Subchronic Treatment with Haloperidol and Clozapine in Rats with Neonatal Excitotoxic Hippocampal Damage

Barbara K. Lipska, Ph.D. and Daniel R. Weinberger, M.D.

We have previously demonstrated that rats with neonatal excitotoxic hippocampal damage manifest abnormal dopamine (DA)-related behaviors after puberty, a phenomenon that has implications for an animal model of schizophrenia. In this study we investigated the effects of subchronic treatment with haloperidol and clozapine in these animals. The ventral hippocampus (VH) of rat pups was lesioned with ibotenic acid on postnatal day 7 (PD7). Starting at PD56, rats were treated for 21 days with either vehicle (VEH), haloperidol (HAL) (0.1 mg/kg, IP), or clozapine (CLOZ) (4 mg/kg, IP). Spontaneous locomotor activity was measured 0.5 hour after the last injection. Apomorphine (APO)-induced stereotypy and locomotion were evaluated five days later. The VH lesioned rats treated with VEH expressed enhanced novelty- and apomorphine-induced hyperlocomotion, as well as potentiated apomorphine-induced stereotypic behaviors as compared to sham-lesioned counterparts. Spontaneous locomotor activity was suppressed by haloperidol but not by clozapine in the sham-operated group, whereas both drugs were effective in suppressing hyperlocomotion in the VH lesioned rats. Withdrawal supersensitivity to apomorphine was seen in the haloperidol but not in the clozapine-treated lesioned rats, and none of the drugs produced significant supersensitivity in the sham-operated animals. These results indicate that the two neuroleptics exerted differential behavioral effects in neurologically intact and hippocampally lesioned animals, and that these effects were also drug-specific. ***[Neuropsychopharmacology 10:199–205, 1994]***

KEY WORDS: *Haloperidol; Clozapine; Neonatal Lesion; Hippocampus; Ibotenic Acid; Stereotypy; Apomorphine*

We have previously reported that rats with neonatal (postnatal day 7, PD7) excitotoxic damage of the ventral hippocampus (VH) express a variety of abnormal behavioral changes, including novelty- and amphetamine-induced hyperlocomotion, increased responsiveness to stress, reduced haloperidol-induced catalepsy, and potentiated stereotypic responses to apomorphine, all of which emerge around the time of puberty (PD56) (Lipska et al. 1993; Lipska and Weinberger 1993b). These behavioral disturbances are thought to be linked to excessive dopaminergic (DA) transmission in the mesolimbic/nigrostriatal systems (Pijenburg and Van Rossum 1973; Kelly et al. 1975; Costall and Naylor 1977; Sanberg 1980; Swerdlow and Koob 1984; Clarke et al. 1988; Robbins et al. 1990). Because this constellation of DA-related behaviors does not emerge until early adulthood despite the presence of a developmental hippocampal lesion, we suggested that this might be a heuristically useful animal model of core features of schizophrenia. In this regard, it was of interest to investigate if antipsychotic drugs suppress abnormal be-

From the Clinical Brain Disorders Branch, National Institute of Mental Health, NIH, Neuroscience Center at St. Elizabeths, Washington, DC.

Address correspondence to: Barbara K. Lipska, Ph.D., Clinical Brain Disorders Branch, Intramural Research Program, National Institute of Mental Health, NIH, Neuroscience Center at St. Elizabeths, 2700 Martin Luther King Ave. SE, Washington, DC 20032.

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haviors in these rats. In an earlier experiment (Lipska et al. 1993), we evaluated the effects of subchronic treatment with haloperidol (0.4 mg/kg for 21 days) and reported suppression of locomotion in both control and VH-lesioned animals. These results raised questions about whether the effects were specific to a typical neuroleptic, and whether a lower and more clinically relevant dose of haloperidol differentially affected intact and VH-lesioned rats.

The present study was designed to compare the effects of the classical neuroleptic, haloperidol (0.1 mg/kg), and the atypical neuroleptic, clozapine (4 mg/kg), on increased spontaneous locomotor activity in the VH-lesioned rats, and their capacities to induce DA receptor supersensitivity, as measured by apomorphine response after withdrawal of the antipsychotic drugs. This dose of haloperidol was chosen because it is subthreshold for producing gross motor deficits in intact rats (Lynch and Carey 1988; Lynch 1990–91; Hollerman et al. 1992) and falls within the range of doses used clinically as antipsychotic treatments (Gilman et al. 1980). Based on its clinical potency, the dose of clozapine was chosen to be roughly equivalent to that of haloperidol (Wyatt 1976; Titeler and Seeman 1980).

