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Cortical Damage Enhances Pemoline-Induced Self-Injurious Behavior in Prepubertal Rats

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CROMWELL, H. C., M. S. LEVINE AND B. H. KING. *Cortical damage enhances pemoline-induced self-injurious behavior in prepubertal rats.* PHARMACOL BIOCHEM BEHAV **62**(2) 223–227, 1999.—Self-injurious behavior (SIB) is a devastating characteristic of several developmental disorders including a number of mental retardation syndromes. The functional neuroanatomy and neuropharmacology of SIB is not well understood. Self-biting behavior (SBB) can be induced in rats by a high dose, systemic injection of pemoline (250 mg/kg, SC). This animal model allows for the investigation of anatomical and pharmacological aspects of SIB. Cortical pathology is a common occurrence in human disorders with SIB, and may be a fundamental pathological factor in producing the behavior. The present experiment was designed to investigate the effects of cortical damage on pemoline-induced SBB in prepubertal rats. Bilateral cortical aspirations were performed in 3–5-week-old rats. One week postsurgery, a pemoline challenge was administered. Behavioral comparisons were completed between the lesion group and an anesthetized-only control group. Results indicated that cortical damage significantly enhanced pemoline-induced SBB, along with some of the other pemoline-induced stereotypical behaviors. These results support the hypothesis that cortical damage influences the expression of stimulant-induced self-injury, and potential mechanisms for this influence are suggested. © 1999 Elsevier Science Inc.

Dopamine Excitatory amino acids Lesch-Nyhan Syndrome Mental Retardation Stereotyped behavior Striatum

SELF-INJURIOUS behavior (SIB) in humans, typically manifest by self-biting, self-hitting, or head-banging, is an extremely debilitating characteristic of several mental retardation syndromes (e.g., Lesch-Nyhan syndrome and Cornelia de Lange syndrome). Cortical pathology is the most common feature of persons with severe mental retardation, and individuals with the most profound cognitive deficits are also the most likely to exhibit repetitive self-injury, irrespective of the underlying cause of the mental retardation (19). Dysfunction of the dopaminergic system has also been identified in at least one mental retardation syndrome characterized by prominent SIB (3,11,40). Currently there is no reliable pharmacotherapy available for reducing these behaviors, and in many cases, physical restraint becomes the most effective treatment option (26).

We have currently been examining the functional neuroanatomy and neuropharmacology of self-injury using an animal model (9,20,21). The model consists of administering a high dose of systemic 2-imino-5-phenyl-4-oxazolidione, pemoline, to produce repetitive self-biting behavior (SBB) in the rat (14,18,31). It is thought that pemoline mainly acts an indirect dopamine agonist similar in mechanisms to amphetamine or cocaine, but with a more prolonged influence upon the dopaminergic system (9,29,32). The aim of the present study was to examine how bilateral neocortical damage would influence the pemoline-induced SBB in the rat. Given the fact that there is a significant evidence that cortical damage enhances stereotypical behavior induced by specific dopamine compounds including amphetamine, apomorphine, and quinpirole (2,16,39), and that the cortical glutamatergic and midbrain dopaminergic systems seem to be highly interactive (13,17,25, 36), it seems likely that self-injury produced from a pemoline injection may be altered by changes in cortical function.

Animals

The Institutional Animal Care and Use Committee, UCLA Harbor Research and Education Institute, reviewed and ap-

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proved all experiments. Experiments used 40 prepubertal male rats (Harlan–Sprague–Dawley, Indianapolis, IN), 30 to 32 days old. Animals were housed individually in clear plastic cages under a 12L:12D cycle with food and water ad lib.

Surgery

The cortical ablation group (n = 17) received a mixture of ketamine/xylazine (80 mg/kg ketamine and 12 mg/kg xylazine). The control group had the injection of anesthetic and underwent a sham operation that included a midline incision followed by suturing (n = 23). Aspiration lesions of the cortex were performed using a suction pump and a 30-gauge needle. Holes over the frontal plate were drilled on both right and left sides. Knife cuts were made through the dura, and suction was applied to the caudal frontal lobe (primary motor, premotor, and frontal agranular regions) and rostral parietal regions (primary sensory cortex) in each experimental animal on each side. Controls did not receive drill holes in the skull because a pilot study showed that at this age, drilling alone produces small amounts of cortical damage.

