to that in experiments 1 and 2. Nevertheless, the mean day of tumor appearance again varied as a function of the shock treatment [$F(3, 36) = 20.96$ $P < .001$]. Mice exposed to only one inescapable shock session exhibited tumors significantly earlier ($\bar{X} = 5.9 \pm 0.30$ days) than the mice among the remaining groups (*8*). Likewise, tumors among mice exposed to five sessions of inescapable shock appeared significantly earlier ($\bar{X} = 7.6 \pm 0.34$ days) than did those of mice exposed to ten shock sessions ($\bar{X} = 9.7 \pm 0.396$ days) or no shock ($\bar{X} = 8.7 \pm 0.367$ days). The difference between the latter two groups approached, but did not reach, an acceptable level of significance (*8*). The mean tumor size over days (Fig. 2) followed from these initial differences, in that mean tumor area varied over days as a function of the shock treatment ($F(39, 468) = 8.95$, $P < .001$). Mice that received a single shock session had significantly larger tumors than did the remaining groups on days 9 through 14. The no-shock control animals and mice that experienced five shock sessions did not differ from one another, but they had significantly larger tumors than did the ten-session group on days 12 to 14 (*8*). Finally, day of death (Fig. 2) revealed that shock treatment influenced mortality [$F(3, 36) = 7.02$, $P < .001$]. As noted earlier, a single session of shock decreased survival time relative to no-shock controls. Five shock treatments likewise reduced survival time, but this effect was absent in the ten-session group. It will be noted that, as in experiment 2, the growth and mortality measures, although roughly comparable, were not entirely congruent.

At first blush it seems paradoxical that tumor exacerbation was not apparent after repeated shock. That is, since tumor appearance begins 48 to 72 hours after a single shock session, tumors in the groups that received five or ten shock sessions should have appeared well before the conclusion of the stress regimen. It is possible that certain physiological aftereffects of shock promote tumor development, but that these physiological states are precluded with repeated shock. Alternatively, stress may differentially influence cells that have been recently transplanted and cells that have had the opportunity to adhere and vascularize over a number of days.

Stress may influence tumorigenicity; however, such an effect is dependent on whether control over stress is possible, as well as on the chronicity of the stress regimen. It is premature to ascribe mechanisms for the stress-induced tumor augmentation and inhibition. Neurochemical, hormonal, and immunological mechanisms may all be involved, although the importance of the latter two in mediating the effect of stress has been questioned (*1*, *11*). Indirect support for the involvement of central transmitters has come from studies showing modification of tumor development following catecholaminergic manipulations (*12*).

Our data lend credence to the human experimentation that provisionally suggests a role for stress in the development of carcinoma (*13*). This is of particular importance since the human research conducted to date has by and large been of a retrospective nature, has not evaluated the psychological factors associated with stress, and has not considered the importance of stress application relative to different stages of tumor development (*13*). Of course, in order to draw a parallel between animal and human work, it is necessary to determine to what extent different tumor systems are influenced by stress, as well as the role of stress upon tumor induction and metastases.

LAWRENCE S. SKLAR
HYMIE ANISMAN
Department of Psychology, Carleton University, Ottawa, Ontario K1S 5B6

