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# Effects of Serotonergic Manipulations on the Behavioral Sensitization and Disinhibition Associated With Repeated Amphetamine Treatment

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OLAUSSON, P., J. A. ENGEL AND B. SÖDERPALM. *Effects of serotonergic manipulations on the behavioral sensitization and disinhibition associated with repeated amphetamine treatment.* PHARMACOL BIOCHEM BEHAV **66**(1) 211–220, 2000.—This study investigated the effects of repeated amphetamine treatment on locomotor activity and behavioral inhibition in the elevated plus-maze, and the influence of serotonin (5-HT) neurotransmission on these behaviors. Acute administration of amphetamine (1.0 mg/kg subcutaneously [SC]) stimulated locomotor activity, which was attenuated by acute citalopram (5.0 mg/kg SC) pretreatment. Repeated daily treatment with amphetamine (15 days) sensitized the rats to the amphetamine-induced locomotor stimulation. Acute pretreatment with the 5-HT precursor l-5-hydroxytryptophan (5-HTP; 25 mg/kg IP) or chronic treatment with the selective 5-HT reuptake inhibitor citalopram (5.0 mg/kg SC, twice daily), did not alter the expression of amphetamine-induced locomotor sensitization. In the elevated plus-maze, animals subjected to repeated amphetamine treatment expressed behavioral disinhibition after amphetamine exposure (1.0 mg/kg SC; −35 min), which was antagonized both by acute 5-HTP and chronic citalopram treatment. In summary, these findings suggest that behavioral sensitization to amphetamine is associated with amphetamine-induced behavioral disinhibition, and that acute 5-HTP as well as chronic citalopram treatment counteract the expression of amphetamine-induced behavioral disinhibition, but not locomotor sensitization. It appears likely that the antagonistic effects of 5-HTP and citalopram on behavioral disinhibition derive from a drug-induced facilitation of brain 5-HT neurotransmission. © 2000 Elsevier Science Inc.

Amphetamine Behavioral sensitization Locomotor activity Elevated plus-maze Conflict behavior Serotonin Citalopram 5-HTP

DRUGS of abuse share the ability to activate the mesocorticolimbic dopamine (DA) system (15,39), a neural pathway which projects from the ventral tegmental area (VTA) to the main terminal regions in the nucleus accumbens (N Acc) and the prefrontal cortex (PFC; 87). This system has been implicated in mechanisms involved in motivational processes and innate drives (49), but also in mechanisms related to drug reward (16,39,87,88). Therefore, the dopaminergic activation produced by the abused drugs has been implicated in their rewarding and reinforcing effects (16,39,88). In support of this hypothesis numerous experiments have demonstrated that animals self-administer the drugs abused by humans, including amphetamine, into the mesocorticolimbic DA system (39,87,88).

Amphetamine elevates the extracellular monoamine levels, i.e., DA (24,40,41,75), serotonin (5-HT; 24,40,41) and no-

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radrenaline (NA; 21,41), in the mesocorticolimbic DA system and several other brain regions via interference with the monoamine reuptake transporters. It is well known that activation of postsynaptic DA receptors in the N Acc stimulate locomotor activity in experimental animals, and, consequently, the mesocorticolimbic DA activation caused by amphetamine and other psychostimulants is associated with enhanced locomotor activity. Interestingly, the locomotor stimulatory properties of psychostimulants are progressively augmented, sensitized, after repeated exposure to the drug (63,66,74). This behavioral sensitization is long-lasting and appears to be attributed to drug-induced neural alterations, occurring both pre- and postsynaptically, which make the mesocorticolimbic DA system hypersensitive (32,52, 63,71). These changes include increased drug-induced elevation of accumbal DA levels (5,58,59,64,89) as well as enhanced postsynaptic DA receptor function (22,23,38,52). The upregulation of the intracellular second messenger (cAMP) pathways and the altered expression of certain transcription factors (e.g., CREB, c-Fos, c-Jun, and Δ-FosB) observed after exposure to psychostimulants appear to have a critical role in the development of locomotor sensitization (52).

