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Clorgyline-Induced Increases in Presynaptic DA: Changes in the Behavioral and Neurochemical Effects of Amphetamine Using In Vivo Microdialysis

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SEGAL, D. S., R. KUCZENSKI AND C. OKUDA. *Clorgyline-induced increases in presynaptic DA: Changes in the behavioral and neurochemical effects of amphetamine using in vivo microdialysis.* PHARMACOL BIOCHEM BEHAV **42**(3) 421–429, 1992. – Microdialysis was used in behaving rats to further characterize the behavioral and regional dopamine (DA) response to the monoamine oxidase (MAO) inhibitor clorgyline and determine how MAO inhibition affects amphetamine (AMPH)-induced changes in behavioral and extracellular DA dynamics. Although clorgyline (4.0 mg/kg) did not significantly alter behavior, it produced prolonged increases in caudate and accumbens extracellular DA and 3MT and corresponding decreases in homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC). Clorgyline pretreatment altered the behavioral response to both low (0.25 mg/kg) and moderate (2.5 mg/kg) doses of AMPH, which was characterized by a shift to more intense forms of stereotypy and corresponding decreases in locomotion. The caudate and accumbens DA response to AMPH (0.25 mg/kg) was also significantly augmented, consistent with an increase in AMPH-releasable cytoplasmic DA. Thus, the potentiated DA response in clorgyline-pretreated animals may be responsible for the changes in the stereotypy profile. Possible implications of these observations for the augmented behavioral response observed with repeated AMPH administration are discussed.

Amphetamine Clorgyline Locomotion Stereotypy Dopamine Sensitization Microdialysis Caudate Accumbens

CONVERGING evidence indicates that amphetamine-induced dopamine (DA) release occurs through an accelerative exchange diffusion process (14). This mechanism, which is dependent upon the DA uptake carrier and independent of impulse flow, appears to involve cytoplasmic DA. By contrast, DA release promoted by neuronal impulse activity involves exocytosis of vesicular DA. Consistent with such a distinction, a variety of pharmacological manipulations that alter impulse-dependent, vesicular DA release have no effect on amphetamine-induced DA release (5,20,33).

Monamine oxidase inhibitors (MAOIs) like clorgyline (9) have been shown to increase tissue levels of DA (7) and more recently to elevate brain extracellular concentrations of this transmitter (4,13,21). The elevation of extracellular DA presumably derives from enhanced vesicular DA since basal extracellular DA is generally thought to reflect impulse-dependent release. In addition, although some of the DA may be taken up by vesicles after MAO is inhibited, the transmitter likely also accumulates in the cytoplasmic pool and, in fact, MAOIs like pargyline have been shown to potentiate the behavioral response to amphetamine (AMPH) (29). In this regard, it has also been suggested that an increase in the size of the AMPH-releasable, cytoplasmic DA pool might be responsible for the enhanced behavioral response to stimulants following repeated AMPH pretreatment (25–27).

The objectives of the present studies were to examine the extent to which the quantitative features of AMPH-induced DA release might be dependent upon the size of the cytoplasmic pool and further evaluate the relationship between extracellular DA and the behavioral profile produced by AMPH. We used in vivo microdialysis in awake rats first to further characterize the behavioral and regional DA response patterns to clorgyline, an allegedly selective MAO-A inhibitor (9). Then, animals were treated with AMPH to determine how MAO inhibition affects AMPH-induced changes in behavioral and DA dynamics.

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METHOD

Male Sprague-Dawley rats (300–350 g) obtained from Harlan Labs were housed four per cage with food and water available ad lib in an animal colony that was maintained at constant temperature and humidity on a 14-h white:10-h red light cycle (white lights on 0500–1900 h). Following at least 1 week of habituation to the animal colony, two guide cannulae extending 2.5 mm below the skull surface were implanted in each animal according to procedures previously described in detail (15). After surgery, animals were housed individually and allowed at least 1 week to recover before receiving any treatment. Concentric-design microdialysis probes (Spectra/Por hollow fiber, MW cut-off 6000, o.d. 250 μm) with an active surface of 3 mm for caudate and 1.25 mm for nucleus accumbens were constructed as previously described (15). Probes were aimed at the medial caudate (1.0 mm anterior to bregma, +2.8 mm lateral, and 6.2 mm below dura) and the nucleus accumbens (2.2 mm anterior, −1.5 mm lateral, 7.8 mm below dura). Probes were perfused with artificial cerebrospinal fluid (in mM: NaCl 147, $CaCl_2$ 1.2, $MgCl_2$ 0.9, KCl 4.0) (2 μl/min) and samples were collected through glass capillary tubing outside the experimental chamber into vials containing 20 μl 0.2 M citrate, pH 3.8, and 20% methanol. Individual probe recoveries, which ranged from 4–6% for caudate and 2–2.5% for nucleus accumbens, were estimated by sampling a standard DA dihydroxyphenylacetic acid (DOPAC) solution in vitro.

Dialysate samples were assayed for DA, DOPAC, homovanillic acid (HVA), and 3-methoxytyramine (3MT) in 40-μl aliquots using HPLC with electrochemical detection (HPLC-EC). The HPLC-EC consisted of a 80 × 4.6 mm ODS-C18 3μm column (Regis, Morton Grove, IL) maintained at 40°C. Mobile phase (0.06 M citric acid, 7% methanol, 0.1 mM Na_2EDTA, and 0.8 mM octane sulfonate, adjusted to pH 4.0–4.7) was delivered at 0.6 ml/min by a Waters, Milford, MA model 510 pump. Amines were detected with a Waters 460 detector with a glassy carbon electrode maintained at +0.65 V relative to an Ag/AgCl reference electrode. Concentrations of extracellular substances, corrected for individual probe recoveries, were estimated from peak areas using a Waters Maxima 820 data station. Although the exact relationship between dialysate concentration and actual extracellular transmitter content is not clear (3,6,32), substances in the dialysates were corrected for individual probe recoveries and are presented as concentration to allow for meaningful comparisons to other data in the literature.

