monaural tone stimulation of either ear. A repeated-measures analysis of variance (*4*) showed the tone stimulus manipulations to have a significant effect ($F = 36.08$; d.f. = 3, 33; $P < .01$). The Newman-Keuls test for individual comparisons among means showed no significant difference between tone stimulation of the left ear alone or the right ear alone although each of these conditions was significantly different from the binaural and silent conditions ($P < .01$ in each case). The binaural condition, too, differed from the silent one ($P < .01$). The results of these statistical analyses coupled with the observation that every subject showed the trend illustrated (Fig. 1) demonstrates that the effects are reliable.

The finding that the tone stimulus presented monaurally produced almost twice as much inhibition as when presented binaurally is surprising since (i) in numerous loudness matching experiments (*5*), binaural acoustic signals are perceived to be slightly louder than the same signals presented monaurally, and (ii) previous investigations (*6*) have always revealed that the inhibitory effect is a function of the intensity of the inhibiting stimulus.

We do not know why monaural stimulation should produce such a strong inhibitory effect. The fact that the effect is not diminished when the tone stimulation is delivered to the contralateral ear argues that the responsible mechanisms must be central, but more research will be necessary before those mechanisms can be identified and understood. In the meantime, the effect enhances the potential of reflex inhibition as an audiometric technique.

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2. This device measures velocity rather than displacement, which is the customary measure of eyelid reflexes; however, the two indices covary over a wide range [E. Hilgard, *J. Gen. Psychol.* **8**, 85 (1933)].
3. Thresholds were determined by the method of R. Carhart and J. Berger [*J. Speech Hear. Disord.* **24**, 330 (1959)], in which the test tone is presented repeatedly in steps of increasing loudness until it becomes audible. Loudness matching was accomplished by alternating between a 70-db SL tone in the better ear and a tone of variable intensity in the less sensitive ear until the subject indicated that the variable tone was of equal loudness. Tones in these procedures were adjusted in 2-db steps rather than the 5-db increments common in clinical practice. To insure that stimuli were of equal intensity in the monaural and binaural conditions, earphones were calibrated under both conditions with a General Radio ANSI Type 1 coupler, P-7 microphone, and 1561-A sound level meter.
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d-Amphetamine–Induced Inhibition of Central Dopaminergic Neurons: Mediation by a Striato-Nigral Feedback Pathway

Abstract. *Lesions of the striato-nigral pathway (that is, crus cerebri or vicinity of the tail of the caudate nucleus) markedly attenuate depressant effects of intravenous* d-*amphetamine on central dopaminergic cell activity. These results, coupled with previous data showing that microiontophoretic application of* d-*amphetamine directly onto dopaminergic cells does not produce significant slowing, provide direct support for the hypothesis that the depressant effect of* d-*amphetamine on these cells is mediated through a striato-nigral neuronal feedback loop.*

In behaviorally effective doses, the primary action of *d*-amphetamine (*d*-AMPH) in the central nervous system appears to be that of increasing the release and blocking the reuptake of the catecholamines (*1*). In 1967, Corrodi *et al.* (*2*), on the basis of biochemical evidence, suggested that some of the effects of *d*-AMPH on dopamine (DA) metabolism might be secondary to a decrease in the firing rate of dopaminergic neurons. They further suggested that this decrease of DA neuronal activity might be due to the ability of *d*-AMPH to cause, indirectly, an increase in the stimulation of postsynaptic DA receptors, leading to a compensatory decrease in the firing rate of DA neurons mediated by a neuronal feedback pathway. Previously, we demonstrated that low doses of *d*-AMPH (0.25 to 2.0 mg/kg, intravenously) cause a marked depression of DA neuronal activity in the zona compacta of the substantia nigra (A9) (Fig. 1) and the ventral tegmental area (A10) (*3*). Furthermore, we provided evidence that this depressant effect of *d*-AMPH on A9 neurons is primarily an indirect action of *d*-AMPH, which is mediated by a neuronal feedback pathway (*4*, *5*). Thus we showed that, whereas postsynaptic cells in the caudate nucleus are very sensitive to microiontophoretically applied amphetamine as well as DA (*6*), microiontophoresis of *d*-AMPH directly onto A9 DA neurons fails to produce any depression of activity at low ejection currents (*5*) [at high ejection currents