References and Notes

1. R. J. Jamasbi and P. Nettesheim, *Br. J. Cancer* **36**, 723 (1977); L. J. Peters, *ibid.* **31**, 293 (1975); ——— and H. Kelly, *Cancer* **39**, 1482 (1977).
2. R. Ader and S. B. Friedman, *J. Comp. Physiol. Psychol.* **59**, 361 (1965); A. Amkraut and G. F. Solomon, *Cancer Res.* **32**, 1428 (1972). See review by R. C. Labarba, *Psychosom. Med.* **32**, 259 (1970).
3. L. L. Gershben, I. Benuck, P. S. Shurrager, *Oncology* **30**, 429 (1974); N. Molomut, F. Lazere, L. W. Smith, *Cancer Res.* **23**, 1097 (1963); B. H. Newberry *et al.*, *Psychosom. Med.* **34**, 295 (1972); B. H. Newberry, J. Gildow, J. Wogan, R. L. Reese, *ibid.* **38**, 1955 (1976); S. N. Pradhan and P. Ray, *J. Natl. Cancer Inst.* **53**, 1241 (1974); H. A. Rashkis, *Science* **116**, 169 (1952).
4. J. M. Weiss, *J. Comp. Physiol. Psychol.* **77**, 1 (1971); *ibid.*, p. 14; *ibid.*, p. 22.
5. H. Anisman, in *Psychopharmacology of Aversively Motivated Behavior*, H. Anisman and G. Bignami, Eds. (Plenum, New York, 1976), pp. 119–172; J. N. Hingtgen, J. E. Smith, P.A. Shea, M. H. Aprison, T. M. Gaff, *Science* **193**, 332 (1976); R. Kvetnansky, A. Mitro, M. Palkovitz, M. Brownstein, T. Torda, M. Vigas, L. Mikulajin, in *Catecholamines and Stress*, E. Usdin, R. Kvetnansky, J. J. Kopin, Eds. (Pergamon, Oxford, 1976), pp. 39–50; E. A. Stone, in *Catecholamines and Behavior*, A. J. Friedhoff, Ed. (Plenum, New York, 1975), vol. 2, p. 31–72; A. M. Thierry, G. Blanc, J. Glowinski, *J. Neurochem.* **18**, 449 (1971); J. M. Weiss, E. A. Stone, M. Harrell, *J. Comp. Physiol. Psychol.* **72**, 160 (1970). J. M. Weiss, H. I. Glazer, L. A. Pohorecky, in *Animal Models in Human Psychobiology*, G. Serban and A. Kling, Eds. (Plenum, New York, 1976), pp. 141–173.
6. L. S. Sklar and H. Anisman, *Soc. Neurosci. Abstr.* **4**, 400 (1978).
7. H. Anisman, D. Decatanzaro, G. Remington, *J. Exp. Psychol. Anim. Behav. Proc.* **4**, 197 (1978).
8. Newman-Keuls multiple comparisons ($\alpha = .05$) were carried out in all instances.
9. Mean [± standard error (S.E.)] on days 9 to 14: no shock = 37.18 ± 4.20, 63.0 ± 5.72, 99.21 ± 8.16, 138.62 ± 9.61, 185.16 ± 10.73, and 219.79 ± 10.63; 75 μA = 64.45 ± 4.82, 91.34 ± 6.97, 132.51 ± 8.54, 168.16 ± 9.78, 231.29 ± 12.06, and 284.69 ± 15.34; 150 μA = 66.66 ± 5.9, 97.62 ± 6.99, 142.80 ± 9.98, 188.40 ± 9.82, 242.03 ± 15.29, and 291.73 ± 20.89.
10. Mean day of appearance (± S.E.) for the 1.1, 2.2, and 3.3 hours of shock exposure: 5.95 ± 0.47, 6.0 ± 0.56, and 5.40 ± 0.52 days, respectively; $P > .10$. Mean survival time (± S.E.) for the 1.1, 2.2, and 3.3 hours of shock exposure: 23.65 ± 1.19, 24.70 ± 1.27, and 24.30 ± 1.32 days, respectively; $P > .10$.
11. A. A. Monjan and M. I. Collector, *Science* **196**, 307 (1977).
12. G. C. Cotzias and L. C. Tang, *ibid.* **197**, 1094 (1977); G. C. Cotzias, S. T. Miller, L. C. Tang, P.S. Papavasiliou, Y. Y. Wang, *ibid.* **196**, 549 (1977); M. M. Wick, *Nature (London)* **269**, 512 (1977); *Science* **199**, 775 (1978).
13. B. H. Fox, *J. Behav. Med.* **1**, 45 (1978).
14. Supported by grant A9845 from the National Research Council of Canada, grant MA6486 from the Medical Research Council of Canada, and by a grant from the Confederation Life Assurance Company. The helpful advice of R. S. Kerbel is gratefully acknowledged.

