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The Neural Substrates for the Motor-Activating Properties of Psychostimulants: A Review of Recent Findings

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SWERDLOW, N. R., F. J. VACCARINO, M. AMALRIC AND G. F. KOOB. *The neural substrates for the motor-activating properties of psychostimulants: A review of recent findings.* PHARMACOL BIOCHEM BEHAV **25**(1) 233–248, 1986.—Several different classes of pharmacological agents produce syndromes of behavioral activation in humans and infrahumans. While many of these agents, including direct and indirect sympathomimetics, methylxanthines, opiates and several neuropeptides have very distinct neurochemical profiles, it is not clear whether their behavioral stimulant action results from their action on a common neural substrate, or instead from their action on parallel but separate activation 'circuits.' Using photocell measurements of motor activity in rats, it has been possible to demonstrate that some agents with very distinct neurochemical identities act on common neural substrates to produce behavioral activation, while other agents act on completely distinct brain regions. Specifically, the locomotor-activating properties of direct and indirect sympathomimetics and opiates appear to result from their action within the basal ganglia, including the ventral striatum and globus pallidus, while the activating properties of caffeine and the neuropeptide, corticotropin releasing factor (CRF) appear to be independent of this circuitry. These findings suggest the presence of at least two separate neural systems capable of mediating behavioral activation.

Locomotor behavior Psychostimulants Photocell cages Sympathomimetics Opiates Methylxanthines Neuropeptides

THE behavioral changes produced by psychomotor stimulants in humans and infrahumans have long been the focus of intense investigation. Behaviors stimulated by acute treatment with these agents often resemble those manifested in a normal individual in conditions of high motivation or arousal [19, 29, 49]. It has therefore been a strategy of many experimenters to study the neural sites of psychostimulant action in hopes of gaining insight into the neural substrates of motivation. Also, chronic exposure to these drugs in man produces behavior that is often characterized by psychotic elements strikingly similar to those exhibited by 'endogenous' psychoses [9, 10, 17, 19, 29]. Thus the study of the neural substrates of psychostimulant action may provide insight into the pathophysiology of psychoses [10, 17, 41–43, 54, 55].

It is apparent from brief scrutiny of the neurochemical and pharmacological profiles of these agents that behavioral activation and other stimulant effects may arise from drug action on many different neural substrates. Thus, indirect sympathomimetics such as amphetamine and cocaine are known to act primarily by enhancing the amount of neurotransmitter released within central catecholamine synapses [19,24], while direct sympathomimetics, like apomorphine and bromocriptine bind directly to post-synaptic dopamine (DA) receptors [7]. Methylxanthines such as caffeine are thought to act primarily at brain adenosine receptors [8]; heroin and other opiates bind opiate receptors probably located on both pre- and post-synaptic sites throughout the CNS [22, 39, 48]. While much is still unknown about the pharmacology of endogenous psychostimulant peptides like corticotropin releasing factor (CRF), both CRF-containing terminals and CRF binding sites have been located in many brain regions [1, 4, 60, 68].

Despite the obvious pharmacological heterogeneity of these agents, there are similarities in the profiles of the behavioral activation that they produce. For example, all of these classes of stimulants produce profound increases in locomotor activity in rats, as measured by photocell activity

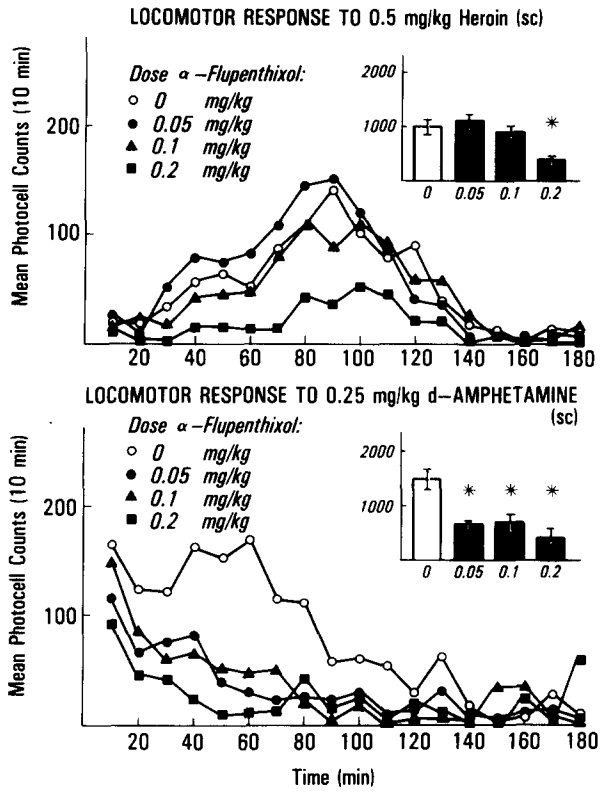

FIG. 1. Top graph. Effects of alpha-flupenthixol on the locomotor response after SC injection of heroin (0.5 mg/kg). Rats were pretreated with alpha-flupenthixol and, 60 min later, habituated to the photocell cages. Ninety min later the rats were injected with heroin. Bottom graph. Effects of alpha-flupenthixol on the locomotor response after SC injection of amphetamine (0.35 mg/kg). Rats were pretreated and tested as in the top graph. *Significantly different from saline, $p<0.05$, Duncan Multiple Range *a posteriori* test. Inset shows the mean total counts for 180 min ±SEM. Based on independent group design, n=8 in each group. Taken from [67].

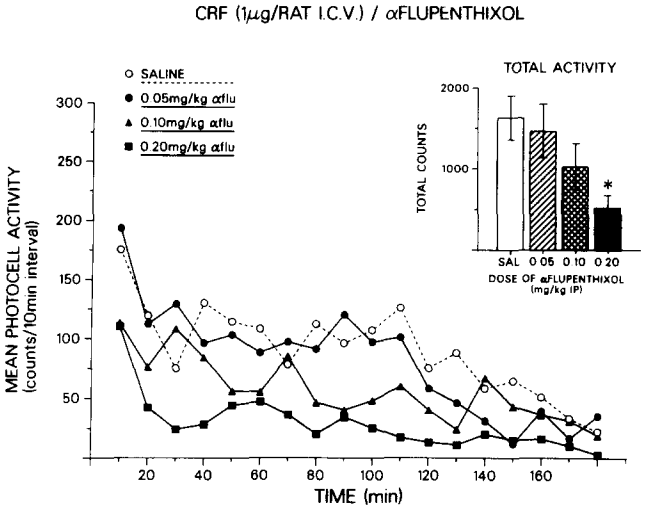

FIG. 2. Effects of alpha-flupenthixol on the locomotor response after intracerebroventricular infusion of CRF (1 μg). Rats were pretreated with alpha-flupenthixol and 60 min later habituated to the photocell cages. Ninety min later the rats received CRF. ○=Saline, ●=0.05, ▲=0.10, ■=0.20 mg/kg alpha-flupenthixol. *Significant difference from saline, $p<0.05$, Newman-Keuls test following ANOVA. Inset shows the mean total counts for 180 min ±SEM for n=8 in each group. Taken from [27].

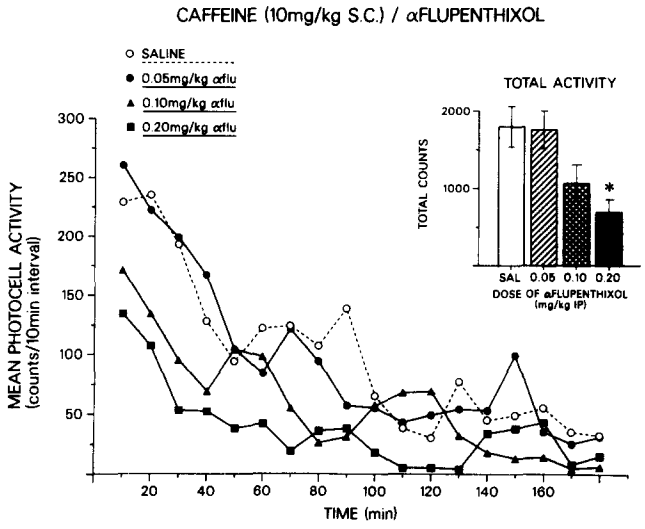

FIG. 3. Effects of alpha-flupenthixol on the locomotor response after SC injection of caffeine (10 mg/kg). Rats were pretreated as in Fig. 2. Notation the same as for Fig. 2. Taken from [27].

in a familiar cage environment during the normally quiescent period of the light-dark cycle [21, 27, 48]. Many of these agents, including amphetamine, caffeine, cocaine and heroin have euphoriant and addictive properties in humans [9, 14, 19], and are self-administered by infrahuman primates and rats [12, 28, 38, 42, 43, 64]. Higher doses of these drugs produce stereotyped patterns of repetitive movements [10, 17, 29] and in humans this results in 'stereotyped' obsessive behaviors and thought patterns [9,46]. Indeed, both caffeine and amphetamine, which display very distinct pharmacological profiles, can stimulate florid psychotic episodes in high doses [9, 11, 46].

