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Corticostriatal and Thalamic Regulation of Amphetamine-Induced Ascorbate Release in the Neostriatum

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BASSE-TOMUSK, A. AND G. V. REBEC. *Corticostriatal and thalamic regulation of amphetamine-induced ascorbate release in the neostriatum.* PHARMACOL BIOCHEM BEHAV **35**(1) 55–60, 1990.—Lesions of cerebral cortex and ventromedial nucleus (VM) of the thalamus were made in rats to investigate the contribution of these structures to amphetamine (AMPH)-induced ascorbate (AA) release in the neostriatum as measured by in vivo voltammetry. Following a recovery period of at least one week, rats were anesthetized, and electrochemically modified, carbon-fiber electrodes were lowered into the neostriatum. Compared to data obtained from sham-operated and unoperated controls, bilateral aspiration lesions of cerebral cortex significantly lowered both the basal level of AA and the amount of AA released by AMPH in the neostriatum. Similar results were obtained after bilateral, but not unilateral electrolytic lesions of the VM thalamus. Collectively, these results suggest that the corticostriatal pathway and the VM thalamic nuclei participate in the regulation of basal and AMPH-induced AA release in the neostriatum.

Amphetamine Ascorbate Corticostriatal pathway In vivo Voltammetry Neostriatum Ventromedial thalamic nucleus

THE ability of amphetamine (AMPH) to release dopamine from axon terminals in the neostriatum is well documented (13, 24, 39). Extracellular dopamine levels may rise by as much as 50% from a baseline of 10 nM. Dopamine, however, is not the only endogenous substance released by AMPH. Extracellular ascorbate (AA) concentrations in the neostriatum, which are normally between 200 to 400 μM (12, 35, 36, 45), increase by more than 100 μM following systemic injections of this drug (12, 18, 28, 46).

Although dopamine has been established as the primary mediator of the behavioral effects of AMPH (30), an accumulating body of evidence suggests that neostriatal AA may exert important modulatory influences. Systemic administration of AA, for example, has been reported to attenuate the behavioral response to AMPH (26,38). Similar effects are seen with intraventricular (43) and intraneostriatal (44) infusions suggesting that these behavioral effects are mediated centrally and are not due to peripheral pharmacokinetic interactions between AA and AMPH. Furthermore, AA has been shown to modulate dopamine receptor binding in neostriatal homogenates (16), and when injected systemically (5) or applied directly by iontophoresis (8), AA accelerates the firing rate of neostriatal neurons. Moreover, although AA enters the central nervous system via the bloodstream, AMPH-induced changes in extracellular AA levels appear to be derived from central rather than peripheral sources (14,46).

AMPH-induced AA release, however, does not appear to be dependent on dopamine release in the neostriatum. Neostriatal dopamine depletions in excess of 95% fail to abolish AMPH-induced AA release in this structure (18). In addition, unilateral nigral infusions of dopamine or AMPH cause an ipsilateral decrease and a contralateral increase in extracellular catechols, while causing a bilateral increase in neostriatal AA levels (46). It appears, therefore, that dopamine terminals in the neostriatum play little, if any, role in the increase in neostriatal AA levels following AMPH administration. Furthermore, because neostriatal infusions of AMPH actually may decrease AA release (46), it is unlikely that intrinsic neostriatal mechanisms, dopaminergic or otherwise, play a major role. In the following experiments, we began an investigation of structures outside the neostriatum that could be involved in the regulation of AMPH-induced neostriatal AA release.

There is evidence that, at least in some instances, rises in extracellular neostriatal AA levels are related to excitatory amino acid release and that the mechanism of this release is a carrier-mediated heteroexchange (15,22). Because the neostriatum receives a large glutamate projection from cerebral cortex, Grünewald and Fillenz (15) suggested that the rise in extracellular AA could be a signal of glutamate uptake following its impulse-evoked release. In support of this hypothesis, they found that a microinfusion of l-glutamate (the naturally occurring isomer) into the neostriatum caused a large increase in extracellular AA, which did not occur after infusion of d-glutamate (22). In addition, unilateral cortical lesions caused a 50 to 80% decrease in the extracellular

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concentration of neostriatal AA (21). It is likely, therefore, that the corticostriatal pathway plays a major role in regulating neostriatal AA levels. To investigate further the role of the corticostriatal pathway in AMPH-induced AA release, AA levels were measured following bilateral cortical lesions using in vivo voltammetry.