METHODS

Surgery

Rat pups (n = 50) were lesioned as described previously (Lipska et al. 1993). Briefly, pregnant Sprague-Dawley rats obtained at 12 to 15 days gestation (Zivic Miller Labs) were housed individually in breeding cages with a 12 hour light/dark cycle and fed ad libitum. Litters of four to eight male pups were formed. On the seventh day of age (PD7 weight 15 to 18 grams), pups within each litter were randomized to SHAM (n = 26) or LESION status (n = 24) and anesthetized by hypothermia (placed on ice for 10 to 20 minutes). An incision was made in the skin overlying the skull and 0.3 µl of ibotenic acid (Sigma, 10 µg/µl) or artificial cerebrospinal fluid was infused bilaterally into the ventral hippocampal formation at a rate of 0.15 µl/min at AP −3.0 mm, ML ± 3.5 mm, VD −5.0 mm, relative to bregma. The needle was withdrawn 4 minutes after completion of the infusion. The pups were placed under a warming lamp and then returned to their mothers.

Drugs

Clozapine (Sandoz, 4 mg/ml) and haloperidol (Sigma Chemical Co., 0.1 mg/ml) were suspended in vehicle (saline/Tween 80 10/1 v/v) before each injection. Apomorphine (Sigma Chemical Co., 0.75 mg/ml) was dissolved in water and used immediately.

Behavioral Testing

On PD56, animals within SHAM and LESION groups were randomly assigned to receive either vehicle (VEH), clozapine (CLOZ) or haloperidol (HAL) (1 ml/kg, IP) once daily at approximately the same time in the morning for 21 days. There were thus six groups of rats: SHAM/VEH (n = 8), SHAM/CLOZ (n = 10), SHAM/HAL (n = 8), LESION/VEH (n = 8), LESION/CLOZ (n = 8), LESION/HAL (n = 8). Half an hour after the last injection when the plasma concentrations of both drugs were expected to be maximal (Ohman et al. 1977, Baldessarini et al. 1993), rats were placed in photocell monitors (Omnitech model RXYZCM) and their spontaneous locomotor activity was recorded for 1 hour. Rats were returned to their home cages until the next behavioral testing.

Five days later, rats were transferred from their home cages to photocell monitors (Omnitech model RXYZCM) equipped with wire grid bottoms. After two hours of acclimatization, freshly prepared apomorphine APO (0.75 mg/kg) was injected subcutaneously. Each rat was observed for 15 seconds at 5 minute intervals during the 60 minute period after injection. Sniffing, licking, biting, and gnawing were scored during each interval. The intensity of stereotypic behavior was scored as follows: 1—fixed sniffing (directed at the floor); 2—short occurrence, 3—occasional bursts, 4—intermittent intense performance, 5—continuous intense performance of either licking, biting, or gnawing (oral stereotypies). During the period of visual assessment, locomotor activity was also recorded at 5 minute intervals by a computerized photocell monitoring system.

Following behavioral testing, all VH-lesioned animals and several sham-operated rats were euthanized by decapitation. Brains were removed and frozen on dry ice. Cresyl violet sections (20 µm) were evaluated by light microscopy.

Statistical Analysis

Locomotion measured at the completion of subchronic treatment was analyzed by a 2-factor ANOVA with lesion Status (Status = SHAM or LESION) and Drug (Drug = VEH, CLOZ, or HAL) as independent factors and total locomotion over the entire testing period as a dependent variable. Withdrawal data were analyzed by a 3-factor analysis of variance (ANOVA) with lesion Status (Status = SHAM or LESION) and Drug (Drug = VEH, CLOZ, or HAL) as independent factors and Time as a within subject repeated variable. When appropriate, further differences were analyzed by Scheffe's post hoc test.

RESULTS

Histological Evaluation of the Lesion

Nissl stained sections illustrated that in the majority of animals neuronal loss and gliosis were confined to the ventral hippocampus, as was reported previously (Lipska et al. 1993). In all rats all cytoarchitectural divisions in the ventral aspects of the hippocampus (CA1–CA4) as well as the subiculum were affected. As previously described (Lipska et al. 1993; Lipska and Weinberger 1993b), in approximately 50% of rats the most temporal portions of the hippocampus formation were spared. Dorsal portions of the hippocampus were spared in all but five subjects in which restricted unilateral damage occurred. Although ibotenic acid has axon sparing properties in most brain regions, due to the atrophy and cavitation some damage to fibers of passage cannot be precluded.

