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Mitigation of the Septal Lesion Syndrome by Pre-Lesion Chronic Treatment with Haloperidol

R. F. MAROTTA[1]

Biopsychology Program, City University of New York, New York, NY 10021

N. LOGAN[2]

Department of Psychology, Hunter College of the City University of New York, New York, NY 10021

S. RIVERSO[3]

College of Mt. St. Vincent, Bronx, NY 10474

AND

E. L. GARDNER[4]

Departments of Psychiatry and Neuroscience, Albert Einstein College of Medicine, Bronx, NY 10461

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MAROTTA, R. F., N. LOGAN, S. RIVERSO AND E. L. GARDNER. *Mitigation of the septal lesion syndrome by pre-lesion chronic treatment with haloperidol.* PHARMAC. BIOCHEM. BEHAV. **16**(5) 769–775, 1982.—The effect of chronic pre-lesion administration of haloperidol, α-methyl-p-tyrosine, apomorphine or phenobarbital on the emergence of and recovery from lesion-induced septal rage was studied in rats. Pre-lesion haloperidol (4 mg/kg/day for 7 days) significantly blocked the post-lesion behavioral syndrome, while the other drugs tested had no effect. These results, together with previous data implicating dopaminergic mechanisms in behavioral recovery from septal lesions, suggest that dopamine receptor blockade may be involved in initiating recovery processes from septal damage.

Septum Septal rage Hyperirritability Recovery of function Haloperidol Emotionality

LESIONS of the septal forebrain area in the rat have long been known to produce a dramatic increase in irritability and reactivity [5,9]. The resulting syndrome, often referred to as "septal rage," is characterized by initially explosive levels of irritability and reactivity, which gradually subside to pre-lesion levels over a fairly prolonged period of behavioral recovery [5,15]. Recovery from this syndrome seems to be a function of time, lesion size and site, and specific type of environmental stimulation [5, 15, 21]. Depending upon the specific experimental conditions, recovery may last as little as 7 or fewer days [15] or as long as several months [5]. When lesion site, lesion size, and environmental stimulation are held constant, a fairly consistent time course of recovery is seen [15].

Although the septal syndrome has been extensively studied and its behavioral sequelae well quantified for more than two decades, little is known about the brain mechanisms subserving the syndrome or its behavioral recovery. Recent evidence, however, points to at least a partial dopaminergic involvement in both the production of irritability and in the process of behavioral recovery following septal damage. For example, the irritability syndrome can be produced by intracisternal [8], intraventricular [35], or localized intraseptal [25,27] injections of the catecholamine neurotoxin 6-hydroxydopamine. Conjunctive administration of desmethylimipramine, to increase the dopaminergic specificity of the 6-hydroxydopamine, does not significantly alter the intensity of the ensuing lesion induced syndrome [25,27]. Also, neurochemical assays of brain tissue from septally-lesioned animals have revealed postoperative decreases in

[1]Present address: Department of Psychiatry, Montefiore Hospital and Medical Center, Bronx, NY 10467.
[2]Present address: Graduate School of Nursing, Pace University, Briarcliff, NY 10510.
[3]Present address: Albert Einstein College of Medicine, Bronx, NY 10461.
[4]Send reprint request to Dr. E. L. Gardner, Department of Psychiatry, Forchheimer Building G54, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461.

forebrain dopamine associated with the lesion-induced hyperirritability [4]. Of possible relevance to this body of evidence is the demonstration, by biochemical assay and histofluorescence microscopy, of dopaminergic fibers running in and around the septal area [22, 31, 32]. These suggestions of a partial dopaminergic involvement in septal hyperirritability do not, however, exclude possible involvement of other neurotransmitter systems as well. In fact, evidence does exist for both a possible cholinergic involvement [38, 42, 44] and localized biogenic amine involvement [11]. The exact lesion locus necessary to evoke septal rage is at present incompletely understood, although a number of investigators have studied the specific contributions of various subareas of septum and associated structures to the syndrome [1,16] and recent work by Munoz and Grossman [34] has shown a behavioral dissection of the syndrome by selective neuronal perikarya destruction induced by kainic acid.

We [28] and others [10,36] have shown that administration of L-dopa following septal lesioning dramatically accelerates the time course of post-lesion behavioral recovery. More recently, we have shown that this capability extends to other dopamine agonists as well, including apomorphine [26].