Several indirect lines of evidence suggest that AA release from the corticostriatal pathway may be regulated, in turn, by a larger circuit that includes the substantia nigra and the ventromedial (VM) thalamus. Because unilateral nigral infusion of AMPH are known to cause a bilateral increase in neostriatal AA release (48), it is possible that dopamine release in the substantia nigra pars reticulata (SNR) may play a role in AA regulation. The VM thalamus, one of the major target areas of the SNR (1, 9, 29), projects to the frontal cortex (2,6) and thus could act as a relay station in the modulation of neostriatal AA levels. Many SNR cells, for example, are responsive to iontophoretic dopamine (32) or systemic AMPH (25). Rebec and Groves (27) reported that SNR neurons displayed a marked increase in firing rate following AMPH administration. That this AMPH-induced excitation involves nigral dopamine is consistent with evidence that dendrites of dopamine neurons in the substantia nigra pars compacta course ventrally into the SNR (19) and that dopamine attenuates the inhibitory effects of iontophoretic or endogenous GABA on SNR neurons (41,42). Thus, by exciting the SNR, AMPH may activate VM thalamus and eventually the corticostriatal pathway that controls neostriatal AA.

Other evidence indicates that changes in the activity of nigrothalamic neurons could affect thalamic, cortical and neostriatal functioning. Use of the [^{14}C]deoxyglucose method revealed that electrical stimulation of the SNR increased local glucose utilization in the thalamus, sensorimotor cortex and neosriatum (33). This metabolic activation appeared to be due to stimulation of the nigrothalamic pathway because it was no longer apparent in animals one week after electrolytic lesion of the VM nucleus of the thalamus (34). Furthermore, electrical stimulation of the nigrothalamic pathway also causes an increase in the release of glutamate in the neostriatum, and this effect is blocked by a similar lesion (10). If AA release is an index of glutamate uptake after its impulse-evoked release, as proposed by Fillenz and co-workers (15,22), activation of this nigro-thalamo-cortical circuit by AMPH would cause the release of AA from corticostriate terminals. To test this hypothesis more directly, AMPH-induced AA release also was monitored following electrolytic lesions of the VM thalamus. Because systemic administration of AMPH causes bilateral activation of the substantia nigra, the effects of both unilateral and bilateral lesions were tested.

METHOD

Lesions

Male, Sprague-Dawley rats, weighing 300 to 400 g, were anesthetized with 2.5 ml/kg Chloropent (Fort Dodge) and placed in a stereotaxic frame. In one group of animals, a portion of the skull anterior to −1.0 mm relative to bregma was removed with the exception of the midline section to protect the venous sinus. Lesions were made by bilateral aspiration of the dorsal aspect of the cortex from 1.0 mm posterior to bregma to the frontal pole. The cavity then was filled with sterile Gelfoam and the wound sutured. To control for nonspecific effects of surgery, another group of rats received sham lesions. The above procedure was used for these lesions except that the cortex remained intact. An additional group of rats had no surgery prior to the recording session.

For both unilateral and bilateral VM lesions, an insulated tungsten electrode was lowered to the following coordinates relative to bregma: 1.25 ML, −2.7 AP and −7.0 DV (23). A 1-mA DC current was applied for 95 sec between the electrode tip (cathode) and an alligator clip (anode) attached to the fascia at the edge of the incision. Bicillin (Wyeth; 90,000 units) was administered intramuscularly (IM) to all surgically treated animals to reduce the risk of infection. All animals then were allowed to recover for 7 to 12 days.

Voltammetry

Carbon fibers (10 μm diameter) were sealed in pulled glass capillary tubes such that the active surface was 400 μm in length. To obtain a voltammetric wave for AA distinct from that for catechols, carbon-fiber electrodes were pretreated electrochemically (11,12). Briefly, the electrode tip was immersed in citrate-phosphate-buffered 0.9% saline, and a triangular wave potential (70 Hz, 0–3 V vs. a saturated calomel electrode, SCE) was applied for 30 sec followed by a 1.5-V constant potential for an additional 30 sec. This procedure alters the active surface of the electrode such that the AA oxidation wave occurs at a lower potential (approximately −50 mV vs. SCE) than at untreated electrodes. A second wave, which appears at more positive potentials, includes DOPAC, a major dopamine metabolite. Data based on this wave will be presented in a separate report.