One explanation for the similarities in the behavioral, but not pharmacological, profiles of these agents is that they may act on different elements of a common neural 'stimulant circuit;' this same circuitry might normally serve to mediate the motivational and pathological states mimicked by different doses of psychostimulants. Alternatively, separate neural substrates may exist that are responsible for the activating properties of pharmacologically distinct stimulants. Such redundancy might underlie functional distinctions between different states of behavioral activation, and might be paralleled by a multiplicity of separate motivational circuits, each triggered by distinct stimuli or contingencies.

In the present review, we will describe experimental evidence that suggests that in the rat, both direct and indirect sympathomimetics and opiates produce behavioral activation through their action on different elements of a single neural circuit. In contrast, caffeine and CRF appear to produce their activating effects independent of this circuitry, but themselves may share a common action within a second separate substrate for stimulant effects.

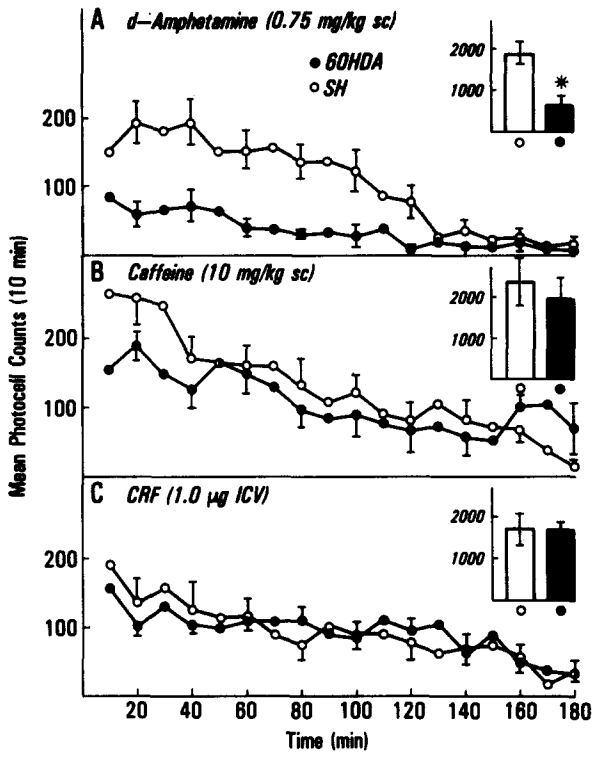

FIG. 4. Locomotor response to (A) 0.75 mg/kg d-amphetamine, (B) 10 mg/kg caffeine and (C) 1.0 μg CRF in rats following sham (○) or 6OHDA (●) lesions of the nucleus accumbens. Ordinate refers to total photocell counts for each 10 min period of a 180 min test. Inset refers to mean total photocell counts ±SEM for 180 min. Taken from [65].

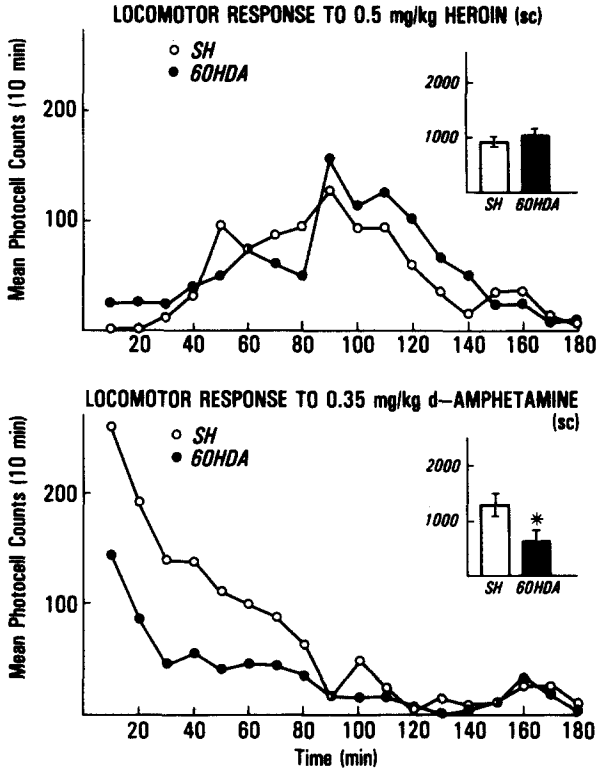

FIG. 5. Top graph. Effects of 6OHDA lesions of the nucleus accumbens on the locomotor response after SC injection of heroin (0.5 mg/kg). Rats were habituated to the photocell cages for 90 min and then injected with heroin. Bottom graph. Effects of 6OHDA lesions of the nucleus accumbens on the locomotor response after SC injection of amphetamine (0.25 mg/kg). Rats were tested as in the top graph. *Significantly different from sham lesion group, $p<0.05$, main effect ANOVA. Inserts show the mean total counts for 180 min ±SEM for eight rats in the sham and lesion group, respectively. Taken from [67].

EFFECTS OF CENTRAL DOPAMINE RECEPTOR BLOCKADE ON STIMULANT-ENHANCED LOCOMOTION

The locomotor-activating properties of several indirect sympathomimetics, including amphetamine, cocaine and methylphenidate, are believed to result largely from their ability to increase brain dopamine (DA) transmission since drugs that block receptors for DA within the central nervous system (CNS) reverse the behaviorally activating properties of these drugs [29, 45, 49]. In order to examine the possible involvement of brain DA transmission as a general neural substrate for stimulant action, we studied the locomotor activation produced by several classes of stimulants in animals that were pretreated with one of four doses of the central DA receptor antagonist alpha-flupenthixol (FLU) [27].

The effects of dopamine receptor blockade on stimulant-enhanced locomotion are seen in Figs. 1–3. Locomotor activity produced by all stimulants was antagonized by FLU, yet significant differences are obvious in the profiles of these stimulant responses to FLU. While the lowest dose of FLU tested significantly blocked amphetamine-stimulated locomotion, only the highest dose of FLU blocked the activation produced by caffeine, CRF or heroin. In fact, while the effective dose 50 percent (ED50) for FLU antagonism of amphetamine-stimulated locomotion was 0.02 mg/kg, the ED50 for antagonism of the other stimulants tested (caffeine—0.14 mg/kg; CRF—0.14 mg/kg; heroin—0.18 mg/kg) was in each case well above the ED50 for FLU-induced catalepsy (known to be 0.10 mg/kg [34]). Thus it appears that while the FLU-induced antagonism of amphetamine-stimulated locomotion results from a specific blockade of a DA receptor population that serves as a critical substrate for amphetamine-stimulated locomotion, the FLU-induced blockade of caffeine-, CRF- or heroin-stimulated locomotion may reflect a more non-specific inability of the animal to move [27].

EFFECTS OF DESTRUCTION OF NUCLEUS ACCUMBENS (N.Acc.) DOPAMINE ON STIMULANT-ENHANCED LOCOMOTION

If increases in central DA transmission form the critical substrate for the locomotor-activating properties of amphetamine, but not caffeine, CRF or heroin, then destruction of central DA terminals might differentially modify the stimulant properties of these drugs. Previous studies have demonstrated that destruction of DA terminals within the nucleus accumbens (N.Acc.) blocks amphetamine-, but not caffeine-stimulated locomotion in the rat [21]. Another consequence of destruction of pre-synaptic DA terminals in the N.Acc. is the development of post-synaptic DA receptor supersensitivity, evidenced biochemically by an increase in DA receptor B max in this region [53], and evidenced behaviorally by a 'supersensitive' locomotor response to the direct DA receptor agonist apomorphine [24].

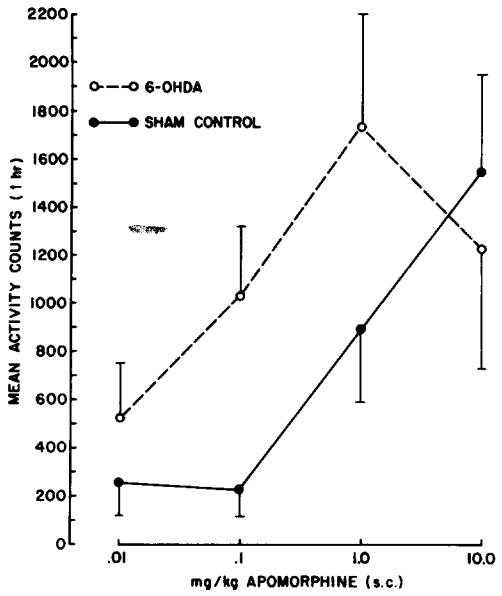

FIG. 6. Locomotor activity elicited by various doses of apomorphine in rats following sham and 6OHDA lesions of the nucleus accumbens. Data represents means (n=4 each dose) ±SEM. Taken from [69].