Behavioral Measures

Seven days postsurgery all animals were given a single injection of pemoline (Sigma; 250 mg/kg SC, suspended in peanut oil vehicle) to produce SBB. Each animal was observed and videotaped for a 1 min period in its home cage at 2, 4, 6, 8, 10, and 24 h following the pemoline injection. Videotapes were scored by two trained observers blind to all treatment conditions and unfamiliar with the outcome of pilot experiments. After taping at each time point, each animal was carefully inspected for evidence of injury. If an animal showed signs of chronic self-biting (macerated tissue at a single site or tissue loss), it was euthanized.

Videotaped observation periods were examined for the presence of a variety of behaviors including self-biting, rotations, locomotion, rearing, stereotyped bob-lick, stereotyped dig/sniff/burrow, resting, and eating/drinking.

Locomotor activity was indicated by the rat moving at least three paws forward in succession; the total number of occurrences was summed for each 1-min sample. Rearing was indicated by counting the number of times the animal lifted both forepaws off the cage floor for at least 3 s. For a subsequent rear to be recorded, the animal must have resumed and maintained contact with the cage floor for at least 1 s. Some animals reared repeatedly in this fashion, while other remained upright throughout the observation period. Occurrences of extended rearing (>10 s) were also recorded.

Stereotyped bob/lick was scored for every 3 s that an animal either bobbed its head in a stereotyped manner or repetitively licked the side or floor of the cage. The behaviors generally cooccurred. Sustained bob/lick activity (>10 s) was separately coded. Stereotyped dig/sniff/burrow was scored for every 3 s an animal engaged in these stereotyped behaviors. Sustained dig/sniff/burrow behavior (>10 s) was coded separately as well.

An episode of SBB was coded for every 3 consecutive seconds of occurrence, with separate designation for extended or continuous (>10 s) exhibition of this behavior.

Histology

At the time of euthanasia, brains were removed and fixed in formalin (10% with 30% sucrose) for histological analysis. Coronal sections were cut at 40 μm using a cryostat and stained with cresyl violet (6). Lesions areas for each coronal slice were determined using vidioimage analysis software (Micromeasure Analysis System). Lesion volume was then determined with the following formula: V(lesion) = t × a(sect); where V(lesion) = the volume of the lesion, t = the distance between sections (400 μm + one section thickness (40 μm), and a(sect) = the sum of lesion areas estimated by the program).

Statistics

Animals with and without lesions were compared across behaviors with a chi-square for the presence or absence of SBB and other stereotyped movements at each time point. For locomotor counts, which were not normally distributed, the Mann–Whitney U-test was used.

RESULTS

Lesion Analysis

The cortical damage varied in size between animals, yet in each case it appeared that damage was located in the precentral area including motor regions in the medical and lateral precentral divisions (22,23). A representative lesion is pictured in Fig. 1. Relative to bregma, this damage ranged from 1.0 mm