In view of these demonstrations that post-surgical administration of dopaminergically active compounds can dramatically alter the recovery period following septal lesions, and in view of other demonstrations that certain pre-surgical manipulations (both pharmacologic and non-pharmacologic) can alter post-lesion recovery periods in both the septal and lateral hypothalamic brain lesion syndromes [2, 3, 12, 13, 18, 19] the present investigation was undertaken to determine whether pre-surgical administration of dopaminergically active compounds could alter the emergence of the septal lesion syndrome.

METHOD

Animals

The experimental subjects were 57 male Long-Evans rats (Blue Spruce, Altamont, NY), weighing approximately 300 grams, maintained on ad lib food and water in individual cages at a constant temperature (22±1°C) on a 12 hour on-12 hour off light-dark cycle.

Pharmacological Manipulations

For seven days prior to septal lesioning, individual groups of animals were administered the following compounds by intraperitoneal injection: haloperidol (4 mg/kg/day; n=8), α-methyl-p-tyrosine (100 mg/kg/day; n=8, apomorphine (20 mg/kg/day; n=8), phenobarbital (60 mg/kg/day; n=8), and saline (1 ml/day; n=10). The volume and pH of each injected compound were as follows: haloperidol (1.0 ml; pH 5.5), α-methyl-p-tyrosine (1.0 ml; pH 4.2), apomorphine (1.0 ml; pH 4.5), phenobarbital (0.5 ml; pH 9.6). All compounds were administered once daily, with the exception of the phenobarbital, which was administered in divided doses twice daily. An additional group of rats (n=5) was given only a single acute administration of 4 mg/kg haloperidol on the day of septal lesioning. Also, a further additional group of rats (n=10) were injected with haloperidol (4 mg/kg/day) for seven days and tested daily for sedation and a variety of other behavioral and physiological effects both during the seven-day period of drug administration and for 10 days thereafter (see below under "Behavioral and Physiological Testing—Haloperidol Sedation Effect").

Lesions

Bilateral radiofrequency thermocoagulative (66°C for 60 sec) lesions of the septal area were performed under pentobarbital anesthesia on all animals by standard surgical and stereotaxic technique. The targeted lesion sites were AP +7.6, L ±0.7, DV ±1.4, according to the atlas of Pellegrino and Cushman [37]. Following completion of all experiments, the animals were killed and reconstruction of each lesion was made by standard histological technique (10% Formalin fixation; 40 μ frozen sections; cresyl violet stain; microscopic examination).

Behavioral Testing—Septal Lesion Hyperirritability

Behavioral evaluation of baseline pre-lesion reactivity and of characteristic post-lesion septal hyperreactivity was performed once daily during the light portion of the light-dark cycle for each animal by standard rating techniques using a modification of the King septal irritability rating scale [21]. The rating scale consisted of seven subscales (each with a range of 0 to 3) for subjective evaluation of each of the following behaviors: (a) biting, (b) jumping (c) vocalization, (d) response to a poke to the flank, (e) magnet reaction, (f) resistance to capture, and (g) resistance to handling. Since all of the subscales had been shown in previous work from this laboratory to be highly correlated and to be proportionally altered by drug manipulations [25–28], subscale scores were combined to yield an overall irritability score ranging from 0 to 21 for each test of each animal. All tests were conducted individually in a special test chamber, and all ratings were done blindly and independently by two different raters. The overall correlation between ratings done by the two raters was highly significant ($r=0.92$, $p<0.001$).

Behavioral and Physiological Testing—Haloperidol Sedation Effect

For the 10 animals given chronic haloperidol and tested daily for sedation and other haloperidol induced effects, the tests were performed once daily during the light portion of the light-dark cycle for each of the seven days of haloperidol administration and each of the 10 following days. The test battery consisted of the following: (1) open-field activity, (2) activity chamber activity, (3) response to stimulation by the experimenter (resistance to capture and resistance to handling), (4) open-field emotionality, (5) heart rate, (6) respiration, and (7) the neurological examination for rats of Bures *et al.* [6]. Activity chamber activity was tested using two Lafayette Instrument Company activity chambers ("jiggle-box" type); each rat was always tested in the same chamber. Resistance to capture and resistance to handling were rated according to the King rating scale criteria (see above). Heart rate and respiration were measured using a modified biotachometer and respiration meter (Narco Biosystems, Inc.). The neurological examination for rats consisted of 10 subcomponents, as follows: (a) flexion reflex, (b) grasping reflex, (c) righting reflexes, (d) placing reactions, (e) equilibrium tests, (f) corneal reflex, (g) pupillary reflex, (h) auditory startle, (i) toe spreading, and (j) head shaking [6]. All testing took place at least five hours after drug administration.

