Pharmacology Biochemistry & Behavior, Vol. 40, pp. 1001–1004. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

BRIEF COMMUNICATION

Dissociation of Haloperidol-Induced "Anhedonia" and Catalepsy by Lesions of the Dorsal Raphe Nucleus

DAVID WIRTSHAFTER AND KAREN E. ASIN[1]

Department of Psychology, M/C 285, The University of Illinois at Chicago, Box 4348, Chicago, IL 60680

Received 22 April 1991

WIRTSHAFTER, D. AND K. E. ASIN. *Dissociation of haloperidol-induced "anhedonia" and catalepsy by lesions of the dorsal raphe nucleus.* PHARMACOL BIOCHEM BEHAV **40**(4) 1001–1004, 1991.—Electrolytic lesions of the dorsal raphe nucleus were found to attenuate haloperidol-induced catalepsy, but did not alter haloperidol's ability to suppress the intake of a highly palatable saccharin/glucose mixture by nondeprived rats. These results suggest that neuroleptic-induced suppression of the drinking of palatable fluids is not secondary to the types of motor deficits that result in catalepsy.

Neuroleptics Haloperidol Reinforcement Anhedonia Dopamine Catalepsy Dorsal raphe nucleus Serotonin

IT is well known that dopamine antagonists are able to reduce the performance of a variety of positively reinforced behaviors, but the nature of the mechanisms mediating these effects has been the subject of much controversy. While some authors have proposed that neuroleptic-induced deficits may reflect an interference with reinforcement mechanisms (1, 11, 30), others have suggested that these effects result from some sort of motor or sensorimotor impairment (3, 20, 25). It should be stressed that the motor and reinforcement interpretations of neuroleptic action are by no means mutually exclusive. It is quite possible that dopamine antagonists may act both to "blunt" reinforcement and to produce a motor deficit, and impairments on a given task may reflect some mixture of these effects (19,27).

The view that the behavioral effects of neuroleptics result primarily from motor impairments gains plausibility from the fact that these drugs are able to induce marked catalepsy. A number of studies have demonstrated that lesions within the midbrain raphe nuclei are able to attenuate neuroleptic-induced catalepsy (5, 8, 14, 17, 22) and we have found that damage to the dorsal raphe nucleus (DR) is primarily responsible for this effect (17). Insofar as catalepsy can be considered an index of neuroleptic-induced motor deficits, this result provides a way of examining the extent to which various effects of neuroleptic drugs are secondary to motor impairments. Thus, if dorsal raphe lesions are able to suppress the cataleptic response to a neuroleptic agent, but fail to reduce some other behavioral effect of the drug, it seems reasonable to conclude that the neuroleptic must be exerting effects in addition to those responsible for the catalepsy.

In the current study we examined the effects of electrolytic dorsal raphe lesions on the ability of haloperidol to induce catalepsy and to suppress the intake of a highly palatable saccharine/glucose mixture by nondeprived rats. The latter task was chosen since it involves a relatively simple motor component and since several studies have provided evidence that neuroleptic-induced suppression of the drinking of palatable fluids is likely to be mediated primarily through alterations in motivational or reinforcement mechanisms (6, 24, 26, 31). Catalepsy was measured by the method of Gumulka et al. (8), which is sensitive to the very mild effects produced by the drug dosages here employed.

METHOD

Animals

Subjects were 26 adult, male Sprague-Dawley derived rats obtained from a colony maintained by the University of Illinois. Rats weighed 280–320 g at the time of surgery and were maintained in individual wire mesh cages with food and water available ad lib, except as described below. Fourteen animals received electrolytic DR lesions and the remainder served as controls.

Surgery

Surgery was conducted under sodium pentobarbitol anesthesia (50 mg/kg). Using standard stereotaxic techniques a stainless steel electrode, 0.2 mm in diameter and insulated except for 0.5 mm at the tip, was placed at coordinates of AP: −0.2; H: −0.5;

[1]Present address: Abbott Labs, D-47H, Abbott Park, IL 60064.

L: 0.0 (21) and a current of 1 mA passed for 8 s to a rectal cathode. The electrode was lowered on the midline following retraction of the superior sagittal sinus (31). In control subjects, the skull was opened but the electrode was not lowered.