The incentive-sensitization theory of addiction (71) proposes that the neurobiologic processes which underlie behavioral sensitization also are involved in drug-seeking and drug-taking behavior, and that conditioned stimuli provide strong motivational impulses for obtaining and consuming the drug by activating the hypersensitive mesocorticolimbic DA system. Supporting this theory, experiments have demonstrated that previous drug experience may increase subsequent self-administration of both amphetamine (48,62,65) and cocaine (25,26). Moreover, sensitization enhances the rewarding effects of different drugs in the conditioned place preference paradigm (46,76) and increases the responding for conditioned reinforcers (85). Together, these and other findings strongly suggest that drug-induced sensitization of the mesocorticolimbic DA neurons may contribute to the increased control of behavior exerted by stimuli associated with the effects of the reinforcing drugs.

Besides the motivational processes possibly related to drug-induced DA sensitization, also the role of inhibitory control in the development of drug abuse have lately received increased attention (30,69). It is well established that drug addicts using different kinds of addictive drugs, including ethanol, nicotine, opiates and psychostimulants, display decreased inhibitory control when assessed in neuropsychologic tests (2,6,10,36,43,51). This may ultimately contribute to the loss of the drug addicts ability to control the drug use (53). It has been proposed that repeated drug exposure produces a state of impaired inhibitory control in addition to the effects on incentive motivation described above (30,54). Together, these behavioral changes have been suggested to contribute to the compulsive drug-seeking and drug-intake encountered in drug addicts (30,54), Evidence also indicates that frontocortical hypofunction contribute to this deficit (30). The effects of repeated drug treatment on inhibitory control can be evaluated using the elevated plus-maze. This behavioral model is generally considered to be an experimental model of anxiety, although there is considerable evidence indicating that disinhibited behavior in conflict models like the elevated plus-maze may also reflect a general loss of inhibitory control, or impulsivity, especially when observed in animals with low 5-HT activity (78,84; see also Discussion).

Serotonin is involved in neuronal processes related to conflict behavior, inhibitory control and impulsivity (18,73,78,79,81), as well as in reward-related mechanisms (8,29,42,44,45,54,55,72). The neuroanatomical as well as the functional substrates for an interaction between the brain 5-HT systems and the mesocorticolimbic DA system are well established (33,80). Interestingly, experiments have suggested that the development of behavioral sensitization to drugs of abuse may involve both dopaminergic and serotonergic mechanisms (34,35,58).

We have recently observed that behavioral sensitization to the locomotor stimulatory effects of nicotine is associated with nicotine-induced behavioral disinhibition in the elevated plus-maze (54). Moreover, chronic treatment with citalopram, the most selective 5-HT reuptake inhibitor (SSRI) presently available (3,28), counteracted the expression both of locomotor sensitization and disinhibition (54). Although there is evidence suggesting that some aspects of the locomotor sensitization produced by nicotine and traditional psychostimulants like amphetamine and cocaine may be qualitatively different, there are many important similarities. Thus, some, but not all, of the mechanisms involved in the induction of sensitization appear to differ between the sensitization to nicotine and amphetamine. Whereas the action of amphetamine in the VTA, but not in the N Acc, appear to be required for the induction of amphetamine sensitization (13), locomotor sensitization can be elicited by repeated infusions of nicotine in both the VTA and the N Acc (37). On the other hand, the neurochemical processes underlying the expression of sensitization share many features. For example, the drug-induced accumbal DA output is enhanced after repeated treatment with both nicotine, cocaine and amphetamine (5,58,64,89), and there is also data suggesting that all drugs enhance postsynaptic DA receptor function (22,23). Moreover, sensitization to either compound enhances the self-administration of cocaine (26,27).

The present study was designed to further investigate the relationship between locomotor sensitization (related to incentive motivation) and behavioral inhibition in the elevated plus-maze (related to inhibitory control) by examining the effects of repeated amphetamine treatment on these behaviors. Moreover, acute l-5-hydroxytryptophan (5-HTP) and chronic citalopram treatment were used to evaluate the effects of enhanced brain 5-HT activity on the behavioral effects of repeated amphetamine treatment.

## METHOD

### *Animals*

Male Sprague-Dawley rats ($n$ = 80), supplied by BeeKay (Sollentuna, Sweden), weighing 250 to 280 grams at the start of the experiment, were used in all tests. The rats were housed four per cage under constant cage temperature (20°C), humidity (40% to 50%) and controlled light-dark conditions (light on at 0600 h and off at 1800 h). The rats had free access to standard laboratory food (BeeKay Feeds) and tap water at all times. The animals were allowed to adapt to the animal department facilities for at least one week before the start of any experiment. The present study was approved by the Ethics Committee for Animal Experiments, Göteborg, Sweden.