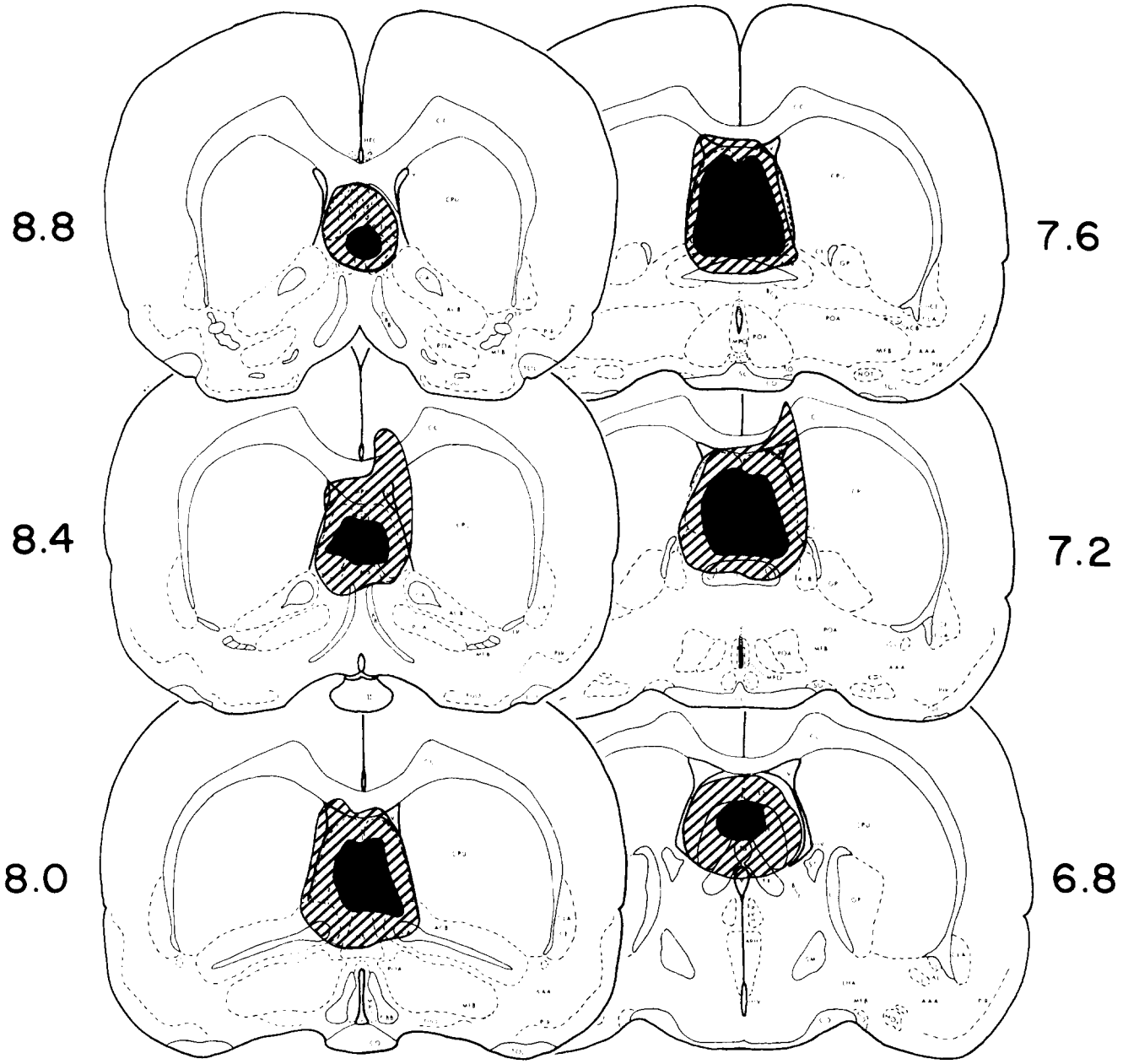

FIG. 1. Reconstruction of the smallest (solid black area) and largest (cross-hatched area plus solid black area) septal lesions in the present series, mapped according to the atlas of Pellegrino and Cushman [37]. The vertical plane coordinates are given in mm anterior to the interaural line.

