STEREOTYPED AND AGGRESSIVE BEHAVIOR INDUCED BY SUSTAINED HIGH DOSE OF THEOPHYLLINE IN RATS

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Abstract Repeated administrations of high doses of theophylline to rats resulted in a series of stages which progressed as treatments were continued, i.e. hypoactivity, stereotypy, killing attack and automutilation, etc. Stereotyped behavior was continuous sniffing with backward locomotion, biting of the cage floor, standing on hind legs with forelimbs-flapping and turning somersaults in the cage. The aggressive behavior associated with theophylline treatment was that seen in affective aggression. The theophyllinized killers vigorously attacked animate as well as inanimate objects including rat-pups but never consumed their prey. Possible mechanisms of the effect of theophylline on aggressive behavior are discussed.

There has not been any demonstration assigning a definite role to methylxanthines in the central nervous system, although Quadbeck and Sachsse (1) have suggested that it may induce an increase in the permeability of the blood brain barrier. Several studies have shown that, of all mammalian tissues, the brain has the highest activity of adenyl cyclase as well as cyclic 3', 5'-nucleotide phosphodiesterase, that is responsible for the destruction of cyclic AMP, and that is inhibited by methylxanthines (2, 3). In addition to these findings, cyclic AMP has a possible involvement as a mediator of behavioral change (4).

This experimental evidence led to the proposal that theophylline may affect fear-motivated behavior in shuttle avoidance responding in rats (in preparation). During the course of these studies, it was observed that some rats chronically injected with theophylline (i.p.) became aggressive and strenuously resisted handling. The purpose of the present study was to observe whether or not theophylline, when administered chronically has effects on aggressiveness, particularly from the point of gross behavior.

MATERIALS AND METHODS

Male albino rats of the Wistar strain, 95-110 days of age at the beginning of the experiment were used. Subjects were housed in groups. Prior to the start of injections, each subject was handled five min a day for two successive days and was housed in an individual cage. On the day following the handling procedure, 28 subjects were randomly divided into 18 as the theophylline group and 10 as the saline control. The dose of theo-

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Phylline used was five mg in one ml saline per 100 g body wt. with the same volume of saline being used for the controls. Each subject was given i.p. injections three times daily for four weeks with a one hr interval between injections, i.e. the daily dose of theophylline amounted to 15 mg per 100 g body wt.

The animals were carefully observed for signs of stereotyped behavior, depilation and scarring before and after every injection. The stereotyped behavior was defined as a single activity which was performed continuously and dominated the subject’s behavior, e.g. continuous sniffing or biting. The subjects were also presented with a series of standardized tests in which their killing responses were measured. The objects used as victims were rat-pups, mice and frogs as animate objects, and stuffed rats, recently deceased rats and immobile and mobile dolls as inanimate objects. The observation was done 60 min after the last injection of each of the first five days and every four days after day six. A victim was introduced into the home cage of the rat, then if a kill did not occur within three min after the confrontation, the victim was removed. Each subject was given a three min trial with each of the objects on each experimental day. A pilot study showed that a kill rarely occurred after three min in the case of the theophyllinized rats.

**RESULTS**

Ten subjects out of 18 in the theophyllinized group died from the toxic effects of the drug, while none of the controls died. As shown in Table 1, the effects of theophylline seemed to develop in a series of stages which progressed as treatments continued. In the hypoactive stage, theophyllinized rats sat still in a crouched posture with piloerection in a corner of a cage and seldom responded to such external stimuli as tapping on the back, pushing the side of the body or blowing air over the body, etc. The animals looked quiet and weak, but they did not lose normal activities, such as eating, grooming, rearing, preening and forward locomotion.

The stereotyped behavior which developed next included continuous sniffing with
backward locomotion, biting of the cage floor, standing on hind legs with forelimbs-flapping, sometimes pressing of the body against the cage wall and turning somersaults, however normal activities were also present.

