Sensitization of Amphetamine-Induced Stereotyped Behaviors During the Acute Response

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ABSTRACT
The quantitative and qualitative features of the behavioral response to amphetamine-like stimulants in rats can be dissociated from the dopamine response. This dissociation is particularly evident in the temporal profiles of the extracellular dopamine and stereotypy responses to higher doses of amphetamine. One possible mechanism contributing to this temporal dissociation is that during the acute response to amphetamine, dopamine receptor mechanisms are enhanced such that stereotyped behaviors can be supported by synaptic concentrations of dopamine which are not sufficient to initiate these behaviors. To further explore the dynamics of stimulant sensitivity during the acute response, we examined the behavioral and extracellular dopamine responses to a low, nonstereotypy-producing dose of amphetamine (0.5 mg/kg) at various times after an acute, priming injection of 4.0 mg/kg when stereotypies had subsided and extracellular dopamine was approaching predrug baseline levels. The low-dose challenge produced intense stereotypies although the regional dopamine responses were not significantly different from control animals. Blockade of the expression of stereotypies during the priming response by the D2 antagonist haloperidol or the D1 antagonist SCH 23390 prevented the expression of an enhanced stereotypy response to the challenge injection. Our results suggest that an exposure to amphetamine results in a rapid sensitization of the stereotypy response which does not involve changes in the extracellular dopamine response but requires activation of dopamine receptors. Such a mechanism may be significantly implicated during binge patterns of stimulant abuse and may also play a role in the sensitization associated with repeated amphetamine administration.

Converging evidence indicates that increases in dopaminergic transmission in the nucleus accumbens (NA) and the caudate-putamen (CP) play a crucial role in the locomotion and stereotypy produced by amphetamine-like stimulants in rats. Consistent with this idea, amphetamine (AMPH) has been shown to increase extracellular dopamine (DA) in these brain regions (Sharp et al., 1987; Carboni et al., 1989; Robinson and Camp, 1990; Kuczenski et al., 1991), and dose-response comparisons suggest a significant relationship between the magnitude and duration of the DA responses and AMPH-induced increases in these behaviors (Sharp et al., 1987; Kuczenski and Segal, 1989). However, evidence now indicates that under a variety of conditions, the quantitative and qualitative features of the behavioral response profile to AMPH-like stimulants can be dissociated from the DA responses (see Segal and Kuczenski, 1994, for a review). The dissociation is particularly evident in the temporal profiles of the DA and stereotypy responses to intermediate and higher doses of AMPH. For example, after 5.0 mg/kg AMPH, maximal CP DA concentrations are achieved within 20 to 30 min after drug administration, corresponding to the onset of oral stereotypies. However, oral stereotypies persist while extracellular DA concentrations, as well as brain and extracellular AMPH concentrations (Kuczenski and Segal, 1989; Kuczenski et al., 1997), rapidly decline to levels less than peak values typically associated with lower, nonstereotypy-producing doses of the drug (Kuczenski and Segal, 1989). One possible mechanism underlying this temporal dissociation is that the high peak DA concentration achieved during the initial response to the drug is required to “trigger” the appearance of focused stereotypies, but that DA is not required for the maintenance of these behaviors. However, in a test of this hypothesis, we found that administration of haloperidol during the declining phase of extracellular DA interrupts the further expression of stereotypies, indicating that continued stimulation of DA receptors is necessary for these behaviors to be maintained (Conti et al., 1997).

An alternative explanation for this temporal dissociation is that during the acute response to AMPH, the sensitivity of DA receptors and/or postreceptor mechanisms is enhanced such that stereotyped behaviors can be supported by synaptic concentrations of DA which are not sufficient to initiate these
behavioral responsivity which occurs during the response to and D2 DA receptor mechanisms are required for the altered dose AMPH challenge, suggesting that activation of both D1 and D2 DA receptor mechanisms.