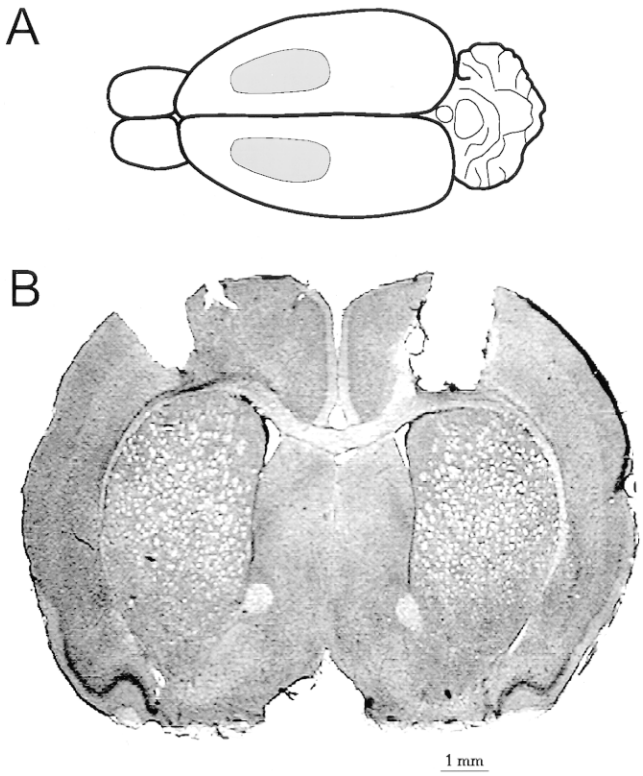

Fig. 1. Drawing of a typical bilateral cortical lesion that involves portions of both frontal cortex and parietal cortex mainly primary sensory regions. (B) Low-magnification photo of a coronal section (AP +0.5) of a bilateral cortical lesion of a rat that had displayed potentiated SIB. These lesions are quite small, mainly involving the medial aspect of the cortex and selective regions in primary motor, premotor, and primary sensory regions.

anterior to −0.4 mm posterior, inclusive (33). Damage was noted in the corpus callosum in several rats. No damage was seen in the underlying striatum in any animal (striatal volumes were not measured). Extensive damage beyond the caudal frontal cortex was rare. The largest lesions included rostral damage into profrontal areas and caudal to secondary sensory regions in the parietal lobe. Medially, damage included the cingulate cortex in the midline longitudinal fissure and laterally extended into parietal areas 1 and 2 (33). Lesion volumes were measured (n = 10). Damage to the left and right sides was found to be comparable (mean volumes were 14 ± 1.1 mm^3 for the right-side and 16 ± 2.3mm^3 for the left side). The volume range for the cortical damage was 9 to 29 mm^3.

Lesion Effects on Pemoline-Induced Self-Biting Behavior

Animals in both intact and cortical lesion groups displayed SBB. The types of injury included biting of the forepaw digits, hindpaws, wrists, thorax, abdomen, and infrequently, the tail. In most cases biting was directed at only one area and was focused and stereotyped. Rats that had cortical aspirations showed significantly greater SBB. This was evident in an average earlier onset and in the overall higher incidence of SBB in the lesion group. SBB was not seen in either group 2 h after pemoline injection. Four hours postpemoline, both groups had members exhibiting SBB. At each time point measured, rats with cortical damage had a higher incidence of SBB compared to intact controls. These results are shown in Fig. 2. The cumulative percentage at 24 h postpemoline was significantly higher in rats with cortex damage compared with intact rats [lesion group = 70.6%, controls = 9%, $\chi^3(1) = 6.1, p < 0.02$]. Measures of cumulative percentage difference permits evaluation of the entire data set (e.g., to include animals that were euthanized prior to the 24 h end point due to significant SBB) from each group, and indicates that cortical damage expressly lowers the threshold for pemoline to induce the stereotypical SBB.

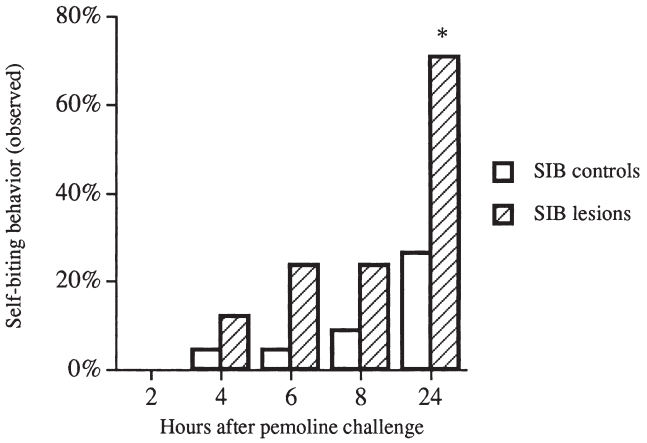

Fig. 2. Self-biting behavior following pemoline challenge in lesioned (n = 17) vs. control animals (n = 23). The percentage of animals in each group displaying the behavior appears at each time point. The 24-h time point is cumulative, indicating the percentage of animals in each group that displayed self-biting behavior of sufficient intensity to produce erythema at any time during the preceeding 24 h. Self-biting behavior over 24 h is significantly greater in lesioned animals than in controls (χ^2 = 6.1 with continuity correction, d.f. = 0.0133).