Between 0700 and 0900 hours, rats from all groups were anesthetized with urethane (1.5 g/kg) and placed in a stereotaxic frame. After exposure of the cortex, the electrode then was lowered 4.5 mm ventral to the brain surface into the anteromedial neostriatum (1.5 mm anterior and 2.5 mm lateral to bregma). In cortically lesioned animals, the Gelfoam was removed carefully from the cavity by aspiration. The electrode then was lowered 2.5 mm ventral to the surface of the corpus callosum at the same coordinates (23).

The stereotaxic frame served as the auxiliary electrode and the SCE was attached to the dural surface via a saline bridge. Staircase voltammetric potential waveforms, −200 mV to +400 mV vs. SCE, were applied at 2-min intervals. Each scan consisted of 32 steps (25 mV/step) of 66.7 msec duration. The scan rate was 100 mV/sec. Current was sampled during the last 33.3 msec of each potential step to allow the faradaic-to-charging current ratio to increase. The short step time ensures that the electrode samples only in the solution pool that surrounds the electrode surface. This allows currents obtained in vivo to be converted to concentrations by comparison to postcalibration values (45). An IBM-XT computer, interfaced with a locally constructed 3-electrode potentiostat, generated the waveforms and stored the sampled current.

After a stable baseline was established, the animal received an intravenous (IV) injection of 2.0 mg/kg d-AMPH sulfate (free base; Sigma) via a femoral catheter. AA concentrations were monitored for 90 min after drug administration. Following completion of the experiment, the electrode was removed and postcalibrated in a citrate-phosphate-buffered solution containing 100 μM AA. In order to mark the approximate location of the recording site, a tungsten wire was lowered to the recording coordinates and current was applied to make a small lesion. Following an anesthetic overdose and a transcardial perfusion, the brain was removed, frozen, sectioned and stained with cresyl violet for histological analysis. Lesioned animals that sustained any direct damage to the neostriatum or animals in which the marking lesion was positioned outside the neostriatum were not included for analysis.

RESULTS

Effects of Cortical Lesions on Neostriatal AA Levels

Figure 1 shows the extent of a representative cortical lesion.

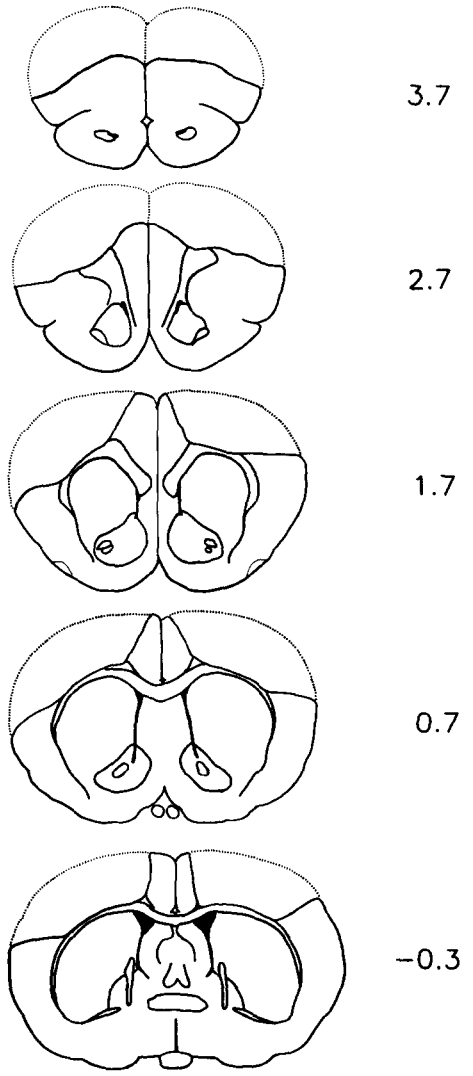

FIG. 1. Representative cortical lesion; dashed areas indicate extent of destruction. AP coordinates are relative to bregma. Histological drawings are based on Paxinos and Watson (23).

Similar lesions have been reported to result in reductions in neostriatal glutamate uptake in excess of 77% (40). Therefore, these lesions would be expected to destroy a large part of the corticostriatal pathway innervating the anteromedial neostriatum.