To test this hypothesis, we examined the behavioral and the CP and NA DA responses to low, nonstereotypy-producing doses of AMPH (0.5–1.5 mg/kg) at various times after an acute "priming" injection of 4.0 mg/kg AMPH when stereotypies had subsided and extracellular DA was approaching predrug baseline levels. Our results revealed that challenge with the low doses of AMPH resulted in the reemergence of intense, focused stereotypies although the CP and NA DA responses were not significantly different from control values. To determine the relative contributions of D1 and D2 receptors to this rapid sensitization during exposure to the priming dose of AMPH, we examined the effects of pretreatment with low doses of haloperidol (HAL) or SCH 23390. Pretreatment with either DA receptor antagonist before the priming dose of AMPH prevented the emergence of intense stereotypies during the subsequent low-dose AMPH challenge, suggesting that activation of both D1 and D2 DA receptor mechanisms are required for the altered behavioral responsivity which occurs during the response to acute AMPH.

Materials and Methods

Subjects. Male Sprague-Dawley rats, weighing 300 to 325 g at the beginning of the experiment, were housed for at least one week before experimental manipulation in groups of two or three in wire mesh cages, with ad libitum access to food and water, in a temperature- and humidity-controlled room, maintained on a 14-h light (5:00 AM to 7:00 PM)/10-h dark cycle. Animals were obtained from Simonsen Labs (Gilroy, CA). All studies adhered to animal welfare guidelines outlined in “Principles of Laboratory Animal Care” (National Institutes of Health Publication no. 85-23).

Three days before the beginning of a drug treatment, animals were placed in individual experimental chambers where they remained for the duration of the experiment. To facilitate habituation to the chambers and procedures, animals were handled and injected with saline once each day. During the remainder of the day and night, animals were not disturbed and their behavior was continuously monitored.

Experimental Chambers. Behavior was monitored in custom-designed activity chambers (Segal and Kuczenski, 1987). Briefly, each of the chambers was located in a sound-attenuated cabinet maintained on a 14-h/10-h light/dark cycle with constant temperature (20°C) and humidity (55 ± 5%). Each chamber consisted of two compartments: an activity/exploratory compartment (30 × 20 × 38 cm) that was connected to a smaller “home” compartment (14 × 14 × 10 cm) in which food and water were available ad libitum. Movements of the animal between quadrants within the activity/exploratory compartment (crossovers) and rearings against the wall, as well as eating and drinking and other vertical (e.g., contact with a hanging stimulus) and horizontal movements (e.g., intercompartment movements) were monitored continuously by computer. In addition to the computer-monitored behaviors, representative animals (n = 5–7 per group) were simultaneously videotaped, typically for 60 s at successive 5-min intervals for up to 6 h to assess the qualitative features of the response. Raters who were unaware of the specific experimental conditions subsequently rated the videotapes on the basis of behavior ethograms and rating procedures established previously (Segal and Kuczenski, 1987). Stereotypy was assessed as the percentage of the observation interval during which the animal displayed each specific behavior. In response to the doses used in the present studies, animals exhibited primarily repetitive head and limb movements and oral behaviors consisting of licking and/or biting directed at the floor of the cage. The appearance of other responses or behavior patterns, undetectable by our automated methods, was noted by the rater after each sampling interval. Raters were highly trained and there were no significant differences between their ratings. In addition, all comparison groups were rated by a single individual to facilitate quantitation of behavioral changes between the experimental groups.

Drugs. Amphetamine sulfate (National Institute on Drug Abuse, Rockville, MD) was dissolved in saline and administered s.c. SCH 23390 (Research Biochemicals, Inc., Natick, MA) was dissolved in saline and administered i.p. Haloperidol (Ortho-McNeil, Raritan, NJ).
NJ) was diluted in saline and administered i.p. Amphetamine doses represent the free base, whereas HAL and SCH 23390 doses were as the salt.

Microdialysis. For dialysis studies, animals were stereotaxically implanted with guide cannulas by procedures previously described in detail (Kuczenski and Segal, 1989). Guide cannulas extended 2.6 mm below the surface of the skull and were aimed at the CP (1.0 mm anterior to bregma, 2.8 mm lateral, and 6.2 mm below dura) or the NA (2.2 mm anterior, 1.5 mm lateral, 7.8 mm below dura). After surgery, animals were housed individually and allowed at least 1 week to recover before receiving any treatment.

