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Habenula Lesions Decrease the Responsiveness of Dorsal Raphe Serotonin Neurons to Cocaine[1]

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PARIS, J. M. AND K. A. CUNNINGHAM. *Habenula lesions decrease the responsiveness of dorsal raphe serotonin neurons to cocaine.* PHARMACOL BIOCHEM BEHAV **49**(3) 555-560, 1994.—The median and dorsal (MR and DR) raphe nuclei are the origin of serotonin (5-HT)-containing neurons that innervate the forebrain. Neurons originating in the medial and lateral habenula provide an extensive afferent input to the midbrain that could serve as a negative feedback circuit. The present study was undertaken to establish whether intact habenula nuclei are required to observe the depressant effects of cocaine on the neural activity of 5-HT somata in the DR. To this end, the spontaneous activity of DR 5-HT neurons was assessed in male rats that had previously received bilateral radiofrequency lesions of the habenula complex either 1-4 h (short term) or 7 days (long term) prior to extracellular recordings of single 5-HT neurons of the DR. In rats with short-term lesions, the inhibitory response to cocaine was significantly attenuated. The mean dose to inhibit activity by 50% (ID_{50}) was increased from 0.68 mg/kg in controls to 2.5 mg/kg in lesioned rats. Short-term habenula lesions also significantly decreased the numbers (but not the firing rates) of 5-HT neurons encountered in the DR. In contrast, the dose-response to cocaine as well as the numbers and firing rates of 5-HT neurons found in rats with long-term habenula lesions did not differ from controls. These results suggest that the inhibitory effects of cocaine on DR 5-HT neuronal activity depend in part on the ability of cocaine to affect habenula control of raphe 5-HT function.

Cocaine Habenula Serotonin (5-HT) Dorsal raphe Electrophysiology Single-unit recording Rat

SEROTONIN (5-hydroxytryptamine; 5-HT) neurons of the dorsal (DR) and median (MR) raphe provide the major source of 5-HT innervation to forebrain (55). These neurons are regulated locally by impulse-regulating 5-HT_{1A} somatodendritic autoreceptors (23,54). Raphe 5-HT cells are also regulated intrinsically via γ-aminobutyric acid (GABA)-containing interneurons and extrinsically by at least three major afferent pathways: 1) an excitatory amino acid pathway from the frontal cortex (24); 2) a noradrenergic component from the locus coeruleus and subcoeruleus (6,7,48); and 3) an extensive input arising in the habenula nuclei (3,22,38). The habenulo-raphe input is particularly interesting because the habenula complex is positioned as a primary link between the limbic forebrain (e.g., nucleus accumbens, substantia innominata, pallidum) and the midbrain (58). In fact, midbrain raphe 5-HT function is influenced by an extensive input from the habenula. For example, stimulation of the lateral habenula results in depression of spontaneously active 5-HT neurons of DR and MR nuclei (56,57,61). As might be predicted, lateral habenula stimulation also decreased [^{3}H]5-HT release in the raphe, substantia nigra, and caudate of cats (47); this effect was blocked by lesions of the fasciculus retroflexus that carry the habenulo-raphe fibers (26). This habenular circuit, which controls DR 5-HT function, appears to be comprised of both a monosynaptic GABAergic pathway (39,56,57,61) and a polysynaptic pathway in which GABA as well as the tachykinin substance P (34,47) and/or an excitatory amino acid (24-26) serves as a component.

The psychostimulant cocaine, which elicits many of its behavioral effects through an enhancement of dopamine (DA) neurotransmission (64), also inhibits the reuptake of 5-HT (49) and elicits a potent, rapid, and reversible inhibition of

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firing of 5-HT DR neurons (14,16,43). Pharmacological studies support the hypothesis that this inhibitory effect of cocaine is due to blockade of 5-HT reuptake at transporters in the raphe (19) and a consequent enhancement of 5-HT available for interaction at raphe impulse-modulating 5-HT_{1A} autoreceptors (14,16,43). However, the prominent actions of cocaine in limbic forebrain regions (10,13,21,59,62) and the hypothesized role for habenular control of 5-HT DR function (above) suggested that, in addition to its direct actions in the raphe, cocaine could also affect raphe function via an influence on forebrain–habenula–raphe feedback pathways. In support of this possibility, acute cocaine administration has been associated with a significant depression of local cerebral glucose utilization in the habenula (29,30,44,45), and continuous cocaine administration reportedly has a neurotoxic effect on habenula neurons (18). The present study was undertaken to test whether intact habenula nuclei are required for the depressant effects of cocaine on 5-HT raphe firing.

METHOD

Young, adult male Sprague–Dawley rats (185–225 g) were purchased from SASCO, Inc. (Houston, TX) and maintained in groups of 3–4/cage in a temperature-, humidity- and light-controlled environment with food and water freely available (lights on 0600 h; lights off 1800 h).