Figure 2 illustrates baseline (time = 0) and post-AMPH levels of AA in the cortically lesioned and control groups (n = 4 in each case). The mean baseline concentration of AA in intact animals was 244 ± 21 μM. This value is consonant with levels reported in previous studies for this region of the neostriatum (12, 35, 36, 45). In contrast, the mean baseline concentration of AA in animals that sustained a bilateral cortical lesion was 62 ± 13 μM, a reduction of 75% compared to intact animals. This decrease does not seem to be merely a result of the surgical procedure as the baseline AA concentration in sham-lesioned animals (290 ± 70 μM) was comparable to that of intact controls.

An IV injection of 2.0 mg/kg d-AMPH caused AA levels to increase by 173 ± 8 μM in the neostriatum of intact animals. A similar increase (192 ± 65 μM) was seen in the sham-lesioned rats.

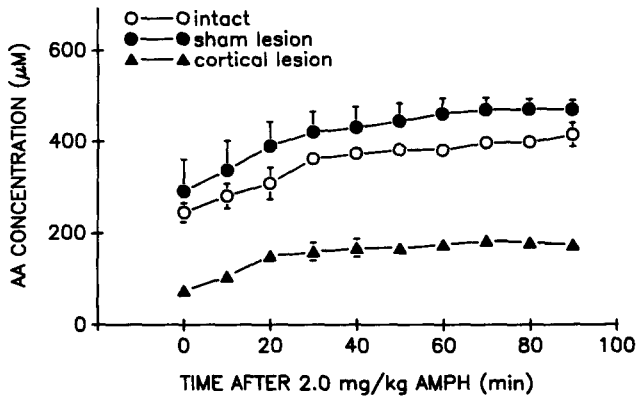

FIG. 2. Mean estimated basal and AMPH-induced AA levels in the neostriatum of sham-lesioned, cortically lesioned and intact control rats (n = 4 in each group). For each animal oxidation current was converted to an estimate of AA concentration based on postcalibration of the electrode. Consistent with previous evidence, AMPH caused an increase in AA release in the sham-lesioned and control groups. Note, however, the large decrease in both the basal and AMPH-induced AA levels in the neostriatum of the cortically lesioned group. Brackets indicate the standard error of the mean (S.E.M.)

In contrast, the response to AMPH in the cortically lesioned animals was severely diminished (112 ± 14 μM); AA levels remained far below the other groups for the duration of the response. As expected, a repeated measures analysis of variance revealed that AA levels were significantly altered by AMPH across all groups, $F(9,81) = 30.01$, $p < 0.001$. There also was a significant lesion effect, $F(2,9) = 29.35$, $p < 0.001$, but no drug-by-lesion interaction, $F(18,81) = 0.81$, $p > 0.6$. A planned comparison indicated that the AMPH-induced AA response in the neostriatum of the cortical lesion group differed dramatically from intact controls, $F(1,9) = 31.35$, $p < 0.001$, whereas AA levels in intact and sham-lesioned rats were comparable, $F(1,9) = 2.93$, $p > 0.1$.

Despite the clear reduction in AA levels following cortical lesions, the AMPH-induced change calculated as a percent of baseline actually increased in this group. Thus, whereas intact controls and sham-lesioned rats had mean increases in AA levels of 66 ± 10.7% and 71 ± 20.3%, respectively, following AMPH, the response of cortically lesioned animals was 181 ± 21.5% of baseline.

Figure 3 shows a representative voltammogram from an animal in the sham (top) and cortically lesioned (bottom) groups both before (stars) and after (circles) AMPH. Note the large increase in the AA wave (approximately −40 mV vs. SCE) in the control rat and the lower AA oxidation current (both pre- and post-AMPH) in the lesioned animal. The electrodes from which these data were obtained were of similar sensitivity based on postcalibration.

The decline in both basal and AMPH-induced AA release in the neostriatum following cortical lesions did not appear to result solely from the effects of surgery because no mean decrease in AA levels was evident in animals with sham lesions. The surgical procedure was not without effect, however, as evidenced by the significantly increased variability, $F(3,3) = 11.3$, $p < 0.05$, in basal AA levels in the sham group. While the variability of AMPH-induced AA levels also was elevated, this increase was significant only at 30, $F(3,3) = 12.0$, $p < 0.05$, and 70, $F(3,3) = 10.0$, $p < 0.05$, min post-AMPH administration.