On the day before the experiment (3:00–4:00 PM), each rat was placed in an experimental chamber and the dialysis probes were inserted to allow for acclimation to the test environment and for adequate equilibration of the dialysis probes. The dialysis chambers were essentially identical with the behavioral chambers described above, with the exceptions that the home compartment and hanging stimulus were removed to prevent interferences introduced by the dialysis methodology. Concentric microdialysis probes were constructed of Spectra/Por hollow fiber (Spectrum, Houston, TX) (molecular weight cut off 6000, o.d. 250 μ) according to the method of Robinson and Whishaw (1988) with modifications as described previously (Kuczenski and Segal, 1989). The length of the active probe membrane was 3 mm for the CP and 1.5 mm for the NA. Probes were perfused with artificial cerebrospinal fluid (147 mM NaCl, 1.2 mM CaCl₂, 0.9 mM MgCl₂, 4.0 mM KCl) delivered by a microinfusion pump (1.5 μl/min) via 50 cm of Micro-line ethyl vinyl acetate tubing connected to a fluid swivel. Dialysate was collected through glass capillary tubing into vials containing 20 μl of 25% methanol and 0.2 M sodium citrate, pH 3.8. Under these conditions, dialysate DA and metabolites were stable throughout the collection and analysis interval. Samples were collected outside the experimental chamber to avoid disturbing the animal. Individual probe recoveries were estimated by sampling a standard DA solution in vitro. At the end of the experiment, each animal was perfused with formalin for histological verification of probe placements.

Dialysate samples were collected every 20 min and were assayed for DA, 3,4-dihydroxyphenylacetic acid, homovanillic acid, and 5-hydroxyindoleacetic acid. The high-performance liquid chromatography-electrochemical detector consisted of a 100 mm × 4.6 mm ODS-C18 3 μ column (Regis Chemical Co., Morton Grove, IL) maintained at 40°C. Mobile phase (0.05 M citric acid, 7% methanol, 0.1 mM Na₂EDTA, and 0.2 mM octane sulfonate adjusted to pH 4.0–4.5) was delivered at 0.6 to 0.8 ml/min by a Waters model 510 pump (Waters Corp., Milford, MA). Amines were detected with a Waters 480 detector with a glassy carbon electrode maintained at +0.65 V relative to
a Ag/AgCl reference electrode. Concentrations were estimated from peak heights with a Waters Maxima 820 data station. Substances in the dialysates were corrected for individual probe recoveries to account for this source of variability and although the exact relationship between dialysate concentration and actual extracellular transmitter content is not clear (Wages et al., 1986; Church et al., 1987; Benveniste et al., 1989; Stahle et al., 1991), values are presented as dialysate concentration to allow for meaningful comparisons to other data in the literature.

Data Analysis. Behavioral and neurochemical data were statistically analyzed with repeated-measures analysis of variance and t-tests with Bonferroni corrections for specific group/time comparisons.

Results

The acute administration of 4.0 mg/kg AMPH resulted in a multiphasic locomotor response profile (Fig. 1) which included an initial phase of enhanced locomotion, an intermediate period during which animals did not locomote but engaged in intense stereotyped behaviors (repetitive head or limb movements and/or oral behaviors), and a poststereotypy locomotor phase. In contrast, the acute administration of 0.5 mg/kg AMPH produced an enhanced locomotor response in the absence of stereotyped behaviors (Fig. 1). To determine whether the low-dose response is altered during the declining phase of the high-dose response, separate groups of animals were injected with 4.0 mg/kg AMPH (primer) and subsequently challenged 3 h later with saline or 0.5 mg/kg AMPH (challenge) during the poststereotypy locomotor phase when focused stereotypies were no longer evident. The responses to the saline and 0.5 mg/kg AMPH challenge injections are summarized in Fig. 2. After administration of saline, there was a brief interruption of locomotion associated with handling, after which animals reengaged in locomotor activation that followed a time course typical for a 4.0-mg/kg dose. In contrast, after administration of 4.0 mg/kg AMPH, intense repetitive movements and oral stereotypies reemerged by the

![Caudate-Putamen](A) and nucleus accumbens (B) DA responses to an injection of 4.0 mg/kg AMPH or saline (at time zero) followed 3 h later by 0.5 mg/kg AMPH, indicated by the arrows. Values are the means ± S.E.M. BL represents the median of the three samples collected immediately before the first injection. The number of animals in each group is indicated in parentheses.

