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A Triggered Hyperkinesia Induced in Rats by Lesions of the Corpus Striatum

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The role of the corpus striatum (caudate, putamen, and globus pallidus) in movement control has been suggested to involve the modulation of sensory traffic to downstream motor mechanisms. We report that kainic acid lesions of the posterior corpus striatum, which preferentially spare fibers of passage while destroying striatopallidal neurons, produce a stimulus-sensitive movement pattern in rats that has a highly specific sensory trigger. The triggered choreic movement pattern is not a motor pathology per se, nor a response to diffuse states of arousal or stress, but rather is activated specifically in response to oral sensory stimulation. This sensory-specific hyperkinesia may be relevant to certain human sensorimotor pathologies.

INTRODUCTION

Involuntary and irrepressible movement patterns are a hallmark of many forms of damage to the corpus striatum in humans. Huntington's chorea is one well known example. But although hyperkinesia such as rapid chorea or more sinuous athetosis frequently accompanies striatopallidal disease in humans, it has not generally been possible to produce reliable hyperkinetic movement patterns in rodents simply by selective focused lesions of the corpus striatum (18).

We report here that an explosive forepaw hyperkinesia, triggered by a spe-

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cific class of oral sensory stimulation, can be elicited reliably in rats by oral stimulation for weeks after damage to the posterior corpus striatum (caudal caudate–putamen plus globus pallidus). The hyperkinesia bears some resemblance to human choreas in that it involves abrupt, rapid, and large-amplitude movements, exhibited in a repetitive pattern. This exaggerated movement pattern can be elicited, without pharmacological treatment, throughout the period of aphagia that typically follows globus pallidus damage (11, 14). The specificity of this hyperkinesia for a single class of oral triggering stimuli (not ordinarily encountered by the rat during aphagia and largely bypassed by the usual nursing regimen using gastric intubation of meals) may be responsible for the choreic action pattern having remained previously hidden. The discovery of a specifically triggered hyperkinesia serves to reinforce the intimate connection of sensory processing with striatal function and action control, which recently has received increased attention in investigations of the corpus striatum (1, 3, 5, 6, 12, 24). This sensory-specific hyperkinesia may be of some use in modeling the mechanisms of pathological hyperkinesia in humans.

METHOD

Bilateral striatopallidal lesions were produced in anesthetized male Sprague–Dawley rats (300 to 350 g) by intrastriatal injection of kainic acid (1.0 μg in 0.5 μl phosphate buffer) delivered during 5 min through a stereotactically placed 30-gauge needle. The needle remained in place an additional 10 min. Diazepam (8 mg/kg) was administered 30 min before and 30 min after kainic acid injections to control convulsant activity and reduce neural damage distant from the injection site caused by kainic acid-induced seizure activity (21). Ten rats received anterior striatal lesions (1.7 mm anterior to bregma, 2.2 mm lateral to sagittal fissure, 5.5 mm ventral to skull surface) and 10 received posterior lesions that included the globus pallidus (0.8 mm caudal to bregma, 3.5 mm L, 6.5 mm V). An additional 10 control rats received striatopallidal injections of the phosphate buffer only (5 anterior; 5 posterior).

Chronic oral cannulae (8) were implanted in all rats to permit later study of responsivity to oral stimulation. These permanent cannulae enter the mouth lateral to the first maxillary molar and exit the head from the dorsal skull. Oral cannulue can deliver taste infusions, and allow the changes in taste reactivity that accompany aphagia to be studied.

Behavioral Testing. Rats were observed in the home cage and in a variety of conditions. Taste reactivity and nonoral sensory stimulation tests were administered during days 3 to 10 after surgery. Defensive burying was tested during days 9 to 14.

Taste Reactivity. Rats were placed in a transparent plastic chamber above a mirror, which reflected a clear view of the face and body to a camera for video recording. A stimulus delivery tube was connected to the oral cannulae. After 5-min habituation, a 1-ml volume of a taste solution was infused into the mouth steadily during 1 min. Taste solutions reflected a range of palatability: 1.0 *M* sucrose, 0.1 *M* HCl, or 3×10^{-4} *M* quinine HCl. One taste stimulus was administered each day, and the order of administration was balanced across rats. Videotaped records were scored in slow motion (frame by frame to $\frac{1}{10}$ normal speed) by an observer blind to the experimental condition of the rat for the occurrence of 11 behavioral responses: locomotion, face washing, paw licking, rhythmic mouth movements, rhythmic midline tongue protrusions, lateral tongue protrusions, gapes, forelimb flails, headshakes, passive dripping of the solution, and paw treading [cf. (7, 8) for detail].