Habenula Lesion Procedures

Short-term (1–4-h) habenula lesions. Rats were anesthetized with urethane (1.5 g/kg, IP; Sigma Chemical Co., St. Louis, MO) and mounted in a stereotaxic holder. An electrode (Radionics type TCZ) with a tip diameter of 0.25 mm and a tip exposure of 0.25 mm was lowered bilaterally to the habenula (AP: β −3.3 mm; ML: ±0.6 mm lateral to the midline; DV: −4.5 mm from the brain surface) (41) and lesions were made using a Radionics radiofrequency lesion maker (RFG-4A) with current (3–5 mA) applied for 90 s per side to maintain a tip temperature between 55–65°. Control animals underwent identical surgical procedures except that the electrode was positioned 1 mm above the habenula and current was not delivered. One to 4 h following completion of the lesion protocol, electrophysiological recordings were conducted (below).

Long-term (7-day) habenula lesions. Rats were anesthetized with sodium pentobarbital (60 mg/kg, IP), treated with atropine methyl bromide (0.4 mg/kg, IP), sodium ampicillin (20 mg/kg, IM), and secured in a stereotaxic frame. Lesions were made as described above. The wound was closed and the animal was allowed to recover on a heating pad; upon full recovery, the rat was housed individually in its home cage. Animals were prepared for single-unit recording 7 days following surgery (below). Control animals underwent identical surgical procedures except that no current was delivered.

Electrophysiological Procedures

Single-unit recording. Following short- or long-term sham or lesion surgery, rats were prepared for single-unit recordings of DR 5-HT neurons. Animals were anesthetized with urethane (1.5 g/kg, IP) and mounted in a stereotaxic frame. Single glass electrodes containing 1% Fast Green in 2 M NaCl (5–8 MΩ) were lowered through a burr hole drilled in the skull overlying the DR (0.4–1.2 mm anterior to the interaural plane) (41). Extracellularly recorded spike activity was passed through a high-input impedance amplifier, filtered, and displayed on an on-line oscilloscope; amplified units were monitored by Brainwave Discovery (Broomfield, CO) and all discriminations were performed by the software that describes and classifies each spike by 10 values (e.g., peak and valley amplitude, time of peak or valley amplitude, etc.). A frequency histogram was graphically recorded (Gould 220) in 10-s intervals from the analog output. Serotonin neurons encountered 4.5–6.5 mm ventral to the surface of the brain were identified on-line by characteristic action potentials (1–2 ms duration, ± spikes) and regular, slow firing rates (0.2–2.5 Hz) (4,14–16). Non-5-HT neurons were also encountered between 4.5 and 6.5 mm ventral to the surface of the brain. These non-5-HT neurons exhibited short duration spikes (<1 ms duration, ± waveform), irregular rhythms, and fast firing rates (>2.5 Hz) (4).

Population sampling. For population cell counts, the electrode was passed vertically three times through a stereotaxically defined block of DR tissue (0.4, 0.8, 1.2 mm anterior to the interaural plane; 0.0 mm lateral to midline). Each cell encountered was recorded for 3–5 min during which basal firing was determined. The number of cells/pass, firing rates, and interspike intervals were compared between sham and lesioned animals using Student's t-test.

Intravenous cocaine injection. In sham or lesioned rats, each 5-HT neuron was recorded for at least 3–5 min prior to drug injections to establish stable basal firing rates. (±)Cocaine HCl (0.125–8.0 mg/kg; Sigma) was dissolved in deionized water and administered intravenously (IV) through a tail vein catheter at 2-min intervals such that each dose doubled the previously administered dose. The percent change from the baseline rate was calculated for each cumulative dose using the mean firing rate during the 2-min epoch between doses. A two-way analysis of covariance for repeated measures was used to determine whether the responsiveness to cocaine differed in sham vs. lesion animals; this analysis was used to assess whether differences between treatment groups were related to variations in the baseline firing rates (covariate) of the sampled cells (63). Subsequent planned comparisons between specific pairs of means were conducted using a Student's t-test. The dose of systemic cocaine predicted to inhibit the baseline firing rate by 50% (ID_{50}) was also determined for each animal

TABLE 1

POPULATION STUDIES: EFFECTS OF SHORT-TERM (1-4 HR) HABENULA LESIONS ON DR 5-HT NEURONS

	Sham (N = 5)	Lesion (N = 6)
No. cells/3 passes	15.0 ± 1.4	9.0 ± 1.0*
No. cells/pass	5.0 ± 0.5	3.0 ± 0.3*
No. 5-HT cells	3.6 ± 0.3	1.9 ± 0.5*
No. non-5-HT cells	1.4 ± 0.4	1.1 ± 0.2
Firing rate (spikes/10 s)	30.1 ± 5.1	40.7 ± 8.0
5-HT cells	11.2 ± 0.95	11.5 ± 0.98
Non-5-HT cells	78.5 ± 15.4	90.4 ± 16.5
Interspike interval (ms)	628 ± 48	499 ± 51

Data are represented as mean ± SEM. 5-HT cells are defined as those cells identified by characteristic action potentials (1–2 ms duration, +/− waveform) and regular, slow firing rates (< 2.5 Hz). Non-5-HT cells are identified by short duration spikes (< 1 ms duration, +/− waveform), irregular rhythms, and fast firing rates (> 2.5 Hz).