Dialysis experiments were conducted in 12 × 12 × 15 in sound-attenuated, temperature- and humidity-controlled chambers, previously described in detail (15,30). Automated behavioral data were collected continuously by computer. Animals were also videotaped to allow direct observational rating of behavior according to procedures we have developed (30). After AMPH administration, the percentage of time during which the animal engaged in specific behaviors was recorded.

Clorgyline (May & Baker, Dagenham, England) and *S*(+)-amphetamine (NIDA, Rockville, MD) were dissolved in saline. Clorgyline (4 mg/kg) was injected intraperitoneally and AMPH (0.25 mg/kg) subcutaneously in a volume of 1 ml/kg body weight. Doses refer to weight of free base.

Each rat was placed in an experimental chamber and the dialysis probes were inserted on the day prior to treatment (1500–1600 h) to allow for acclimation to the test environment and for adequate equilibration of the dialysis probes. At about 9:00 a.m. the following morning, animals were injected with clorgyline or saline, followed 6 h later by AMPH. Baseline DA and its metabolites were defined as the median of the three 20-min dialysis samples prior to injection. Following administration of clorgyline or saline, 20-min samples were collected for 2 h followed by 40-min samples for the next 4 h. After AMPH administration at about 3:00 p.m., samples were collected for 2 h at 20-minute intervals. At the end of the experiment, each animal was perfused with 4% formalin and the brain was removed and fixed in formalin for histological verification of probe placement.

A separate series of experiments were designed to more thoroughly characterize the effects of clorgyline on spontaneous and AMPH-induced behavioral activity. The same procedures were used as described above with the exception that only the behavioral response to treatment was monitored. Therefore, in the absence of constraints imposed by the dialysis apparatus our two-compartment test chamber could be used to obtain additional behavioral measures to more accurately assess treatment-induced effects [see (30) for detailed description of experimental chamber]. Briefly, the chamber is divided into a relatively small "home" compartment, in which food and water are continually accessible, and a larger activity compartment identical to the one used for the dialysis study with the exception that a hanging wire mesh stimulus is available for monitoring investigatory activity.

As in the dialysis study, animals were exposed to the chamber on the day prior to treatment at about 3:00 p.m. and then injected the following day with either saline or clorgyline at about 8:00 a.m., 6 h prior to administration of either 0.25 or 2.5 mg/kg AMPH. Behavior was monitored continuously, as described above, using both automated and videotape procedures, from the time of clorgyline injection to about 6 h after AMPH administration.

Behavior and amine data were tested for significance with an analysis of variance (ANOVA). For each analysis that yielded a significant F ratio, t-tests with Bonferroni adjustment were applied for posthoc comparisons within or between groups. Where only one comparison was assessed, a paired or unpaired Student's t-test was utilized.

RESULTS

Clorgyline (4 mg/kg) did not significantly alter locomotion (crossovers and rearings; Fig. 1), although over the 6-h period prior to AMPH injection drug-treated animals showed a somewhat lower level of locomotor activity compared to controls [40 ± 9 and 67 ± 9, respectively; $t(10) = 2.15$, $p = 0.057$]. Observational ratings revealed no qualitative differences in the behavioral responses between the two groups of animals.

In contrast to its behavioral effects, clorgyline produced profound, long-term changes in caudate (Fig. 2) and accumbens (Fig. 3) DA dynamics. Caudate DA (Fig. 2A) was significantly elevated by 20–40 min after injection ($p = 0.046$) and achieved peak extracellular concentrations (about 340% of baseline) within the subsequent hour. This increased level of DA persisted for at least 4 h (DA concentrations at 100–120 min, 75 ± 4; at 320–360 min, 79 ± 9; NS).

Both caudate DOPAC (Fig. 2B) and HVA (Fig. 2C) were markedly reduced and the pattern of change was relatively similar for the two metabolites. Although the rate of decrease