Effects of VM Thalamic Lesions on Neostriatal AA Levels

The data from the animals that received electrolytic lesions are

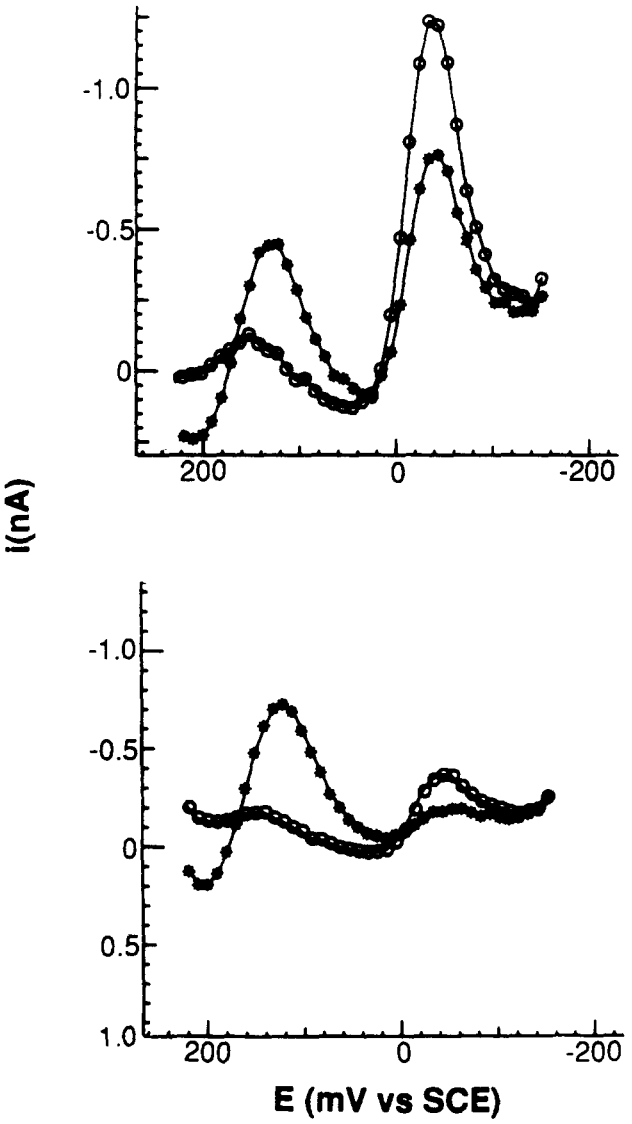

FIG. 3. Example of pseudoderivative voltammograms for a sham-lesioned (top) and cortically lesioned animal (bottom) both before (stars) and after (circles) an IV injection of 2.0 mg/kg AMPH. The voltammetric wave for oxidation of AA is observed at approximately −40 mV versus SCE and the wave for DOPAC occurs at approximately +130 mV versus SCE. There is a clear increase in the voltammetric wave for AA in the sham-lesioned animal after AMPH administration and a large decrease in the amplitude of both the pre- and post-AMPH AA peak in the lesioned animal. Note the differences in the current scale on these graphs.

separated into two groups. Animals (n = 7) that received unilateral VM thalamic lesions are included in Group 1. In some cases, lesions were not limited to the VM thalamus, but included damage to ventrolateral, gelatinosus and ventroposterior thalamic nuclei. Although these lesions varied in size and extent of VM damage, these variations had no effect on mean AA concentrations. Group 2 was comprised of animals that sustained bilateral damage to the VM thalamus (n = 4). Figure 4 illustrates the largest and smallest extent of thalamic tissue destroyed by lesions in Group 2. Other damaged areas included ventrolateral, gelatinosus, ventroposterior, reticular, paracentral and centrolateral thalamic nuclei. Because the VM thalamus is the only common area of damage among all animals in this group, it is unnlikely that damage to these other

