"Hypersexuality" and Behavioral Changes in Cats Caused by Administration of p-Chlorophenylalanine

Abstract. *The behavior of 26 male cats was systematically observed before, during, and after daily administration of the tryptophan hydroxylase inhibitor,* p-*chlorophenylalanine. These observations established that "hypersexuality," increased aggression, and perceptual disorientation are sequelae of the chronic administration of the drug in cats.*

During an electroencephalographic study of sleep patterns in cats undergoing treatment with the tryptophan hydroxylase inhibitor, *p*-chlorophenylalanine (PCPA), rather striking changes in sexual behavior were noted in one of the animals (*1*). This observation suggested that the induction of major behavioral disturbances by chronic administration of PCPA was a viable possibility, despite the lack of behavioral findings other than the induction of insomnia attributable to the chronic administration of PCPA (*2, 3*). Accordingly, we undertook systematic and comprehensive observations of a variety of feline behavior patterns, and, in addition, we made polygraphic recordings. We summarize here the most dramatic behavioral findings of the overall study, portions of which have been presented elsewhere (*4*).

Twenty-six adult, male cats, each weighing 2 to 5 kg, were the subjects. Thirteen were observed according to a standard protocol on at least four occasions before the onset of treatment (base line) and throughout the treatment period (group A). The remaining 13 animals (group B) were studied according to the same systematic procedure during the course of other PCPA experiments, but less regularly.

The data were derived mainly from standard behavioral test sessions, each 1 hour long, during which the cats were continuously observed in a specially constructed, isolated room. During each session they were sequentially presented with tuna fish, Purina cat chow, a live rat, a passive but otherwise normal male cat (or an anesthetized male), and finally the dominant male of the entire cat colony. A trained observer tape-recorded a running commentary throughout these sessions, utilizing standard terminology for behavioral ratings together with a free-flowing narrative description of the behavior. The commentary was later scored for relevant behavioral variables.

After a base-line or adaptation period, PCPA suspended in a neutral citric acid–phosphate buffer was administered subcutaneously each day to the cats. The daily dose for cats in group A was 150 mg/kg whereas the dose for cats in group B ranged between 75 and 300 mg/kg. The cats in group A had six to nine 1-hour-long observation periods during the first 9 days of PCPA treatment. The number of observation sessions ranged between 3 and 32 per cat for the combined groups. The PCPA treatment periods were 5 to 37 days. In addition to the standard observation sessions, notations were made by all laboratory personnel whenever appropriate throughout the day and night.

Pronounced changes in behavior developed rapidly in every one of the experimental animals after a latency of 3 to 5 days from the initial injection. These changes did not appear to be modified by the variation in PCPA dosage among the group B animals. Of the constellation of emergent behavioral changes, the appearance of "hypersexuality" was perhaps the most dramatic. By "hypersexuality," we mean the marked tendency of one male cat to mount and attempt intercourse with another male cat (*5*). Although homosexual behavior has been occasionally reported in presumably normal cats (*6*), under the conditions prevailing in our laboratories over the past several years countless opportunities for such interactions among male cats have produced only one or two undocumented instances of mounting. These many opportunities have included specific test situations similar to those used in the study reported here (*7*).

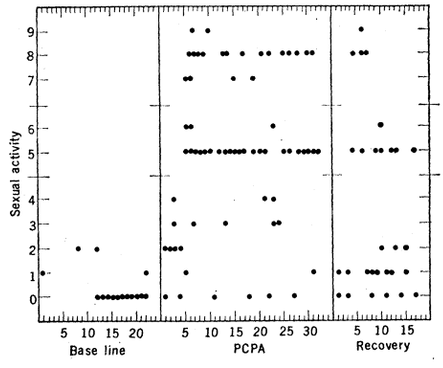

Fig. 1. The daily sexual activity of one cat observed before, during, and after PCPA administration. The abscissa is divided into days. Scoring categories for sexual behavior are represented by the following numbers on the ordinate: 0, not observed for sexual activity; 1, no interaction, ignores other cat; 2, sniffs other cat casually; 3, grooms its own genitals; 4, grooms other cat anywhere; 5, makes a sexual cry; 6 pursues other cat, sniffing it; 7, tries to mount but is easily discouraged; 8, mounts in an integrated deliberate manner; and 9, mounts reflexly, almost involuntarily, in a stereotyped fashion. Categories 1 to 4 are normal patterns of behavior among cats; 5 and 6 are preliminary sexual maneuvers; and 7 to 9 are overt sexual acts. Category 10 (will fight to mount or stay mounted) was not seen in this cat. On some days more than one observation was made.

There is a fairly definite and easily graded sequence of behaviors which constitute a complete sexual act for the cat (see Fig. 1). For the sake of simplicity, we have divided the sequence into preliminary maneuvers (sniffing, pursuing, vocalizations) and complete mounts (mounting though easily discouraged, persistent mounting, disorganized mounting). Only one instance of complete mounting was seen during the 78 base-line sessions with cats of group A. After administration of PCPA, 10 of the 13 cats in group A spontaneously mounted other male cats in a total of 52 out of 128 encounters during the test situation. Seven cats from group B were exposed to other male cats after PCPA treatment either during test situations or by chance. Five of these animals were observed to execute complete mounts. The time course of the development of hypersexuality depicted in Fig. 1 is representative of all the cats. Soon after PCPA treatment was initiated, there was an increase in preliminary maneuvers ($P < .02$), culminating in complete mounts between day 3 and day 6 after the start of the drug treatment. Many of the observation sessions during PCPA treatment in which mounting was not seen occurred in the first days of drug administration.