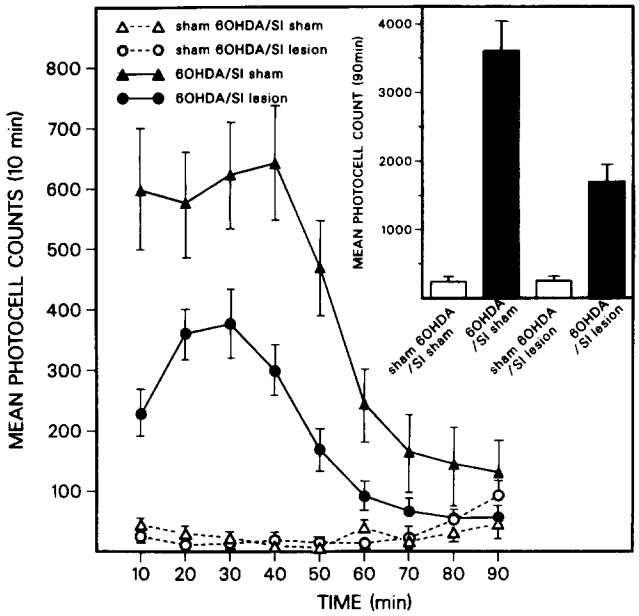

FIG. 7. Locomotor response after SC injection of 0.1 mg/kg apomorphine. Ordinate refers to total photocell counts for each 10 min period of a 90-min test. Data represents means±SEM. (SI—substantia innominata; for lesion histology, see [62]). Taken from [62].

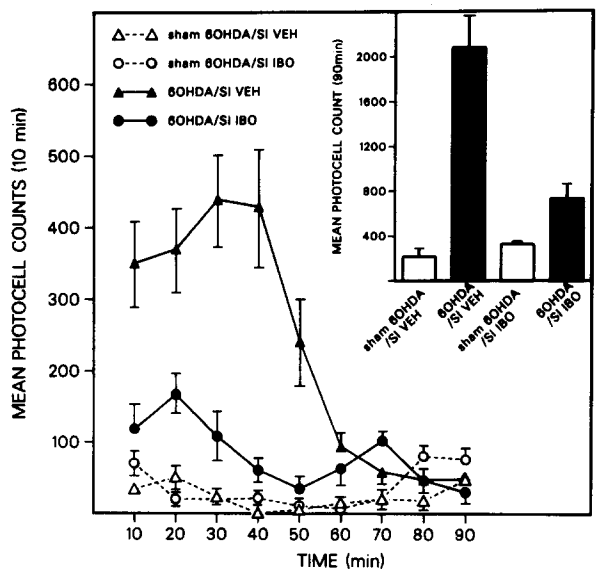

FIG. 8. Locomotor activity following SC injection of 0.1 mg/kg apomorphine. Ordinate refers to mean photocell counts for each 10 min period for the groups represented as follows: △, sham 6OHDA/SI vehicle (n=6); ○, sham 6OHDA/SI ibotenic acid (n=6); ▲, 6OHDA/SI vehicle (n=10), ●, 6OHDA/SI ibotenic acid (n=9). Statistical analysis was accomplished with a two-way analysis of variance with repeated measures on time, with significance taken at $p<0.05$. (SI—substantia innominata; IBO—ibotenic acid; for lesion histology, see [63]). Taken from [63].

The effects of destruction of N.Acc. dopamine on stimulant-enhanced locomotion are seen in Figs. 4–6. Compared to vehicle-injected controls, 6OHDA-injected rats showed a significantly decreased response to 0.35 and 0.75 mg/kg d-amphetamine. In contrast, the locomotor response to caffeine, CRF or heroin was not significantly diminished over the 180 min test [67]. Animals tested with apomorphine showed a clear dose-dependent activation that was greatly potentiated in 6OHDA-injected animals, as indicated by a ten-fold increase in sensitivity to apomorphine in 6OHDA-compared to vehicle-injected animals [68]. The highest dose of apomorphine (10.0 mg/kg) produced intense gnawing in 6OHDA-injected animals, with a resultant decrease in locomotor activity [68].

These results are consistent with the finding that pharmacological blockade of brain DA receptors antagonizes amphetamine-, but not caffeine-, CRF- or heroin-stimulated locomotion. While the integrity of pre-synaptic DA terminals within the N.Acc. is required for amphetamine-stimulated locomotion, the activating properties of caffeine, CRF and heroin are apparently independent of their effects on N.Acc. DA. Furthermore, the results from tests with apomorphine in this experiment directly implicate the post-synaptic DA receptor within the N.Acc. as a substrate of stimulant-enhanced locomotion. This conclusion follows from the finding that the sensitivity of animals to the locomotor-activating properties of the DA receptor agonist apomorphine is increased ten-fold by a treatment which has been shown to increase the number of post-synaptic DA receptors within the N.Acc. [53]. These results do not address, however, the means by which elevated DA receptor activation within this brain region, whether produced indirectly by amphetamine or directly by apomorphine, might be translated to lower circuitry to produce behavioral activation.

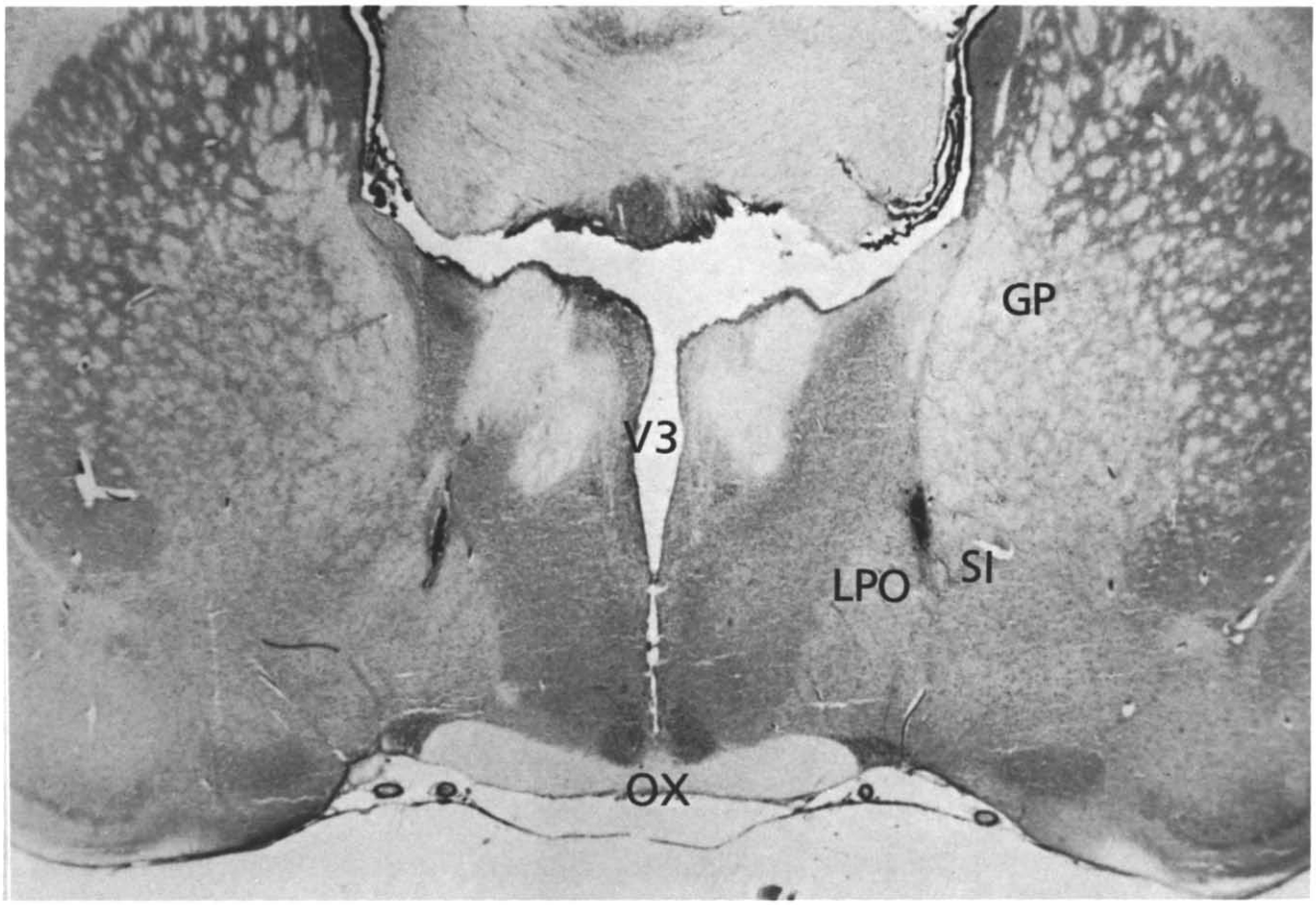

FIG. 9. Frontal section showing typical site of bilateral injector tips within the SI/LPO region. Abbreviations: SI—substantia innominata; LPO—lateral preoptic area; GP—globus pallidus; OX—optic chiasm; V3—third ventricle. Taken from [61].