Data Analyses

Statistical analyses of changes in lesion-induced hyperirritability were performed as appropriate [43] using the Friedman non-parametric analysis of variance (χ^2_r), the Kruskal-Wallis one-way analysis of variance by ranks (H), and the Mann-Whitney rank test for independent samples (U).

RESULTS

Lesions

All animals were found to have large bilateral lesions of both the medial and lateral septal areas, with varying additional involvement of immediately adjacent structures. Lesion placement and extent did not differ between drug groups. Lesion size and location are illustrated in Fig. 1.

Drug Effects on Lesion Sequelae

Animals given seven days of saline injections prior to surgery exhibited a standard course of behavioral recovery with a statistically significant, $\chi^2_r=57.8$, $p<0.001$, decrease in irritability during the 7 days following septal lesion. The length and pattern of this recovery was essentially identical to that which we have routinely observed for non-injected septally-lesioned animals [27,28] and for septally-lesioned animals given saline injections following surgery [26]. Animals given seven days of α-methyl-p-tyrosine (100 mg/kg/day), apomorphine (20 mg/kg/day) or phenobarbital (60 mg/kg/day) prior to surgery showed post-lesion recovery patterns similar to that shown by the saline animals (Fig. 2A). There were no statistically significant differences between the saline, α-methyl-p-tyrosine, apomorphine, or phenobarbital groups in either overall intensity of post-lesion syndrome or rate of behavioral recovery, $H<3.89$, p=n.s., for each of the 10 days post-lesion.

In contrast, the animals treated chronically for seven days prior to surgery with haloperidol (4 mg/kg/day) showed dramatically lower levels of post-lesion septal irritability than the other groups (Fig. 2B). At 24 hours post-lesion, these animals showed a median level of irritability that was approximately 75% less than that shown by the saline-injected controls. By 48 hours post-lesion, the chronic haloperidol-injected animals had returned to baseline irritability levels, there being no statistically significant difference between their median pre-lesion irritability and their median irritability at 48 hours post-lesion, $\chi^2_r=4.83$, p=n.s. The post-lesion difference in irritability between the chronic haloperidol-injected animals and the chronic saline-injected controls was statistically highly significant, $U=0$, $p<0.001$, for each of the first seven days post-lesion. There was, in fact, no overlap in irritability scores between animals in the chronic haloperidol and the saline groups for the first seven days after surgery. Other than exhibiting acute sedation, the chronic haloperidol animals showed no other behavioral or physiological effects from the haloperidol. The 10 rats given chronic haloperidol and tested daily on the behavioral and physiological test battery described above also showed no behavioral or physiological effects other than obvious acute sedation. The sedation, though initially pronounced, showed rapid tolerance, and was no longer detectable (by behavioral measures of open-field activity, activity-chamber activity, and response to stimulation by the experimenter) by the fifth day of haloperidol treatment (pre-lesion day 3). At no time was the haloperidol-induced acute sedation as severe as that seen in the phenobarbital-treated animals, who were markedly sedated and ataxic following each drug dose. In addition, the chronic haloperidol-treated rats did exhibit hyperirritability on post-lesion day 1 (see Fig. 2B), indicating that if any subtle behavioral and physiological dysfunctions were produced by the haloperidol they were not sufficiently strong to abolish hyperirritability. Furthermore, if the chronic haloperidol had produced long-lasting dysfunctions of sufficient severity to disrupt hyperirritability, post-lesion irritability might be expected to rise with each succeeding post-lesion day, as any long-lasting haloperidol effects wore off. In fact, this did not occur (Fig. 2B).

In marked contrast to the post-lesion behavior of the animals given chronic haloperidol prior to surgery, the animals given only a single acute administration of haloperidol on the day of septal lesioning exhibited a full-blown classic post-lesion septal syndrome (Fig. 2B), which slowly attenuated over the course of the ensuing eight days, $\chi^2_r=48.4$, $p<0.001$. In fact, the post-lesion syndrome shown by these acute haloperidol animals was of even greater intensity and duration than that shown by the chronic saline control animals, $0\leq U\leq 1.5$, $p<0.001$, for each of the first seven days post-lesion.