Spontaneous Locomotor Activity at Completion of Subchronic Treatment

ANOVA performed on total distance traveled over the entire testing period (60 minutes) showed significant main effects of Status ($F_{1,42} = 10.6$, $p = .002$) and Drug ($F_{2,42} = 8.5$, $p = .0008$) as well as a significant Status × Drug interaction ($F_{2,42} = 3.7$, $p = .03$). In accordance with our previous data (Lipska et al. 1993; Lipska and Weinberger 1993b), LESION/VEH rats expressed higher exploratory activity than the SHAM/VEH group ($p < .05$). HAL ($p < .05$) but not CLOZ significantly reduced spontaneous locomotion in sham-operated animals as compared with the SHAM/VEH group. Hyperlocomotion evident in lesioned animals was significantly reduced by both drugs, but HAL produced a more pronounced effect than CLOZ (LESION/HAL vs LESION/CLOZ, $p < .05$), Fig. 1.

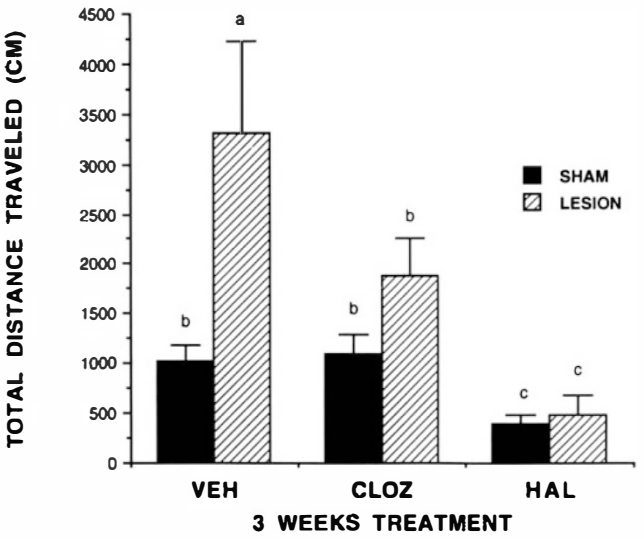

Figure 1. Total distance traveled over 60 minutes by rats with SHAM or ibotenic acid (LESION) lesions of ventral hippocampal formation tested half an hour after the last injection of either saline with Tween (VEH), clozapine (CLOZ 4 mg/kg), or haloperidol (HAL 0.1 mg/kg) that was administered intraperitoneally for 21 days. SHAM/VEH, SHAM/HAL, LESION/VEH, LES/CLOZ, LESION/HAL, $n = 8$/group; SHAM/CLOZ, $n = 10$, a > b > c, $p < .05$.

Withdrawal Effects

The analysis of apomorphine-induced stereotypic behaviors revealed main effects of Status ($F_{1,45} = 9.8$, $p = .003$), Drug ($F_{2,42} = 7.1$, $p = .002$) and Time ($F_{11,495} = 24.9$, $p < .001$) but no significant 2- or 3-way interactions, except for Status × Time ($F_{11,495} = 6.9$, $p < .0001$). There were no differences between VEH, CLOZ, or HAL treated sham-operated animals. However, LESION/HAL rats expressed accentuated stereotypies and differed significantly from the two other LESION groups (VEH or CLOZ) as well as from SHAM animals ($p < .05$). In contrast, CLOZ did not produce a hypersensitivity response in LESION rats (LESION/CLOZ vs LESION/VEH, NS), Fig. 2.

For apomorphine-induced locomotor activity, ANOVA showed main effects of Status ($F_{1,39} = 8.7$, $p = .005$) and Time ($F_{11,429} = 16.1$, $p < .001$) and a trend for a Drug effect ($F_{2,39} = 1.8$, $p < .1$). There was a significant Status × Time interaction ($F_{11,429} = 7.4$, $p < .0001$) and a trend for a significant Drug × Time interaction ($F_{22,429} = 1.3$, $p < .1$). All other interactions were not significant. Similarly, as for apomorphine-induced stereotypies, withdrawal of either drug had no significant effect in sham-operated animals. Withdrawal of HAL, however, profoundly potentiated locomotor activity in lesioned rats (LESION/HAL vs LESION/VEH and LESION/CLOZ, $p < .05$), whereas CLOZ treatment did not result in the development of locomotor hypersensitivity to apomorphine, Fig. 2.