Nonoral Sensory Stimulation. Diffuse, arousing stimuli of various sorts were presented in the home cage or test chamber; e.g., handling, sudden noise (hand clap), tail pinch, or local tactile stimulation of a region of the face or body with a pointed probe. Behavioral responses were noted or videotaped.

Defensive Burying. Pilot studies using the taste-reactivity test suggested a powerful facilitation of paw treading by striatopallidal damage. A natural treading-like motion of the forepaws is seen in normal rats during defensive burying of a foreign or noxious object. Rats respond to a noxious object, such as a stationary electrified prod or a poison-paired piece of food, by burying it using a forepaw treading motion temporally and morphologically similar to the treading elicited by aversive tastes (8, 16). In order to examine whether or not lesion-induced changes in paw treading applied equally across the different contexts in which treading may occur, all rats were tested in the defensive burying paradigm beginning 1 week after surgery.

The rats were preexposed to the $40 \times 30 \times 40$-cm plastic test chamber (without the electrified prod) for 30-min periods on each of 3 consecutive days. The chamber was filled with a 5-cm layer of clean gravel. On the 4th day, an electrified, wire-wrapped, $6.5 \times 0.5 \times 0.5$-cm prod was inserted into the chamber through a hole in the center of the wall at one end 2 cm above the gravel layer. This shock circuit delivered shocks averaging 4 mA for the duration of contact. Each rat remained in the chamber until 15 min after it initially touched the prod and clearly received a shock (i.e., flinched or jumped). If the rat did not touch the novel prod within 30 min, the procedure was repeated on subsequent days until it did. All behavior was videotaped for subsequent analysis [cf. (16)].

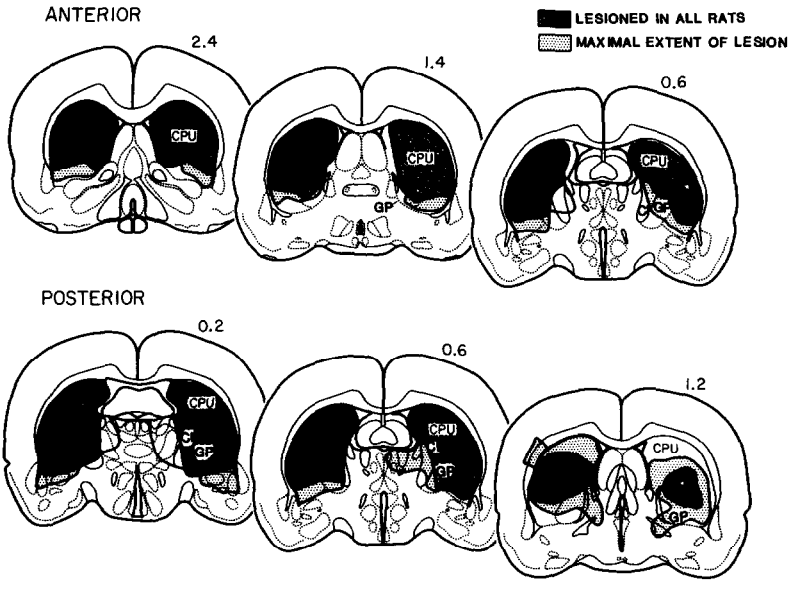

FIG. 1. Extent of kainic acid-induced lesions. The dark gray portion depicts area of neuronal cell body loss and gliosis shared by all members of a lesion group. The light gray portion depicts the maximal extent of individual lesions. Abbreviations: CPU—caudate-putamen, GP—globus pallidus, CI—internal capsule.

Histology. At the conclusion of the experiment each rat was deeply anesthetized and perfused. Brains were frozen, sectioned, mounted on slides, and stained with cresyl violet. Sections were microscopically examined to assess gliosis and the loss of neuron cell bodies.

RESULTS

Lesion Histology. Kainic acid produced marked gliosis and neuron loss in the nucleus caudate–putamen (neostriatum) and globus pallidus. Cell loss in the globus pallidus and nucleus basalis was much more extensive in the posterior striatal injection group. Typical and maximal extent of kainic acid lesions is shown in Fig. 1. Marked cell loss was also seen in the anterior lateral thalamic nuclei in two of the posterior-injected rats, and in the lateral septum, anterior hypothalamus, and amygdala in one posterior-injected rat. No damage typically was observed in the nucleus accumbens or the overlying neocortex.