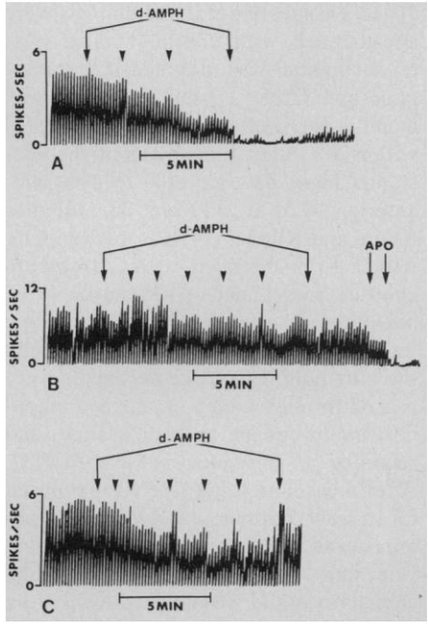

Fig. 1. (A) Typical *d*-AMPH–induced depression of the activity of a zona compacta (A9) dopaminergic neuron in an unlesioned animal. *d*-Amphetamine, in a total dose of 1.6 mg/kg (0.2, 0.2, 0.4, and 0.8 mg/kg, at arrows), temporarily stopped this cell. Recovery was very slow. Control lesioned animals yielded identical results. (B) Effect of *d*-AMPH and apomorphine (*APO*) on dopaminergic cell activity after lesion of the ipsilateral crus cerebri. *d*-Amphetamine, in a total dose of 25.6 mg (0.4, 0.4, 0.8, 1.6, 3.2, 6.4, and 12.8 mg/kg), produced a minimal slowing of this cell. In contrast, apomorphine (0.05 and 0.05 mg/kg) produced its usual depressant effect despite the presence of the lesion. (C) Effect of *d*-AMPH on A9 dopaminergic cell activity after an ipsilateral lesion of the tail of the caudate nucleus. *d*-Amphetamine, in a total dose of 25.6 mg/kg, produced a temporary 30 percent decrease in neuronal activity. All drugs were administered intravenously. Drug dosages are given in terms of the weight of their salts.

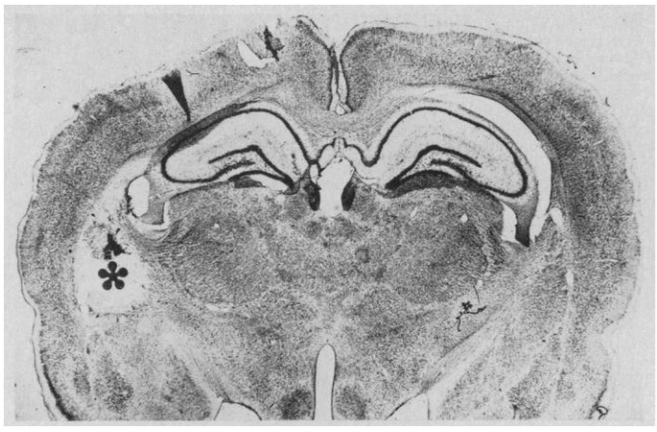

Fig. 2. Bright-field photomicrograph illustrating the area typically destroyed by a radio-frequency lesion of the tail of the caudate nucleus. The asterisk marks the site of the lesion.

these cells are markedly depressed because of a local anesthetic effect of *d*-AMPH (*7*)] and transection of the brain between the caudate nucleus and substantia nigra greatly attenuates the depressant effect of intravenous *d*-AMPH even at doses 14 times that necessary to markedly depress these cells in an unlesioned animal (*5*). In contrast to the lack of effect of microiontophoretically applied *d*-AMPH on A9 DA neurons, both DA and apomorphine markedly depressed these cells when applied in the same manner (*8*). This depression was blocked by intravenous haloperidol (a DA receptor blocker) (0.25 mg/kg). From these experiments we concluded that DA receptors were present on the dendrites or cell bodies of DA neurons in the substantia nigra, which might play a significant role in the mediation of the pharmacological effects of some drugs affecting the DA system (*7, 9*). On the other hand, our combined lesion and microiontophoretic data suggested that the behavioral, biochemical, and electrophysiological effects of *d*-AMPH could not have been mediated through an action at this site, but were mediated indirectly through a postsynaptic activation of DA receptors, leading to a decrease in DA cell firing rate mediated by a neuronal feedback pathway.