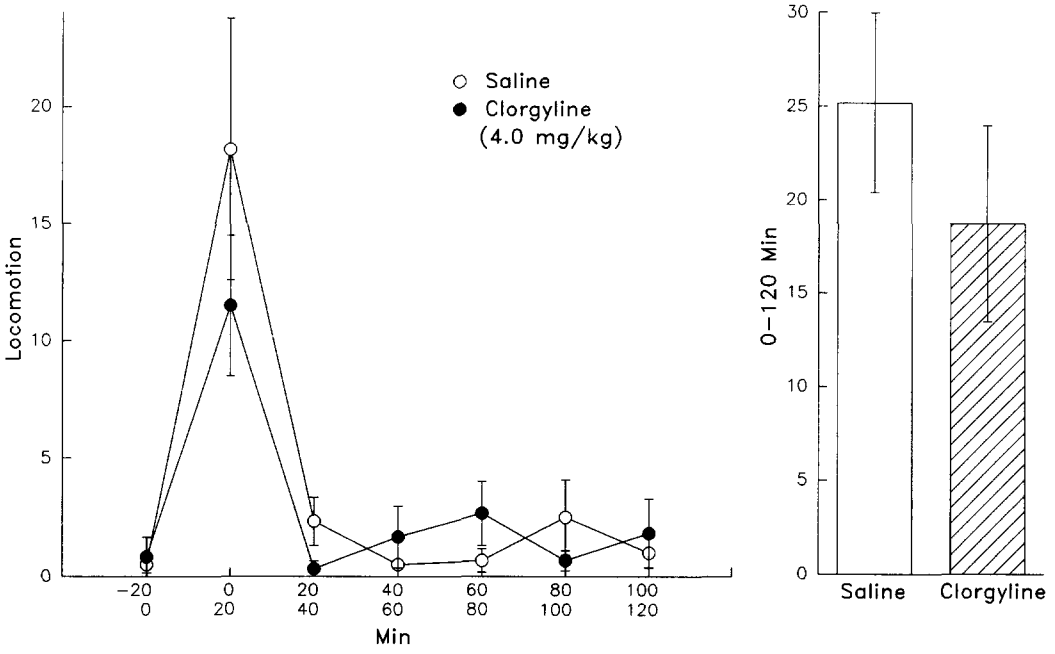

FIG. 1. Left: Temporal pattern of the locomotor response to the intraperitoneal administration of saline (n = 6) or 4 mg/kg clorgyline (n = 6). Locomotion (crossovers + rearings) is presented as the mean ± SEM. Right: Cumulated locomotor response during the initial 2 h following treatment.

was somewhat greater for DOPAC (17% baseline as compared to 33% baseline for HVA by 1 h after injection), both metabolites were reduced to a maximum level of about 10% of baseline by 2 h and remained at about peak levels of reduction for the following 4–5 h.

As with DA, caudate 3MT (Fig. 2D) was significantly increased by clorgyline. However, unlike DA, 3MT continued to rise until about 3 h after injection (100–120 min, 215 ± 10; 160–200 min, 316 ± 14; p = 0.001), and then remained at this level (320–360 min, 329 ± 24; NS) for at least the next 3 h.

The clorgyline effect on accumbens DA dynamics (Fig. 3) closely paralleled the caudate response profiles. Dopamine (Fig. 3A) gradually increased, achieving peak concentrations at about 1–2 h after injection (450% of baseline), which persisted for at least 4–5 h (100–120 min, 55 ± 8; 320–360 min, 56 ± 11; NS). As compared to caudate DA, accumbens DA levels increased more rapidly, achieving significance during the initial 20-min interval (p = 0.015).

Both accumbens DOPAC and HVA displayed a marked and persistent decrease after clorgyline. As with caudate, accumbens HVA declined at a somewhat slower rate (30% of baseline by 1 h after injection as compared to 13% of baseline for DOPAC), although both metabolites achieved a maximum reduction to about 10% baseline by 2 h and remained at that level during the subsequent 4–5 h. Also like the caudate 3MT response to clorgyline, the increase in accumbens 3MT concentration did not peak until about 3 h after injection (100–120 min, 114 ± 11; 160–200 min, 141 ± 15; p = 0.004).

The low dose of AMPH (0.25 mg/kg) produced a typical pattern of behavioral activation that lasted for less than 2 h and was characterized by increased crossovers and rearings (locomotion, Fig. 4). In addition, there was evidence of mild stereotypy consisting primarily of focused sniffing and intermittent episodes of repetitive head movements. Clorgyline pretreatment did not significantly alter locomotion over most of the duration of the response (about 1 h), although this behavior was reduced during the first 20-min interval (saline pretreatment, 76 ± 13; clorgyline pretreatment, 38 ± 12; p = 0.059). However, the stereotypy response shifted toward a more intense, that is, higher dose, profile including a relative decrease in focused sniffing and a significant increase in repetitive head and limb movements (Fig. 4).

A similar but more pronounced clorgyline-induced shift in the AMPH response profile was observed in animals whose behavior was assessed using the two-compartment chamber. In fact, locomotion was reflected by two indices of horizontal (crossings within the activity compartment and between the two compartments) and of vertical (rearings and hanging stimulus contacts) activity was significantly reduced throughout most of the duration of the response (Fig. 5, top). In addition, as with the dialyzed animals, clorgyline pretreatment produced a shift in the AMPH response from focused sniffing to repetitive movements (Fig. 5, top).

The response to 2.5 mg/kg AMPH was also significantly altered by clorgyline (Fig. 5, bottom). After clorgyline, the multiphasic locomotor response typical of this dose of AMPH exhibited a temporal pattern more characteristic of a higher dose including a more marked reduction in locomotion (30–90 min) after the initial period of activation (Fig. 5, bottom) and a more prolonged poststereotypy hyperactivity phase (180–240 min: saline 71 ± 12, clorgyline 148 ± 28; $t(35)$ = 2.51, p = 0.19).

Clorgyline pretreatment also produced a corresponding change in the qualitative features of stereotypy during the period of depressed locomotion (30–90 min) (Fig. 5, bottom). Thus, whereas a 2.5-mg/kg dose of AMPH typically produces primarily repetitive head movements and some focused sniff-