Fig. 3. Temporal profile of the caudate-putamen (A) and nucleus accumbens (B) DA responses to an injection of 4.0 mg/kg AMPH or saline (at time zero) followed 3 h later by 0.5 mg/kg AMPH, indicated by the arrows. Values are the means ± S.E.M. BL represents the median of the three samples collected immediately before the first injection. The number of animals in each group is indicated in parentheses.
second 10-min interval (190–200 min after the initial 4.0 mg/kg AMPH primer), and persisted for an additional 30 to 50 min. The locomotor response that emerged after stereotypy was not greater than an acute, 0.5-mg/kg response (see Fig. 1), although the duration was longer.

A parallel microdialysis study was conducted to determine whether the 4.0 mg/kg AMPH primer altered the extracellular DA response profiles in the CP or the NA to a subsequent 0.5 mg/kg AMPH challenge and the results are presented in Fig. 3. Animals that were administered saline and then challenged 3 h later with 0.5 mg/kg AMPH exhibited an increase in CP and NA extracellular DA about 5-fold over baseline levels. Priming with 4.0 mg/kg AMPH had no significant effect on either the CP or NA DA responses to the 0.5 mg/kg AMPH challenge 3 h later (Fig. 3). In contrast, the 0.5 mg/kg AMPH challenge in the 4.0 mg/kg AMPH-pretreated group resulted in the reemergence of intense stereotypies (data not shown) similar to the profile described above (Fig. 2).

To determine whether context-dependent conditioning is a factor in the enhanced stereotypy response to the 0.5-mg/kg AMPH challenge after the 4.0 mg/kg primer, the injection procedure was modified to minimize association of drug administration with the experimental chamber. For 4 days before drug testing, all animals were removed from the experimental chambers each day at about 8:00 AM, injected with saline, and placed in opaque plastic containers (11.5 × 7.25 × 5 inches). Three hours later, they were injected with saline and replaced into the experimental chambers until the following day. On the fifth day, the rats were removed from the experimental chamber, administered the saline or 4.0 mg/kg AMPH primer, and then placed into the plastic chambers. Three hours later, all animals were administered the 0.5-mg/kg AMPH challenge dose and then transferred to the experimental chamber. The number of animals in each group is indicated in parentheses. Animals receiving a priming injection with 4.0 mg/kg AMPH exhibited significantly more stereotyped behaviors (repetitive head and limb movements and oral stereotypies) in response to the 0.5 mg/kg AMPH challenge (Inset; \( t = 47.40, P < .001 \)).

Fig. 4. Effects of a priming dose of 4.0 mg/kg AMPH in one environment on the locomotor stereotypy responses to 0.5 mg/kg AMPH in a different environment. For 4 days before drug testing, all animals were removed from the experimental chambers each day at about 8:00 AM, injected with saline, and placed in opaque plastic containers (11.5 × 7.25 × 5 inches). Three hours later, they were injected with saline and replaced into the experimental chambers until the following day. On the fifth day, the rats were removed from the experimental chamber, administered the saline or 4.0 mg/kg AMPH primer, and then placed into the plastic chambers. Three hours later, all animals were administered the 0.5-mg/kg AMPH challenge dose and then transferred to the experimental chamber. The locomotor and stereotypy responses to the 0.5-mg/kg AMPH challenge are summarized in Fig. 4. Saline-pretreated animals exhibited an enhanced locomotor profile typical of this dose. In contrast, animals primed with 4.0 mg/kg AMPH exhibited a period of intense stereotypy consisting of repetitive head or limb movements and oral behaviors.
To examine the persistence of the enhanced stereotypy response to the low dose of AMPH, separate groups of animals were injected with 0.5 mg/kg AMPH at 3, 4, or 5 h after an initial injection of saline or 4.0 mg/kg AMPH, and the results are presented in Fig. 5. In saline-pretreated animals, 0.5 mg/kg AMPH promoted a behavioral response profile consisting of locomotion in the absence of focused stereotypies, and because there were no significant differences among the three groups, these data were combined. In animals receiving the 4.0 mg/kg-AMPH priming dose, the enhanced stereotypy and corresponding decrease in locomotion were most pronounced in the 3-h time group. In the 4-h group, some AMPH-pretreated animals still exhibited episodes of repetitive head movements in response to the 0.5-mg/kg AMPH injection, and as a consequence, the locomotor response was significantly less than that for the saline-pretreated group. By 5 h, both saline- and AMPH-pretreated groups exhibited only locomotion and the magnitude of the locomotor responses of the two groups was not significantly different. However, the time course of this sensitization effect was dose-dependent because in response to a higher challenge dose of AMPH (1.5 mg/kg), intense stereotyped behaviors (repetitive head and limb movements) could still be elicited for at least 5 h after priming with a 4.0 mg/kg dose of AMPH (Fig. 6).

