fiat, P. NMR studies of catecholamines. Interactions with adenine nucleotides and divalent metal ions in aqueous solution. Journal of the American Chemical Society. 1977, 99, 4963-4968.

Grant, E. C. An analysis of the social behavior of the male laboratory rat. Behaviour. 1963, 21, 260-281.

Greenberg, A., and Coleman, M. Depressed whole blood serotonin levels associated with behavioral abnormalities in the de Lange syndrome. Pediatrics. 1973, 51, 720-724.

Gutensohn, W., and Guroff, G. Hypoxanthine guanine-phosphoribosyl transferase from rat brain (purification, kinetic properties, development and distribution). Journal of Neurochemistry. 1972, 19, 2139-2150.

Harlow, H. F. The heterosexual affectional system in monkeys. American Psychologist. 1962, 17, 1-9.

Haulica, I., Ababei, L., Branisteanu, D., and Topoliceany, F. Preliminary data on the possible hypnogenic role of adenosine. Journal of Neurochemistry, 1973, 21, 1019-1020.

Johnson, G. G., Nyhan, W. L., Shear, C., Ekman, P., and Friesen, W. A. A behavioral phenotype in the De Lange syndrome. Pediatric Research. 1976, 10, 843-850.

Jolles, J., Rompa-Barendregt, J., and Gispen, W. H. Novelty and grooming behavior in the rat. Behavior Neurology and Biology. 1979, 25, 563-572.

Jones, I. H., Congiu, L., Stevenson, M. B., Strauss, N., and Frei, D. A. A biological approach to two forms of human self-injury. Journal of Nervous and Mental Disease. 1979, 167, 74-78.

Kelley, W. N. Hypoxanthine-guanine phosphoribosyltransferase deficiency in the Lesch-Nyhan syndrome and gout. Federation Proceedings. 1968, 27, 1047-1052.

Kelley, W. N., and Wyngaarden, J. B. The Lesch-Nyhan syndrome. In J. B. Stanbury, J. B. Wyngaarden, and D. S. Gredrickson (Eds.), The Metabolic Basis of Inherited Disease (3rd. ed.). New York: Mc Graw Hill, 1972.

Krooth, R. S., May, S. R., and Stern, H. J. A theory for the chemical mediation of the excitability of the brain, with special reference to natural and drug-induced sleep. Journal of Theoretical Biology. 1977, 66, 595-652.

Lake, C. R., and Ziegler, M. G. Lesch-Nyhan syndrome: Low dopamine-β-hydroxylase activity and diminished sympathetic response to stress and posture. Science. 1977, 196, 905-906.

Lau, K. F., and Henderson, J. F. Inhibitors of purine metabolism in Ehrlich Ascites tumor cells in vitro. Cancer Chemotherapy Reports (part 2). 1972, 3, 95-109.

Lippa, A. S., Klepner, C. A., Younger, L., Sano, M. S., Smith, W. V., and Beer, B. Relationship between benzodiazepine receptors and experimental anxiety in rats. Pharmacology Biochemistry and Behavior. 1978, 9, 853-856.

Maitre, M., Ciesielski, L., Lehmann, A., Kempf, E., and Mandel, P. Protective effect of adenosine and nicotinamide against audiogenic seizure. Biochemical Pharmacology. 1974, 23, 2807-2816.

Maj, J., Sowinska, H., Baran, L., and Kapturkiewicz, Z. The effect of clonidine on locomotor activity in mice. Life Sciences. 1972, 11, 483-491.

Mason, W. A., and Sponholz, R. R. Behaviour of rhesus monkey raised in isolation. Journal of Psychiatric Research. 1963, 1, 299-306.

McIlwain, H. Regulatory significance of the release and action of adenine derivatives in cerebral systems. Biochemical Society Symposia. 1974, 36, 69-85.

Meyer-Holzapfel, M. Abnormal behavior in zoo animals. In F. W. Fox (Ed.), Abnormal Behavior in Animals. Philadelphia: Saunders, 1968.

Mizuno, T., and Yugari, Y. Self-mutilation in Lesch-Nyhan syndrome. Lancet. 1974, 1, 761.

Morgan, L. L., Schneiderman, N., and Nyhan, W. L. Theophylline: Induction of self-biting in rabbits. Psychonomic Science. 1970, 19, 37-38.