DISCUSSION

The results of this study indicate that subchronic treatment with haloperidol or clozapine produces differential behavioral effects in neurologically intact or in neonatally VH-lesioned animals, and that these effects are also drug-specific. In particular, the VH-lesioned rats appear to be relatively more sensitive to the suppressive effects of clozapine on spontaneous locomotor activity than control animals, whereas both groups potently respond to haloperidol. Moreover, the VH-lesioned rats express increased sensitivity to withdrawal of the typical neuroleptic. Withdrawal of haloperidol but not of

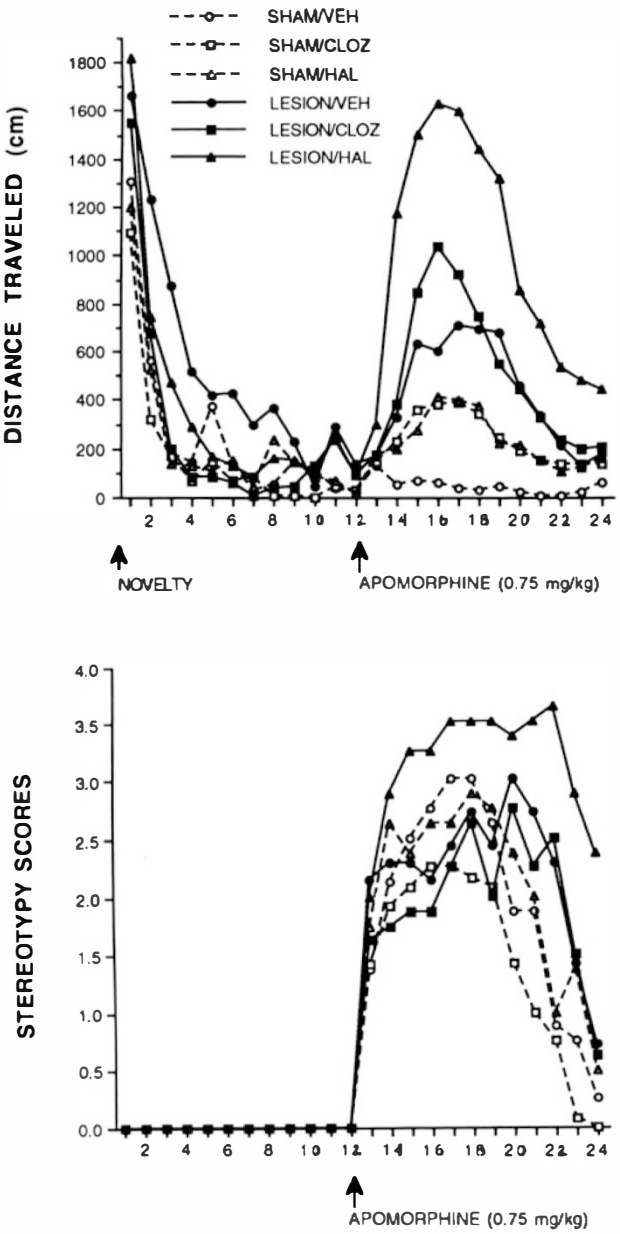

Figure 2. Locomotor (upper panel) and stereotypic (lower panel) response to apomorphine (0.75 mg/kg, subcutaneously) in rats with SHAM or ibotenic acid (LESION) lesions of the ventral hippocampal formation. Rats were previously treated for 21 days with either saline with Tween (VEH), clozapine (CLOZ, 4 mg/kg), or haloperidol (HAL, 0.1 mg/kg). Testing was performed five days after the last injection of the drug. Rats were placed in the photocell monitors (Novelty) and their locomotor activity was measured for 1 hour. They were then injected with apomorphine and visually scored for the presence or absence of stereotypic behaviors every five minutes for 1 hour. Numbers of rats per group as in Fig. 1.

clozapine induced profound hypersensitivity to apomorphine in the VH-lesioned rats without significantly affecting the neurologically intact controls. These data show that neuroleptic drugs may exert more profound or even qualitatively different effects in an already dysfunctional DA system than in an intact one, and may have implications for studying mechanisms of action of drugs used in schizophrenia.