EFFECTS OF ELECTROLYTIC- OR IBOTENIC ACID-INDUCED DESTRUCTION OF THE SUBSTANTIA INNOMINATA/LATERAL PREOPTIC AREA ON STIMULANT-ENHANCED LOCOMOTION

Efferent projections from the N.Acc. to the globus pallidus, substantia innominata, lateral preoptic area, substantia nigra, thalamus and reticular formation have been described [14, 18, 33, 35, 57–59, 70]. In an earlier attempt to determine the first-order efferent projections from the N.Acc. to the neurons that may eventually activate the spinal 'final common pathway,' we [62,63] studied the 'supersensitive' locomotor response to apomorphine in rats that received bilateral electrolytic or ibotenic acid-induced damage to a major recipient of N.Acc. efferent fibers. The 'supersensitive' locomotor response was chosen so as to functionally exaggerate the role of DA receptors in an easily quantifiable behavioral paradigm. The lesion site chosen for this work was an area ventral to the globus pallidus that includes the substantia innominata/lateral preoptic area (SI/LPO). This region of the ventral pallidum (VP) has been shown by autoradiographic, retrograde transport, anterograde degeneration, immunohistochemical and electrophysiological techniques to receive a dense projection of fibers from the N.Acc. [18, 33, 36, 57, 58, 70].

As seen in Fig. 7, compared to animals that received N.Acc. sham (vehicle) injections, 6OHDA-injected animals showed a significantly potentiated locomotor response to apomorphine. Subsequent electrolytic lesions within the SI/LPO depressed the locomotor response to apomorphine in 6OHDA-injected animals by 52.7%, but did not depress the response in sham (vehicle) injected animals. Figure 8 shows the results from animals following vehicle- and ibotenic-acid injections within the SI/LPO. Compared to the animals that received sham (vehicle) 6OHDA injections, 6OHDA-injected animals showed a significantly potentiated locomotor response to apomorphine. Injections of ibotenic acid within the SI/LPO significantly diminished (by 65%) the locomotor response to apomorphine in 6OHDA-injected animals, but not in vehicle-injected animals.

These results indicate that the first-order efferent projection from the N.Acc. onto cells within the ventral pallidum forms a critical output for the behavioral expression of N.Acc. DA receptor stimulation. Thus, locomotor activation produced by stimulation of 'supersensitive' DA receptors within the N.Acc. was significantly decreased by destruction of either cells and fibers within the SI/LPO region—using electrolytic lesions—or by destruction of only cells in this area—using the fiber-sparing neurotoxin ibotenic acid [47]. Apparently, the efferent circuit that translates forebrain DA receptor activation into activation of spinal motoneurons synapses first within this region of the ventral globus pallidus.

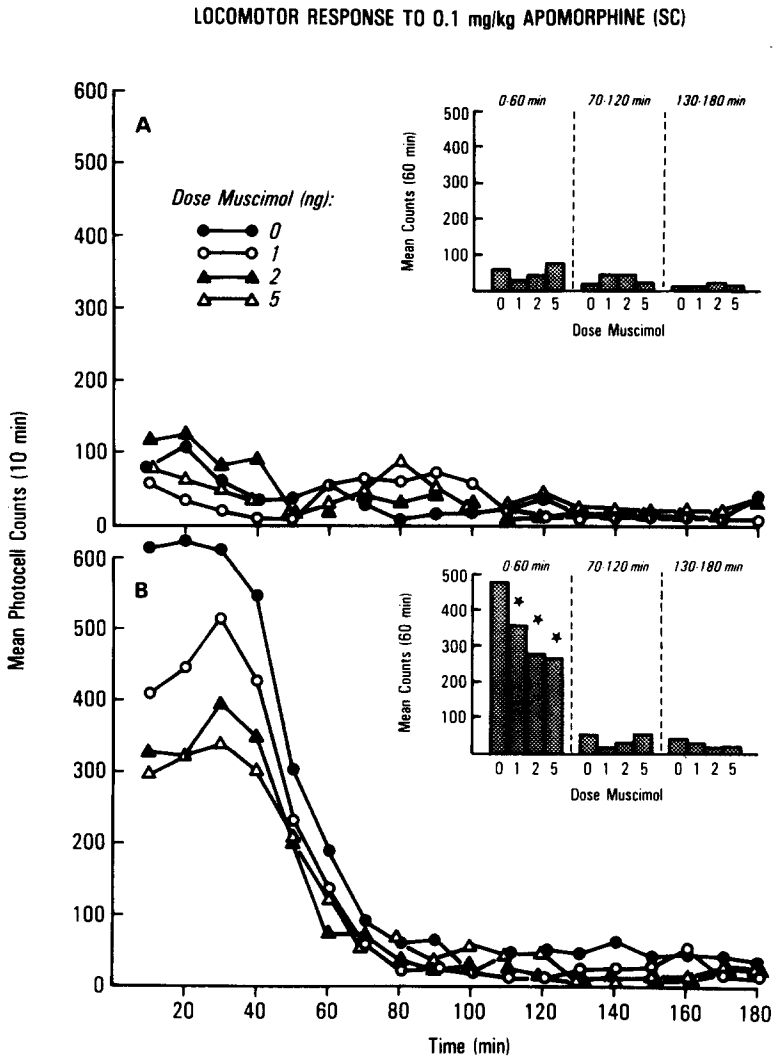

FIG. 10. Locomotor response to 0.1 mg/kg apomorphine SC in vehicle—(A) and 6OHDA-injected (B) rats following intracerebral injection of 0, 1, 2, or 5 ng muscimol into the SI/LPO regions. Insert histogram indicates total locomotor activity collapsed over 60 min intervals. *Significantly different from 0 dose muscimol ($p<0.05$, Newman-Keuls test following a significant dose × time interaction). Taken from [61].

NEUROCHEMICAL IDENTITY OF THE FIRST-ORDER EFFERENT PROJECTION FROM THE N.Acc. MEDIATING STIMULANT-INDUCED LOCOMOTION

Anatomical, pharmacological and neurochemical evidence has led to the hypothesis that gamma amino butyric acid (GABA)-containing fibers constitute the efferent projections involved in the locomotor response to activation of the N.Acc. First, while fibers from the N.Acc. containing GABA, enkephalin (ENK) and substance P innervate the SI/LPO [71], ENK-containing fibers do not appear to contribute to the 'supersensitive' locomotor response to apomorphine since high doses of naloxone do not alter this response [61]. Second, locomotor activation produced by direct application of DA into the N.Acc. is attenuated by infusion of GABA into the SI region [30]. While this DA-stimulated locomotion is distinct from the 'supersensitive' response that follows 6OHDA-induced denervation, the findings nonetheless suggest that the locomotor-activating properties of DA stimulation within the N.Acc. are opposed by GABAergic transmission within the SI/LPO. One parsimonious explanation for this finding is that DA acts within the N.Acc. to inhibit the release of GABA from terminals within the ventral pallidum, and that this inhibition results in increased locomotor activity.

A series of experiments were conducted to determine whether the locomotor-activating properties of 'supersensitive' DA activity within the N.Acc., as well as those of the stimulants amphetamine, heroin, caffeine, and CRF results from the interruption of GABAergic transmission within the VP. If such is the case, then stmulation of GABA receptors in the SI with a GABA agonist would be expected to oppose these drug actions.