*$p < 0.05$ vs. sham controls.

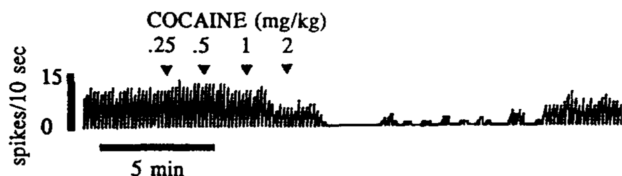
TABLE 2

POPULATION STUDIES: EFFECTS OF LONG-TERM (7-DAY) HABENULA LESIONS ON DR 5-HT NEURONS

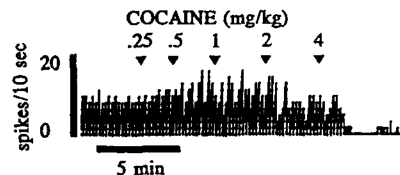
	Sham (N = 4)	Lesion (N = 5)
No. cells/3 passes	11.2 ± 1.4	11.0 ± 3.5
No. cells/pass	3.7 ± 0.5	3.7 ± 0.6
No. 5-HT cells	3.0 ± 0.4	3.1 ± 0.8
No. non-5-HT cells	0.7 ± 0.2	0.6 ± 0.4
Firing rate (spikes/10 s)	21.9 ± 2.8	26.1 ± 5.7
5-HT cells	12.0 ± 1.7	14.0 ± 0.9
Non-5-HT cells	62.7 ± 11.6	51.4 ± 4.9
Interspike interval (ms)	513 ± 153	506 ± 79

See Table 1 footnote for details.

SHAM



1-4 HRS POST-LESION



7 DAYS POST-LESION

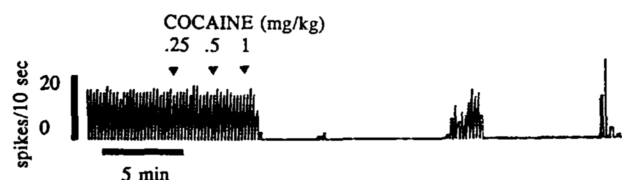


FIG. 1. The neuronal response of 5-HT DR cells to intravenous cocaine in habenula-lesioned rats. Cocaine elicited a reversible inhibition of the activity of a 5-HT DR neuron from a rat with a short-term (1-4-h) sham lesion (top) with a dose to completely inhibit activity of 2 mg/kg. In a 5-HT neurons recorded from a rat with a short-term (1-4-h) habenula lesion (middle), the ability of cocaine to suppress spontaneous activity was attenuated (dose to inhibit completely activity = 4 mg/kg). The suppressant effects of cocaine in a long-term (7-day)-lesioned rat were no different than in sham controls (bottom). In these frequency histograms, the arrows indicate the time at which the infusion of the specified doses was complete.

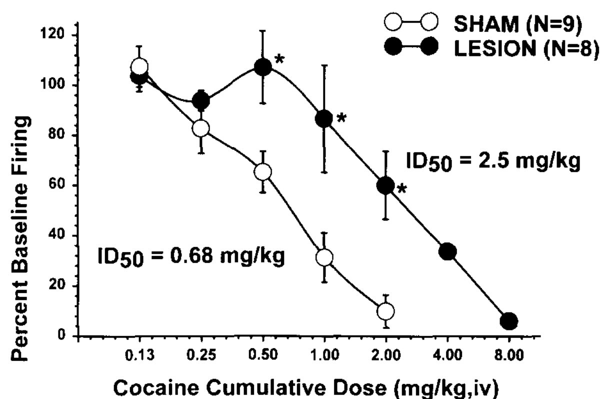


FIG. 2. Short-term (1-4-h) habenula lesions: dose-response curves for the inhibition of 5-HT DR neurons induced by cocaine. Drugs were administered IV at 2-min intervals such that each dose doubled the previously administered dose. Circles represent the mean ± SEM percentage of baseline firing rate observed at each dose of cocaine (ordinate). Open and closed circles denote the percentage of baseline firing rate observed in response to IV cocaine in sham or short-term (1-4-h)-lesioned rats, respectively. Asterisks represent doses at which sham and lesioned rats differed ($p < 0.05$).

using log-probit analysis; Student's t-tests were used to compare ID_{50}s for cocaine by treatment groups.

At the conclusion of each recording session, cathodal current was passed through the recording electrode (15 μA for 20 min). The resulting dye spot deposited at the site of the electrode tip and the extent of the lesion damage were histologically identified. Only data derived from experiments in which the recording electrode and the lesion were properly placed were included for further analysis.