Various killing behaviors, whether the victim was animate or inanimate, developed almost at the same stage. A kill did occur in about 60% of the theophyllinized rats, in which case all these killing responses were provoked within several sec after a victim was introduced into a home cage of the theophyllinized rat. Once the killing behavior was established, it continued for the remainder of the experiment. The extreme and persistent attack was directed not only against live victims, but also against inanimate objects including stuffed rats. The killing behavior produced in the theophyllinized rats never resulted in the consumption of the prey. Theophylline-treated rats killed by biting their victims through the spinal cord in the cervical region. The killer was very likely to hold the victim with his teeth and struggle vigorously, when the victim was removed from a cage. These killing patterns did not change until the end of the experiment, whether the victim was animate or inanimate, including rat-pups.

![Fig. 1. Automutilation around the root of the tail in a rat treated with sustained high dose of theophylline.](image)

Rats on theophylline also mutilated themselves by biting and tearing their paws and the tail and the skin around the root of the tail, shown in Fig. 1, in the same manner as described by Seegmiller (5). There were no apparent differences between the sexes concerning elicitation. The hair over the abdomen or the legs fell off gradually and scars were sometimes evident on the limbs and the tail. The theophyllinized rats responded much more quickly to noises than did the controls, and consumed their food more rapidly. None of the control animals revealed any of the behavior observed in the theophylline-treated animals.

**DISCUSSION**

It has been considered that the methylxanthines have in common a stimulant action. There is considerable controversy, however, as to whether this is also true at all dose levels.
Recent studies have shown that caffeine and theophylline at mild or strong doses produce apparent sedation, lack of movement (6, 7) and anxiety-reducing activity (8), though reversal of effects is observed only after acute drug administration. The behavioral hypoactive effects observed herein during acute administration of theophylline support this finding. The present study was primarily concerned with behavioral changes which developed during the course of chronic administration of theophylline. Emphasis is, therefore, placed on the fact that the effects of theophylline under conditions of chronic administration developed not only in the hypoactive stage as the initial effect of the drug, but were also observed in such a series of stages as stereotypy, killing attack and automutilation, etc.

The types of stereotyped behavior in these theophyllinized rats are somewhat similar to those seen with several stimulant drugs represented by amphetamine. Many findings indicate that the development of stereotypy induced by classical stimulants is associated with dopaminergic mechanisms in the corpus striatum, in which the dopamine of the brain is highly concentrated (6). Although additional research is necessary to elucidate the biochemical mechanisms involved in eliciting stereotypy, Waldeck (9) has indicated that methylxanthines increase the turnover of noradrenaline and dopamine in the mouse brain when given in sufficiently large doses, and inferred that the effect of methylxanthines on catecholamines could be due to inhibition of the catabolism of intraneuronal cyclic AMP.

The aggressive behavior associated with theophylline treatment is consistent with that seen in affective aggression. Moyer (10) classifies the various types of aggression into seven categories in which the affective aggressions are characterized by the following responses: attack is not followed by the consumption of prey, a wide variety of inanimate as well as animate objects is attacked, and the range of stimuli which will elicit affective aggression is extremely broad. These characteristic traits are consistent with the behavioral responses seen in theophyllinized rats, which responded vigorously to noises, while intense noise is normally ineffective in producing fighting behavior in rats (11). In addition, once theophylline treatment induced the rats to kill, these rats attacked inanimate as well as animate objects without consuming them, though attackers, developed in other procedures, interrupt the attacking response toward dolls as well as stuffed mice and rats (11, 12). Myer (13) shows that olfactory cues control inhibition of killing rat-pups in mouse killing rats and Karl et al. (12) suggest that the production of the killing response results from the suppression of an active inhibition mediated through the olfactory pathways which inhibit the facilitating influence of the killing response exerted by the central nucleus of the amygdala. On the other hand, the fact that serotonin has a depressant action on the activity of amygdaloid neurons led them to observe an important reduction of the serotonin content in the amygdala in consequence of the removal of the olfactory bulbs (12). These studies suggest that the behavioral mechanism observed in the development of the killing of rat-pups may depend on the biochemical breakdown of the inhibitory mechanism through the olfactory pathways, which theophylline may have as an effect on the CNS of rats.
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