Behavior. Hyperactivity (spontaneous locomotion and paw treading) was evident immediately upon recovery from anesthesia. This disappeared

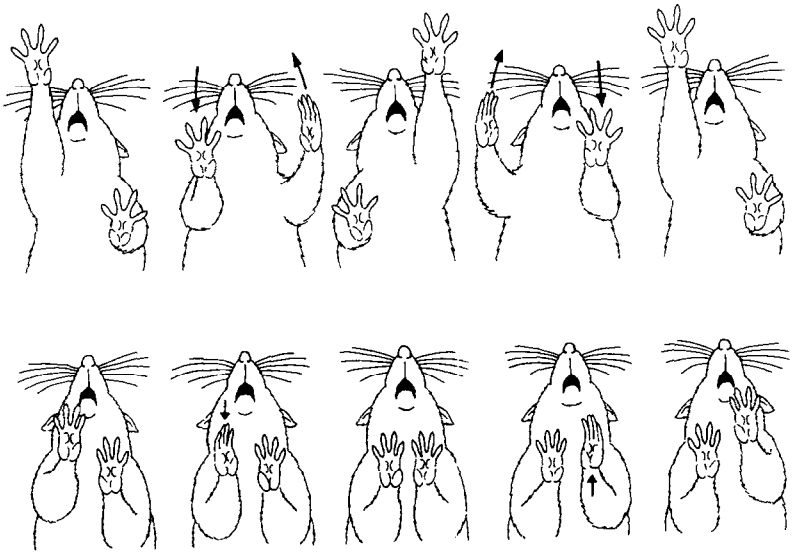

FIG. 2. Paw treading. Rhythmic forward and backward extension of the forepaws, with the two paws 180° out of phase. Top row depicts treading with maximal extension. Bottom row depicts low-amplitude treading. Each row sequence depicts approximately 0.3 s of treading.

within 12 h (10). A period of aphagia or hypophagia, lasting at least 2 weeks, followed all posterior lesions and some anterior lesions. Rats were fed a liquid diet three times daily by gastric intubation during this period.

During the first 10 days after the lesion, rats typically evinced no spontaneous hyperkinesia, nor could any movement pattern other than startle or brief orientation or locomotion be induced by diverse mild stressors or arousing stimuli such as handling, tail pinch, pinprick, air puff, or a sudden loud noise. In the taste-reactivity test, however, an explosive and persistent forepaw treading (Fig. 2) was triggered by oral stimuli in 90% of posterior-lesion and in 30% of anterior-lesion rats. Descriptively, a posterior-lesion rat, quiescent before the oral infusion, typically burst into forepaw treading within seconds of the infusion onset. Treading was well coordinated, with the two paws 180° out of phase ranging in amplitude from a complete maximal extension of the forelimbs alternately forward and backward (with a cycle frequency of approximately 3.5 Hz), to mere rapid substrate pats with no horizontal extension. When elicited by the oral infusion, treading persisted for the duration of the stimulus and bouts of vigorous paw treading were often seen to occur intermittently up to 5 min after the stimulus had ended.

As a general rule, choreic treading could be elicited throughout the entire period of aphagia in posterior-lesion rats. The correlation between treading

and aphagia appeared quite strong. Those rats with posterior lesions that showed the strongest aphagia, never touching either cereal mash or food pellets, tended to show also the most exaggerated and prolonged treading bursts. In addition, the three rats from the anterior lesion group that tested positive for elicited treading also showed aphagia lasting 5 to 8 days, longer than any other rat from the anterior group. These three rats had lesions extending posteriorly well into the globus pallidus. No other clear correlation between lesion histology and treading could be found, although future studies with smaller lesions might find more success in this regard.