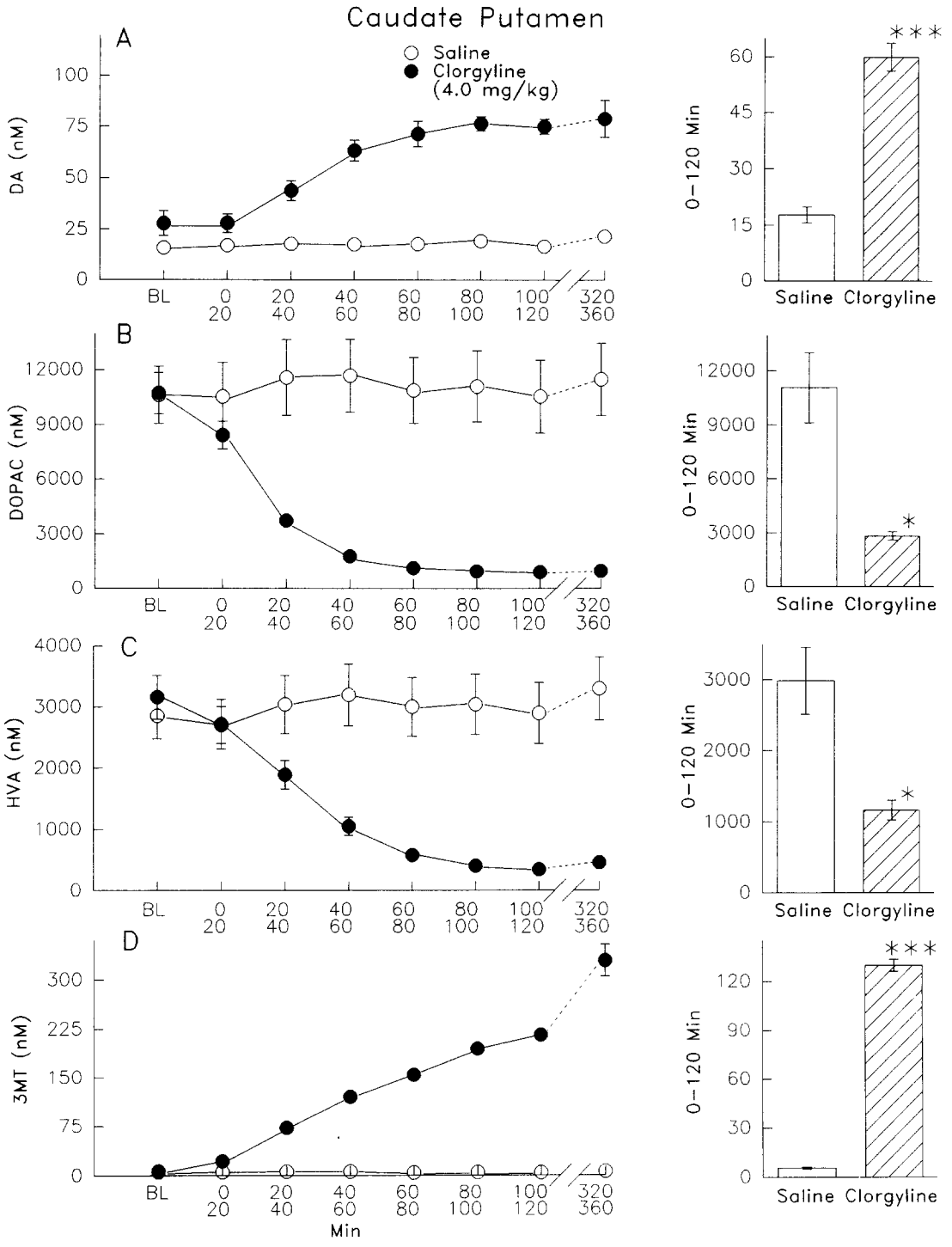

FIG. 2. Effects of clorgyline on caudate-putamen extracellular DA dynamics. Left: Temporal pattern of the response of DA and its metabolites following the intraperitoneal administration of saline (n = 5) or 4 mg/kg clorgyline (n = 5). Values are presented as mean dialysate concentrations ± SEM, corrected for probe recoveries. Baseline (BL) values, defined as the median of the three samples preceding injection, were not significantly different between the two groups. Right: Histograms represent the cumulative response to saline or clorgyline during the initial 2 h after treatment. *$p < 0.05$; ***$p < 0.001$.