### *Drugs*

Citalopram bromide, (5.0 mg/kg SC), generously supplied by Lundbeck A/S (Denmark) and d-amphetamine, (1.0 mg/kg sc; Sigma, USA), l-5-hydroxytryptophan (25 mg/kg ip; Sigma, USA) and benserazide (25 mg/kg IP), a gift from Roche AB (Sweden) were dissolved in saline (0.9% NaCl). Amphet-

amine was injected in a volume of 2 ml/kg while benserazide, 5-HTP and citalopram were injected 5 ml/kg. All doses are expressed as the weight of the salt.

### *Behavioral Methods*

*Locomotor Activity.* Locomotor activity was measured using computerized activity meters (Digiscan animal activity monitor, Omnitech Electronics, USA) that were placed in 8 identical sound- and light-attenuating boxes containing a weak light and a fan. The activity meter was equipped with three rows of infrared photosensors, each row consisting of 16 sensors placed 2.5-cm apart. Two rows were placed in a 90 degree angle along the front and side of the floor of the cage. The third row was placed 10 cm above the floor to measure vertical activity. The activity meters were connected to an analyzer system (Omnitech Electronics, USA) and data was collected using LabVIEW software (National Instruments, USA). All experiments were performed between 0900 h and 1800 h in a balanced order.

*Behavioral Inhibition.* Behavioral inhibition was investigated using Montgomery's elevated plus-maze. The experimental apparatus consisted of a plus-formed maze with mesh-wire floor, elevated approximately 0.75 m above the floor in a semi-illuminated room. The arms of the plus-maze were 40-cm long and 10-cm wide. Two opposing arms were surrounded by 10-cm high black walls (closed arms), while the other arms were devoid of walls (open arms). The animals were initially allowed at least 1 h of habituation to the testing room, after which they were treated with drugs according to the test paradigm (see below). In order to be able to measure both increased and decreased behavioral inhibition the spontaneous exploratory behavior was stimulated. Therefore, each rat was initially put into an unfamiliar environment (a dark box with a grid floor) for approximately 5 min before it was placed in the center of the plus-maze facing a closed arm. Entry into one arm was defined as the animal placing all four paws into the arm. The investigator was situated 2 meters from the center of the maze. After every tested animal the maze was carefully wiped with a wet cloth. The time spent in, and the number of entries made into, open and closed arms were recorded during a 5 min-test session, and the time and number of entries made into open arms were expressed as percent of the total time and total entries made into both open and closed arms. All experiments were performed between 0900 and 1800 h in a balanced order.

This conflict model is based on the observation that the contrast between the elevated open and closed arms in the elevated plus-maze inhibits the exploratory behavior normally displayed by rats placed in a novel environment (50,61). The exploration of open arms is thus suppressed, and in the present setting, a nontreated, normal rat spends only about 15% to 30% of the total arm time on open arms. Manipulations which increase the percentage of time and entries made onto the open arms are therefore considered to produce behavioral disinhibition, whereas treatments which increase the total number of entries are considered to stimulate locomotor activity.

Several elegant studies published by File and co-workers (20,56,61), using factor analysis and correlation procedures, have demonstrated that the measures of inhibition/disinhibition (i.e., % time and % entries spent on/made onto the open arms) describe the same behavior and account for the same variable effects, although the % time spent on open arms appear to be a measure more sensitive to drug effects. On the other hand, the total number of entries made in the plus-maze is an independent behavior reflecting general locomotor activity (see above).

## EXPERIMENTAL DESIGN

### *The Citalopram Experiment*

*General Design.* Rats ($n = 40$) were randomly divided into five groups ($n = 8$) which were assigned to the following treatments: 1) vehicle + vehicle (veh + veh; 2 groups); 2) vehicle + amphetamine (1.0 mg/kg SC; veh + amph); and 3) citalopram (5.0 mg/kg SC bid) + vehicle (cit + veh) 4. citalopram (5.0 mg/kg SC bid) + amphetamine (1.0 mg/kg SC; cit + amph). Citalopram or vehicle pretreatment was injected at 0900h, 60 min before amphetamine/vehicle treatment. To maintain a chronic SSRI effect, citalopram (5.0 mg/kg SC) or the corresponding vehicle was injected also at 1700 h, according to the drug treatment schedule. This treatment lasted for 15 days, and the effects of these drug treatments on locomotor activity were recorded on treatment days 1 and 15. On day 17, i.e., when the locomotor activity studies were completed, all rats were subjected to the elevated plus-maze.