Naturally emitted actions can be quantified either in terms of mean duration (or total number) of the response for a group of animals or in terms of response incidence (the number of animals per group showing the action at all). Paw treading to oral stimulation was enhanced dramatically after striatal lesions by both measures. A duration analysis showed marked differences in paw treading among vehicle control, anterior lesion, and posterior lesion groups for each of the three tastes: sucrose, HCl, and quinine ($P < 0.01$, ANOVA in each case). Specifically, rats with posterior striatal kainic acid lesions showed greater treading duration ($\bar{x} = 32 \pm 74$ s of the 60-s trial for all tastes combined) than either vehicle control ($\bar{x} = 0 \pm 0$ s for all tastes combined; $P < 0.01$ for each taste separately by t test) or anterior lesion rats ($\bar{x} = 4 \pm 1$ s for all tastes combined, $p < 0.01$ for each taste separately). Paw treading was thus increased after posterior striatal damage, regardless of whether the eliciting taste would normally be perceived as palatable or unpalatable. An analysis based on response incidence supported the conclusion that paw treading to tastes was elevated in posterior lesion groups compared with either anterior lesion or control groups ($P < 0.05$ in every case, paired z test of proportions). All the other natural actions were either suppressed or unchanged by striatopallidal damage. Figure 3 portrays the quantitative changes in each action's incidence and in paw treading duration, in response to either (normally palatable) sucrose or (normally unpalatable) quinine.

Sporadic paw treading is a natural response shown occasionally by normal rats to particularly unpalatable tastes (7, 8). No taste infusion, however, elicits treading of this persistence and amplitude in normal rats. The treading of posterior corpus striatum lesion rats, which was shown even to normally highly palatable tastes such as sucrose (Fig. 2), is exaggerated by orders of magnitude above treading's normal expression both in terms of its probability (the number of rats showing it) and its intensity (duration or number of treads) once elicited.

Because a much reduced form of treading can be elicited in at least some normal rats by at least some tastes, we wondered whether or not posterior corpus striatum lesions might specifically multiply the power of all *natural*

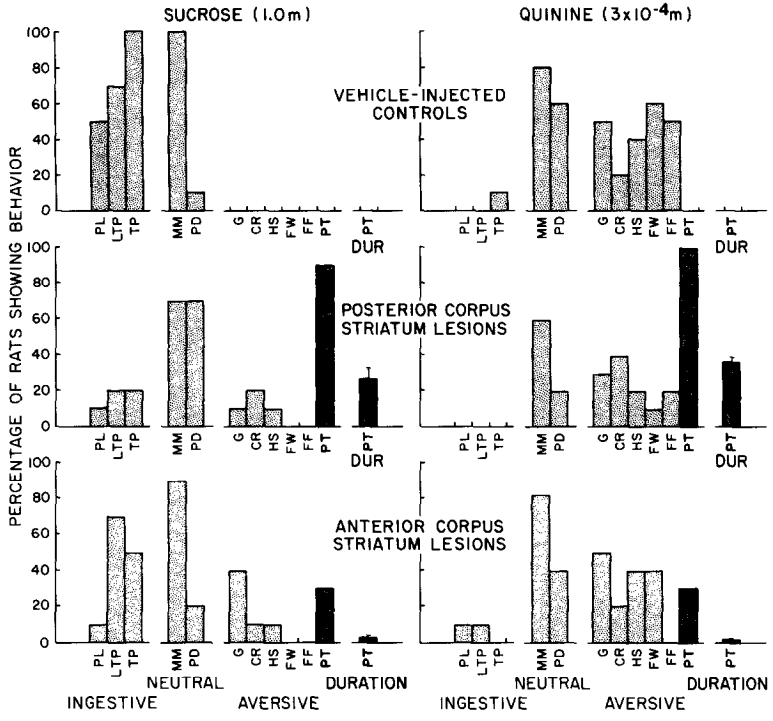

FIG. 3. Behavior elicited by oral infusions of 1.0 *M* sucrose and 3×10^{-4} *M* quinine in vehicle control, posterior lesion, and anterior lesion groups. Ingestive responses are paw licking (PL), lateral tongue protrusions (LTP), and midline tongue protrusions (TP). Neutral responses are rhythmic mouth movements (MM), and passive dripping of the solution (PD). Aversive responses are gapes (G), chin rubs (CR), headshakes (HS), face washing (FW), forelimb flails (FF), and paw treads (PT).

elicitors of forepaw treading (for example, by releasing this motor pattern from tonic inhibition). The defensive-burying test, in which treading-like movement is elicited from rats by a noxious object placed in a sandbox, was used to discover if striatal lesions would facilitate treading to other natural elicitors of treading. Although rats with lesions explored the box and touched the prod (and thus received brief paw shocks) at least as often as control rats, virtually no treading was shown by lesion rats in this situation. Neither duration nor incidence analyses showed significant differences in treading between the groups.