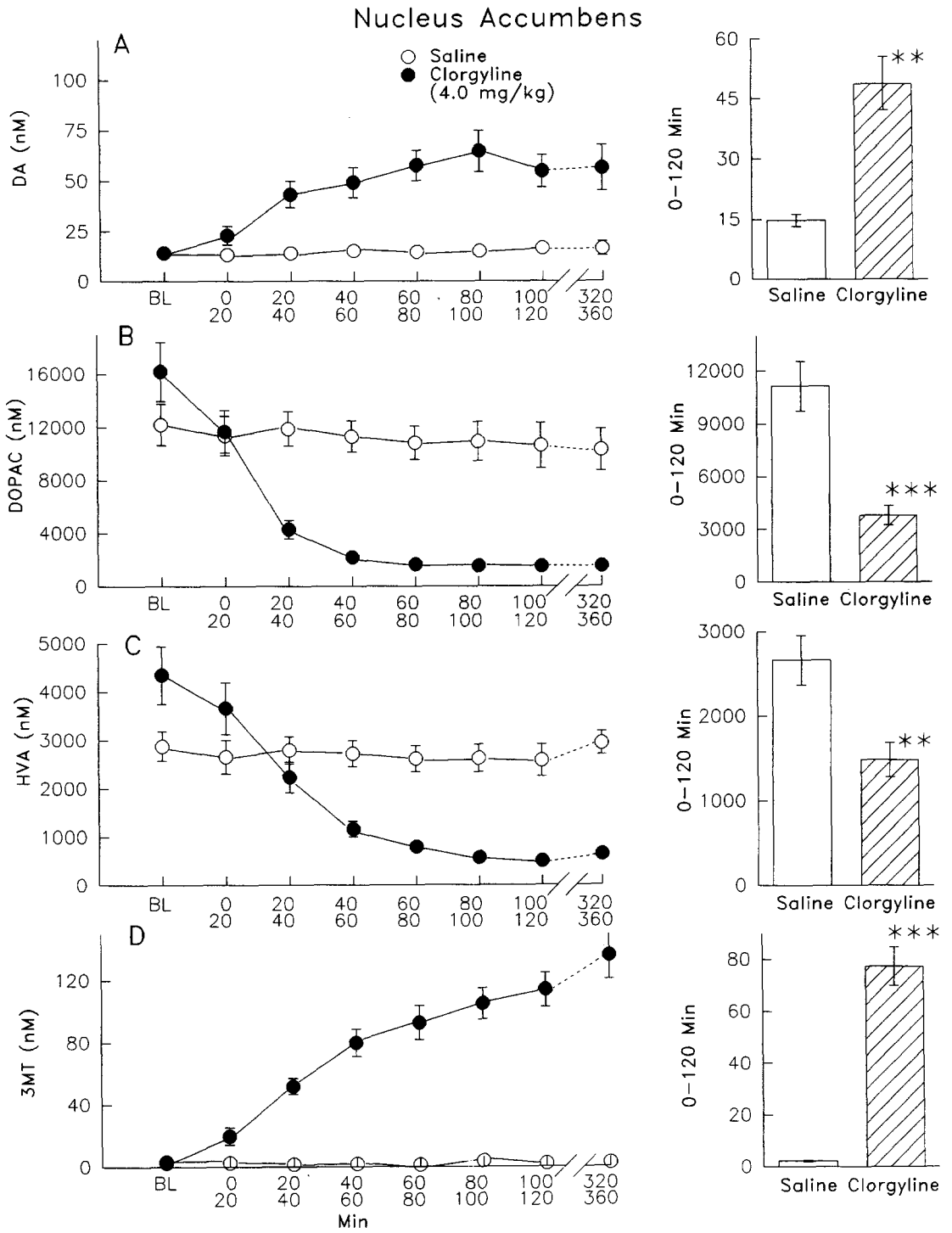

FIG. 3. Effects of clorgyline on nucleus accumbens extracellular DA dynamics. Left: Temporal pattern of the response of DA and its metabolites following the intraperitoneal administration of saline (n = 5) or 4 mg/kg clorgyline (n = 6). Values are presented as mean dialysate concentrations ± SEM, corrected for probe recoveries. Baseline (BL) values, defined as the median of the three samples preceding injection, were not significantly different between the two groups. Right: Histograms represent the cumulative response to saline or clorgyline during the initial 2 h after treatment. $^{**}p < 0.01$; $^{***}p < 0.001$.