Catalepsy Measurement

Catalepsy was measured by a slight modification of the method of Gumulka et al. (8), which involves placing the animal sequentially in each of ten different positions. The animals were twice placed with both forepaws elevated 4″ on a wood block. The next four placements involved individually elevating each of the fore- and hindpaws 2″. Next both of the right and then both of the left paws were raised 2″. Finally, both of the hindpaws were elevated 4″ and this position was repeated. Subjects received one point for each position that was maintained for more than fifteen seconds, except for the first two positions, which were scored two points each. The maximal catalepsy score was thus 12 points.

Biochemistry and Histology

Following the completion of behavioral studies, 8 randomly selected lesioned and 5 control subjects were sacrificed by cervical fracture and their brains rapidly removed. Samples of striatal tissue were removed by the hole punch technique, as we have described elsewhere (29), and assayed for serotonin content by HPLC (13). The brain stems were placed in 10% formalin. The remaining subjects were sacrificed by transcardial perfusion, under deep pentobarbital anesthesia, with saline followed by 10% formalin. At least two weeks later, 64 micron cryostat sections were prepared through the lesion sites and stained with cresyl violet.

Procedure

After one week of recovery from surgery animals were placed on a daily regimen in which food and water were removed from their cages and two hours later a graduated drinking tube filled with a mixture of 0.2% saccharin and 5% glucose was placed on their cages. Intakes were measured one hour later at which time food and water were returned to the animals. Two weeks were allowed for intakes to stabilize before drug testing began. On test days the rats were weighed and then injected with haloperidol (0, 0.075, 0.1 or 0.15 mg/kg SC) 30 min before being given the saccharine/glucose solution. Intakes were recorded one hour later at which time catalepsy was tested as described above. (Catalepsy was not measured following vehicle injections as pilot work had indicated that both normal and DR lesioned rats fail to maintain any of the positions in the absence of haloperidol.) The various doses of haloperidol were administered in a counterbalanced order and drug tests were separated from each other by at least three days. Rats were allowed one hour access to the saccharin/glucose mixture on nontest days.

RESULTS

All of the lesions were centered in the DR and examples of the lesions are shown in Fig. 1. Biochemical assays indicated that the DR lesions depleted striatal serotonin by 72.7%, $t(11) = 4.72$, $p<0.01$.

Catalepsy data are shown in panel A of Fig. 2. A multivariate analysis of variance (MANOVA), using the profile technique to handle repeated measures, indicated that the DR lesions produced a significant attenuation of haloperidol-induced catalepsy, $F(1,24) = 20.05$, $p<0.001$. The haloperidol dose effect was not significant, $F(2,23) = 2.177$, $p>0.1$.

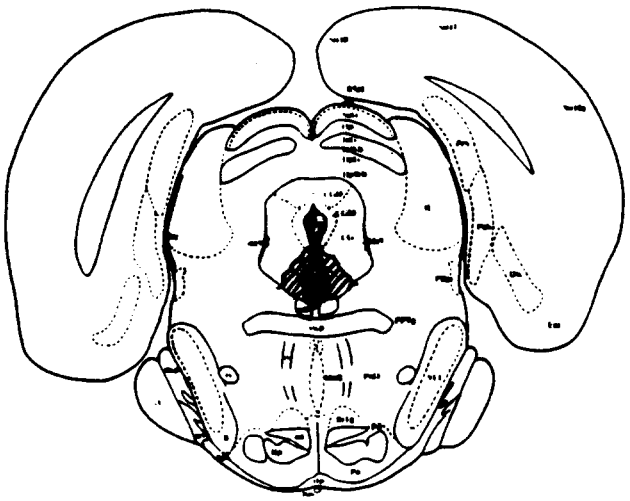

FIG. 1. Tracings through the maximal extent of the largest and smallest dorsal raphe lesions.