However, a recent study in which the effects of *d*-AMPH on the activity of single and multiple units in the caudate-putamen and substantia nigra were determined by direct infusion of *d*-AMPH into these structures has suggested that the effect of *d*-AMPH on DA cell activity is not mediated by a neuronal feedback pathway, but rather through an ability of *d*-AMPH to increase and block reuptake of DA at DA dendro-dendritic synapses in the substantia nigra (*10*). We report here further evidence that a feedback pathway is the main mechanism by which *d*-AMPH, when administered intravenously in behaviorally relevant doses, induces the slowing of A9 DA neurons.

Using the horseradish peroxidase technique for the retrograde mapping of afferent connections in the brain (*11*), we recently identified several inputs to the rat substantia nigra, including projections from the prefrontal cortex, dorsal raphe nucleus, globus pallidus, head of the caudate nucleus (except for medial central core), and tail of the caudate nucleus (*12*). Several of these could be links in neuronal feedback pathways to the substantia nigra which might mediate the depressant effects of *d*-AMPH on DA zona compacta neurons. In addition, confirming the work of others (*13*), we determined that many of the rostral afferent projections travel through the crus cerebri to reach the substantia nigra. If the depressant effects of *d*-AMPH on A9 DA neurons is mediated by a neuronal feedback pathway, then discrete lesions of one or more of these areas should markedly attenuate the depressant effect of *d*-AMPH on these cells.

Male Sprague-Dawley rats weighing 240 to 300 g were used. The animals were anesthetized with chloral hydrate. After the animal was mounted in a stereotaxic apparatus, a 3-mm burr hole was made in the skull at varying coordinates within the outer dimensions of the substantia nigra [lateral, 1200 to 2400 μm; anterior, 1270 to 2420 μm, according to König and Klippel (*14*)]. A micropipette with a 1-μm tip filled with 2*M* sodium chloride (impedance at 1000 hertz, 4 to 8 megohms) saturated with a green dye (fast green) was then lowered through the burr hole. Electrode potentials were passed through a high-impedance amplifier, monitored on an oscilloscope, and recorded as previously described (*15*). After a baseline firing rate was recorded for at least 5 minutes, *d*-AMPH was administered intravenously through a tail vein. Only one cell was studied in each animal to avoid possible residual drug effects. Body temperature was monitored and maintained at 36° to 37°C. At the end of each experiment the site of the electrode tip was marked by iontophoretic ejection of fast green (*16*). After perfusion with 5 percent glutaraldehyde in saline, 50-μm serial frozen sections of each brain were cut and stained with cresyl violet. A fast green spot approximately 40 μm in diameter marked each recording site. In one series of experiments (N = 8) discrete lesions of the crus cerebri were made using a stereotaxically placed fine wire retractable knife (anterior, 3180 μm). Great care was taken not to damage the adjacent median forebrain bundle containing the DA nigro-striatal fibers. In other experiments discrete radio-frequency lesions were used to destroy the tail of the caudate nucleus and a small portion of the lateral border of the internal capsule (N = 4) (Fig. 2). Numerous control lesions (N = 24) were also made. These included destruction of the median forebrain bundle, entire head of the caudate nucleus, globus pallidus, entire ipsilateral cerebral cortex, amygdala, and claustrum, as well as transection of the brain posterior to the substantia nigra, and transection of the dorsal half of the brain and the contralateral side of the brain in the same area where the lesions of the crus cerebri were placed. Immediately after each lesion was made, the ability of *d*-AMPH to depress A9 DA cell activity was determined. We had previously characterized A9 DA neurons electrophysiologically using combined single unit recording and fluorescence histochemical techniques (*3, 17*). The rate and firing pattern of A9 cells is specific for these neurons in that no other cells in the area have the same characteristics. They cannot be confused with non-DA zona reticulata cells because these cells spontaneously fire at much faster rates (15 to 45 spikes per second) and often have a regular rhythm. In each of the experiments reported, electrical activity of only one A9 cell was recorded.