An equally impressive change in rage behavior also occurred. As one test of this, a large laboratory rat was routinely released in the observation room with group A animals. Only one cat attacked and killed rats before the drug was given. During the period of drug treatment, however, in repeated instances 6 of the 13 cats killed rats. As the treatment period progressed, the attacks became more confused and

savage, and the cats would bat and tear at the rat, then gnaw on it, and, if allowed, eat it completely. In several years of utilizing rat-cat interactions as a test of aggression, we had never seen a cat eat a rat after killing it. Although most animals became much more vicious when subjected to PCPA treatment (several cats actually attacked and severely mauled experienced technicians—not to mention other cats—entirely without provocation), a few unpredictably became more affectionate and would even prefer rubbing against the observer's legs to eating tuna fish.

A third category of changes seemed to involve perceptual processes. Their complexity and individuality resisted simple description and quantification. Every animal receiving PCPA showed a variety of perceptual disturbances, the development of which was consistently related to the time course of the drug. In general the first change was an episode of prolonged wakefulness which usually occurred at around 50 to 60 hours after the first PCPA injection. The animals moved around restlessly in their cages, and even when they were crouched in one place they constantly shifted their weight from one side to the other. In the observation room they ceaselessly explored, sniffing and looking at each object many times. After this period of hyperactivity was well established, episodes of unusual perceptual behavior began to occur. At first the animals seemed to overreact to slight noises, and occasionally they looked wildly around the room when a single moving stimulus such as a rat was present. They often stared at a fixed point for long intervals. Eventually all of the cats showed episodes of looking around the room as though they were watching some obscure object moving in the air. Precautions were taken to assure that the cats were not, in fact, watching something real (for example, a fly). Rapid darting eye movements, orienting movements of the ears, and extensive sniffing often accompanied this visual searching. The extreme of these perceptual disturbances was seen in two-thirds of the cases when animals appeared to interact emotionally with stimuli not apparent to the observer. The animals were observed to hiss and back into a corner in a typical fear response, to strike out at unseen objects, and even to interrupt ongoing activity such as mounting another animal to attend to nonexistent stimuli.

It has been shown that the insomnia associated with PCPA treatment in cats can be markedly reduced by administration of the serotonin precursor 5-hydroxytryptophan (5-HTP) (*3*, *8*). Two animals were given single injections of the precursor in very small dosage (1 mg/kg). As a result there was a definite reduction of abnormal behavior in the waking state (that is, the animals did not mount, kill rats, or exhibit other aggressive behavior). After about 8 hours abnormal behavior returned to its level before treatment with 5-HTP.

After 5 or 6 days of PCPA administration the intensity of the behavioral changes appeared to diminish in most cats. This was much more true of spontaneous behavior such as eating, drinking, grooming, and pacing than of elicited behavior. Thus after ten or more days on PCPA a cat might just sit if left alone but would still become violently enraged from a pinch on the tail and would still mount if presented with another male cat.

Thirteen of the animals in this study, and, in addition, nine animals who were not undergoing behavioral testing, were killed and perfused with saline for biochemical analysis of brain tissue. Serotonin was assayed fluorimetrically with tissue extraction either by solvent extraction with butanol or by ion-exchange chromatography with Bio-Rex 70 (a weakly acidic resin containing carboxylic acid exchange groups). The fluorescence assay was performed after the addition of hydrochloric acid, and similar results were obtained with both procedures (*9*).

The concentrations of serotonin in the brainstems of cats ($N = 3$) that were treated with PCPA for 5 days at a daily dose of 150 mg/kg changed from 0.65 μg/g in controls to 0.06 μg/g in experimental animals. After PCPA treatment for 9 days the concentration of brainstem serotonin was 0.03 μg/g ($N = 5$). Single animals killed at various times thereafter up to 37 days of treatment showed similar low concentrations of brainstem serotonin.

Eight cats were studied during the period of recovery from the drug treatment (*10*). Fifteen days after treatment with PCPA was discontinued, this group of animals no longer exhibited unusual behavior patterns. Although systematic observations were not continued beyond this point, we felt that the animals' subsequent behavior was essentially normal.

Nearly all the cats studied showed marked alterations in sexual, aggressive, and perceptual behaviors during chronic administration of PCPA, and all animals were definitely changed by the drug in one or more of these categories of behavior. In addition, all animals suffered a reduction in total amount of sleep (*11*). These findings of totally altered behavioral patterns in cats are in marked contrast with the paucity of behavioral consequences of PCPA treatment reported in earlier investigations (*2*, *3*). However, a recent report on the effects of PCPA in rats has documented simultaneous enhancement of sexual, aggressive, and grooming behaviors (*12*). Augmentation of sexual behavior in rats treated with PCPA has been confirmed (*13*), and incidental observation of mouse-killing tendencies in rats treated with PCPA presumably confirms the enhancement of aggressive behavior (*14*).