All studies were conducted under the strictest compliance with the PHS Policy on the Humane Care and Use of Laboratory Animals and the NIH *Guide for the Care and Use of Laboratory Animals.*

RESULTS

Population Studies: Effects of Short-Term (1-4-h) and Long-Term (7-Day) Habenula Lesions

To determine whether habenula lesions affected the number of cells encountered in the DR as well as their firing rates, population sampling of neurons in the DR was conducted. The number of spontaneously active (5-HT and non-5-HT) cells found per pass was decreased in rats with short-term habenula lesions ($p < 0.05$) (Table 1). When the number of cells/pass was examined more closely, a significant decrease in the number of slower firing, presumably 5-HT neurons (rate < 2.5 Hz) was observed in short-term-lesioned rats ($p < 0.05$). The firing rates of these 5-HT neurons, however, were unchanged in habenula-lesioned rats.

The numbers of cells/pass, firing rates, and interspike intervals did not differ between rats with sham vs. long-term habenula lesions (Table 2).

Cocaine Inhibition of DR 5-HT Activity: Effects of Short-Term (1-4-h) and Long-Term (7-Day) Habenula Lesions

The effects of cocaine on 5-HT cell firing following a sham, short-term (1-4-h) or long-term (7-day) lesion of the

habenula are illustrated in representative frequency histograms shown in Fig. 1. Cocaine elicited a reversible inhibition of the spontaneous activity of a 5-HT neuron recorded in a short-term sham animal (Fig. 1, top). The cocaine-elicited suppression of a 5-HT neuron recorded in a short-term-lesioned rat (Fig. 1, middle) was significantly attenuated (dose to complete inhibition of firing = 4 mg/kg). However, by 7 days postlesion, the effects of cocaine are similar to those observed in sham animals (Fig. 1, bottom). The cumulative dose–response curve for inhibition of DR-5-HT firing following short-term or sham lesions is shown in Fig. 2; the dose–response for cocaine in lesioned rats was significantly different than that of controls, $F(1, 37) = 6.08, p = 0.0298$. The mean dose to inhibit activity by 50% (ID_{50}) was increased from 0.68 mg/kg in controls to 2.5 mg/kg in lesioned rats. As shown in Fig. 3, the cocaine-induced depression of spontaneous activity did not differ between sham rats ($N = 6$) and rats with long-term (7-day) habenula lesions ($N = 7$), $F(1, 42) = 0.54, p = 0.477$.

DISCUSSION

The lateral habenula provides a major efferent projection to the midbrain raphe and has been demonstrated to regulate neuronal outflow of midbrain raphe 5-HT neurons (22,38). In the present study, the basic electrophysiological characteristics of 5-HT DR neurons in vivo and the sensitivity of these 5-HT neurons to cocaine administration was assessed following habenula or sham lesions made 1–4 h or 7 days prior to single-unit recordings of DR 5-HT neurons. Population sampling of 5-HT and non-5-HT neurons in the DR indicated that significantly fewer spontaneously active 5-HT cells were found in rats 1–4 h after habenula lesions, although the firing rates and interspike intervals of identified 5-HT cells were unchanged. In contrast, neither the numbers, firing rates, nor interspike intervals of non-5-HT neurons were altered in lesioned animals; thus, the lesion-associated loss of 5-HT neurons cannot be related to the "masking" of these neurons as faster-firing, non-5-HT neurons. Presumably, therefore, the reduction in numbers of 5-HT cells in habenula- vs. sham-lesioned rats must be related to a cessation of neural activity in a subpopulation of 5-HT cells. Spontaneously firing 5-HT cells exhibit a slow regular discharge pattern that is regulated by the tonic pacemaker properties of the cell (1,2,9,11), but dependent

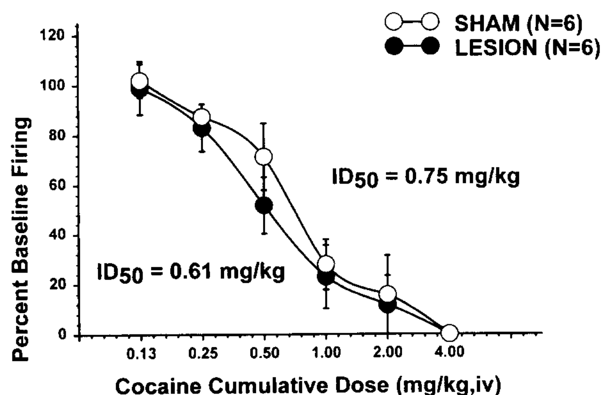


FIG. 3. Long-term (7-day) habenula lesions: dose–response curves for the inhibition of 5-HT DR neurons induced by cocaine. Symbols as in Fig. 2.