After lesions of either the crus cerebri or the tail of the caudate, A9 cells were firing faster than in control animals. In every case in which the crus cerebri or the tail of the caudate nucleus and lateral border of the internal capsule was destroyed, the depressant effect of intravenous *d*-AMPH was markedly attenuated. Doses of *d*-AMPH up to 25.6 mg/kg (a lethal dose) failed to produce more than a 50 percent decrease in DA cell activity (Fig. 1). However, apomorphine (N = 6), a direct DA receptor stimulator, continued to exert its usual depressant effect (0.05 to 0.1 mg/kg, intra-

venously) (Fig. 1) and this effect was readily reversed by intravenous haloperidol (0.1 mg/kg). In contrast, none of the control lesions diminished the ability of *d*-AMPH to markedly depress these cells at low doses (Fig. 1A). Destruction of the median forebrain bundle, which contains the ascending axons of A9 cells, led to an increase in their spontaneous rate but did not prevent *d*-AMPH–induced depression of these cells.

Thus discrete lesions in the crus cerebri and the vicinity of the tail of the caudate nucleus effectively blocked the depressant effects of *d*-AMPH on DA cell firing rate even when it was given in nearly lethal doses. These findings, coupled with the relatively weak effect of microiontophoretically administered *d*-AMPH on DA cell activity (*5*), strongly suggest that the depressant effect of *d*-AMPH on these cells is mediated predominantly by a neuronal feedback pathway rather than as a direct or indirect action on DA receptors located on A9 DA cell bodies or dendrites. The finding that such lesions cause an increase in the spontaneous rate of firing of A9 cells suggests that they have been freed from an inhibitory input. The degree of block induced by the lesions varied from almost total to 50 percent. When *d*-AMPH did induce a partial depression of A9 cell activity in lesioned animals, it did so usually at a relatively low dose (0.8 to 1.6 mg/kg). The depression seen under these circumstances may be due either to an incomplete lesion that missed some feedback pathway fibers or to an action of *d*-AMPH either directly or indirectly on dopaminergic autoreceptors on the dendrites of A9 cells, as suggested by Groves *et al.* (*10*). In animals with chronic lesions of the crus cerebri, preliminary studies showed, in a few cases, some return of the ability of *d*-AMPH to depress A9 cells. The mechanism responsible for this return is unclear, but it could be due to the development of supersensitivity in some portion of the feedback pathway or some other compensatory mechanism.

Although in this study we have considered mainly feedback effects in the nigrostriatal system, the presence of DA-sensitive autoreceptors on DA neurons appears well established (*8, 18*) and it is intriguing to speculate on the possible physiological significance of DA receptors on dopamine cell bodies or dendrites. If present, dendro-dendritic synapses between DA neurons would imply a physiological role for DA receptors at such junctions. The published evidence for such synapses is, as yet, not conclusive (*19*). The pharmacological significance of DA autoreceptors appears much clearer. Directly acting DA receptor agonists and antagonists have been shown to interact at these receptors, thereby inducing changes in the activity of DA neurons (*7, 8*). At least one behavioral effect has been attributed to an action of a drug at this site (*20*). As we suggested previously, when considering the mechanism and site of action of a drug that affects the DA system, one must now take into consideration its effects on presynaptic receptors or autoreceptors as well as its postsynaptic actions. However, in the specific case of *d*-AMPH it would appear that in a pharmacological dose its ability to induce depression of A9 DA neurons is mediated largely through its effect on a neuronal feedback pathway whose cells of origin are in the caudate nucleus and whose axons travel by way of the crus cerebri to the substantia nigra.

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Stable and Plastic Unit Discharge Patterns during Behavioral Generalization

Abstract. *A movable microelectrode was implanted in adult cats trained to respond differentially to two different frequencies of light flicker. Unit responses were recorded along cortical and thalamic trajectories. The late components of the poststimulus response of 29 percent of the cells examined showed statistically significant differences when data from different behavioral outcomes to the same neutral generalization stimulus were compared.*

Numerous reports from human as well as animal experiments have established that the same physical stimulus can elicit diverse evoked response waveshapes. While the actual features of the stimulus seem to be represented by exogenous, stimulus-bound components of short latency, these waveshapes show differences usually manifested in relatively long latency components. Such phenomena have been observed in situations where the same stimulus is interpreted in different ways (*1*), or where the information delivered by the stimulus depends upon the features considered relevant by the subject, the relative probability of the stimulus, or its relationship to other events (*2*). The endogenous nature of these processes is most unequivocally established by potentials which appear when an expected event fails to occur (*3*).

In some of these studies, the different endogenous processes were accurate fac-