Fluid intakes are shown in panel B of Fig. 2. A MANOVA conducted on intake scores indicated that haloperidol produced a significant attenuation of drinking, $F(3,22) = 196.97$, $p<0.001$. Analysis of contrasts indicated that the suppression of fluid in-

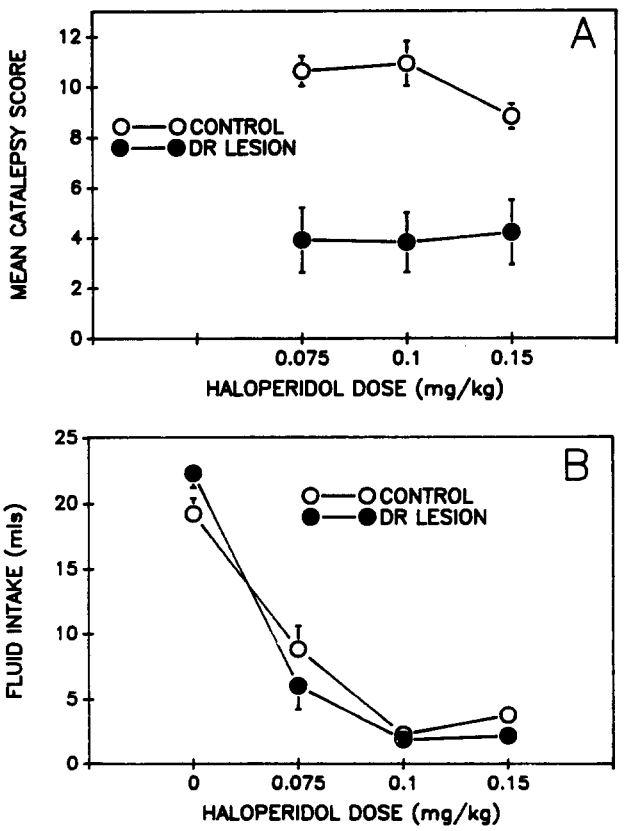

FIG. 2. The effects of dorsal raphe lesions on haloperidol-induced catalepsy (A) and on haloperidol-induced suppression of the intakes of a saccharin/glucose mixture (B).

take was significant at the 0.075 mg/kg dose of haloperidol, $F(1,24)=66.875$, $p<0.001$, and that the 0.1 mg/kg dose of haloperidol produced a significantly larger suppression of drinking than did the 0.075 mg/kg dose, $F(1,24)=21.049$, $p<0.001$. In contrast, intakes did not differ significantly following injections of 0.1 and 0.15 mg/kg of haloperidol, $F(1,24)=1.902$, $p>0.1$. Neither the lesion effect, $F(1,23)<1$, nor the lesion × dose interaction, $F(3,22)=1.939$, $p>0.1$, approached statistical significance.

DISCUSSION

The results of the current experiment are in agreement with previous reports that electrolytic DR lesions are able to attenuate neuroleptic-induced catalepsy (5, 8, 14, 17, 22). It is unlikely that this effect results from generalized hyperactivity, since DR lesions produce much smaller effects on locomotor activity than do lesions of the median raphe nucleus (MR) (2) which, in our hands, fail to alter catalepsy (17). Although the DR lesions resulted in a significant reduction in striatal serotonin levels, it should not be concluded that serotonin depletion necessarily underlies the reduction in catalepsy, since the lesions also damaged nonserotonergic cells and fibers within the DR. In other studies (17) we have not been able to detect alterations in neuroleptic-induced catalepsy following intra-DR injections of the specific serotonergic neurotoxin 5,7-dihydroxytryptamine.

In marked contrast to their effects on catalepsy, DR lesions in the present study failed to influence the suppression of drinking induced by haloperidol. Since haloperidol depressed drinking in a dose-dependent fashion, it is unlikely that our failure to observe an effect of DR lesions could have resulted from an insensitivity of the intake measure. For example, control animals receiving the 0.75 mg/kg dose of haloperidol drank more than did the lesioned animals treated with the 1.0 mg/kg dose even though the former animals displayed greater catalepsy than did the latter. These findings suggest that different neural mechanisms underlie the ability of dopamine antagonists to elicit catalepsy and to inhibit the intake of palatable solutions. Results compatible with this conclusion have also been obtained by Ljungberg (18) who found that systemic treatment with the antimuscarinic agent scopolamine, which is well known to inhibit neuroleptic-induced catalepsy [e.g., (23)], had no effect on haloperidol's suppression of deprivation-induced drinking. [The present results are, in some regards, easier to interpret than those of Ljunberg (18) since DR lesions, unlike scopolamine treatment, did not alter baseline intakes.] These findings demonstrate that it is possible to dissociate the cataleptic and antiingestive effects of neuroleptics. It should be stressed that our results do not directly support the notion that the effects of dopamine blockers on drinking result from interference with reinforcement mechanisms, but rather only suggest that the suppression of drinking does not result from the same neural alterations as does the catalepsy. It is possible, for example, that neuroleptic-induced inhibition of drinking may reflect a type of motor deficit which is not indexed by catalepsy. It should be noted that central dopamine blockade has been reported to alter lap volume and tongue extension during drinking (12). It is not clear, however, that these changes are truly indicative of a motor deficit; under some conditions, for example, lap volume varies as a function of the flavor of the fluid being ingested (J. D. Davis, personal communication).