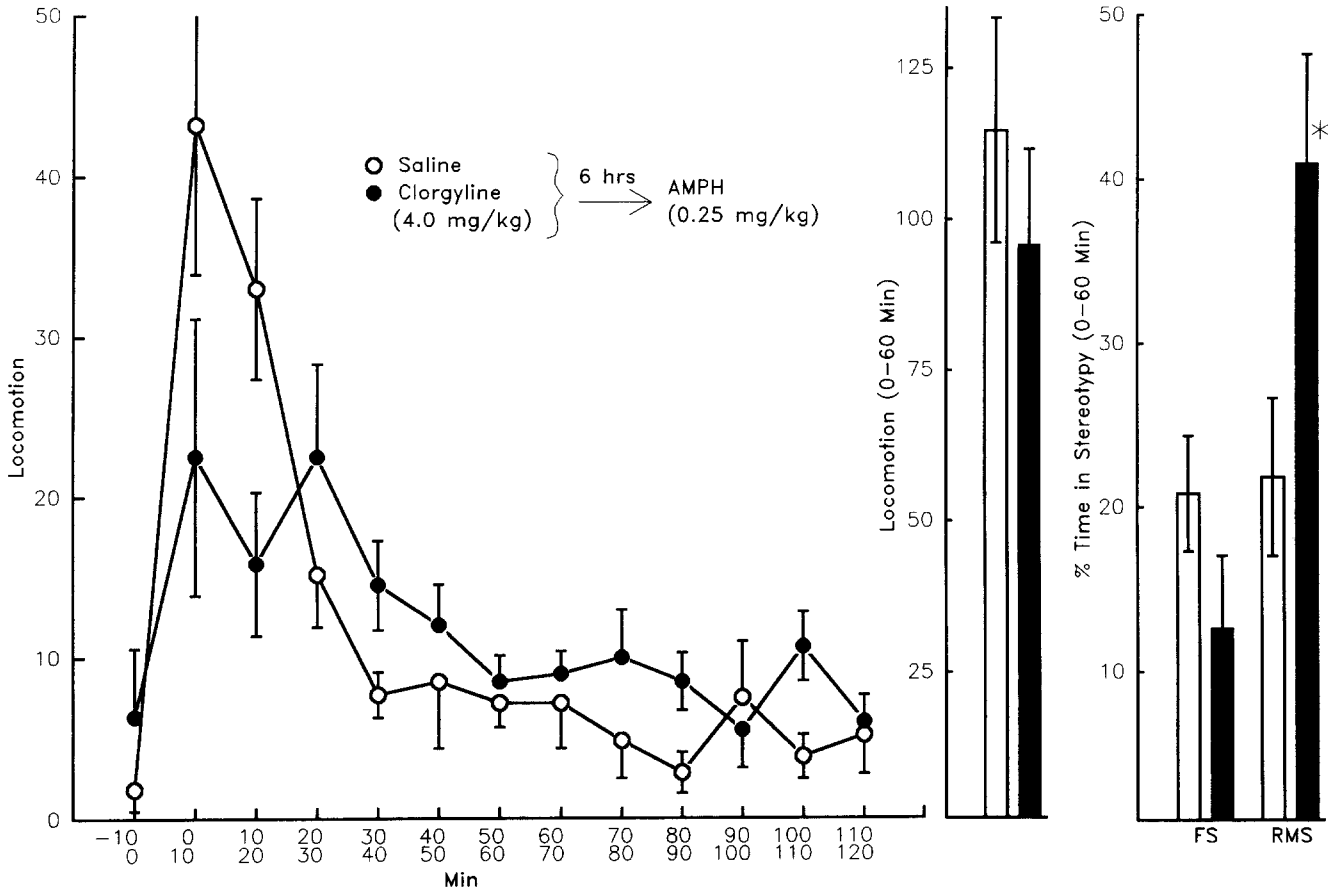

FIG. 4. Effects of clorgyline pretreatment on the behavioral response to 0.25 mg/kg AMPH. Left: Temporal profile of the locomotor (crossovers + rearings) response to the subcutaneous administration of 0.25 mg/kg AMPH 6 h following pretreatment with saline (n = 6) or clorgyline (n = 6). Right: Histograms represent the locomotor and stereotypy (FS, focused sniffing; RMS, repetitive movements) response profiles cumulated over the initial 60 min after AMPH administration. *$p < 0.05$.

ing, oral stereotypy emerged as the predominant form of perseverative behavior in clorgyline-pretreated animals.

Amphetamine (0.25 mg/kg) significantly increased caudate DA in saline-pretreated animals, $F(6, 30) = 25.3$, $p = 0.001$ (Fig. 6, top) to a peak extracellular concentration of about 400% of baseline within the first 40 min after injection (baseline, 23 ± 2; 0–20 min, 88 ± 14; $p = 0.003$). Clorgyline significantly enhanced the AMPH-induced DA response within the initial 60 min (Fig. 6), even when the DA level was corrected for preinjection differences in concentration (Fig. 6, top right). Amphetamine also significantly decreased both DOPAC, $F(6, 30) = 13.2$, $p = 0.001$, and HVA, $F(6, 30) = 6.4$, $p = 0.001$, to a maximum of 55 and 75% of baseline, respectively. Comparable temporal patterns were observed in clorgyline-pretreated animals [DOPAC: $F(6, 24) = 13.8$, $p = 0.001$; HVA: $F(6, 24) = 4.6$, $p = 0.003$].

Amphetamine produced a similar response profile in accumbens DA dynamics (Fig. 6, bottom). Extracellular DA was significantly increased, $F(6, 24) = 5.4$, $p = 0.001$, and achieved an approximately four-fold increase within 1 h after AMPH injection (baseline, 16.3; 0–20 min, 62.1; $p = 0.044$). Similarly, as with the caudate response, clorgyline pretreatment significantly enhanced the AMPH-induced elevation of DA even when DA was corrected for preinjection differences in concentration (Fig. 6, bottom right). The pattern of change in the DA metabolites was similar to that observed in the caudate.

DISCUSSION

The responses of caudate and accumbens DA dynamics to clorgyline are consistent with irreversible inhibition of type A MAO (9). As we (21) and other (4,13) have previously reported for caudate, this drug produced persistent decreases in extracellular DOPAC and HVA and corresponding increases in extracellular DA and 3MT in accumbens as well. The decreases in DOPAC and HVA presumably result from inhibition of MAO-A in DA nerve terminals. MAO-A inhibition likely augments the vesicular DA pool in addition to the cytoplasmic pool, leading to elevated basal DA (i.e., impulse-mediated release).

The prolonged elevation of 3MT presumably derives from the enhanced extracellular levels of DA since catechol-*O*-methyl-transferase is localized outside DA nerve terminals (10,12,24). In addition, elevated 3MT concentrations may also reflect a reduction in 3MT metabolism to HVA since MAO-A