In the doses administered, both antipsychotic drugs suppressed excessive spontaneous locomotor activity in the neonatally VH-lesioned rats, but only haloperidol produced this effect also in control animals. This observation might suggest that the dose of haloperidol used in this study is relatively higher than that of clozapine. The rationale for using 0.1 mg/kg of haloperidol was that it was a low enough dose not to induce gross motor impairments such as catalepsy, rigidity, or immobility (Lynch and Carey 1988, Hollerman et al. 1992). Moreover, target doses of both drugs reflect daily clinical doses used in the control of schizophrenia, increased five times to account for the increased metabolism in the rat. They were chosen to be roughly equivalent based on their clinical potencies (Wyatt 1976, Gilman et al. 1980). Our pilot investigations after acute injections (unpublished data) showed that even doubling the dose of clozapine (8 mg/kg) did not affect spontaneous locomotor activity in intact rats, whereas 0.1, 0.2, and 0.4 mg/kg of haloperidol suppressed locomotion to a similar extent. Lynch and Carey (1988) reported a slight reduction in locomotor activity associated with an acute injection of 0.1 mg/kg of haloperidol, and a significant suppression after a 21-day treatment (Lynch 1990–91). Our haloperidol data are consistent with this report. Our findings of the differential effects of prolonged treatment with these two neuroleptics on spontaneous locomotor activity in control rats are in agreement with other studies (Rupniak et al. 1985) that used similarly equivalent, albeit considerably higher, doses of haloperidol (1.4 to 1.6 mg/kg) and clozapine (24 to 27 mg/kg). According to these studies, treatment for 1 to 3 months with haloperidol but not with clozapine resulted in a reduction of spontaneous locomotion in intact rats (Rupniak et al. 1985). It thus cannot be excluded that a lower dose of halperidol than that used in our study might exert differential effects in sham vs lesioned rats (i.e., no blockade and reduction of locomotion, respectively). Clozapine, however, even if administered in substantially higher doses than in our study, seems unlikely to suppress locomotion in controls.

Because spontaneous locomotion is believed to be primarily mediated by the mesolimbic DA system (Pijenburg and Van Rossum 1973), these results suggest that mesolimbic DA receptors were blocked during continuous exposure to haloperidol but not to clozapine. Although this, indeed, may be true for neurologically intact rats, blockade of mesolimbic DA transmission by prolonged clozapine administration might have occurred, as inferred from our data, in the VH-lesioned animals. However, since other neurotransmitter sys-

tems including cholinergic, GABA-ergic, and serotonergic may also play a role in mediating locomotor activity (Mogenson et al. 1979, Vaccarino et al. 1986, Day et al. 1991), it is plausible that other factors, besides a blockade of the mesolimbic DA system, may account for suppression of spontaneous locomotion by clozapine in rats with neonatal VH lesions.

Clozapine is a potent blocker of serotoninergic, muscarinic cholinergic, and adrenergic receptors (Deutch et al. 1991). It has also been recently demonstrated to bind to dopamine D4 receptors expressed primarily in limbic and prefrontal cortices (Tol et al. 1991). By whatever mechanism, a low dose of clozapine administered subchronically exerts potent behavioral effects in the neonatally VH-lesioned rats despite the failure to affect spontaneous locomotion in controls. This is consistent with other studies demonstrating that doses of antidopaminergic agents (haloperidol or spiroperidol) that were subthreshold in intact rats produced gross deficits in 6-OHDA-treated rats (Zigmond and Stricker 1973, Heffner et al. 1977, Hollerman et al. 1992) and indicates that a dysfunctional DA system is more susceptible to being affected by additional demands.