The effects of injections of the GABA-agonist muscimol into the SI/LPO on apomorphine-stimulated locomotion are

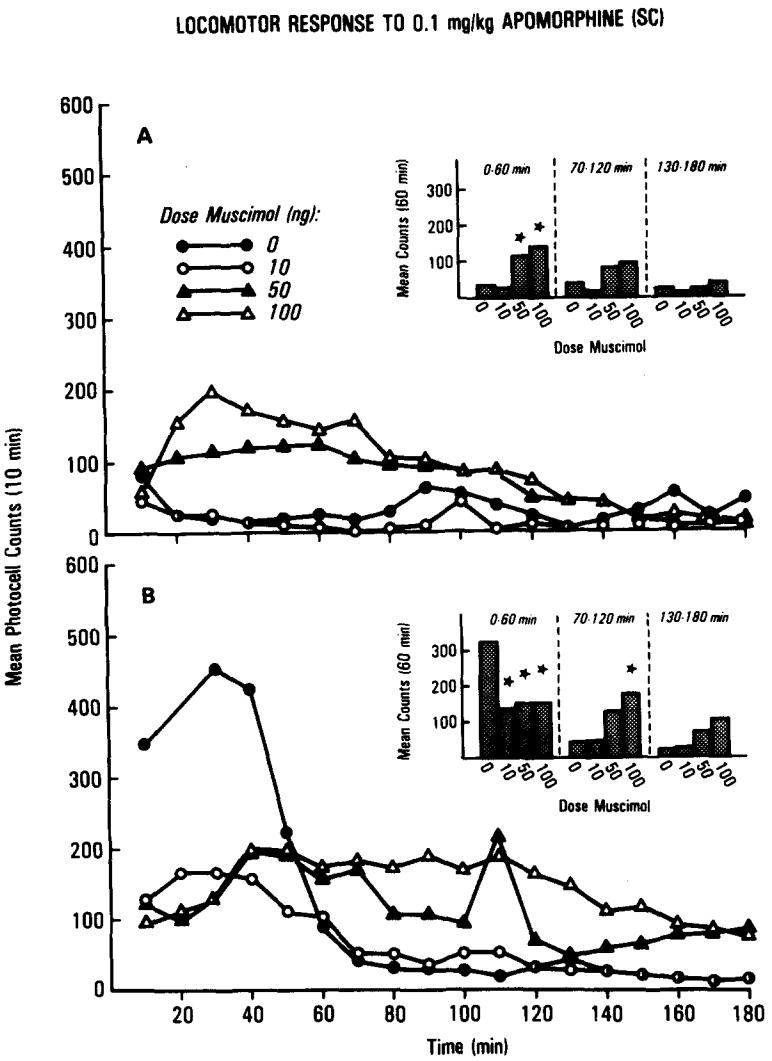

FIG. 11. Locomotor response to 0.1 mg/kg apomorphine SC in vehicle—(A) and 6OHDA-injected (B) rats following intracerebral injection of 0, 10, 25, or 50 ng muscimol into the SI/LPO region. Insert histogram indicates total locomotor activity collapsed oer 60 min intervals. *Significantly different from 0 dose muscimol ($p<0.05$, Newman-Keuls test following a significant dose × time interaction). Taken from [61].

seen in Figs. 9–11. Injection of low doses of muscimol decreased the locomotor response to apomorphine in 6OHDA-injected animals in a dose-dependent manner, but had no reliable effect on the locomotor response to apomorphine in vehicle-injected animals (Fig. 10). Higher doses of muscimol (>10 ng) produced an initial blockade of apomorphine-stimulated locomotion (Fig. 11), but in both 6OHDA- and vehicle-injected animals, these higher doses produced a prolonged increase in locomotor activity, that reached its maximum approximately 90 min following muscimol injection, at a point when the 'supersensitive' locomotor response in 6OHDA-injected rats had subsided.

The locomotor response to amphetamine, heroin, caffeine, and CRF following injection of saline or 10 ng muscimol into the SI/LPO are seen in Fig. 12. Within-subject comparison revealed that muscimol injections significantly decreased the locomotor response to amphetamine and heroin, but not to caffeine or CRF. Thus, injection of the GABA-agonist muscimol into the ventral pallidum differentially blocks the locomotor-activating properties of several stimulants: locomotion stimulated by apomorphine, amphetamine and heroin is antagonized by these muscimol injections, while locomotion stimulated by caffeine and CRF is not significantly opposed by these injections.

These results are consistent with growing evidence from behavioral investigations that a GABAergic projection from the N.Acc. into the VP provides the first link in the expression of mesolimbic DA stimulation. First, locomotor activation produced by injection of DA into the N.Acc. is disrupted by injection of GABA [30] or ethanolamine O-sulfate (EOS), an inhibitor of GABA metabolism [40], into the VP. Second, locomotor activation resulting from stimulation of supersensitive DA receptors within the N.Acc. is blocked by destruction of cells within the SI/LPO (see above) or by

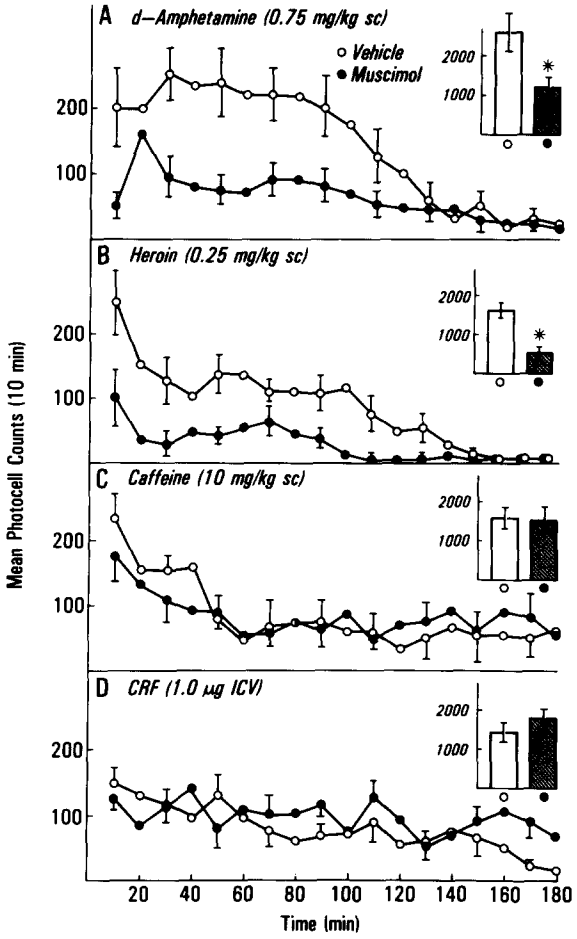

FIG. 12. Locomotor response to (A) 0.75 mg/kg d-amphetamine, (B) 0.25 mg/kg heroin, (C) 10 mg/kg caffeine and (D) 1.0 μg CRF in rats following injection of vehicle (○) or 10 ng muscimol (●) into the SI/LPO region. Ordinate refers to total photocell counts for each 10 min period of a 180 min test. Insets refer to total photocell counts (means±SEM) for 180 min. Taken from [65].

injection of the GABA agonist muscimol into the SI/LPO area [61].

The effects of muscimol injections into the SI/LPO on amphetamine-, caffeine- and CRF-induced locomotor activity are strikingly similar to those produced by depletion of DA within the N.Acc., i.e., amphetamine-, but not caffeine- or CRF-stimulated locomotion is blocked by these injections. In contrast, heroin-induced activation, which is not disrupted by depletion of N.Acc. DA, is clearly opposed by muscimol injections into the SI/LPO. We have suggested that these findings provide evidence for some differentiation in the neural mechanisms of psychostimulant action. Thus, amphetamine-activation may depend on two specific sequential neural events: an increase in DA transmission within the N.Acc., and a subsequent inhibition of GABAergic transmission within the ventral pallidum. Heroin-activation is known to result from its action on opiate receptors within the N.Acc., since heroin-stimulated activation is opposed by injection of the lipophobic opiate receptor antagonist methyl-naloxonium HCl directly into the N.Acc. [2]. Furthermore, the present findings suggest that the locomotor-activating properties of heroin, like those of amphetamine and apomorphine, might also depend on the inhibition of GABAergic transmission within the ventral pallidum. In contrast, the activating properties of caffeine and CRF may be mediated by other neural substrates.

The role of limbic-cortical afferent activation of this N.Acc.-ventral pallidal circuitry in locomotor activation in the rat has been addressed by Mogenson and Nielsen [31]. In this work, locomotor activation produced by infusion of carbachol directly into the dentate gyrus of the hippocampus was disrupted by infusion of the glutamate antagonist glutamate acid diethyl ester HCl (GDEE) into the N.Acc., or by infusion of GABA into the ventral pallidum. Interestingly, rat exploratory activation within a novel open-field environment was also inhibited by N.Acc. GDEE infusion or by ventral pallidal GABA infusion [32]. These findings suggest that 'endogenous' goal-oriented activation may depend on limbic-cortical activation of this N.Acc.-ventral pallidal circuit; furthermore, these results provide evidence that environment- and psychostimulant-induced behavioral activation in the rat share greatly overlapping neural substrates.