12 December 1978; revised 2 April 1979

Dissociations Between the Effects of LSD on Behavior and Raphe Unit Activity in Freely Moving Cats

Abstract. *The hypothesis that the action of hallucinogenic drugs is mediated by a depression of the activity of brain serotonergic (raphe) neurons was tested by examining the behavioral effects of* d*-lysergic acid diethylamide (LSD) while studying the activity of raphe neurons in freely moving cats. Although the results provide general support for the hypothesis, there were several important dissociations. (i) Low doses of LSD produced only small decreases in raphe unit activity but significant behavioral changes; (ii) LSD-induced behavioral changes outlasted the depression of raphe unit activity; and (iii) raphe neurons were at least as responsive to LSD during tolerance as they were in the nontolerant condition.*

The phenomenological effects of *d*-lysergic acid diethylamide (LSD) and theories concerning the biological bases of its action have had a major impact on psychiatry, psychology, and pharmacology over the past 25 years. A large body of evidence now suggests that brain 5-hydroxytryptamine (serotonin) may play an important role in mediating the dramatic psychobiological effects of LSD (*1*, *2*). The most compelling of these data come from electrophysiological studies demonstrating that small quantities of LSD, administered either intravenously or microiontophoretically, markedly depress the discharge rate of serotonin-contain-

0036-8075/79/0803-0515$00.50/0

ing neurons in rats (*3, 4*). These data, however, are insufficient for establishing a causal relationship between the effects of LSD on serotonergic neurons and on behavior. First, these electrophysiological studies have been conducted exclusively with either anesthetized or immobilized animals. Since the activity of serotonergic neurons is strongly influenced by the state and activity of the organism (*5*), either restraint or anesthesia could dramatically influence the response of these neurons to LSD. Second, anesthetization and paralysis obviously preclude the concomitant analysis of the behavioral effects of LSD along with the changes in unit activity.

An electrophysiological technique that permits stable and long-term recordings from central nervous system neurons in the freely moving cat has been developed (*5, 6*). In addition, an animal-behavior model for studying the actions of LSD and related hallucinogens, which is specific to this class of drugs and which parallels the major characteristics of the actions of LSD in humans, has also been recently described (*7, 8*). We have combined these two techniques and examined the effects of LSD on the activity of serotonin-containing neurons while simultaneously scoring the behavioral changes induced by the drug. This is, to our knowledge, the first attempt to analyze a drug effect on the activity of serotonin-containing neurons concomitantly with behavior.

Single-unit activity from neurons in the dorsal raphe nucleus of 14 adult female cats was recorded with 32- and 62-μm-diameter Nichrome wires, as previously described (*5, 6*). This method produces spike amplitudes of 80 to 400 μV and signal-to-noise ratios of 2 : 1 to 16 : 1 (Fig. 1). Electroencephalogram (EEG), electrooculogram (EOG), and neck electromyogram (EMG) leads were also implanted. (All electrical potentials were led from the cat by means of a cable and slip-ring assembly.) During a 3- to 4-week period after the operation, the cats were habituated to a sound-attenuating chamber (65 by 65 by 95 cm high) with two 12-V d-c lights and a 66-dB masking noise. Food, water, and a litter pan were available during the entire recording procedure. During experimental sessions, the cats were placed in the recording chamber, and 0.5 to 4 hours of baseline unit data were obtained. Baseline unit activity was stable over time for a given behavioral state, showing less than 5 percent variation. The cat was then administered either LSD tartrate (10 or 50 μg per kilogram of body weight, injected intraperitoneally), a bromo derivative of LSD (BOL) (50 μg/kg), or saline (0.5 ml/kg) (drug doses expressed as the salt). Unit activity was continuously monitored on an oscilloscope and on a polygraph along with the EEG, EOG, and EMG recordings. Behavior was continuously monitored on a television screen and scored on polygraph paper (*8*). Unit activity and behavior were examined for periods of 1 to 8 hours after the injection. Cats receiving 50 μg/kg of LSD received the same treatment 24 hours after the initial injection, and unit activity and behavior were monitored for 1 hour after the injection. At the completion of the study, recording sites were determined with the Prussian blue reaction in conjunction with a neutral red stain of 50-μm sections through the midbrain.