In all of this work it would appear that the behavioral response to PCPA administration is more intense and more enduring and involves more specific modalities of behavior in the cat than in the rat. The same applies to the effect of PCPA on sleep patterns in the rat where the reported changes range from moderate changes to none at all (*15*). However, before one concludes that a profound and encompassing behavioral effect of PCPA administration is unique to the cat, further studies with long-term administration of PCPA at several concentrations and continuous observation of many behavioral modalities in the rat should be done. It is possible that discrepancies in the response to PCPA across species would be reflected in differential changes in other compounds during PCPA administration (*16*).

It is worth noting that the behavioral changes associated with long-term PCPA administration are provocatively similar to the changes associated with prolonged selective deprivation of rapid eye movement (REM) sleep in both cats (*7*, *17*) and rats (*18*), although the effects of the manipulation of REM sleep are somewhat less intense. Furthermore, the administration of amphetamine to rats deprived of REM sleep intensifies the syndrome to the point where compulsive mounting and aggressive posturing occur spontaneously (*19*). Finally, the above-mentioned behavior of rats given amphetamine and deprived of REM sleep is identical with the behavior of rats who

are treated with reserpine and then given amphetamine (*19, 20*).

The data presented here on the effect of PCPA treatment in cats represent minimum estimates of change. They include only positive identification of behavior patterns made during relatively short—although daily—observation periods. They are sufficient, however, to show that long-term administration of PCPA has a pronounced and encompassing effect and to suggest that serotonin may have a pervasive role in regulating drive and behavior in the cat.

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References and Notes

1. Ordinarily we did not allow cats to interact during experiments in order to minimize the possibility of a cat fight with damage to a valuable animal or its implanted electrodes. Thus it would have been possible to complete a whole study without seeing two cats interact in the suggestive manner described here. In this particular instance, the cat treated with PCPA was brought into the recording room while another cat was still out of his recording cage receiving wound care and temperature measurement. The cat treated with PCPA leaped out of the experimenter's arms and was instantly upon the other male cat in a typical feline sexual mount.
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10. Three of the 26 cats were killed after 5 days of PCPA treatment and another four died during the course of the experiments from causes unrelated to the experimental manipulation. Of the remaining animals, six were killed after nine or more days of treatment; and five died from presumed toxic effects of the drug, thus leaving eight for observations during the recovery period.
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6 October 1969; revised 16 January 1970 ■

Brain Norepinephrine: Enhanced Turnover after Rubidium Treatment

Abstract. *After biosynthesis of norepinephrine was inhibited, treatment of rats for 10 days with rubidium chloride (0.6 milliequivalent per kilogram of body weight) caused an increase in the rate of disappearance of norepinephrine in the brainstem but not in the telencephalon. Also the utilization of intracisternally injected tritiated norepinephrine was increased and was accompanied by a shift in the pattern of norepinephrine metabolism to normetanephrine. These data suggest that greater amounts of neuronally stored norepinephrine were released to central adrenergic receptors.*

The action of rubidium on central excitability in monkeys has been described (*1*). The effectiveness of another alkaline earth cation, lithium, in the treatment of mania has been tentatively associated with the effect of this ion on brain amine metabolism (*2*) which is perhaps related to an interaction with other cations intimately involved in adrenergic neurotransmission. In contrast to the effects of lithium in both humans and infrahuman species, rubidium causes hyperactivity, increased aggressiveness, and electroencephalographic activation. We examined the effects of short-term rubidium treatment on gross behavior and on the metabolism of brain catecholamines in rats.

Our experiments were performed on male Long-Evans rats that weighed 250 to 300 g at the start of the study. The rats, housed in groups of four, were injected daily with saline or with rubidium chloride (0.6 meq per kilogram of body weight; intraperitoneally) for ten consecutive days. Twenty-four hours after the last injection, groups ($n = 16$) of both the control rats and those treated with rubidium were injected with 200 mg/kg (intraperitoneally) of the methyl ester of DL-α-methyl-*p*-tyrosine (αMT), an inhibitor of catecholamine biosynthesis which can be used to measure the rate of utilization of catecholamines (*3*). Animals were killed at intervals thereafter.

Brains were dissected into stem (comprising diencephalon, metencephalon, and myelencephalon) and telencephalon fractions for amine determination. After the fractions were homogenized in 0.4*N* perchloric acid, the supernatants were adjusted to *p*H 6.5 and passed over IRC-50 resin. Norepinephrine (NE), dopamine (DA), and 5-hydroxytryptamine (serotonin, 5-HT) were assayed spectrophotofluorimetrically after elution from the resin by 0.5*N* acetic acid. Values for brain NE and DA concentrations were subjected to regression analysis by least-square fitting to obtain rate constants for their disappearance after inhibition of catecholamine biosynthesis.

In a second experiment, control rats and those treated with rubidium were given an intracisternal injection of [^{3}H]NE (8.3 μc; specific activity, 7 c/mmole; New England Nuclear).