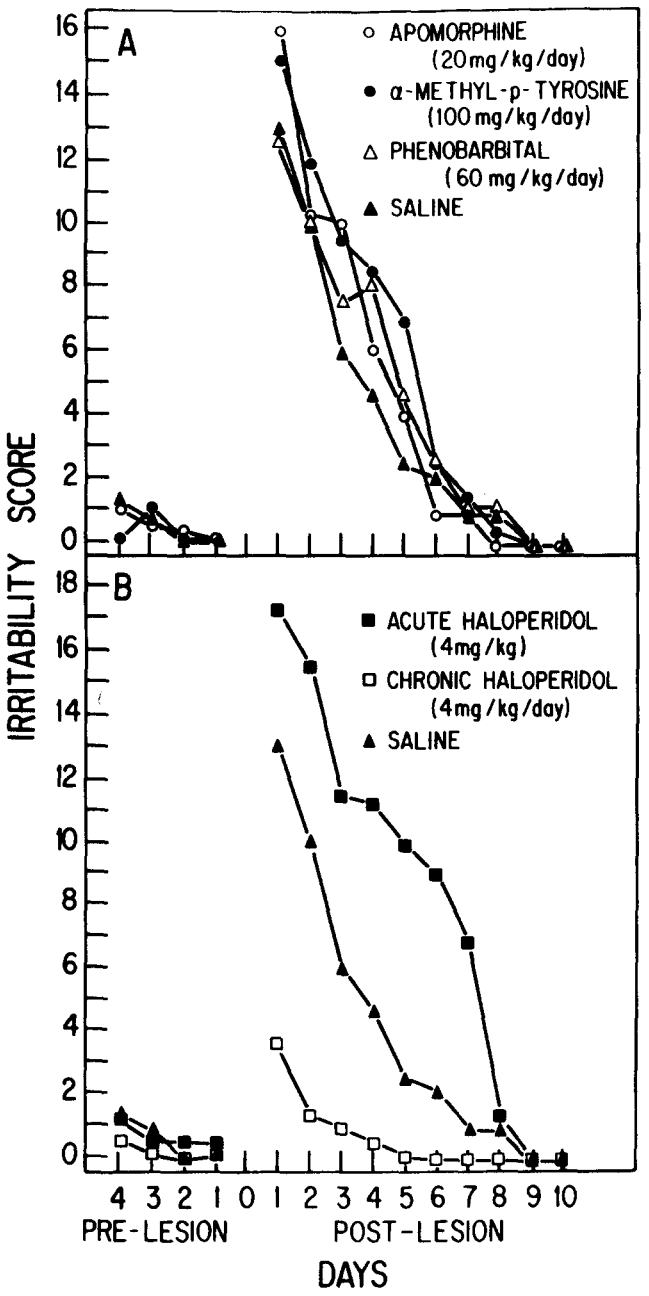

FIG. 2. Pre- and post-lesion irritability in septal lesion rats given 7 days of chronic pre-lesion injections of α-methyl-p-tyrosine (●), apomorphine (○), haloperidol (□), phenobarbital (△), or saline (▲), or given an acute injection of haloperidol on day of lesion (■). The saline values shown are identical for parts A and B.

DISCUSSION

The present findings indicate that it is possible to significantly attenuate the hyperirritability syndrome that follows septal lesions by appropriate pre-lesion pharmacological treatment. Thus, seven days of chronic haloperidol prior to septal damage significantly mitigated the intensity and duration of the post-lesion behavioral sequelae. That this was not due to simple sedation from the haloperidol is shown by the lack of effect on septal hyperirritability of chronic administration of a clearly sedative dose of phenobarbital. Interestingly, Harrell and Balagura [18] have reported that septal irritability can be mitigated by five days of pre-surgical treatment with p-chlorophenylalanine. It appears, therefore, that there exist at least two pharmacological agents, haloperidol and p-chlorophenylalanine, which, when given pre-lesion, are capable of modifying the post-lesion appearance of the septal hyperirritability syndrome. On the basis of the present data and those presented by Harrell and Balagura [18] haloperidol seems to be the more effective agent. While p-chlorophenylalanine produces considerable depletion of brain serotonin by tryptophan hydroxylase inhibition [29], it also inhibits tyrosine hydroxylase, resulting in depletion of brain catecholamines [29,39], including dopamine [47]. Thus, the present data, along with evidence from other laboratories and data collected in other experimental paradigms, suggest that pre-lesion pharmacological modification of septal lesion sequelae may involve catecholaminergic mechanisms, although, obviously, other neurochemical mechanisms cannot at this stage be ruled out. This is concordant with findings by other investigators studying the neuropharmacological substrate of affective behavior in animals [14,40]. Recently, we have extended the present findings with pre-lesion chronic haloperidol to pilot studies using the more specifically dopaminergic antagonist pimozide (Marotta and Gardner, unpublished results). In these studies, chronic pimozide (2 mg/kg/day for 10 days pre-lesion) is as effective in mitigating the post-lesion emergence of septal hyperirritability as chronic haloperidol.