DISCUSSION

These experiments demonstrate a marked context-dependent alteration in motor activity after posterior striatal damage. The contrast between the very

low levels of spontaneous forepaw activity in rats with lesions and the powerfully enhanced treading elicited by the oral stimulation of a taste solution suggests that posterior striatopallidal lesions do not enhance general forepaw motor activation, but rather enhance a mechanism that produces action in response to stimulation. The failure of diffuse arousing stimuli such as noise, tail pinch, or handling to elicit this choreic hyperkinesia argues further that the effective elicitor is neither sensory stimulation per se nor general emotional arousal or distress. Finally, the failure of treading facilitation to transfer to defensive burying shows clearly that posterior striatopallidal lesions do not enhance equally the elicitation of treading-like behavior by all releasing stimuli. Rather these lesions appear to create the hyperkinesia by restructuring stimulus-response relations, elevating treading dramatically as a specific response to oral stimulation. Whether the effective stimulus can be narrowed further to a subclass of oral stimuli (intraoral versus perioral, gustatory vs. tactile) or whether multiple subclasses are equally able to function as elicitors, remains an open question. However, we can at least be certain from our present observations that no *particular* gustatory cue is required: a wide range of different tastants and even distilled water are able to effectively elicit treading in the first week after a posterior striatal lesion. Choreic movements in response to visual sensory stimuli have been reported in monkeys with corpus striatum lesions (4), but the present report appears to be the first discovery of a reliable and long lasting, stimulus-specific hyperkinesia in a rodent induced by striatal damage (10, 13, 18).

The corpus striatum receives massive sensory cortical projections. In the cat, a full 25% of neostriatal neurons respond to tactile stimulation of the mouth and face (20). Numerous investigators have proposed that the corpus striatum may function to bring behavior under the control of the *appropriate* stimulus by tonically or dynamically enhancing and suppressing the receptivity of various sensorimotor loops in ways that are appropriate to the behavioral context (1, 3, 4, 9, 12, 17, 19, 22). Sensory-triggered hyperkinesia after striatal damage may reflect the loss of tonic inhibition of particular sensorimotor loops (rather than of particular *motor* outputs downstream). The resultant high gain activation of such loops could then ineluctably result in abnormal action whenever the appropriate sensory stimulus is present. It may be conceivable that even the spontaneous chorea and other hyperkinesia that can accompany striatopallidal disease in humans reflects the operation of such a mechanism acting upon ordinary baseline rates of neural activity in sensory pathways. The observation that psychological stress often worsens the symptoms of such patients (15) is consistent with this hypothesis, given the reported facilitation of sensorimotor responsiveness by stress (acting in part through the nigrostriatal system (2, 23, 25)). The reliable and

dramatic sensory-specific hyperkinesia reported here may provide a tool to explore further the mechanisms underlying such human movement disorders involving the corpus striatum.