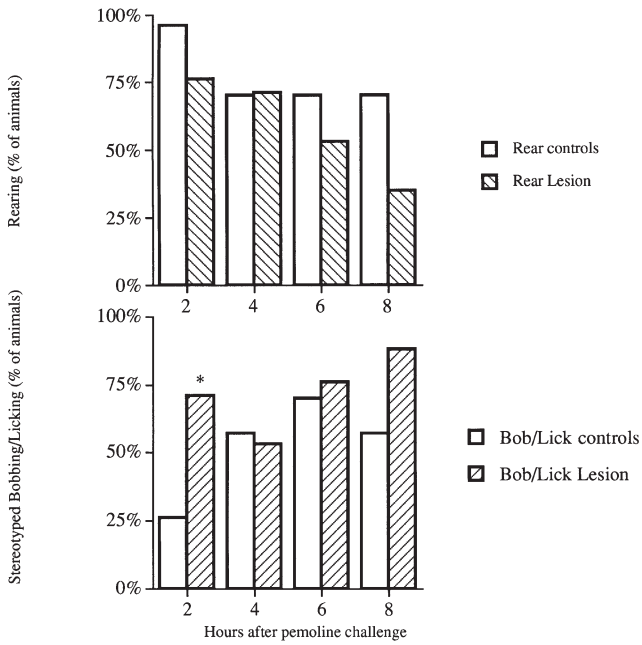

Fig. 3. Rearing (top panel) and stereotyped head bobbing/licking behavior following pemoline challenge in lesioned (n = 17) vs. control animals (n = 23). The percentage of animals in each group displaying the behavior appears at each time point. Bobbing/licking behavior at 2 h is significantly greater in lesioned animals than in controls. (χ^2 = 6.1 with continuity correction, d.f. = 1, p = 0.0133).

Lesion Effects on Other Pemoline-Induced Stereotypical Behaviors

General stereotypy and locomotion were also measured. Stereotyped movements were measured by videotape analysis and because most observations tended to be rated "continuous" or for extended periods (longer than any 1 min viewing), the incidence of behavior was used as an index of a difference between groups. A higher percentage of rats with cortical lesions showed pemoline-induced stereotyped bob/licking. This

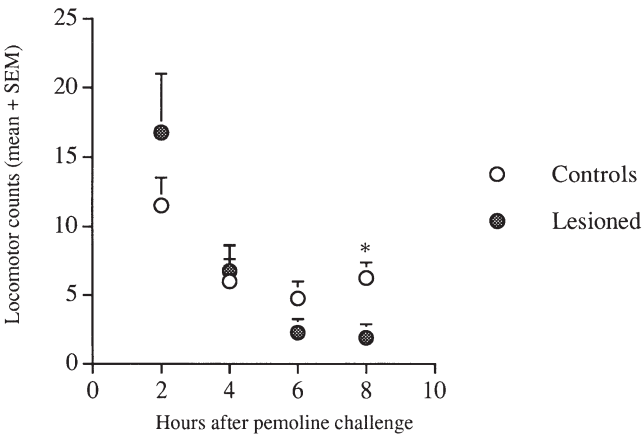

Fig. 4. Locomotor activity following pemoline challenge in lesioned (n = 17) vs. control animals (n = 23). Locomotor activity is significantly greater in control animals at 8 h (Mann–Whitney U-test, Z-corrected for ties = −3, p = 0.0031).

significant increase in incidence was observed early after the pemoline injection [2-h time point; $\chi^2(1) = 6.1, p < 0.02$]. Results are shown in Fig. 3. The same relationship at the 8-h time point occurred between groups, but the difference was not significant, $\chi^2(1) = 3.3, p = .069$. In contrast, rats with cortical lesions displayed less rearing at three out of the four time points measured with the greatest difference observed at the 8-h observation period ($p = 0.07$).

At this same time point, rats with cortical damage displayed less locomotor activity compared to controls (lesion = 1.8 ± 1 counts; control = 6.2 ± 1.1 counts, Mann–Whitney U, $p < 0.01$). Results are shown in Fig. 4. This decrease in locomotor activity could be related to the increased levels of SBB and bob/licking actions in the same group at similar times.