Although recovery from septal rage may at least partially involve dopaminergic systems, the specific mechanisms underlying such recovery are as yet unknown. However, on the basis of both the present data and previous evidence from our laboratory [25,26] and others [2–4, 7, 8, 10, 12, 13, 18, 19, 23, 24, 30, 33, 41, 46], some hypotheses appear suggestive. Among these suggested mechanisms for recovery from brain lesions are habituation [9], axonal sprouting [24], enzyme induction [23], diaschisis [23], and denervation supersensitivity [30]. This last mechanism, post-synaptic supersensitivity, has, in fact, been suggested as the mechanism underlying behavioral recovery from lesions of the lateral hypothalamus [13]. In this regard, it is of interest that the pharmacological agents known to facilitate recovery from both the septal and lateral hypothalamic syndromes, upon chronic pre-lesion administration, are direct or indirect neurotransmitter antagonists [13, 18, 19]. Given the extensive evidence for antagonist-induced neurotransmitter supersensitivity [33,41], it seems possible that chronic pre-lesion antagonist administration may produce supersensitivity in one or more neurotransmitter systems. If post-lesion recovery does involve supersensitivity processes [13], such pre-lesion antagonist administration may give the experimental animals a head start on those processes necessary for recovery.

Such processes can also be viewed in the context of a diaschitic model of recovery from brain damage [23,46]. Thus, in the present experiments, the haloperidol pretreatments may have produced a change (supersensitivity) in the functional level of dopaminergic receptor membranes functionally linked to the septal area, resulting in partial compensatory protection against a loss of tonic dopaminergic input caused either directly or indirectly by the brain lesion. The exact anatomical location of such functional links remains to be elucidated, although dopaminergic innervation of portions of the septal area is well established [22, 31, 32] and other work from our own laboratory is suggestive of an involvement of the mesencephalic dopaminergic nuclei [25].

On the other hand, if induction of dopaminergic receptor supersensitivity were the sole mechanism underlying the attenuated rage and accelerated recovery of the haloperidol pre-treated animals, the lack of effect of α-methyl-p-tyrosine becomes problematic, in view of its ability to also induce dopaminergic supersensitivity [17,45]. In the present experiments, the dose of α-methyl-p-tyrosine used (100 mg/kg/day) is well above the minimum dose required to induce supersensitivity [45] and is the same dose found by Hynes *et al.* [19] to significantly enhance recovery from lateral hypothalamic lesions when chronically administered pre-lesion. Since only the haloperidol pretreatments facilitated recovery from the present septal lesions, it may be that direct receptor blockade is essential for pre-lesion pharmacological attenuation of septal irritability, since haloperidol is a direct receptor blocking agent while α-methyl-p-tyrosine is an indirect antagonist. Haloperidol and α-methyl-p-tyrosine also differ in that dopamine synthesis is increased, via feedback regulatory mechanisms (secondary to the direct receptor blockade), by haloperidol but not α-methyl-p-tyrosine [20]. Thus, increased dopamine turnover secondary to receptor blockade may also be involved in the mechanisms subserving the presently observed phenomenon. In addition, the course of chronic haloperidol administration employed in the present study was shorter than what is usually necessary for a significant supersensitive response [33], although effects with very short courses of neuroleptic administration have also been reported [7].

With regard to the present lack of effect from chronic apomorphine, it should be noted that apomorphine's pharmacological effects are of short duration, especially in comparison to the sustained effects of chronic high-dose haloperidol. At the dose of apomorphine used in the present experiments (20 mg/kg/day), intense and prolonged apomorphine-induced behavioral stereotypy was observed in all animals, rendering the use of higher doses impossible. Also, it has been shown in other behavioral paradigms (e.g., stereotypy) that chronic agonist administration does not always produce effects opposite to those produced by chronic antagonist administration. Thus, we do not feel that the lack of effect from apomorphine necessarily argues against the suggestion that chronic dopamine receptor blockade may be involved in initiating recovery processes from septal damage.

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