upon external synaptic influences, including a tonic excitatory noradrenergic and excitatory amino acid input (6,7,36,60). Loss of this tonic excitatory input (e.g., in a midbrain slice) does decrease the number of spontaneously discharging 5-HT cells (60), although a subpopulation of neurons retains firing characteristics similar to those seen in vivo. Although it has been hypothesized that this excitatory input is noradrenergic (6,7,60), excitatory amino acid or tackykinin input could be important as well; thus, the habenula (24–26) could be one source of excitatory innervation of DR 5-HT neurons (37,60). However, depression of 5-HT neuronal activity is the most prominent consequence of habenula stimulation (72–88%), with excitation observed in only 9–21% of neurons (40,56). Perhaps maintenance of impulse activity in this later group of cells, which respond with excitation upon habenula stimulation, is dependent upon excitatory habenula input and, in the absence of the habenula, these 5-HT neurons become quiescent. Alternatively, loss of inhibitory (GABA) input to excitatory neurons impinging directly upon some DR 5-HT neurons might result in disinhibition of this excitatory input and subsequent depolarization blockade (and cessation of activity) of these 5-HT DR neurons; while not yet shown for 5-HT neurons, depolarization blockade occurs in DA neurons following excessive glutamate activation [for review (8)]. Although these explanations are largely speculative, the concept that 5-HT neurons may be heterogenous is supported by other evidence, such as distinctions in the morphology of axon terminals and the sensitivity to the neurotoxic effects of substituted amphetamines. Thus, although the majority of 5-HT neurons in the DR possess fine, nonbeaded axons that are sensitive to MDMA toxicity, a subpopulation of DR (and a majority of MR) 5-HT neurons possesses thick, beaded axons that are resistant to amphetamine toxicity (31). Electrophysiological and pharmacological studies also indicate distinctions among 5-HT neurons that might be functionally relevant (12,42,53). Perhaps one of the defining characteristics for this subgroup of 5-HT cells is the extent of excitatory input from habenula and, perhaps, frontal cortex (24) and coeruleus (6,7,48).

Serotonin DR neurons recorded 1–4 h after lesion of the habenula responded with an attenuated suppression of firing in response to cumulative intravenous dosing with cocaine. These data suggest that, in addition to local inhibition of 5-HT reuptake in raphe (16), the depressant effects of cocaine on 5-HT cellular activity may be related to activation of negative feedback, habenulo-raphe pathways; when this pathway is removed, the response to cocaine is attenuated. It is unlikely that the potency of cocaine was reduced due to altered activity levels because differences in firing rates of 5-HT neurons were not observed between lesion and control rats. To more fully address this point, it will be necessary to determine whether habenula lesions alter the inhibitory effects of other drugs (e.g., *d*-lysergic acid diethylamine) thought to act locally in raphe. Of note, brain transections did not alter the depressive effects of a selective 5-HT reuptake inhibitor (chlorimipramine) or releaser (*p*-chloroamphetamine), suggesting that long-loop feedback from the forebrain did *not* mediate the depressive effect of these indirect 5-HT agonists (33). However, cocaine is not a selective 5-HT reuptake inhibitor (20, 27,49). Many of its in vivo effects are attributed to its potentiation of DA neurotransmission, particularly within mesolimbic DA circuits (64). Perhaps the dopaminergic actions of cocaine in mesolimbic regions, such as the nucleus accumbens, activate negative feedback via the habenulo-raphe pathways to influence the function of 5-HT neurons. Of note, habenula

neurons have been identified to receive afferents from the nucleus accumbens, a mesolimbic area crucial to the behavioral effects of cocaine (64); these same habenula neurons send axons to the DR (28). In further support of this hypothesis, the efficacy of cocaine as an inhibitor of spontaneous activity of 5-HT and DA neurons is greater when cocaine is administered intravenously (vs. iontophoretically) (14,17). Studies of local cerebral glucose utilization have also demonstrated that, although most limbic structures show *stimulated* metabolic activity after cocaine administration, that of the lateral habenula is significantly *depressed* by cocaine (29, 30,44,45) as well as other stimulants and DA agonists (32,35, 46). The present findings illustrate the complexity of cocaine's net effects on neurotransmission and the importance of establishing a comprehensive picture of its actions in the brain.

At 7 days postlesion, the number of 5-HT neurons recorded in the DR and the inhibitory response to cocaine had returned to unlesioned, control levels. Thus, these observed electrophysiological and pharmacological modifications may be a consequence of transient functional deficits in the habenulo-raphe pathway despite the fact that no significant alterations in the firing rates of either 5-HT or non-5-HT neurons were noted. Alternatively, compensatory mechanisms in the habenulo-raphe circuitry may have developed as a consequence of the loss of this important afferent pathway. A thorough analysis of the basic electrophysiological characteristics and pharmacological sensitivities of 5-HT DR neurons at additional time points following habenula lesions would provide insight into this possibility.

Like the diminished suppressive effects of cocaine following short-term lesions, the destruction of the habenula nuclei attenuated the inhibitory effects of another stimulant, methamphetamine, on DA neurons in the substantia nigra (51,52). Similar lesions, which included destruction of the medial thalamus, have also been shown to block the effects of amphetamine on frontal cortical-evoked neostriatal potentials (50). However, an important caveat of these, as well as the current study, is that the lesions of the habenula nuclei destroyed both fibers of passage and neuronal somata, and extended into other brain structures, in particular, the thalamus, which may also project to the raphe (5). Thus, to definitively ascribe the observed effects of habenula lesions to a specific loss of habenula cell bodies requires studies with more localized and selective means of lesioning (e.g., ibotenic acid).