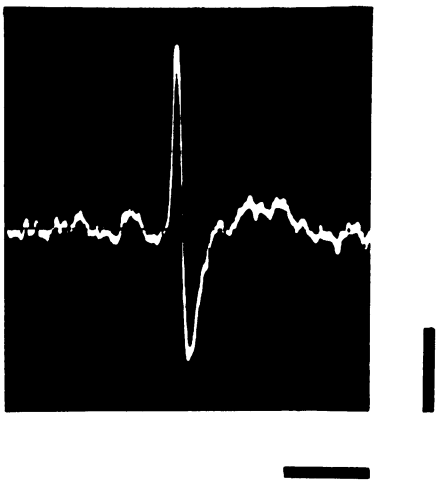

Fig. 1. Oscilloscopic trace of raphe unit discharge in a freely moving cat. Calibrations: 1 msec; 50 μV.

During baseline recordings, 53 of the neurons examined displayed the slow regular activity (mean discharge rate, 3.44 ± 0.18 spikes per second during active waking) characteristic of serotonergic neurons recorded both in vivo and in vitro (*3, 5, 9*). When examined histologically, these 53 cells were found to be localized on or near the midline within the dorsal raphe nucleus, which has been shown by fluorescence histochemistry to be densely populated with serotonin-containing neurons (*10*). Seven neurons in our study displayed irregular, high-frequency discharge rates and were found outside (lateral or ventral to) the dorsal raphe nucleus.

After LSD administration, cats displayed characteristic behavior consisting of limb flicking, abortive grooming, head shaking, staring, and investigatory responses (*7, 8*). Of these, the limb flick is the most sensitive and reliable behavioral index of the central action of hallucinogenic drugs and was therefore used for the quantitative behavioral analysis in this study (*7, 8*). Cats were typically more active and attentive and showed more head shaking and investigatory behavior within the first 5 to 10 minutes after injection. The first limb flicks usually appeared within 10 minutes after the 50 μg/kg dose of LSD [approximately the peak behavioral dose (*8*)], and the full-blown behavioral effects were typically present within 15 to 20 minutes. LSD (50 μg/kg) significantly decreased raphe unit activity from an active waking baseline [F (6,174) = 4.37, $P < .01$], with a mean maximal decrease of 48 percent (standard error = 7) 1 hour after the injection (Figs. 2 and 3). The peak behavioral effect also occurred approximately 1 hour after injection. The discharge rate of 28 of the 30 raphe units was significantly decreased by the 50 μg/kg dose of LSD. This dose produced a 25.1 percent decrease in unit activity [$t(29) = 2.62$, $P < .02$] as soon as 5 minutes after injection, and a significant increase in the rate of limb flicking [$t(29) = 2.97$, $P < .01$] after 10 minutes. Although unit activity remained significantly depressed for only 3 hours after the injection, the rate of limb flicking remained significantly above the baseline for at least 8 hours. Twenty-four hours after the initial dose of LSD (50 μg/kg), a second dose of 50 μg/kg was virtually without behavioral effect (for example, only 0.3 limb flicks per hour), but it produced an even greater decrease (− 62.4 percent) in raphe unit activity (Fig. 2) [$t(27) = 3.19$, $P < .01$].

There were no phasic changes in the discharge rate of raphe units in association with limb flicks. After LSD administration, the activity of several raphe units was completely suppressed for up to 30 seconds during staring and increased during digging or grooming behavior. In general, the raphe neuron discharge rates were much more variable from minute to minute after LSD than before.