To determine whether the development of the sensitized stereotypy response required activation of D1 and/or D2 DA receptors, we used SCH 23390 (0.05–0.20 mg/kg) or HAL (0.1 mg/kg) at doses thought to be relatively selective between the D1 and D2 receptors, respectively (Hyttel, 1978, 1981, 1983; Christensen et al., 1984). Preliminary studies were conducted involving systematic manipulation of dose and time parameters to establish treatment conditions which 1) blocked the expression of stereotyped behaviors in response to a priming injection of 4.0 mg/kg AMPH and 2) did not interfere with the stereotypy response to 2.5 mg/kg AMPH injected at time corresponding to challenge injection. This dose of AMPH was selected because it produces a response that closely resembles the behavioral profile of the response to the 1.5 mg/kg AMPH challenge 5 h after the 4.0 mg/kg challenge.
AMPH primer. Also in this regard, we chose to examine the role of D1 and D2 receptor activation with the 1.5 mg/kg challenge paradigm at 5 h to minimize potential direct effects of the DA receptor antagonists on the challenge response. The locomotor and stereotypy responses to 2.5 mg/kg AMPH in animals pretreated 5 h earlier with saline or the highest HAL and SCH 23390 doses used were not significantly different (analysis of variance (ANOVA), stereotypy response, 10–100 min, \( F_{(2,19)} = 0.99, P = 0.39 \); ANOVA, locomotion, 0–10 min, \( F_{(2,19)} = 0.83, P = 0.46 \)). Based on these results, groups of animals were pretreated with saline, SCH 23390, or HAL 15 to 30 min before the administration of 4.0 mg/kg AMPH. Five hours after the AMPH treatment, all animals were subsequently administered a 1.5-mg/kg AMPH challenge injection. HAL completely prevented the expression of stereotyped behaviors (which were replaced by locomotor activation) during the response to the 4.0 mg/kg AMPH (Fig. 7A). HAL pretreatment also blocked the enhanced responsiveness to subsequent challenge with 1.5 mg/kg AMPH (Fig. 7B).

A somewhat similar pattern of response was evident in SCH 23390-pretreated animals (Fig. 8). However, examination of the locomotor and stereotypy profiles for individual animals revealed a wide range of individual variation in sensitivity so that at both doses of SCH 23390 used, some animals displayed a typical stereotypy response to the 4.0 mg/kg AMPH primer (Fig. 9, A and C). Furthermore, sub-grouping of animals based on their stereotypy responses to the primer after antagonist administration revealed divergent responses to the challenge injection. Thus, for both SCH 23390 doses tested, blockade of stereotypies during the response to the priming dose prevented the appearance of a sensitized stereotypy response to the 1.5 mg/kg challenge. In contrast, animals which exhibited a stereotypy response during the priming dose also displayed stereotyped behavior to the subsequent injection of 1.5 mg/kg AMPH (Fig. 9 B and D).

**Discussion**

The acute administration of AMPH-like stimulants results in a variety of dose-dependent behavioral effects, and converging evidence implicates NA and CP DA in the locomotion and stereotypy induced by these drugs. Although most studies have suggested dose-response relationships between the intensity and duration of the behavioral and extracellular DA responses, there appears to be no simple quantitative...
relationship between relative extracellular DA concentrations and specific components of the stimulant-induced locomotor and stereotypy profiles. In the present studies, we confirmed our previous observation (Kuczenski and Segal, 1989; Kuczenski et al., 1997) that intense focused stereotypies in response to a moderate dose of AMPH (4.0 mg/kg) persisted during the pronounced decline in extracellular DA. In addition, we now show that after the stereotypy initiated by this “priming” dose had completely subsided, this behavior could be reinitiated in response to a low dose of AMPH (0.5 mg/kg) which by itself produces only locomotor activation. Importantly, this enhanced behavioral response occurred without a corresponding increase in extracellular DA to levels typically associated with intense stereotypies.