In summary, intravenous cocaine appears to elicit its potent inhibitory actions on 5-HT neurons via both somatodendritic impulse-regulating 5-HT_{1A} autoreceptors and inhibitory habenulo-DR feedback processes. The extent to which cocaine activates habenulo-raphe feedback as a consequence of its actions as an indirect DA agonist in forebrain DA circuits will be an interesting hypothesis to test.

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REFERENCES

1. Aghajanian, G. K.; VanderMaelen, C. P. Intracellular identification of central noradrenergic and serotonergic neurons by a new double labeling procedure. J. Neurosci. 2:1786–1792; 1982.
2. Aghajanian, G. K.; VanderMaelen, C. P. Intracellular recordings from serotonergic dorsal raphe neurons: Pacemaker potentials and the effect of LSD. Brain Res. 238:463–469; 1982.
3. Aghajanian, G. K.; Wang, R. Y. Habenular and other midbrain raphe afferents demonstrated by a modified retrograde tracing technique. Brain Res. 122:229–242; 1977.
4. Aghajanian, G. K.; Wang, R. Y.; Baraban, J. Serotonergic and non-serotonergic neurons of the dorsal raphe: Reciprocal changes in firing induced by peripheral nerve stimulation. Brain Res. 153: 169–175; 1978.
5. Andersen, E.; Rigor, B.; Dafny, N. Electrophysiological evidence of concurrent dorsal raphe input to caudate, septum, habenula, thalamus, hippocampus, cerebellum and olfactory bulb. Int. J. Neurosci. 18:107–116; 1983.
6. Baraban, J. M.; Aghajanian, G. K. Suppression of firing activity of 5-HT neurons in the dorsal raphe by alpha-adrenoceptor antagonists. Neuropharmacology 19:355–363; 1980.
7. Baraban, J. M.; Aghajanian, G. K. Noradrenergic innervation of serotonergic neurons in the dorsal raphe: Demonstration by electron microscopic autoradiography. Brain Res. 204:1–11; 1981.
8. Bunney, B. S.; Chiodo, L. A.; Grace, A. A. Midbrain dopamine system electrophysiological functioning: A review and new hypothesis. Synapse 9:79–94; 1991.
9. Burlhis, T. M.; Aghajanian, G. K. Pacemaker potentials of serotonergic dorsal raphe neurons: Contribution of a low-threshold Ca^{2+} conductance. Synapse 1:582–588; 1987.
10. Callahan, P. M.; Cunningham, K. A. Electrophysiological effects of cocaine in amygdala nuclei: Relationship to dopamine and serotonin actions. Soc. Neurosci. Abst. 21:679; 1991.
11. Crunelli, V.; Forda, S.; Brooks, P. A.; Wilson, K. C. P.; Wise, J. C. M.; Kelly, J. S. Passive membrane properties of neurons in the dorsal raphe and periaqueductal grey recorded in vitro. Neurosci. Lett. 40:263–268; 1983.
12. Cunningham, K. A.; Bryan, S. K. Cocaine sensitization: Responsivity of serotonin (5-HT) neurons to iontophoretic 5-HT. Soc. Neurosci. Abst. 22:1238; 1992.
13. Cunningham, K. A.; Callahan, P. M.; Lekan, H. L. Cocaine: Electrophysiological characterization of effects in amygdala nuclei. Soc. Neurosci. Abst. 15:1098; 1989.
14. Cunningham, K. A.; Lakoski, J. M. Electrophysiological effects of cocaine and procaine on dorsal raphe serotonin neurons. Eur. J. Pharmacol. 148:457–462; 1988.
15. Cunningham, K. A.; Lakoski, J. M. The interaction of cocaine with serotonin dorsal raphe neurons: Single unit extracellular recording studies. Neuropsychopharmacology 3:41–50; 1990.
16. Cunningham, K. A.; Paris, J. M.; Goeders, N. E. Chronic cocaine enhances serotonin autoregulation and serotonin uptake binding. Synapse 11:112–123; 1992.
17. Einhorn, L. C.; Johansen, P. A.; White, F. J. Electrophysiological effects of cocaine in the mesoaccumbens dopamine system: Studies in the ventral tegmental area. J. Neurosci. 8:100–112; 1988.
18. Ellison, G. Continuous amphetamine and cocaine have similar neurotoxic effects in lateral habenular nucleus and fasciculus retroflexus. Brain Res. 598:353–356; 1992.
19. Gobi, M.; Cervo, L.; Taddei, C.; Mennini, T. Autoradiographic localization of [^{3}H]paroxetine specific binding in the rat brain. Neurochem. Int. 16:247–251; 1990.
20. Heikkila, R. E.; Orlansky, H.; Cohen, G. Studies on the distinction between uptake inhibition and release of [^{3}H]-dopamine in rat brain tissue slices. Biochem. Pharmacol. 24:847–852; 1975.
21. Henry, D. J.; White, F. J. Repeated cocaine administration causes persistent enhancement of D1 dopamine receptor sensitivity within the rat nucleus accumbens. J. Pharmacol. Exp. Ther. 258:882–890; 1991.
22. Herkenham, M.; Nauta, W. J. H. Efferent connections of the habenular nuclei in the rat. J. Comp. Neurol. 187:19–48; 1979.