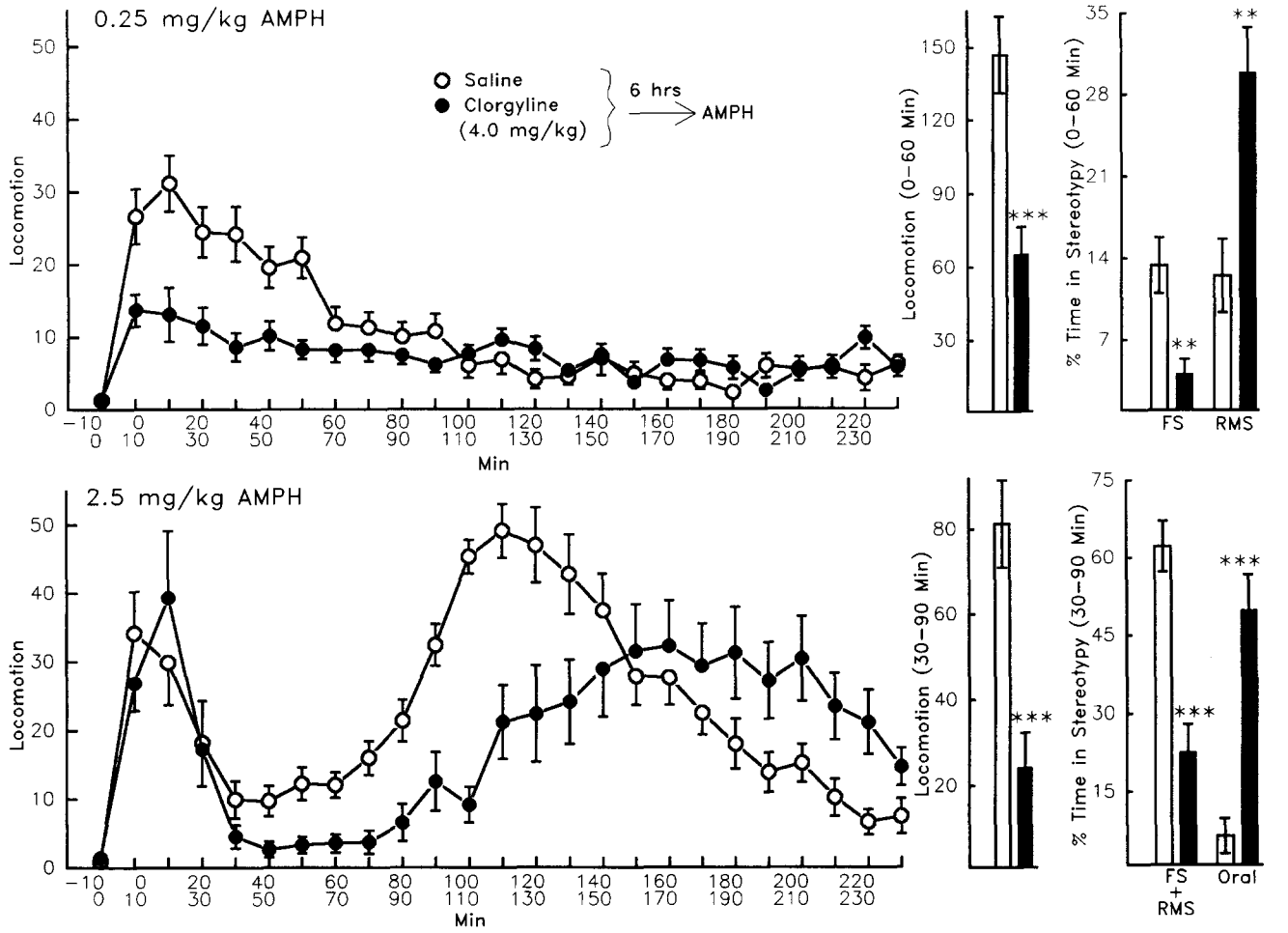

FIG. 5. Effects of clorgyline pretreatment on the behavioral response to AMPH. Left: Temporal pattern of the locomotor response (horizontal + vertical measures; see the Results section for further details) to 0.25 mg/kg (top: saline, $n = 20$; clorgyline, $n = 19$) and 2.5 mg/kg (bottom: saline, $n = 18$; clorgyline, $n = 19$) AMPH. Right: Locomotor and stereotypy (top: saline, $n = 10$; clorgyline, $n = 9$; bottom: saline, $n = 18$; clorgyline, $n = 19$) responses to AMPH, cumulated over the indicated interval. (FS, focused sniffing; RMS, repetitive movements.) $^{**}p < 0.01$; $^{***}p < 0.001$.

may also participate in this conversion. Indeed, if this dose of clorgyline is relatively specific for MAO-A then pronounced accumulation of 3MT and persistent suppression of HVA would suggest that little conversion of 3MT to HVA occurs through MAO-B in either caudate or accumbens.

We have previously noted that, despite the substantial increase in caudate extracellular DA following clorgyline administration, no changes in behavior could be observed (21). The present data confirm those results and extend this apparent dissociation between behavioral activity and DA to the accumbens. In fact, although both caudate and accumbens exhibited four- to five-fold increases in extracellular DA, locomotion did not significantly change (Fig. 1). As we have previously discussed (21), the emergence of compensatory adjustments (such as receptor desensitization) in response to the gradual rise of synaptic DA might have offset the effects of the increases in DA. Alternatively, MAO-A inhibition may not, by itself, produce the pattern of neurochemical changes that are critical for inducing behavioral activation.

In contrast to this apparent dissociation between spontaneous activity and extracellular DA, clorgyline pretreatment produced a significant increase in both the DA and behavioral responses to AMPH. The behavioral change for both the low (0.25 mg/kg) and moderate (2.5 mg/kg) doses of AMPH was characterized by a shift to more intense forms of stereotypy and corresponding decreases in locomotion. This pattern of enhanced responsiveness closely resembles the changes in stereotypy that occur with increasing dose. The caudate and accumbens DA response to AMPH was also significantly augmented, consistent with an increase in AMPH-releasable cytoplasmic DA. In this regard, we previously speculated (15) that the dose-dependent AMPH-induced increase in extracellular DA concentrations may be related to the progressive increase in response preservation associated with increasing doses of the drug. Thus, the potentiated DA response in clorgyline-pretreated animals may be responsible for the changes in the stereotypy profile. It should be noted, however, that MAO-A inhibitors such as clorgyline are alleged to block the metabolism of other monoamines including NE and serotonin, both of which have been implicated in the AMPH re-