A dose of 10μg/kg also significantly decreased raphe unit activity [$F(6,132) = 2.34$, $P < .05$], with a maximum decrease of 18 percent 1 hour after the injection (Fig. 3). The peak behavioral effect of this dose also occurred at approximately 1 hour (mean limb flicks = 12 per hour). Unit activity was significantly decreased for 2 hours after the injection [$t(22) = 2.44$, $P < .05$], whereas the limb flick rate was significantly above baseline for at least 4 hours [$t(22) = 2.69$, $P < .02$].

Neither saline (N = 7) nor BOL (a nonhallucinogenic congener of LSD that is as effective as LSD in blocking serotonin's peripheral action) (N = 6) had any significant effect on either raphe unit activity or behavior. LSD (50 μg/kg) produced no significant effect on nonserotonergic cells (N = 7) outside the dorsal raphe nucleus.

The following model has been proposed to account for LSD-induced hallucinogenesis (*4*, *11*). LSD depresses the activity of serotonin-containing midbrain raphe neurons; because serotonin has an inhibitory postsynaptic effect in the forebrain (*4*), this disinhibition increases in the activity of the postsynaptic target neurons (*11*). There are dense serotonergic inputs to visual and limbic system structures (*12*), and the LSD-induced release from tonic serotonergic inhibition of these structures can explain the prominent visual hallucinations and changes in affect that follow LSD administration (*1*).

Our data provide general support for a causal relationship between LSD's inactivation of central serotonergic neurotransmission and the behavioral effects of the drug. (i) Doses of 10 and 50 μg/kg significantly depressed raphe unit activity and increased several behaviors specific to LSD and related hallucinogens; (ii) the magnitude and duration of both the unit and behavioral changes were dependent on dosage; (iii) the peak behavioral and unit changes were temporally correlated; and (iv) these effects were somewhat specific to LSD (the changes in behavior and raphe unit activity were not seen in response to BOL, and LSD produced no significant changes in the activity of nonserotonergic cells).

There were, however, three important dissociations between raphe unit activity and the behavioral changes. (i) Low doses of LSD produced only small decreases (10 to 20 percent) in raphe unit activity, but produced significant behavioral changes. This result may simply be evidence that subtle changes in the activity of these neurons may precipitate dramatic behavioral changes. It probably also reflects the additional actions of LSD, such as dopaminergic effects (*13*), in eliciting the behaviors under study. (ii) The behavioral changes following both doses of LSD significantly outlasted the raphe unit changes. This finding may be explained by the continuing depression of serotonin release after raphe unit activity has returned to baseline (*14*). It may also be due to a rapid change in sensitivity of neurons receiving a serotonergic projection from the raphe. (iii) Raphe neurons were at least as responsive to LSD during tolerance as during the nontolerant condition [these unit data support a previous electrophysiological study in rats (*15*)]. Our data imply that the decrease in raphe unit activity during tolerance may be offset by a compensatory neuronal change, perhaps in raphe target neurons. We have recently gathered evidence in support of this hypothesis from studies of receptor binding (*16*).

Placing emphasis on these dissociations between raphe unit activity and behavior might suggest abandoning the serotonin hypothesis of hallucinogenic drug action. When these data are considered in the broader context of the entire literature on the mechanism of action of hallucinogenic drugs (*1*, *2*, *17*), however, they do provide some support for a primary role of serotonin neurons in this process. For example, in studies of the molecularly simpler hallucinogen 5-methoxy-*N*, *N*-dimethyltryptamine, we have found a much closer relationship between the behavioral changes and the effects upon raphe neurons (*17*). Therefore, rather than abandoning the serotonin hypothesis of hallucinogenesis, it should be modified to reflect the fact that