There are a number of possible explanations for this profound dissociation between the intensity of stereotypy and levels of DA. For one, it could be argued that extracellular DA does not provide an accurate index of synaptic DA dynamics and that the functionally relevant synaptic DA response pattern is substantially different from the extracellular pool. However, this possibility seems unlikely for several reasons. First, most evidence suggests that physiological and pharmacological manipulations of DA function result in changes in DA in the extracellular space, assessed by either microdialysis or in vivo electrochemistry, that parallel predicted changes in synaptic DA (see Di Chiara, 1991; Westerink, 1995; Blaha and Phillips, 1996, for reviews). Second, particularly relevant to the present studies, we have previously shown that after AMPH administration, extracellular DA concentrations are highly correlated with extracellular concentrations of AMPH, and that the rate constants for the decline of extracellular DA, extracellular AMPH, and tissue levels of AMPH are comparable (Kuczenski et al., 1997). Based on the mechanism of action of AMPH, the release of DA into the synaptic cleft should be proportional to extracellular and/or tissue levels of the drug. Therefore, it is most reasonable to conclude that AMPH-induced changes in the concentration of DA in the synaptic cleft will parallel AMPH pharmacokinetics. Thus, at least in the presence of AMPH, extracellular DA seems to provide an accurate reflection of

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**Fig. 7.** Effect of HAL on the locomotor and stereotypy responses to the subsequent administration of 4.0 mg/kg AMPH (A, priming response) and, 5 h later, 1.5 mg/kg AMPH (B, challenge response). Groups of animals received saline (SAL) or 0.1 mg/kg HAL 15 min before the priming dose of AMPH (4.0 mg/kg). After an additional 5 h, the animals were challenged with 1.5 mg/kg AMPH. Histograms represent the stereotypy (repetitive head and limb movements and oral behaviors) cumulated over the indicated interval. All values represent means ± S.E.M. The number of animals in each group is indicated in parentheses. Priming response: ***P < .001, t = 8.37, compared to SAL-SAL; **P < .01, t = 9.56 compared with HAL-AMPH. Challenge response: ***P < .001, t = 7.46 compared with SAL-SAL; **P < .01, t = 9.56 compared with SAL-AMPH.
synaptic DA dynamics. Therefore, the persistence of intense stereotypies after acute AMPH administration during the rapid decline in synaptic DA and AMPH, as well as the reinitiation of intense stereotypies in response to the low-dose AMPH challenge, likely reflects altered responsivity to AMPH-induced neurochemical changes other than DA release.

One mechanism which could contribute to such an enhanced response is an increased sensitivity of DA receptors. Our results, that the appearance of stereotyped behaviors after acute AMPH administration during the rapid decline in synaptic DA and AMPH, as well as the reinitiation of intense stereotypies in response to the low-dose AMPH challenge, likely reflects altered responsivity to AMPH-induced neurochemical changes other than DA release.

Fig. 8. Effect of SCH 23390 on the locomotor and stereotypy responses to the subsequent administration of 4.0 mg/kg AMPH (A, priming response) and 5 h later, 1.5 mg/kg AMPH (B, challenge response). Groups of animals received saline (SAL), 0.05 or 0.2 mg/kg SCH 23390 15 min before the priming dose of AMPH (4.0 mg/kg). After an additional 5 h, the animals were challenged with 1.5 mg/kg AMPH. The number of animals in each group is indicated in parentheses. ANOVA revealed a significant effect of pretreatment on the stereotypy response to 4.0 mg/kg AMPH (F(2,25) = 7.04, P < .004). ANOVA also revealed a significant effect of pretreatment on the stereotypy response to the subsequent 1.5 mg/kg AMPH challenge (F(2,27) = 6.87, P < .004).