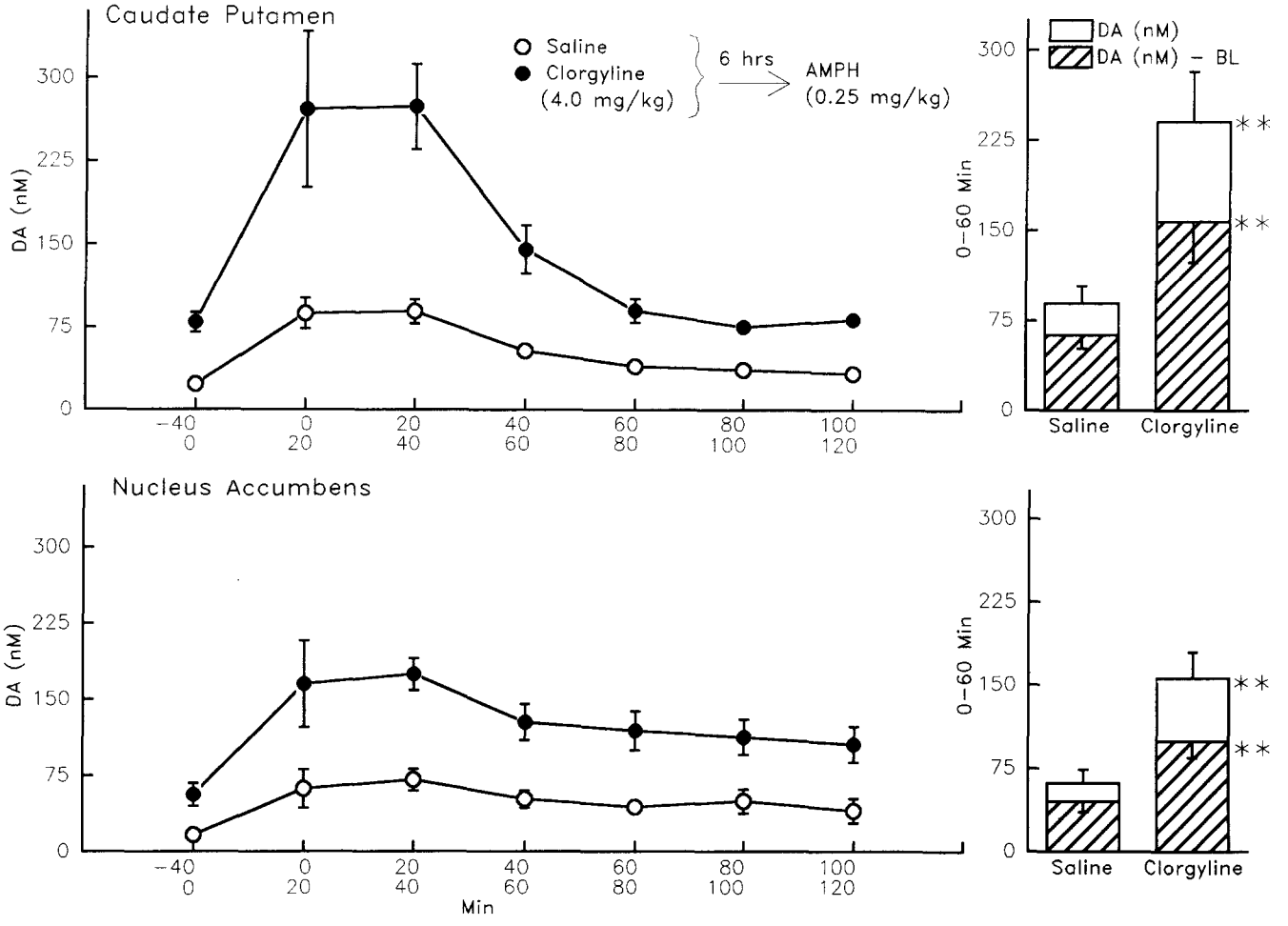

FIG. 6. Effects of 0.25 mg/kg AMPH on extracellular DA in caudate-putamen (top: saline, $n = 6$; clorgyline, $n = 5$) and nucleus accumbens (bottom: saline, $n = 5$; clorgyline, $n = 6$). Left: Temporal profile of dialysate DA concentration in response to AMPH. Right: Histograms represent the cumulated DA response during the initial 60 min following AMPH administration. Data are presented as absolute concentration (open bar) or corrected for corresponding baseline (BL) values (hashed bar). For this analysis, baseline is defined as the dialysate DA concentration detected during the 40-min interval immediately preceding AMPH administration. **Significantly different from corresponding saline-pretreated group ($p < 0.01$).

sponse (8,17,19,28). Therefore, it is possible that, as with DA, clorgyline pretreatment may also enhance AMPH-induced increases in NE (17) and serotonin (15). In fact, as we have previously argued (15,16,18), our converging evidence suggests that changes in extracellular DA alone do not appear to fully account for the quantitative features of the behavioral activation induced by AMPH. Thus, all of these neurochemical changes resulting from MAO-A inhibition may contribute to the changes in the AMPH behavioral profile.

Our observations regarding the AMPH response following clorgyline pretreatment have potentially important implications for the augmented behavioral response observed with repeated AMPH administration since an increase in AMPH-releasable DA has been proposed to underlie stimulant sensitization (25-27). In fact, several investigators have reported an enhanced DA response to AMPH challenge following repeated AMPH pretreatment (1,22,27) and it has been suggested (25-27) that an augmented presynaptic DA pool may mediate this increased DA response. Since MAO inhibition, which presumably leads to elevated DA levels in both the cytoplasmic and vesicular pools, did in fact result in a significantly greater AMPH-induced DA release and stereotypy response, our results following clorgyline pretreatment are consistent with such a mechanism. However, although the DA response to AMPH was enhanced in both caudate and accumbens following clorgyline pretreatment, a potentially important difference between the effects of clorgyline and repeated AMPH administration is that only the MAO inhibition alters basal DA dynamics. That is, as discussed above, basal DA is persistently increased after clorgyline pretreatment, whereas repeated AMPH does not appear to significantly alter baseline DA levels (2,11,22,23,27,31). Our results indicate that an increase in cytoplasmic DA elevates vesicular DA, presumably through the dynamic equilibrium that exists between these pools. Thus, the absence of increased basal DA after repeated AMPH is not readily compatible with an increase in either vesicular or cytoplasmic DA, and therefore the mechanism underlying the enhanced DA response to AMPH challenge

following repeated AMPH pretreatment remains to be determined.

Furthermore, the role of DA in AMPH-induced behavioral sensitization is further complicated by our recent findings of a decreased caudate and accumbens DA response in animals exhibiting an augmented behavioral response following previous exposure to multiple injections of AMPH (31). These results appear to suggest that, at least under some experimental conditions, other processes or mechanisms, including a role for non-DA systems, may be implicated in the sensitization phenomenon that results from repeated AMPH administration.

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