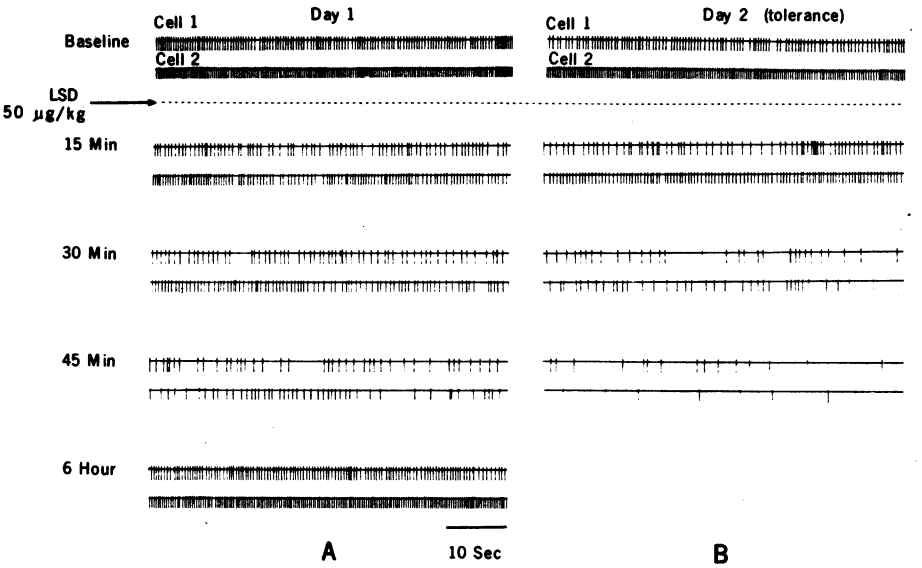

Fig. 2. (A) Effects of LSD on the activity of two simultaneously recorded neurons in the dorsal raphe nucleus. A significant depression is evident by 15 minutes after the injection and was maximal by 45 minutes. Both cells fully recovered by 6 hours after the injection. (B) A second dose of LSD administered 24 hours after the initial dose produced an even greater decrease in unit activity. No data are shown for the 6-hour time point on day 2, because the time course for the return of unit activity to baseline during tolerance was not recorded. The spikes in this figure are not action potentials; they are the triggered standard pulse output of a spike height discriminator written out on polygraph paper.

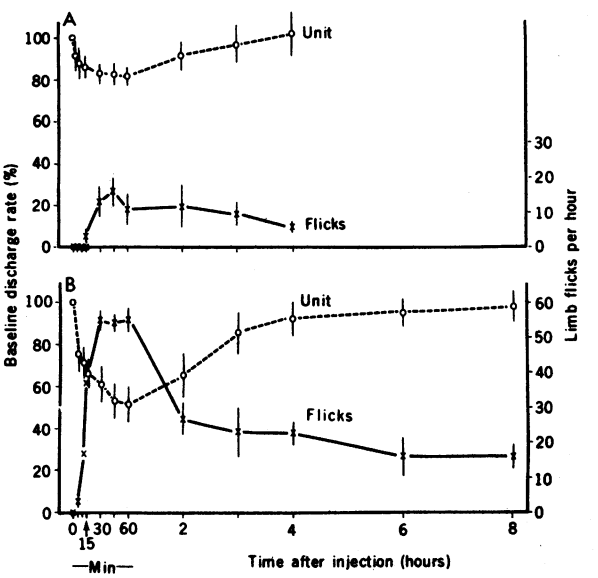

Fig. 3. Time course for the effects of LSD [(A) 10 μg/kg; (B) 50 μg/kg] on the activity of dorsal raphe neurons (○) and the rate of occurrence of limb flicks (X). Vertical bars represent standard errors of the means.

this system of neurons may exert subtle modulatory influences and therefore not mediate behavioral changes in a simple one-to-one fashion. The initiation of the behavioral effects of LSD may directly depend on changes in the activity of serotonin-containing neurons, whereas other aspects of its action, such as its peak effects, its duration, and development of tolerance, may depend on factors such as other neurotransmitter systems and synaptic plasticity involving raphe target neurons.