23. Jacobs, B. L.; Azmitia, E. C. Structure and function of the brain serotonin system. Physiol. Rev. 72:165–229; 1992.
24. Kalen, P.; Karlson, M.; Wiklund, L. Possible excitatory amino acid afferents to nucleus raphe dorsalis of the rat investigated with retrograde wheat germ agglutinin and D-^{3}H-aspartate tracing. Brain Res. 360:285–297; 1985.
25. Kalen, P.; Pritzel, M.; Nieoullon, A.; Wiklund, L. Further evidence for excitatory amino acid transmission in the lateral habenular projection to the rostral raphe nuclei: Lesion induced decrease of high affinity glutamate uptake. Neurosci. Lett. 68:35–40; 1986.
26. Kalen, P.; Strecker, R. E.; Rosengren, E.; Bjorklund, A. Regulation of striatal serotonin release by the lateral habenula dorsal raphe pathway in the rat as demonstrated by in vivo microdialysis: Role of excitatory amino acids and GABA. Brain Res. 492: 187–202; 1989.
27. Komiskey, H. L.; Miller, D. D.; LaPidus, J. B.; Patil, P. N. The isomers of cocaine and tropacocaine: Effects on ^{3}H-catecholamine uptake by rat brain synaptosomes. Life Sci. 21:1117–1122; 1977.
28. Li, Y.-Q.; Takada, M.; Mizuno, N. Demonstration of habenular neurons which receive afferent fibers from the nucleus accumbens and send their axons to the midbrain periaqueductal gray. Neurosci. Lett. 158:55–58; 1993.
29. London, E. D.; Wilkerson, G.; Goldberg, S. R.; Risner, M. E. Effects of L-cocaine on local cerebral glucose utilization in the rat. Neurosci. Lett. 68:73–78; 1986.
30. London, E. D.; Wilkerson, G.; Ori, C.; Kimes, A. S. Central action of psychomotor stimulants on glucose utilization in extrapyramidal motor areas of the rat brain. Brain Res. 512:155–158; 1990.
31. Mamounas, L. A.; Mullen, C. A.; O'Hearn, E.; Molliver, M. E. Dual serotonergic projections to forebrain in the rat: Morphologically distinct 5-HT axon terminals exhibit differential vulnerability to neurotoxic amphetamine derivatives. J. Comp. Neurol. 314: 558–586; 1991.
32. McCulloch, J.; Savaki, H. E.; Sokoloff, L. Influence of dopaminergic systems on the lateral habenular nucleus of the rat. Brain Res. 194:117–124; 1980.
33. Mosko, S. S.; Jacobs, B. L. Electrophysiological evidence against negative neuronal feedback from the forebrain controlling midbrain raphe unit activity. Brain Res. 119:291–303; 1977.
34. Nishikawa, T.; Scatton, B. Inhibitory influence of GABA on central serotonergic transmission. Involvement of the habenuloraphe pathways in the GABAergic inhibition of ascending cerebral serotonergic neurons. Brain Res. 331:81–90; 1985.
35. Orzi, F.; Dow-Edwards, D.; Jehle, J.; Kennedy, C.; Sokoloff, L. Comparative effects of acute and chronic administration of amphetamine on local cerebral glucose utilization in the conscious rat. J. Cereb. Blood Metab. 3:154–160; 1983.
36. Pan, Z. Z.; Williams, J. T. GABA and glutamate mediated synaptic potentials in rat dorsal raphe neurons in vitro. J. Neurophysiol. 61:719–726; 1989.
37. Pan, Z. Z.; Williams, J. T. Differential actions of cocaine and amphetamine on dorsal raphe neurons in vitro. J. Pharmacol. Exp. Ther. 251:56–62; 1989.
38. Paris, J. M.; Lorens, S. A. Afferent projections to the median raphe nucleus in the rat. Soc. Neurosci. Abst. 14:1183; 1988.
39. Park, M. R. Monosynaptic inhibitory postsynaptic potentials from lateral habenula recorded in dorsal raphe neurons. Brain Res. Bull. 19:581–586; 1987.
40. Patel, S.; Millan, M. H.; Meldrum, B. S. Decrease in excitatory transmission within the lateral habenula and the mediodorsal thalamus protects against limbic seizure in rats. Exp. Neurol. 101: 63–74; 1988.
41. Paxino, G.; Watson, C. The rat brain in stereotaxic coordinates. Sydney: Academic Press; 1986.
42. Piercy, M. F.; Lum, J. T.; Palmer, J. R. Effects of MDMA ('ecstasy') on firing rates of serotonergic, dopaminergic, and noradrenergic neurons in the rat. Brain Res. 526:203–206; 1990.
43. Pitts, D. K.; Marwah, J. Electrophysiological effects of cocaine on central monoaminergic neurons. Eur. J. Pharmacol. 131:95–98; 1986.