animals, but had little effect in the remaining animals. It appears, therefore, that a critical threshold (subject to individual variation) governs the stereotypy-antagonistic actions of these drugs. Nevertheless, activation of both receptors during the priming phase appears to influence the development of the subsequent sensitized response. Thus, it is possible that subthreshold concentrations of DA are capable of maintaining and/or reinitiating stereotypy because of enhanced DA receptor responsivity. However, ongoing behavioral studies with DA receptor agonists have revealed subtle changes in the qualitative and quantitative features of responsivity to these agents which are not entirely consistent with a simple increase in the sensitivity of DA receptors (unpublished results). Additional behavioral studies, as well as neurochemical characterization of DA receptor function will be required to further assess the role of changes in receptor sensitivity in the acute AMPH sensitization effect. Another possible explanation for these effects is based on the premise that AMPH affects a neural system(s) which inhibits or competes with the expression of focused stereotypies. For example, some evidence suggests that...
AMPH-induced DA release acting on D2 receptors in the frontal cortex can inhibit drug-induced stereotyped behaviors (Karler et al., 1997; Bedingfield et al., 1997; Karler et al., 1998). The rapid development of tolerance or tachyphylaxis to DA release in the frontal cortex could then result in the disinhibition of CP DA effects. Several observations regarding the pharmacodynamics of AMPH-like stimulants are generally consistent with a disinhibition hypothesis. For one, as previously discussed, focused stereotypies persist in response to moderate doses of AMPH whereas DA and AMPH concentrations rapidly decline below levels which are required to initiate these behaviors (Kuczenski and Segal, 1989; Kuczenski et al., 1997). In addition, the onset of stereotypies after the acute administration of a high dose of AMPH is markedly delayed relative to the appearance of peak extracellular DA concentrations; i.e., after i.v. AMPH, for example, extracellular CP DA peaks within the first 2 min after drug administration, but oral stereotypies do not appear for an additional 20 min, during which time DA concentrations have declined by 50% (Cho et al., 1998). These apparent discrepancies between the temporal patterns of CP DA and behavioral activation by AMPH might be reconciled if the initial pharmacological effect of AMPH includes activation of an “inhibitory” neural system that rapidly develops tolerance. Thus, during the initial interval after high-dose AMPH administration, focused stereotypies would be suppressed until tolerance or tachyphylaxis developed to the effects of AMPH on this inhibitory system, at which time CP dopaminergic activation would prevail and stereotypy would emerge. Furthermore, with continued tachyphylaxis of this inhibitory influence, stereotypy could then persist in spite of the decline of extracellular DA to levels which do not normally initiate these behaviors. In addition, the ability of a low, normally nonstereotypic dose of AMPH to reinitiate stereotypies would also reflect the continued presence of tachyphylaxis in such an inhibitory system.

The acute sensitization phenomenon may be especially important within the context of binge patterns of stimulant abuse involving frequent administration of the drug at short intervals. In addition, these observations could also have
implications for the mechanisms underlying certain aspects of the behavioral sensitization associated with repeated intermittent stimulant administration. One hallmark feature of the sensitized response profile associated with moderate doses of AMPH is a more rapid onset and intensification of AMPH-induced stereotyped behaviors (see Segal and Kuczenski, 1994, for a review), and, in the present experiments, the rapid emergence of intense stereotypy in response to a low-dose AMPH challenge parallels those features of the sensitized response. It is conceivable, therefore, that with repeated AMPH administration, a more persistent alteration in receptor mechanisms and/or tolerance in a system that is inhibitory to the expression of stereotyped behaviors could lead to both a more rapid onset and an intensification of these behaviors to subsequent exposure to the drug. However, the enhanced responsivity which we report above appears to be relatively specific for AMPH-induced stereotypes; i.e., the locomotor response to a challenge injection of 0.5 mg/kg AMPH at 5 h after the priming dose is not different from that of controls (Fig. 5), whereas at this same time point, behaviors are intensified in response to 1.5 mg/kg of the drug (Fig. 6). Therefore, it appears that several mechanisms likely contribute to the altered behavioral profile associated with repeated AMPH administration, and our results suggest that the locomotor sensitization may involve different mechanisms that require a longer time course. In this regard, our past results (Leith and Kuczenski, 1982) support a different temporal pattern for the development of locomotor and stereotypy sensitization.

In summary, an acute exposure to AMPH results in a rapid sensitization of the stereotypy response to a subsequent injection of the drug. This sensitization appears to require both D1 and D2 DA receptor activation and does not involve changes in presynaptic dopaminergic transmission, but may reflect altered DA receptor sensitivity. Alternatively, a mechanism may be involved which is inhibitory to the expression of focused stereotypes, and which rapidly develops tolerance/tachyphylaxis to AMPH’s actions. These mechanisms may be significantly implicated in changes which occur during binge patterns of stimulant abuse and may also play a role in the sensitization which is associated with repeated AMPH administration.

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References


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