MICHAEL E. TRULSON
BARRY L. JACOBS

Program in Neurosciences,
Department of Psychology,
Princeton University,
Princeton, New Jersey 08544

References and Notes

1. G. K. Aghajanian, H. J. Haigler, J. L. Bennett, in *Handbook of Psychopharmacology*, L. L. Iversen, S. D. Iversen, S. H. Snyder, Eds. (Plenum, New York, 1975), pp. 63–96.
2. D. X. Freedman and A. E. Halaris, in *Psychopharmacology: A Generation of Progress*, M. A. Lipton, A. DiMascio, K. F. Killam, Eds. (Raven, New York, 1978), pp. 347–359.
3. G. K. Aghajanian, W. E. Foote, M. H. Sheard, *Science* **161**, 706 (1968).
4. H. J. Haigler and G. K. Aghajanian, *J. Pharmacol. Exp. Ther.* **188**, 688 (1968).
5. M. E. Trulson and B. L. Jacobs, *Brain Res.* **163**, 135 (1979); D. J. McGinty and R. M. Harper, *ibid.* **101**, 569 (1976).
6. B. L. Jacobs and D. J. McGinty, *Exp. Neurol.* **33**, 1 (1971); R. M. Harper and D. J. McGinty, in *Brain Unit Activity During Behavior*, M. I. Phillips, Ed. (Thomas, Springfield, Ill., 1973), pp. 80–104.
7. B. L. Jacobs, M. E. Trulson, W. C. Stern, *Science* **194**, 741 (1976); M. E. Trulson and B. L. Jacobs, *Brain Res.* **132**, 315 (1977); D. B. Rusterholz, J. L. Spratt, J. P. Long, C. F. Barfknecht, *Commun. Psychopharmacol.* **1**, 589 (1977); D. E. Nichols, W. R. Pfister, G. K. W. Yim, *Life Sci.* **22**, 2165 (1978).
8. B. L. Jacobs, M. E. Trulson, W. C. Stern, *Brain Res.* **132**, 301 (1977). No claim is being made that the cats given LSD are hallucinating since it is impossible to know what a nonverbal organism is experiencing. The behavioral syndrome, especially the limb-flick response, is a useful animal model for studying the actions of hallucinogenic drugs because (i) these behaviors are elicited specifically by LSD and related hallucinogens, and (ii) they parallel the major characteristics of the action of these drugs in humans. Furthermore, these behavioral changes are dose-dependent, sensitive to doses within the human range, robust, reliable, and easy to quantify.
9. G. K. Aghajanian and H. J. Haigler, *Brain Res.* **81**, 364 (1974); S. S. Mosko and B. L. Jacobs, *Physiol. Behav.* **13**, 589 (1974); *Neurosci. Lett.* **2**, 195 (1976).
10. C. Pin, B. Jones, M. Jouvet, *C. R. Soc. Biol.* **162**, 2136 (1968); D. Poitras and A. Parent, *J. Comp. Neurol.* **179**, 699 (1978).
11. G. K. Aghajanian and H. J. Haigler, *Psychopharmacol. Commun.* **1**, 619 (1975).
12. K. Fuxe, *Acta Physiol. Scand. Suppl. 257* **64**, 41 (1965); U. Ungerstedt, *Acta Physiol. Scand. Suppl. 367* (1971).
13. L. Pieri, M. Pieri, W. Haefely, *Nature (London)* **252**, 586 (1974); M. E. Trulson, A. D. Stark, B. L. Jacobs, *Eur. J. Pharmacol.* **44**, 113 (1977); B. L. Jacobs, M. E. Trulson, A. D. Stark, G. R. Christoph, *Commun. Psychopharmacol.* **1**, 243 (1977); G. R. Christoph, D. M. Kuhn, B. L. Jacobs, *Life Sci.* **21**, 1585 (1977).
14. D. W. Gallager and G. K. Aghajanian, *J. Pharmacol. Exp. Ther.* **193**, 785 (1975).
15. M. E. Trulson, C. A. Ross, B. L. Jacobs, *Neuropharmacology* **15**, 771 (1977).
16. M. E. Trulson and B. L. Jacobs, *Life Sci.* **24**, 2053 (1979).
17. ———, *Eur. J. Pharmacol.* **54**, 43 (1979).
18. Supported by National Institute of Mental Health grant MH23433 and the Alfred P. Sloan Foundation. We thank R. M. Paternoster for excellent technical assistance.