It is possible that, owing to the simplicity of the responses involved, neuroleptic-induced suppression of the drinking of palatable fluids may provide a measure of "anhedonia" which is relatively uncontaminated by motor impairments. In contrast to their inability to alter the effects of neuroleptics on ingestive behavior, raphe lesions (15,16), and treatment with antimuscarinic drugs (3,7), have been shown by several workers to reduce the suppression of operant behavior produced by neuroleptics. Although these results could be taken to suggest that motor effects play a significant role in neuroleptic-induced suppression of operant responding, it should be noted that, under certain conditions, both antimuscarinics (4, 9, 10) and raphe lesions (2) are able to attenuate the suppression of operant responding produced by nonreinforcement. It is clear that a considerable amount of further effort will be necessary in order to clarify the nature of the behavioral suppression produced by dopamine blockade.

ACKNOWLEDGEMENTS

This work was supported, in part, by NIH grant NS21350. The authors thank Christina Vassilatos for her excellent technical assistance.

REFERENCES

1. Asin, K. E.; Wirtshafter, D. Evidence for dopamine involvement in reinforcement obtained using a latent extinction paradigm. Pharmacol. Biochem. Behav. 36:417–420; 1990.
2. Asin, K. E.; Wirtshafter, D.; Kent, E. W. Straight alley acquisition and extinction and open field activity following discrete electrolytic lesions of the midbrain raphe nuclei. Behav. Neural Biol. 25:242–256; 1979.
3. Carey, R. J. Reversal of haloperidol induced deficits in self-stimulation by anti-Parkinsonian drugs. Behav. Brain Res. 10:405–411; 1983.
4. Carlton, P. L. Brain acetylcholine and inhibition. In: Tapp, J., ed. Reinforcement and behavior. New York: Academic Press; 1969.
5. Costall, B.; Fortune, D. H.; Naylor, R. J.; Marsden, C. D.; Pycock, C. Serotonergic involvement with neuroleptic catalepsy. Neuropharmacology 14:859–868; 1975.
6. Davis, J. D.; Schneider, L. H.; Gibbs, J.; Smith, G. P. D-1 and D-2 receptor antagonists reduce initial rate of intake in sham feeding rats. Soc. Neurosci. Abstr. 12:1557; 1986.
7. Fibiger, H. C.; Zis, A. P.; Phillips, A. G. Haloperidol induced disruption of conditioned avoidance responding: Attenuation by prior training or by anticholinergic drugs. Eur. J. Pharmacol. 30:309–314; 1975.
8. Gumulka, W.; Kostowski, W.; Czlonkowski, A. Role of 5-HT in the action of some drugs affecting the extrapyramidal system. Pharmacology 10:363–372; 1973.
9. Hearst, E. Effects of scopolamine on discriminated responding in the rat. J. Pharmacol. Exp. Ther. 126:349–358; 1959.
10. Herblin, W. F. Extinction reversal by scopolamine. Psychonom. Sci. 13:43–44; 1968.
11. Horvitz, J. C.; Ettenberg, A. Haloperidol blocks the response reinstating effects of food reward: A methodology for separating neuroleptic effects on reinforcement and motor processes. Pharmacol. Biochem. Behav. 31:861–865; 1989.
12. Jones, D. L.; Mogenson, G. J. Oral motor performance following central dopamine receptor blockade. Eur. J. Pharmacol. 59:11–21; 1979.
13. Kilts, C. D.; Breese, G. R.; Mailman, R. B. Simultaneous quantification of dopamine, 5-hydroxytryptamine and four metabolically related compounds by means of reversed phase liquid chromatography with electrochemical detection. J. Chromatogr. 225:347–357; 1981.
14. Kostowski, W.; Gumulka, W.; Czlonkowski, A. Reduced cataleptogenic effects of some neuroleptics in rats with lesioned midbrain raphe and treated with p-chlorophenylalanine. Brain Res. 48:443–446; 1972.
15. Kostowski, W.; Plaznik, A. Decreased disrupting effect of neuroleptics on conditioned avoidance in rats with lesions in the mid-brain