THE EFFECTS OF LESIONS OF SI/LPO EFFERENT FIELDS ON APOMORPHINE-STIMULATED LOCOMOTION

While it appears that the circuitry underlying the stimulant action of at least some psychostimulants involves a GABAergic projection from cells within the N.Acc. onto cells within the SI/LPO, it is still not clear how this circuitry translates drug effects at the level of the ventral pallidum into changes in spinal motoneuron activity. Efferent projections of the SI/LPO region have been described to include massive cholinergic projections which traverse rostrally through medial prefrontal cortex (MFC) and then spread caudally to innervate much of the neocortex [18], as well as fibers that innervate the dorsomedial thalamic nucleus (DMT) [72] and the region of the pedunculopontine nucleus (PPN) [59] which is thought to form a rat homologue to the mesencephalic locomotor region [16]. In order to examine which of these regions, if any, forms the critical link from the SI/LPO to lower motor circuitry responsible for translating the effects of forebrain DA receptor stimulation into behavioral activation, we studied the effects of lesions of the MFC, DMT and PPN on the 'supersensitive' locomotor response to apomorphine.

Despite massive lesion damage (Figs. 13–15), of the three regions tested, only lesions of the DMT produced a reliable decrease of 'supersensitive' apomorphine-stimulated locomotion (Fig. 18). Especially impressive was the fact that large lesions of the PPN (Fig. 17), an area believed to send monosynaptic projections to spinal motoneurons, in fact produced a tendency (non-significant) towards increased apomorphine-stimulated locomotion. Furthermore, while extensive damage to the DMT did decrease the 'supersensitive' response, the effect was not one of complete blockade. These results suggest that while some of the SI/LPO efferents critical to the behavioral expression of N.Acc. DA stimulation pass to or through the DMT, other separate critical terminal fields may exist. Clear from these findings, however, is that SI/LPO efferent projections to the areas of MFC and PPN described above do not serve as a critical substrate for N.Acc. DA-mediated locomotor activation.

GENERAL DISCUSSION

A crucial step in designing an experimental approach

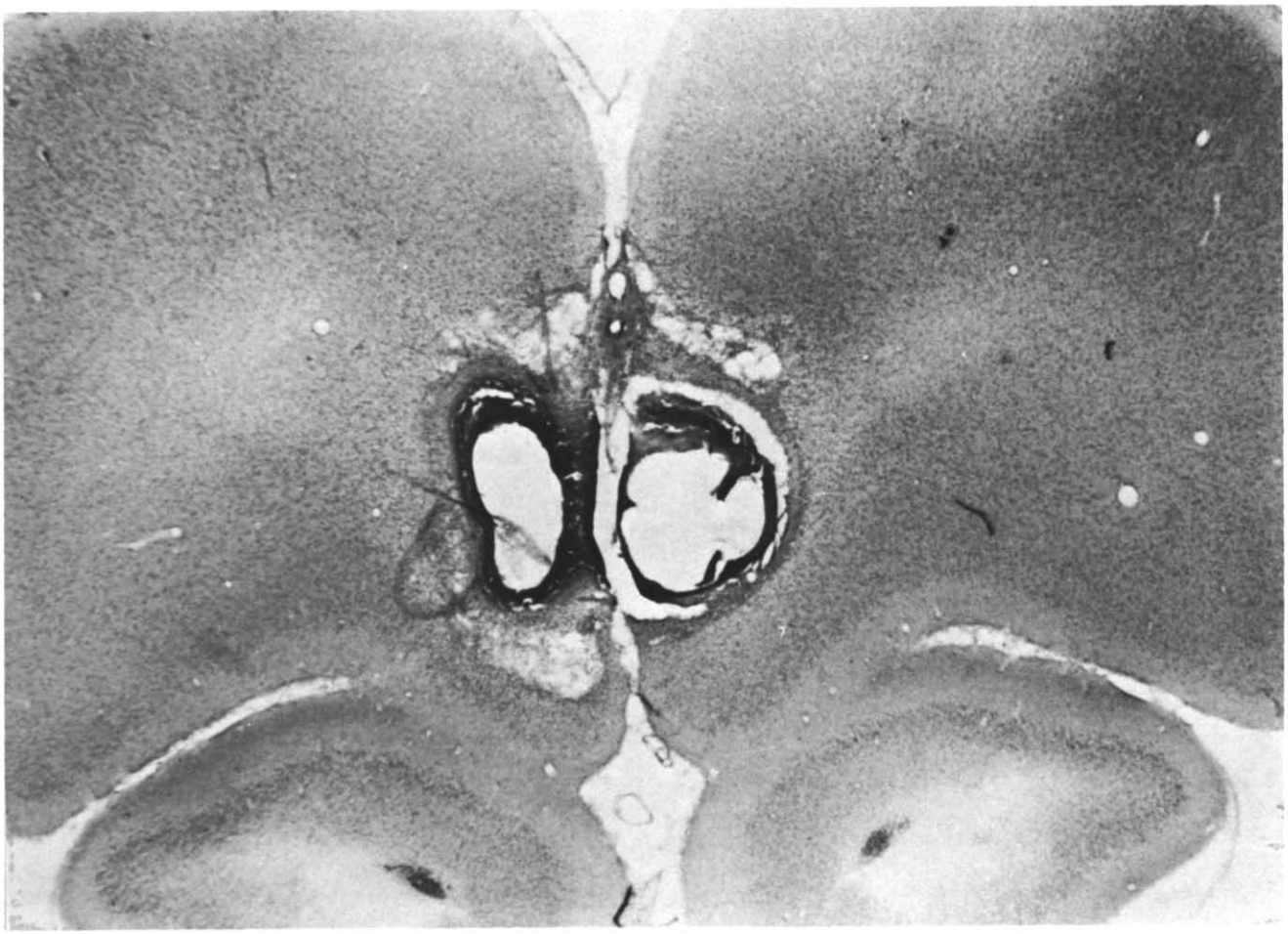

FIG. 13. A photomicrograph to show the typical extent of bilateral electrolytic damage to the medial frontal cortex. Nissl-stained frontal section.

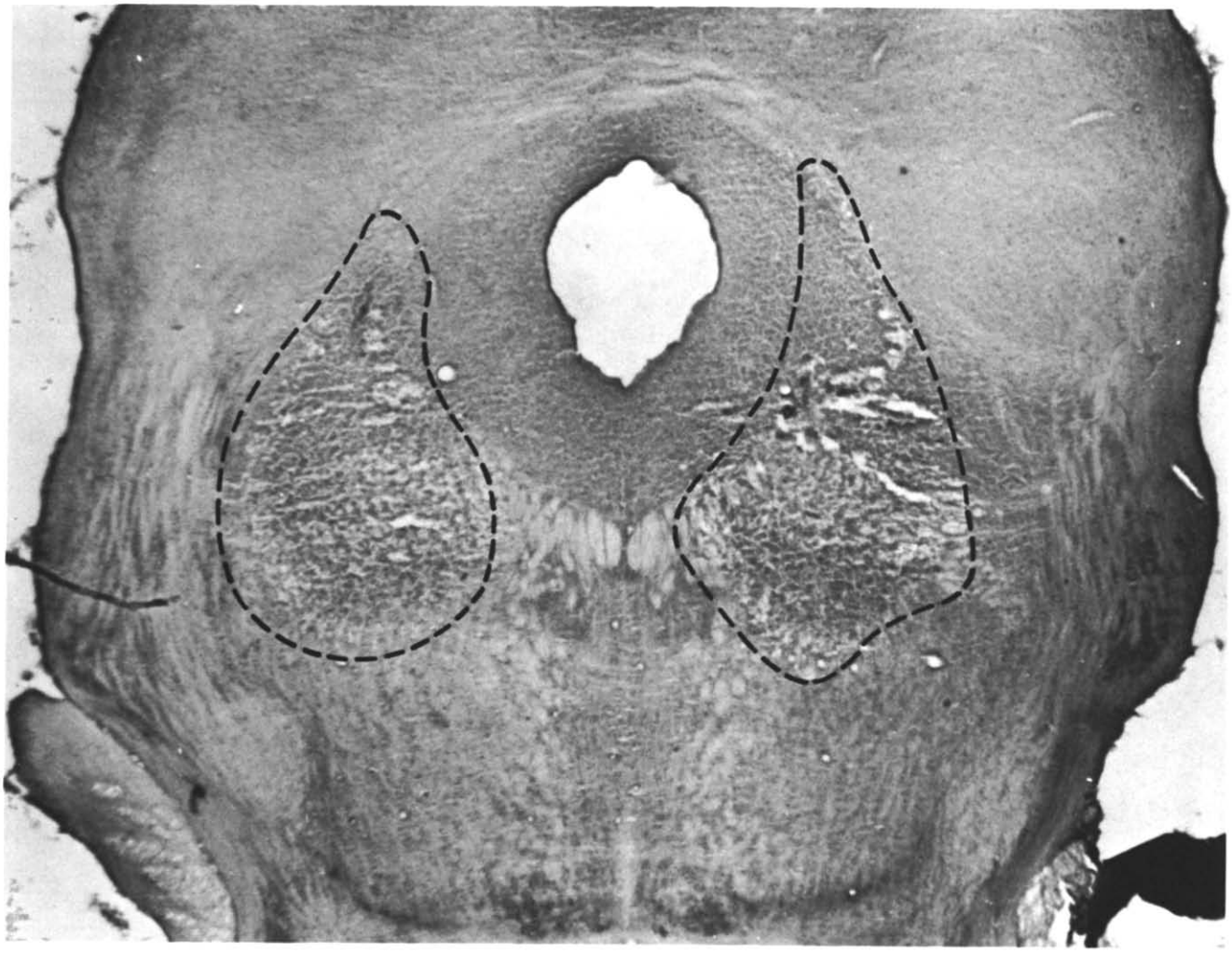

FIG. 14. A photomicrograph to show the typical extent of bilateral ibotenic acid lesions of the pedunculopontine nucleus (dashed lines). Nissl-stained frontal section.