44. Porrino, L. J. Functional consequences of acute cocaine treatment depend on route of administration. Psychopharmacology (Berlin) 112:343–351; 1993.
45. Porrino, L. J.; Domer, F. R.; Crane, A. M.; Sokoloff, L. Selective alterations in cerebral metabolism within the mesocorticolimbic dopaminergic system produced by acute cocaine administration in rats. Neuropsychopharmacology 1:109–118; 1988.
46. Porrino, L. J.; Lucignani, G.; Dow-Edwards, D.; Sokoloff, L. Correlation of dose-dependent effects of acute amphetamine administration on behavior and local cerebral metabolism in rats. Brain Res. 307:311–320; 1984.
47. Reisine, T. D.; Soubrie, P.; Artaud, F.; Glowinski, J. Involvement of lateral habenula-dorsal raphe neurons in the differential regulation of striatal and nigral serotonergic transmission in cats. J. Neurosci. 2:1062–1071; 1982.
48. Roizen, M. F.; Jacobowitz, D. M. Studies on the origin of innervation of the noradrenergic area bordering on the nucleus raphe dorsalis. Brain Res. 101:651–568; 1976.
49. Ross, S. B.; Renyi, A. L. Inhibition of the uptake of tritiated 5-hydroxytryptamine in brain tissue. Eur. J. Pharmacol. 7:270–277; 1969.
50. Ryan, L. J.; Young, S. J.; Groves, P. M. Amphetamine alteration of amplitude and timing of cortical neostriatal interactions. Neuropsychopharmacology 1:71–79; 1987.
51. Sasaki, K.; Suda, H.; Wantanabe, H.; Kaneko, S.; Nomura, Y.; Nishino, H.; Ono, T. Habenular lesion attenuates methamphetamine-induced inhibition of dopamine neuronal activity in the substantia nigra pars compacta of rats. Neurosci. Lett. 86:67–71; 1988.
52. Sasaki, K.; Suda, H.; Watanabe, H.; Yagi, H. Involvement of the entopeduncular nucleus and the habenula in methamphetamine-induced inhibition of dopamine neurons in the substantia nigra of rats. Brain Res. Bull. 25:121–127; 1990.
53. Sinton, C. M.; Fallon, S. L. Electrophysiological evidence for a functional differentiation between subtypes of the 5-HT_1 receptor. Eur. J. Pharmacol. 157:173–181; 1988.
54. Sprouse, J. S.; Aghajanian, G. K. Electrophysiological responses of serotonergic dorsal raphe neurons to 5-HT_{1A} and 5-HT_{1B} agonists. Synapse 1:3–9; 1987.
55. Steinbusch, H. W. M. Serotonin-immunoreactive neurons and their projections in the CNS. In: Bjorklund, A.; Hokfelt, T.; Kuhar, M. J., eds. Handbook of chemical neuroanatomy: Classical transmitters and transmitter receptors in the CNS. Amsterdam: Elsevier; 1984:68–125.
56. Stern, W. C.; Johnson, A.; Bronzino, J. D.; Morgane, P. J. Effects of electrical stimulation of the lateral habenula on single-unit activity of raphe neurons. Exp. Neurol. 65:326–342; 1979.
57. Stern, W. C.; Johnson, A.; Bronzino, J. D.; Morgane, P. J. Neuropharmacology of the afferent projections from the lateral habenula and substantia nigra to the anterior raphe in the rat. Neuropharmacology 20:979–989; 1981.
58. Sutherland, R. J. The dorsal diencephalic conduction system: A review of the anatomy and functions of the habenular complex. Neurosci. Biobehav. Rev. 6:1–13; 1982.
59. Uchimura, N.; North, R. A. Actions of cocaine on rat nucleus accumbens neurones in vitro. Br. J. Pharmacol. 99:736–740; 1990.
60. VanderMaelen, C. P.; Aghajanian, G. K. Electrophysiological and pharmacological characterization of serotonergic dorsal raphe neurons recorded extracellularly and intracellularly in rat brain slices. Brain Res. 289:109–119; 1983.
61. Wang, R. Y.; Aghajanian, G. K. Physiological evidence for habenula as major link between forebrain and midbrain raphe. Science 197:89–91; 1977.
62. White, F. J.; Hu, X. -T.; Henry, D. J. Electrophysiological effects of cocaine in the rat nucleus accumbens: Microiontophoretic studies. J. Pharmacol. Exp. Ther. 266:1075–1084; 1993.
63. White, F. J.; Wang, R. Y. A10 dopamine neurons: Role of autoreceptors in determining firing rate and sensitivity to dopamine agonists. Life Sci. 34:1161–1170; 1984.
64. Woolverton, W. L.; Johnson, K. M. Neurobiology of cocaine abuse. Trends Pharmacol. Sci. 13:193–200; 1992.