REFERENCES

1. ABERCROMBIE, E., AND B. L. JACOBS. 1984. Dopaminergic involvement in the processing of sensory information in the striatum. *Soc. Neurosci. Abstr.* **10:** 349.
2. ANTELMAN, S. M., H. SZECHTMAN, P. CHIN, AND A. E. FISHER. 1975. Tail pinch-induced eating, gnawing, and licking behavior in rats: dependence on the nigrostriatal dopamine system. *Brain Res.* **99:** 319–337.
3. COOLS, A. R. 1985. Brain and behavior: hierarchy of feedbck systems and control of input. Pages 109–168 in P. P. G. BATESON AND P. M. KLOPFER, Eds., Plenum, New York.
4. DENNY-BROWN, D., AND N. YANAGISAWA. 1976. The role of the basal ganglia in the initation of movement. Pages 115–149 in *The Basal Ganglia,* M. D. YAHR, Ed., Raven Press, New York.
5. DUNNETT, S. B, AND S. D. IVERSEN. 1982. Sensorimotor impairments following localized kainic acid and 6-hydroxydopamine lesions of the neostriatum. *Brain Res.* **248:** 121–127.
6. EVARTS, E. V., D. KIMURA, R. M. WURTZ, AND O. MIKOSAKA. 1984. Behavioral correlates of activity in basal ganglia neurons. *Trends Neurosci.* **7:** 447–453.
7. GRILL, H. J., AND K. C. BERRIDGE. 1985. Taste reactivity as a measure of the neural control of palatability. Pages 1–61 in J. SPRAGUE AND A. N. EPSTEIN, Eds., *Progress in Psychobiology and Physiological Psychology,* Vol. 11. Academic Press, New York.
8. GRILL, H. J., AND R. NORGREN. 1978. The taste-reactivity test. *Brain Res.* **143:** 263–297.
9. HRUSKA, R. E., AND E. K. SILBERGELD. 1979. Abnormal locomotion in rats after bilateral intrastriatal injection of kainic acid. *Life Sci.* **25:** 181–194.
10. IVERSEN, S. D. 1979. Behavior after neostriatal lesions in animals. Pages 195–212 in I. DIVAC AND R. G. E. OBERG, Eds., *The Neostriatum.* Pergamon, New York.
11. LEVINE, M. S., AND J. S. SCHWARTZBAUM. 1973. Sensorimotor functions of the striatopallidal system and lateral hypothalamus and consummator behavior in rats. *J. Comp. Physiol. Psychol.* **85:** 615–635.
12. LIDSKY, T. I., C. MANETTO, AND J. S. SCHNEIDER. 1985. Considerations of sensory factors involved in motor functions of the basal ganglia. *Brain Res. Rev.* **9:** 133–146.
13. LILES, S. L., AND G. D. DAVIS. 1969. Athetoid and choreiform hyperkinesias produced by caudate lesions in the cat. *Science* **164:** 195–197.
14. MORGANE, P. J. 1961. Alterations in feeding and drinking behavior of rats with lesions in globi pallidi. *Am. J. Physiol.* **201:** 420–428.
15. NARABAYASHI, H., T. CHIDA, AND T. KONDO. 1979. Analysis of two factors influencing involuntary movement: psychological stress effect and motor effect. Pages 361–371 in L. J. POIRIER, T. L. SOUKES, AND P. J. BEDARD, Eds., *Advances in Neurology* Vol. 24. Raven Press, New York.
16. PINEL, J. P. J., AND D. TREIT. 1983. The conditioned defensive burying paradigm and behavioral neuroscience. Pages 212–234 in T. E. ROBINSON, Ed., *Behavioral Approaches to Brain Research.* Oxford Univ. Press, New York.
17. SABOL, K. E., AND D. B. NEILL, S. A. WAGES, W. H. CHURCH, AND J. B. JUSTICE. 1985. Dopamine depletion in a striatal subregion disrupts performance of a skilled motor task. *Brain Res.* **335:** 33–43.

18. SCHNEIDER, J. S. 1984. Role of the basal ganglia in a chemically induced dyskinesia in rat. *Exp. Neurol.* **84:** 524–532.
19. SCHNEIDER, J. S., F. J. DENARO, AND T. I. LIDSKY. 1982. Basal ganglia: motor influences mediated by sensory interactions. *Exp. Neurol.* **77:** 534–543.
20. SCHNEIDER, J. S., AND T. I. LIDSKY. 1981. Processing of somatosensory information in the striatum of behaving cats. *J. Neurophysiol. (London)* **85:** 841–851.
21. SPERK, G., H. LASSMANN, H. BARAN, F. SEITELBERGER, AND O. HORNYKIEWICZ. 1985. Kainic acid-induced seizures: dose-relationship of behavioural, neurochemical, and histopathological changes. *Brain Res.* **338:** 289–295.
22. TEUBER, H. L. 1976. Complex functions of the basal ganglia. Pages 151–168 in M. D. YAHR, Ed., *The Basal Ganglia.* Raven Press, New York.
23. VALENSTEIN, E. S. 1980. Stereotypy and sensory-motor changes evoked by hypothalamic stimulation: possible relaton to schizophrenic behavior patterns. Pages 39–52 in A. ROUTTENBERG, Ed., *Biology of Reinforcement.* Academic Press, New York.
24. VILLABLANCA, J. R., R. J. MARCUS, AND C. E. OLMSTEAD. 1976. Effects of caudate nuclei or frontal cortical ablations in cats. *Exp. Neurol.* **52:** 389–420.
25. WISE, R. A., AND M. A. BOZARTH. 1985. Interaction of drugs of abuse with brain mechanisms of reward. Pages 111–113 in B. BLUM AND L. MANZO, Eds., *Neurotoxicology.* Dekker, New York.