raphe nuclei. Physiol. Behav. 29:621–626; 1982.
16. Kozlowski, A.; Wirtshafter, D.; Asin, K. E. Electrolytic median raphe lesions reduce the ability of haloperidol to suppress an instrumental response. Soc. Neurosci. Abstr. 9:1171; 1983.
17. Kozlowski, A.; Wirtshafter, D.; Asin, K. E. Role of the midbrain raphe nuclei in the attenuation of neuroleptic induced catalepsy. Soc. Neurosci. Abstr. 10:260; 1984.
18. Ljungberg, T. Scopolamine reverses haloperidol-attenuated lever pressing for water but not haloperidol-attenuated water intake in the rat. Pharmacol. Biochem. Behav. 29:205–208; 1988.
19. Ljunberg, T. Blockade by neuroleptics of water intake and operant lever pressing for water in the rat: Anhedonia, motor deficit or both? Pharmacol. Biochem. Behav. 27:341–350; 1987.
20. Mason, S. T.; Beninger, R. J.; Fibiger, H. C.; Phillips, A. G. Pimozide-induced suppression of responding: Evidence against a block of food-reward. Pharmacol. Biochem. Behav. 12:917–923; 1980.
21. Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. New York: Academic Press; 1982.
22. Przewlocka, B.; Kukulka, L.; Tatarczynska, E. The effect of lesions of raphe nuclei on the cataleptic action of neuroleptics. Pol. J. Pharmacol. Pharm. 28:581–589; 1977.
23. Setler, P.; Sarau, H.; McKenzy, G. Differential attenuation of some effects of haloperidol in rats given scopolamine. Eur. J. Pharmacol. 39:117–126; 1976.
24. Schneider, L. H.; Davis, J. D.; Watson, C. A.; Smith, G. P. Similar effect of raclopride and reduced sucrose concentration on the microstructure of sucrose sham feeding. Eur. J. Pharmacol. 186:61–70; 1990.
25. Tombaugh, T. N.; Szostak, C.; Voorneveld, P.; Tombaugh, J. W. Failure to obtain functional equivalence between dopamine receptor blockade and extinction: Evidence supporting a sensory-motor conditioning hypothesis. Pharmacol. Biochem. Behav. 16:67–72; 1982.
26. Towell, A.; Muscat, R.; Willner, P. Effects of pimozide on sucrose consumption and preference. Psychopharmacology (Berlin) 92:262–264; 1987.
27. Wirtshafter, D.; Asin, K. E. Haloperidol and nonreinforcement produce different patterns of response slowing in a food reinforced runway task. Pharmacol. Biochem. Behav. 22:661–663; 1985.
28. Wirtshafter, D.; Asin, K. E.; Kent, E. W. Simple technique for midline stereotaxic surgery in the rat. Physiol. Behav. 23:409–410; 1979.
29. Wirtshafter, D.; Klitenick, M. A.; Asin, K. E. Is dopamine involved in the hyperactivity produced by injections of muscimol into the median raphe nucleus: Pharmacol. Biochem. Behav. 30:577–583; 1988.
30. Wise, R. A. Neuroleptics and operant behavior: the anhedonia hypothesis. Behav. Brain. Sci. 5:39–87; 1982.
31. Xenakis, S.; Sclafani, A. The effects of pimozide on the consumption of a palatable saccharin-glucose solution in the rat. Pharmacol. Biochem. Behav. 15:435–442; 1981.