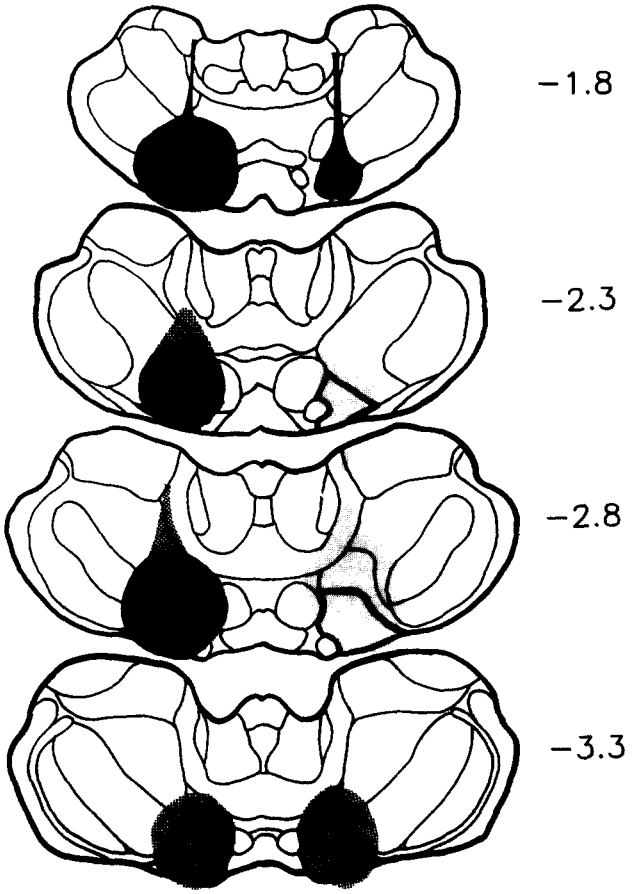

FIG. 4. Diagrammatic representation of the thalamus on serial coronal brain sections showing the extent of the smallest (dark shade) and the largest (light shade) bilateral lesions of the VM thalamus. The VM thalamus is outlined in thick black lines. AP coordinates are relative to bregma. Histological drawings based on Paxinos and Watson (23).

structures could account for our results.

Baseline (time = 0) and post-AMPH levels of AA in the two groups that received electrolytic lesions are shown in Fig. 5. In addition, data from the intact control group are displayed again for comparison. Note that the mean baseline concentration of AA in animals with unilateral lesions of the VM thalamus (269 ± 25 μM) was comparable to that of intact controls (243 ± 21 μM), whereas this value dropped substantially in bilaterally lesioned rats (158 ± 26 μM). Furthermore, while AMPH caused an increase in AA release in all groups, the increase in the bilaterally lesioned animals (124 ± 29 μM) was smaller than that seen in either control animals (173 ± 7 μM) or in unilaterally lesioned animals (182 ± 15 μM). A planned comparison performed in conjunction with the repeated measures analysis of variance revealed that bilateral VM thalamic damage significantly lowered AMPH-induced neostriatal AA release compared to intact controls, $F(1,12) = 6.72$, $p < 0.025$. No difference emerged between the intact animals and those with unilateral VM lesions, $F(1,12) = 1.10$, $p > 0.3$. All three groups, however, showed similar increases in AA following AMPH administration when expressed as a percentage of the baseline levels: intact control = 66 ± 10.7%, unilateral VM lesion = 68 ± 13.7%, and bilateral VM lesion = 78 ± 15.9%.

DISCUSSION

Despite the fact that systemic AMPH increases extracellular

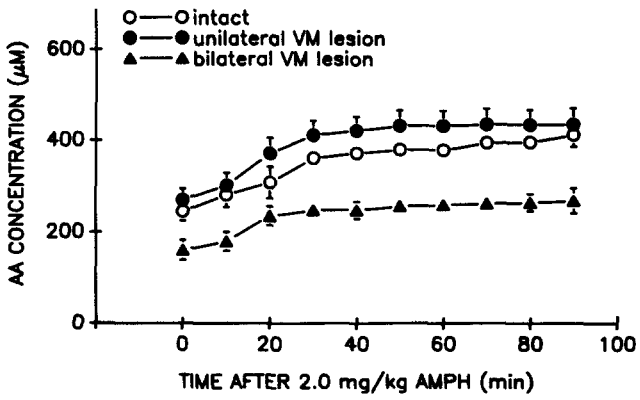

FIG. 5. Mean estimated basal and AMPH-induced AA levels in the neostriatum of rats that received unilateral (group 1; n=7) or bilateral (group 2; n=4) lesions of the VM thalamus. Data from intact control animals (n=4) are displayed again for comparison. Note that bilateral, but not unilateral VM thalamic lesions reduced basal and AMPH-induced AA release. Brackets indicate the S.E.M.