It should be noted that, since animals housed in groups are less sensitive to the effects of psychostimulants, including amphetamine, than isolated rats (1,77), repeated treatment with the amphetamine dose used in the present study has previously been observed to produce locomotor sensitization in both isolated and group housed rats (77).

*Locomotor Activity.* In the citalopram experiment, rats were injected with citalopram (5.0 mg/kg SC) or vehicle, placed in transparent plastic boxes and put into the activity meters. The animals were then allowed a 60-min habituation period, after which they were taken out, injected with amphetamine (1.0 mg/kg SC) or vehicle, and replaced in the boxes. Locomotor activity was recorded for 60 min starting 5 min after drug injection in order to avoid nonspecific injection-induced hypermotility. All experiments were performed between 0900 h and 1800 h in a balanced order.

*Behavioral Inhibition.* In the citalopram experiment, rats were injected with citalopram (5.0 mg/kg SC) or vehicle according to the drug treatment schedule and were returned to their home cages. Sixty minutes later, the animals were injected with amphetamine (1.0 mg/kg SC) or vehicle and, again, returned to their home cages for 30 min before they were subjected to the elevated plus-maze experiment procedures. The design of the present plus-maze experiments was based on the results from the locomotor activity study. Therefore, the animals were tested in the elevated plus-maze at a time period (35 to 40 min post amphetamine injection) during which the level of amphetamine-induced locomotor-stimulation peaked.

### *The 5-HTP Experiment*

*General Design.* Rats ($n = 40$) were treated with vehicle ($n = 24$) or amphetamine (1.0 mg/kg SC; $n = 16$) for 15 days, and the drug-induced locomotor activity was recorded on treatment days 1 and 15. The rats were then divided into five groups ($n = 8$), three vehicle-treated and two amphetamine-treated. On day 16, the effect of acute 5-HTP pretreatment on amphetamine-induced locomotor stimulation was investigated. On day 17, the effects of acute 5-HTP and repeated amphetamine treatment on behavioral inhibition were studied in the elevated plus-maze.

As mentioned above, animals housed in groups are less sensitive to the effects of psychostimulants, including amphet-

amine, than isolated rats (1,77). Thus, it should be noticed that repeated treatment with the amphetamine dose here used has previously been observed to produce locomotor sensitization in both isolated and group housed rats (77).

*Locomotor Activity.* In the 5-HTP experiment, rats were injected with the peripheral decarboxylase inhibitor benserazide (25 mg/kg IP), in order to avoid effects induced by synthesis of 5-HT in the periphery, or vehicle and returned to their home cages. Thirty minutes later, the benserazide-treated rats received 5-HTP (25 mg/kg IP) and the vehicle-treated rats were injected with vehicle, placed in transparent plastic boxes and put into the activity meters. The animals were then allowed a 60-min habituation period, after which they were taken out, injected with amphetamine (1.0 mg/kg SC) or vehicle, and replaced in the boxes. Locomotor activity was recorded for 60 min starting 5 min after drug injection in order to avoid nonspecific injection-induced hypermotility.

*Behavioral Inhibition.* Rats were injected with the peripheral decarboxylase inhibitor benserazide (25 mg/kg IP), and returned to their home cages. Control rats received the equivalent volume of vehicle. Thirty minutes later, the benserazide-treated rats received 5-HTP (25 mg/kg IP) and the vehicle-treated rats were once again injected with vehicle, and returned to their home cages. Another 60 min later the animals were injected with amphetamine (1.0 mg/kg SC) or vehicle and, again, returned to their home cages for 30 min, before the elevated plus-maze experiment was initiated. The design of the present plus-maze experiments was based on the results from the locomotor activity study. Consequently, the animals were tested in the elevated plus-maze at a time period (35 to 40 min post amphetamine injection) during which the level of amphetamine-induced locomotor-stimulation peaked.