10 January 1979; revised 4 April 1979

6-Hydroxydopamine Potentiates Acute Herpes Simplex Virus Infection of the Superior Cervical Ganglion in Mice

Abstract. *Treatment of mice with 6-hydroxydopamine increased herpes simplex virus replication in the superior cervical ganglion while it decreased the subsequent prevalence of latent infection. Preganglionic neurectomy failed to block this effect. These observations suggest that intrinsic neural events modify the outcome of viral infections of the nervous system.*

It is recognized that each cell type in the nervous system may differ in viral susceptibility; however, individual cells within the nervous system are usually assumed to be ontogenetically fixed in their response to infection (*1*). To account for variability in the outcome of infection, attention has been focused almost exclusively on factors extrinsic to the nervous system, such as the dose and neurotropism of the infecting viral strain, the access of virus to neural tissue, and immunologically specific and nonspecific systemic host defenses, while little effort has been directed at defining whether changes in the intrinsic metabolic or functional state of neural cells might influence the character of nervous system viral infection (*1*). To explore this question, I have used a model of herpes simplex virus (HSV) infection of the superior cervical ganglion (SCG) of the autonomic nervous system, and now report that treatment of mice with 6-hydroxydopamine (6-OHDA), a drug that selectively injures adrenergic nerves (*2*), markedly alters the course of infection in this ganglion.

Infection of the SGC occurs after inoculation of the ipsilateral eye with HSV, and the virus reaches the ganglion principally over neural pathways (*3*, *4*). The ganglion infection is conveniently considered in two phases: an acute phase, lasting less than 10 days, in which active HSV replication can be monitored by measuring viral titers in homogenates of the ganglion, and a latent phase, during which infectious virus is no longer detected in ganglion homogenates, but the persistence of the viral genome can be demonstrated when virus is reexpressed in ganglia assayed by explantation-cocultivation techniques (*3*, *4*). In all aspects tested, SCG infection closely resembles experimental sensory ganglion infection with HSV (*5*).

Systemically administered 6-OHDA is selectively taken up by and destroys adrenergic nerve terminals, resulting in widespread sympathectomy (*2*). In the mature animal, neuronal cell bodies survive and the damaged nerve terminals regenerate. The drug 6-OHDA was selected for this study in order to extend the observation that surgical postganglionic neurectomy, when performed after virus reaches the ganglion, augments HSV replication in the SCG (*4*). As an experimental tool, 6-OHDA offers several advantages over surgical neurectomy in avoiding operative trauma and producing a more uniform and circumscribed lesion.

Four- to six-week-old BALB/c female mice (Charles River) were infected by unilateral intraocular inoculation of 8×10^4 plaque-forming units (PFU) of the F strain of HSV type 1. Methods of virus preparation, inoculation, and assay of ganglia and eyes ipsilateral to the side of inoculation by homogenization and explantation have been described (*3*, *4*). 6-Hydroxydopamine hydrobromide (Regis; 250 mg/kg) was dissolved in 0.9 percent sodium chloride containing ascorbic acid (Calbiochem; 0.8 mg/ml) immediately before intraperitoneal injection; control mice received ascorbate vehicle under identical conditions. Previous studies have shown that passive immunization of mice with antibody to HSV reduces the extent of viral replication in the SCG acutely while actually enhancing the subsequent prevalence of latency (*4*), and that immunization protects the integrity of the ganglion (*6*). In addition, enhancement of virus replication by surgical postganglionic neurectomy was most readily recognized in passively immunized mice in which background virus replication was minimal during the acute phase of infection (*4*). For these reasons, both unimmunized mice and mice passively immunized by intraperitoneal injection of 0.2 ml of rabbit antiserum to HSV possessing a neutralizing antibody titer of > 2000 (given 1 day after intraocular HSV challenge) were used in the present studies.

0036-8075/79/0803-0518$00.50/0