AA in the neostriatum, a direct infusion of AMPH into this structure causes either a slight decrease or no change in neostriatal AA (48). AMPH, therefore, must be acting at sites outside the neostriatum. Our results implicate the cerebral cortex as one of these sites. Cortical lesions not only cause a decline in the basal level of neostriatal AA, they significantly attenuate the AMPH-induced rise in AA levels. AMPH is known to increase the activity of cortical neurons (3,37), and to the extent that these cells contribute to the glutaminergic corticostriatal pathway, their activation may result in neostriatal AA release.

A functional link between glutamate-containing corticostriatal terminals and neostriatal AA is supported by evidence that iontophoretically applied AA appears to enhance the excitatory effects of glutamate on neostriatal neurons (8). To the extent that AA is released from corticostriatal terminals following the impulse-induced release of glutamate, as Fillenz and co-workers propose (15), extracellular AA may serve to prolong the synaptic action of this excitatory neurotransmitter. If, as our results suggest, AA also is released from corticostriatal terminals by AMPH, AA could interact with glutamate to play a direct role in altering neostriatal functioning following AMPH administration. In fact, neostriatal infusions of AA have been reported to attenuate the AMPH-induced behavioral response (44).

Because neostriatal AA levels increase following nigral infusions of AMPH, we hypothesized that AMPH-induced dopamine release in the SNR could activate the corticostriatal pathway indirectly via nigrothalamic and thalamocortical systems. Consistent with this view, we found that lesions of the VM thalamus, one of the major targets of the nigrothalamic tract, attenuate AMPH-induced AA release in the neostriatum. Note, however, that this effect was seen with bilateral, but not unilateral, VM lesions, arguing for a substantial contralateral influence. Indeed, both ipsi- and contralateral projections have been identified in the nigrothalamic (9) and corticostriatal (7) pathways. Thus, to the extent that VM thalamus is part of a circuit that controls AA release from corticostriatal terminals, the circuit must include a contralateral component. In support of this hypothesis, unilateral nigral infusions of AMPH cause a bilateral increase in neostriatal AA release (48).

That activation of the nigrothalamic pathway will activate, in turn, the corticostriatal system is consistent with evidence that electrical stimulation of the SNR increases neostriatal glutamate release and that this effect is abolished by VM thalamic lesions (10). Moreover, a direct infusion of GABA, the alleged neurotransmitter in the nigrothalamic pathway, into VM thalmus also elevates neostriatal glutamate release (4). Presumably, GABA exerts this effect through thalamic interneurons, which then cause a disinhibition of the excitatory thalamocortical projection (31).

Although cortical lesions significantly lowered the absolute change in AA levels produced by AMPH, the percentage change from baseline was enhanced in these animals. This finding suggests that compensatory mechanisms may be at work either in the remaining corticostriatal terminals or in other systems to cause a greater-than-normal increase above baseline following an AMPH challenge. It is important, therefore, to monitor absolute levels of AA rather than calculate AA changes simply as a percentage change from baseline. In fact, basal levels in cortically lesioned animals also may be elevated above what may be expected on the basis of surviving corticostriatal terminals alone, though this possibility is difficult to confirm. Interestingly, VM thalamic lesions did not appear to engage AA compensatory mechanisms in the neostriatum. Animals with these lesions showed the same AMPH-induced percentage change from baseline as control rats.

The cortical lesion procedure may have had a nonspecific effect on AA in that we noticed an occasional increase in variability in AA levels in sham-lesioned animals. It is unlikely, however, that the absolute decreases in basal and AMPH-induced AA levels that we observe following cortical or VM thalamic lesions can be attributed to surgery because such decreases failed to appear in rats that sustained either sham cortical or unilateral VM lesions. In fact, sham-lesioned animals actually displayed a slight mean increase in basal AA levels, arguing against a surgical influence on the AA decline in the cortical lesion group.

Although our results suggest a nigro-thalamo-corticostriatal system in the control of AMPH-induced AA release in the neostriatum, other systems and pathways may play an important modulatory role. The corticostriatal projection, for example, could be influenced by dopamine released from either mesocortical or mesolimbic terminals. Indeed, both D-1 and D-2 dopamine receptors have been implicated in AA release (20,28). Moreover, serotonin depleting lesions, for example, have been shown to increase AMPH-induced neostriatal AA release (17), while lesions of the crus cerebri, which contains several ascending and descending pathways, cause both a decline in basal AA levels and virtually abolish the AA response to AMPH (47). Further research on these and other forebrain systems may help to clarify the neural mechanisms underlying neostriatal AA release.

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