Similarly differential behavioral effects were observed in the intact or VH-lesioned rats after drug withdrawal. Five days after discontinuation of subchronic administration of low doses of either clozapine or haloperidol did not trigger a significant hypersensitive reaction to apomorphine in control rats. There was no increase in a stereotypic response to apomorphine and only a slight increase in apomorphine-induced locomotor activity in intact neuroleptic-treated rats as compared to vehicle-treated controls. Many previous studies have shown that repeated administration of haloperidol (0.25 to 5.0 mg/kg for 1 to 7 weeks), when followed by drug withdrawal (2 to 21 days), induces behavioral supersensitivity to apomorphine (Muller and Seeman 1978; Hussain et al. 1992) and increases the density of DA D2 receptors in the striatum (Muller and Seeman 1978; Rupniak et al. 1984). Unlike haloperidol, clozapine does not produce such withdrawal effects (Sayers et al. 1975; Muller and Seeman 1978). The data are inconsistent, however, since some investigators (Gianutsos and Moore 1977; Seeger et al. 1982; Rupniak et al. 1984) point out that withdrawal from prolonged clozapine administration results in behavioral supersensitivity that is limited exclusively to the mesolimbic DA system (i.e., produces apomorphine-induced hyperlocomotion), in contrast to haloperidol that affects both mesolimbic and nigrostriatal systems (i.e., produces potentiation of apomorphine-induced locomotion and stereotypy). The action of neuroleptics in the mesolimbic pathway is thought to be associated with their antipsychotic properties, whereas the potency in the nigrostriatal system is considered to be related to adverse side effects such as tardive dyskinesia (TD) (Ljunberg and Ungerstedt 1978; Chiodo and Bunney 1983; White and Wang 1983; Chiodo and Bunney 1985). Neuroleptic-induced hypersensitivity of striatal dopamine receptors as measured by exaggerated stereotyped response to acute dopamine agonist challenge or by increased DA receptor density in the striatum after long-term treatment has been proposed as a rat model of TD (Sayers et al. 1975; Burt et al. 1977). In the majority of animal studies, however, the effects of prolonged administration of neuroleptic drugs were investigated in neurologically intact subjects, and thus may not be relevant to pathological states such as schizophrenia. In our study the doses of both drugs might have been too low to produce supersensitivity to apomorphine in control rats. This observation is consistent with the report by Lynch (1990–91), who also did not find postsynaptic supersensitivity as measured by a stereotypic response to a lower dose of APO 0.07 mg/kg) after 48-hour withdrawal from 21-day treatment with 0.1 mg/kg of haloperidol. However, in our study, the discontinuation of this same low dosage treatment with haloperidol triggered a very profound hypersensitive response to apomorphine in the VH-lesioned animals. Both exaggerated apomorphine-induced hyperlocomotion and stereotypy were evident in the haloperidol-treated VH-lesioned rats despite a very limited effect in controls. Clozapine, on the other hand, failed to produce any of these supersensitive reactions in the VH-lesioned rats. The differences in pharmacokinetic profiles of both drugs are unlikely to account for these effects. In fact, a considerably longer elimination half-life from both brain and plasma of haloperidol (4 to 14 hours [Ohman et al. 1977]) or even several days after chronic treatment [Cohen 1992]) as compared with a very rapid elimination rate of clozapine (1 to 2 hours [Baldessarini et al. 1993]) would indicate that in the rat, haloperidol could still attain detectable levels in brain 5 days after cessation of treatment. This possibility would, if anything, lead to blockade rather than potentiation of the effects of apomorphine.

If withdrawal supersensitivity after prolonged neuroleptic treatment in the rat indeed models some aspects of TD, these data suggest that animals with a preexisting dysfunction within the ventral hippocampus and developmentally related brain systems (Lipska et al. 1993) may be more prone to develop adverse side effects after treatment with haloperidol but not with clozapine than could be inferred from studies in neurologically intact subjects. To the extent that our experimental lesion may model some aspects of schizophrenia, such as postpubertal emergence of DA-related abnormal behaviors, developmental structural hippocampal defect and medial prefrontal cortical dysfunction (Jaskiw and Weinberger 1992; Lipska and Weinberger 1993a; Lipska et al. 1993), investigating the response to antipsychotics in rats with this neonatal VH lesion might provide better insight not only into the therapeutic action of these

drugs in patients with schizophrenia but also on the mechanisms of developing TD.

There are several limitations to the present findings that require clarification. First, the study involved only single doses of haloperidol and clozapine. Dose response experiments would certainly provide more information, but they would be technically difficult to perform in that they would require lesioning and testing large numbers of animals for prolonged periods of time. On the other hand, even if they were to show that the differences were dose dependent, the fact that the VH lesion could shift dose response characteristics would represent a further elaboration of the essential point of this study, that is, changes in susceptibility of the lesioned brain to pharmacological actions of these drugs. Second, we did not perform pharmacokinetic studies to assure a similar disposition and/or metabolism of administered neuroleptics in the control and lesioned rats. It is unclear, however, how our lesion could introduce a systematic bias in this regard. Third, we demonstrated the differential effects of both drugs in both groups of animals on a limited number of behavioral parameters. It would certainly be of interest to explore if antipsychotic treatment normalizes other behavioral disturbances in the VH-lesioned rats. Fourth, treatment with other representatives of atypical and classical neuroleptics would be needed to draw broader conclusions about whether these two classes of drugs induce differential effects in intact and VH-lesioned animals. We are currently working on elucidating these issues. Nevertheless, despite its limitations, this study provides potentially important data on the differential action of neuroleptics in intact and hippocampally lesioned animals indicating that the latter may be more sensitive to both therapeutic and adverse neurological effects of antipsychotic treatment.

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