Morpurgo, C. Aggressive behavior induced by large doses of 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride (ST155) in mice. European Journal of Pharmacology. 1968, 3, 374-377.

Nyhan, W. L. The Lesch-Nyhan syndrome. Annual Review of Medicine. 1973, 24, 41-60.

Nyhan, W. L. The Lesch-Nyhan syndrome. In J. Hamburger, J. Crosnier, and M. H. Maxwell (Eds.), Advances in Nephrology (vol. 3). Chicago: Yearbook Medical Publishers, 1974.

Nyhan, W. L. Behavior in the Lesch-Nyhan syndrome. Journal of Autism and Childhood Schizophrenia. 1976, 6, 235-252.

Peters, J. M. Caffeine toxicity in starved rats. Toxicology and Applied Pharmacology. 1966, 9, 390-397.

Peters, J. M. Caffeine-induced hemorrhagic automutilation. Archives Internationale de Pharmacodynamie et de Therapie. 1967, 169, 139-146.

Post, R. M. Cocaine psychosis: A continuum model. American Journal of Psychiatry. 1975, 132, 225-231.

Phillis, J. W., and Kostopoulos, G. K. Adenosine as a putative transmitter in the cerebral cortex. Studies with potentiators and antagonists. Life Sciences. 1975, 17, 1085-1094.

Phillis, J. W., Kostopoulos, G. K., and Limacher, J. J. A potent depressant action of adenine derivatives on cerebral cortical neurones. European Journal of Pharmacology. 1975, 30, 125-129.

Plotnikoff, N. Magnesium pemoline: Enhancement of learning and memory of a conditioned avoidance response. Science. 1966, 151, 703-704.

Razzak, A., Fujiwara, M., Ogawa, N., and Ueki, S. Characteristics of abnormal behavior induced by 2-(2,6-dichlorophenylamino)-2-imidazoline (ST 155) in mice. Japanese Journal of Pharmacology. 1973, 23 (Suppl.), 67.

Razzak, A., Fujiwara, M., Oishi, R., and Ueki, S. Possible involvement of a central noradrenergic system in automutilation induced by clonidine in mice. Japanese Journal of Pharmacology. 1977, 27, 145-152.

Razzak, A., Fujiwara, M., and Ueki, S. Automutilation induced by clonidine in mice. European Journal of Pharmacology. 1975, 30, 356-359.

Rockson, S., Stone, R., VanDer Weyden, M., and Kelley, W. N. Lesch-Nyhan syndrome: Evidence for abnormal adrenergic function. Science. 1974, 186, 934-935.

Rose, G., and Schubert, P. Release and transfer of H^3 adenosine derivatives in cholinergic septal system. Brain Research. 1977, 121, 353-357.

Sakata, T., and Fuchimoto, H. Stereotyped and aggressive behavior induced by sustained high dose of theophylline in rats. Japanese Journal of Pharmacology. 1973, 23, 781-785.

Schallert, T., and Wishaw, I. Q. Two types of aphagia and two types of sensorimotor impairment after lateral hypothalamic lesions: Observations in normal weight, dieted, and fattened rats. Journal of Comparative and Physiological Psychology. 1978, 92, 720-741.

Schubert, P., Lee, K., West, M., Deadwyler, S., and Lynch, G. Stimulation dependent release of H^3-adenosine from central axon terminals to target neurons. Nature. 1976, 260, 541-542.

Schulman, J. D., Greene, M. L., Fujimoto, W. Y., and Seegmiller, J. E. Adenine therapy for Lesch-Nyhan syndrome. Pediatric Research. 1971, 5, 77-82.

Shear, C. S., Nyhan, W. L., Kirman, B. H., and Stern, J. Self-mutilative behavior as a feature of the de Lange syndrome. Journal of Pediatrics. 1971, 78, 506-509.

Skolnick, P., Marangos, P. J., Goodwin, F. K., Edwards, M., and Paul, S. Identification of inosine and hypoxanthine as endogenous inhibitors of (^{3}H) diazepam binding in central nervous system. Life Sciences. 1978, 23, 1473-1480.

Soumireu-Mourat, B., and Caido, B. Activity and learning in rats after magnesium pemoline. Psychopharmacology. 1968, 12, 258-262.

Tinklepaugh, O. L. The self-mutilation of a male Macacus rhesus monkey. Journal of Mammology. 1928, 9, 293-300.