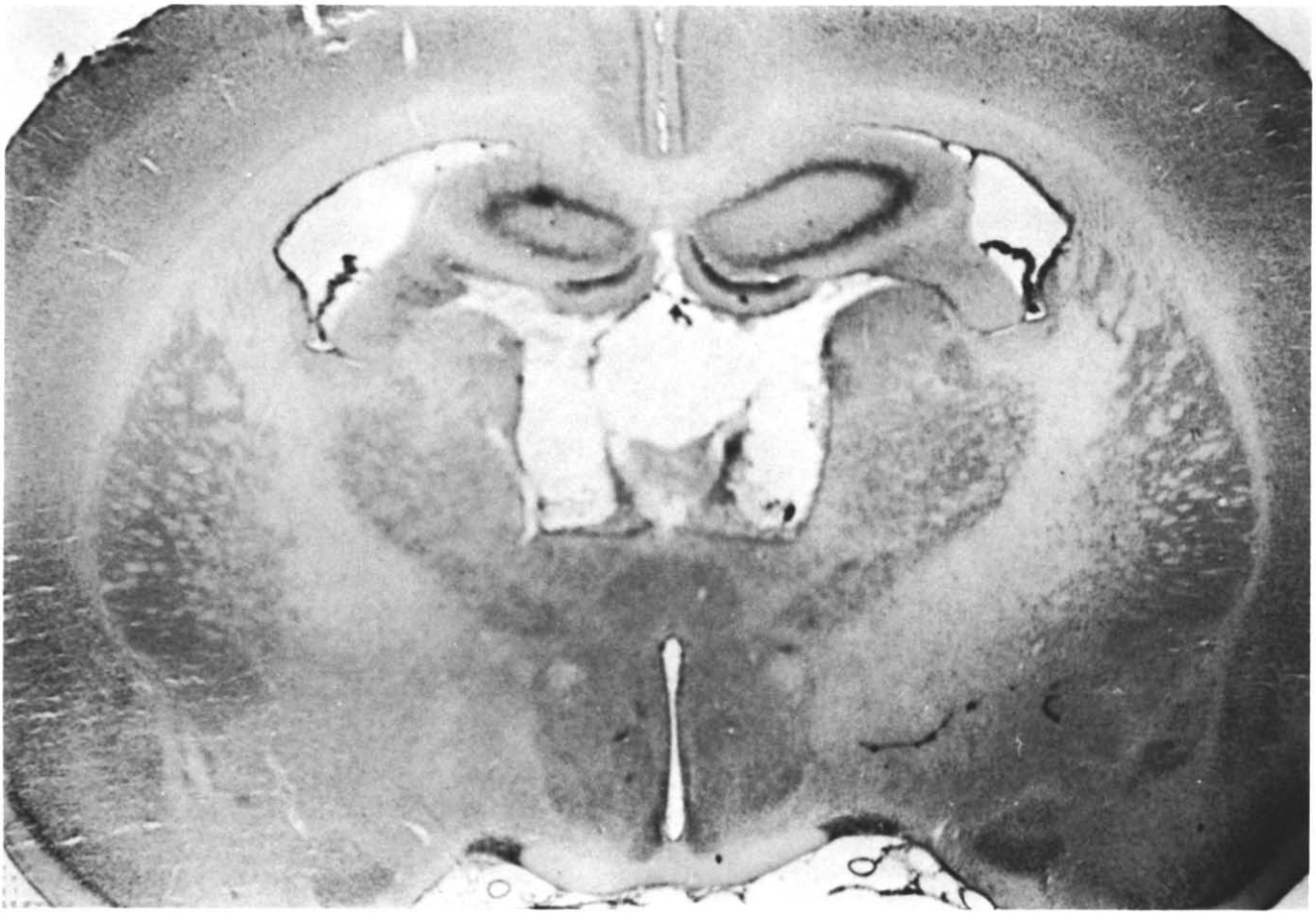

FIG. 15. A photomicrograph to show the typical extent of bilateral electrolytic damage to the dorsomedial nucleus of the thalamus. Nissl-stained frontal section.

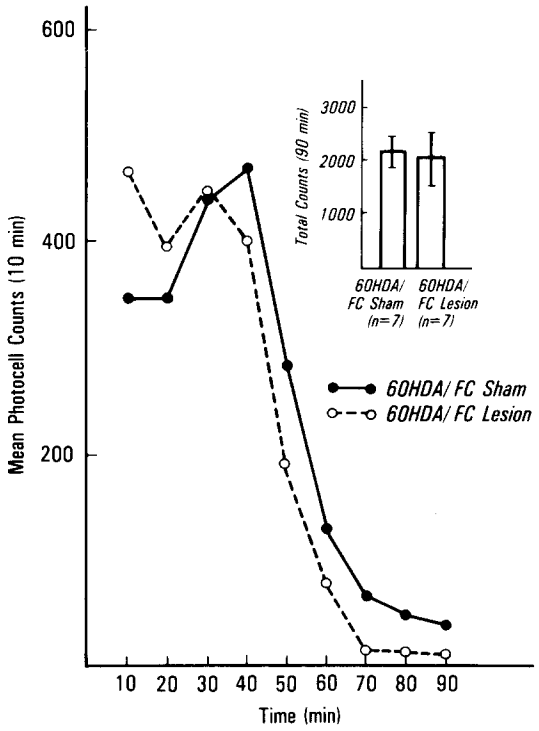

FIG. 16. Effects of electrolytic damage to the medial frontal cortex on the supersensitive locomotor response to apomorphine in rats following 6OHDA-induced denervation of the nucleus accumbens.

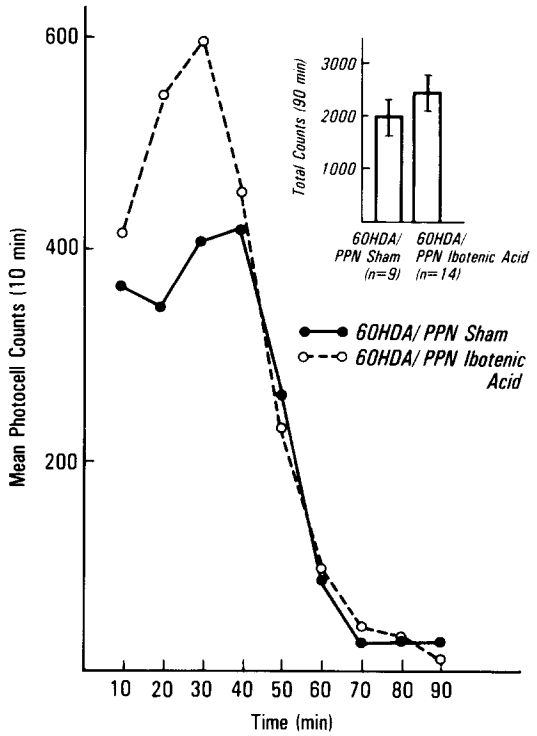

FIG. 17. Effects of ibotenic acid lesions of the pedunculopontine nucleus on the supersensitive locomotor response to apomorphine in rats following 6OHDA-induced denervation of the nucleus accumbens.