DISCUSSION

The primary finding of the present study was that animals with cortical damage showed an enhancement of SBB following a pemoline challenge. These results suggest that cortical damage can influence a consequent drug-induced behavior that is believed to be primarily caused by prolonged dopamine release (27,31). This finding supports the idea that cortical damage in patients who display SIB may have a critical influence on the degree of SIB, and pharmacotherapies in the future may need to focus more on modulating neurotransmitter systems specific to the cortex (e.g., glutamate). In addition, animals with cortical lesions displayed different degrees of pemoline-induced stereotypies. Rats with cortical damage display greater bobbing and licking movements early in the cascade of events following pemoline injection. This effect remained present but somewhat diminished at the later time points when the cortical-lesioned rats show a coincident decrease in locomotion and rearing. This result may arise at these later time points because these animals are displaying more intense self-biting behavior. Self-biting behavior and stereotyped bobbing and licking may occur coincidentally because of their similar action organization, whereas locomotion may decrease at the expense of the increased oral and head-centered movements.

Small cortical damage seems to be adequate to produce the enhancement in young animals. In earlier pilot studies, we noticed that control animals with sham operations that included drilling through the skull also showed enhanced SBB when cortical damage was observed. In comparing the degree of SBB with the lesion size, we have found that smaller lesions are just as potent in enhancing pemoline-induced SBB compared to larger lesions. Further investigations are needed to probe this idea in more detail. In any case, the variability of our methods for making sham lesions could lead to a hypothesis that the stress of the surgery (with drilling) plays a key role in the observed enhancement. We believe this is not so, based upon earlier work examining the effects of unilateral striatal lesions upon pemoline-induced self-injury. We found that animals with these lesions, which included a similar operation (stress level) as our cortical lesion group in the present study, did not show an enhancement of SBB when the cortex was intact (37).

A number of mechanisms could influence the enhancement of pemoline-mediated behaviors produced by cortical damage. Postlesion plasticity in the cortex as well as in subcortical structures is most likely such an influence. Cortical damage alters the neurophysiological properties of subcortical structures (1,7,8,24), changes neurotransmitter levels available for release (30,38), transforms the synaptic relationships, and modifies several indices of plasticity in a number of subcortical regions (34,35). Cortex damage also produces *N*-methyl-D-asparate (NMDA) and non-NMDA receptor upregulation in the striatum (41). The striatum has been found to be important for the production of many stereotyped movements (16), and an increase in glutamate receptor number could produce a facilitating effect upon cortical glutamate release following the lesion. Of course, this facilitation would depend upon enough remaining viable cortex after the damage. Ablation of cortex also decreases D_2 receptor levels in the striatum (28). Such a change has been attributed to the loss of the presynaptic D_2 receptors on corticostriatal terminals (12), and could lead to abnormally high levels of D_1 receptors. Recent electrophysiological studies have shown that D_1 receptor stimulation has an enhancing effect upon the NMDA-induced response in both the cortex (4) and striatum (5,25). This dopamine/glutamate interaction in the striatum was examined in slices of rat corticostriatal tissue taken from animals displaying SBB (10). The results of the study indicated that rats that display self-injury have an anomalous dopamine-induced increase of the glutamate-mediated striatal synaptic response. This result supports the idea that the phenomenon of pemoline-induced SBB is related to an alteration in glutamate transmission, and that this alteration is influenced by dopamine modulation. These relationships would certainly be changed by cortical pathology and the plasticity that follows such damage.

Previously, it has been shown that there are distinct behavioral alterations that follow damage to different cortical subareas, and that these alterations depend upon the developmental stage in which the damage occurs (22). Whether damage to different cortical subareas yields different outcomes in terms of influencing pemoline-induced SBB will be an important area of investigation, as these variables may be critical in the etiology of SIB in humans. Furthermore, the delineation of critical developmental aspects that interact in the relationship between cortical pathology and pemoline-induced SBB may provide clues to the prevention or remediation of SIB in persons with profound mental retardation.

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