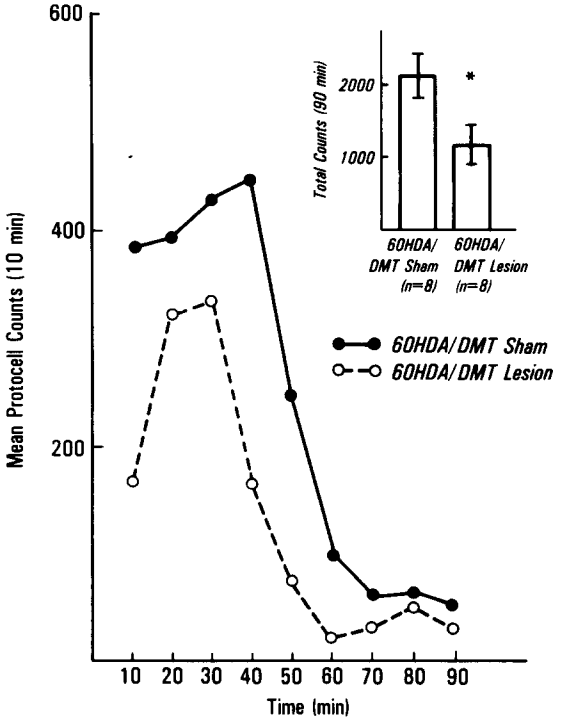

FIG. 18. Effects of electrolytic damage to the dorsomedial nucleus of the thalamus on the supersensitive locomotor response to apomorphine in rats following 6OHDA-induced denervation of the nucleus accumbens. *Significantly different from DMT sham group, two-way ANOVA with repeated measures on time, $p<0.05$.

aimed at understanding infrastructural organization of any biological system involves the choice of the measure that will monitor changes within that system. In the above set of experiments, the measure used to monitor stimulant-induced changes within the rat CNS was locomotor activity quantified in photocell activity cages. This assay, permits the study of pharmacological interactions between different classes of agonists and antagonists: since this measure is quantified and extremely sensitive, it is also possible to make simple predictions to test the internal consistencies of the measurements. For example, using this locomotor response it was clear that the effects of the DA agonist amphetamine were extremely sensitive to the DA receptor antagonist properties of FLU. Using this same approach, we have previously demonstrated that the effects of the opiate agonist heroin are extremely sensitive to the opiate receptor antagonist properties of naloxone [64]. Thus with these 'consistencies' as a reference source, it is possible to study the response of other stimulants to pharmacological antagonists, and to use this information to make inferences regarding the structural organization of the underlying neural circuitry.

A major advantage to this locomotor measure is that it permits an anatomical as well as pharmacological analysis of the neural substrates that are critical to the behavioral expression of stimulant action. Thus, through the use of electrolytic and fiber-sparing lesions, it is possible to demonstrate that the stimulant effects of N.Acc. DA activity are dependent on the integrity of cells within the ventral pallidal region including the SI and LPO. Through the use of local intracerebral injections, it was possible to determine that this

critical efferent projections is GABAergic, and thus assign both anatomical and neurochemical identity to this second link in the stimulant 'circuit.' While the third link in this 'output' circuitry remains in question, it is apparent from the results presented that fibers projecting to or through the DMT relay at least some of the pallidal information to lower motor circuitry (Fig. 12).

Using the measure of rat locomotor activity, we have previously speculated that a functional DA-opiate interaction might occur pre-synaptic to mesolimbic DA receptors within the N.Acc. [64]. This hypothesis is based on the finding [64] that naloxone antagonizes amphetamine-stimulated locomotion, which depends on pre-synaptic release of DA onto DA receptors within the N.Acc., however naloxone does not antagonize locomotion stimulated by the direct action of apomorphine on post-synaptic DA receptors following denervation of the N.Acc. [61]. Furthermore, it is possible to predict that this pre-synaptic opiate-DA interaction is independent from the central substrate for opiate stimulant properties, since heroin-stimulated locomotion is not antagonized by destruction of the DA-containing fibers innervating the N.Acc. [67].

Another advantage to the locomotor measure is that the index studied is a functional integrated response in a largely intact organism. Thus, while the experimenter can adopt a parametric approach to studying locomotion, the response changes can also be interpreted for their functional significance within the animals' behavioral repertoire. For example, the neural substrates for the behaviorally-activating properties of amphetamine, apomorphine and heroin appear to correlate highly with the regions believed to mediate the positively-reinforcing properties of these and related agents [3, 12, 28, 35, 38, 42, 43, 51, 52, 57, 66, 69].

The apparent overlap of neural substrates for DA- and opiate-stimulated behavioral activation and those for positive reinforcement leads to the intriguing suggestion that endogenous stimulation of N.Acc. DA and opiate transmission may normally underlie goal-oriented behavioral activation in the rat. It would be unlikely, however, that integrated behavioral displays could be initiated by simple increases and decreases in N.Acc. neurotransmission. It is conceivable, however, that initiation of goal-oriented behavior might follow activation of limbic-cortical glutamate afferents to the N.Acc., which have been shown by Nielsen and Mogenson [31,32] to be a critical substrate for rat exploratory behavior. Interactions between ascending N.Acc. DA afferent and intrinsic N.Acc. Spiny I circuitry have been proposed to provide a 'filter' function that limits the amount or nature of the cortical information that passes beyond the N.Acc. to activate lower motor circuitry [16]. Drugs that alter DA transmissions within the N.Acc. may modify these interactions, and thus change the pattern of information that reaches the ventral pallidum.

It is not yet known how ventral pallidal efferents activate goal-oriented behaviors, although it seems highly unlikely that the complexity of the motor patterns that underlie these behaviors could be supported exclusively at a subcortical level. It is more reasonable to presume that the ultimate 'final common pathway' for these behaviors must be the cortico-spinal pathway, which could provide somatotopic organization to the sequences of muscle activation. Activity within pallido-thalamic efferent fibers, and subsequently within thalamo-cortical fibers, might thus serve to direct limbic-cortical information to appropriate effector motor groups through the cortico-spinal pathway. According to the findings reviewed here, stimulation of these substrates can be achieved at many sites proximal to the 'final common pathway'—by carbachol infusions into the hippocampus [31], glutamate infusions into the N.Acc. [31], DA- [30] or opiate [2] activation of the N.Acc., or blockade of GABA transmission within the ventral pallidum [30]. The quantitative and qualitative contribution of each link in this neural circuit to the nature of the resulting behavioral activation is an important issue that awaits further systematic study.

One finding that emerges repeatedly through the series of experiments reviewed herein is that the stimulant properties of caffeine and CRF differ markedly from amphetamine, apomorphine and heroin in their pharmacological and anatomical profiles. Thus, locomotor activity stimulated by caffeine and CRF are not antagonized by selective blockade of receptors for DA or opiates, nor are they antagonized by the destruction of N.Acc. DA terminals or infusion of muscimol into the SI/LPO region. Apparently, these agents exert their stimulant properties through a set of neural elements very distinct from that responsible for the stimulant properties of sympathomimetics and opiates.

Aside from sharing a common insensitivity to the antagonistic effects of several pharmacological and surgical manipulations, caffeine and CRF produce behavioral changes that are strikingly similar. While amphetamine, apomorphine and heroin produced behavioral activation that consisted of an initial period (60–90 min) of very high levels of locomotion followed by relative sedation, caffeine- and CRF-induced locomotor activity is more prolonged, without an initial period of intense activation. In addition, while amphetamine-, apomorphine- and heroin-stimulated locomotion consists of apparently organized and continuous 'exploratory' movements—sniffing and rearing—caffeine and CRF-stimulate discontinuous bursts of locomotion, in which periods of relative quiescence are interspersed with periods of very high activity.

The similarity of the pharmacological and behavioral profiles of CRF- and caffeine-activation suggest that hypotheses as to a common mechanism of action should be considered. It is possible that this mechanism might share at least some common elements with the neural substrates of stress-induced behavioral activation, since CRF is known to be released into the CSF during periods of stress [6], and has been shown to enhance the stress response to novel environments [5,56]. Such a function might employ mechanisms of arousal not involved in the activation produced by the neural circuitry underlying amphetamine-, apomorphine- and heroin-stimulation locomotion.

In summary, the nucleus accumbens, located at the interface of the limbic projections from amygdala, hippocampus and cingulate cortex [14,18] and receiving extrapyramidal fibers from midbrain DA-containing nuclei [34] is well situated to form neural circuitry that mediates the behaviorally-activating properties of several stimulants. Efferent GABAergic fibers projecting from the nucleus accumbens to the ventral pallidum translate integrated limbic and extrapyramidal information to lower motor circuitry; some of this information appears to be carried by ventral pallidal efferent fibers projecting to the dorsomedial nucleus of the thalamus. A qualitatively and quantitatively distinct form of behavioral activation is produced by other stimulants, including caffeine and CRF, that act independent of these neural substrates. It seems very possible that activation of this circuitry by positive reinforcing environmental stimuli, through the release of endogenous DA or opiate compounds,

might contribute to activation crucial to motivated behavior. Indeed, several 'endogenously generated' appetitive behaviors are known to be blocked by disruption of this circuitry following destruction of N.Acc. DA terminals [41]. It is also tempting to speculate that pathological changes in activity within this system might disrupt normal reinforcement contingencies, and contribute to the affective components of both psychiatric and neurologic disease states.

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