## STATISTICS

Data from the acute locomotor activity studies were statistically evaluated using a factorial analysis of variance (ANOVA) followed by Fisher's protected least significant difference (PLSD) test. The data from the chronic locomotor activity experiments were analyzed with an ANOVA for repeated measures followed by the paired *t*-test. The data obtained in the plus-maze study were evaluated with a factorial ANOVA, followed by Fisher's PLSD test. Multiple comparisons were corrected for using Holm's procedure (25), which is a sequentially rejective test procedure, and a weighted improvement of the Bonferroni-Dunn procedure. Correlations were evaluated with the Paired Correlation Analysis followed by Fisher's *r* to *z* test. A probability value ($p$) less than 0.05 was considered statistically significant.

## RESULTS

### *Effects of Acute and Chronic Citalopram Treatment on Amphetamine-Induced Locomotor Stimulation on Day 1 and 15*

On day 1, there were statistically significant differences between the effects of the drug treatments on locomotor activity ($F(3, 28) = 24.797$; $p < 0.0001$). Post hoc analysis demonstrated that acute amphetamine (1.0 mg/kg SC) increased locomotor activity compared with vehicle, both in rats pretreated with citalopram (5.0 mg/kg SC; $p < 0.0001$) and vehicle ($p < 0.0001$). Acute citalopram pretreatment attenuated the locomotor stimulation produced by amphetamine in previously drug naive animals ($p < 0.05$; Fig. 1).

On day 15, after repeated drug treatment for 15 days, there were statistically significant differences between the experimental groups ($F(3, 28) = 40.187$; $p < 0.0001$). The locomotor response was altered with the duration of the drug treatment ($F(1, 28) = 28.081$; $p < 0.0001$). Repeated daily treatment with amphetamine (1.0 mg/kg SC) enhanced the locomotor stimulatory effect compared with day 1, both in rats receiving vehicle ($p < 0.01$) and citalopram (5.0 mg/kg SC bid; $p < 0.01$) in addition to amphetamine. Repeated treatment with vehicle or citalopram alone had no significant effect (Fig. 1).

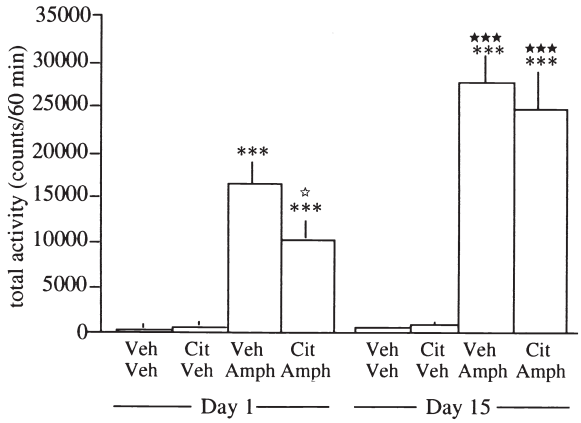


FIG. 1. Effect of citalopram (5.0 mg/kg SC, twice daily) on the development of sensitization to the locomotor stimulatory effects of amphetamine (1.0 mg/kg SC). Shown are the mean + SEM; $n = 8$, all groups. Statistics: Factorial ANOVA followed by Fisher's PLSD test (acute effects) or the ANOVA for repeated measures followed by the paired *t*-test (chronic effects). Multiple comparisons were corrected for using Holm's procedure. *** $p < 0.001$ compared with vehicle treated groups; ☆ $p = 0.05$ compared with veh + amph; ★★★ $p < 0.001$ compared with corresponding treatment day 1.

### *Effect of Chronic Citalopram Treatment on Acute Amphetamine-Induced Locomotor Stimulation*

Chronic citalopram (5.0 mg/kg SC, twice daily) treatment for 15 days did not alter the locomotor response to an acute injection of amphetamine (1.0 mg/kg SC). Veh-treated 19561 ± 1649 vs. cit-treated 18684 ± 2200 (counts/60 min; $p = 0.7565$).

### *Effects of Acute 5-HTP Treatment on Amphetamine-Induced Locomotor Stimulation After Repeated Amphetamine Treatment*

After repeated drug treatment for 15 days there were statistically significant differences between the experimental groups ($F(1, 30) = 72.77$; $p < 0.0001$). The locomotor response was altered with the duration of the drug treatment ($F(1, 30) = 51.933$; $p < 0.0001$). Repeated daily treatment with amphetamine (1.0 mg/kg SC) enhanced the locomotor stimulatory effect compared with day 1 ($p < 0.0001$). Repeated treatment with vehicle had no significant effect per se (Fig. 1). Acute treatment with 5-HTP (25 mg/kg IP) did not alter the expression of amphetamine-induced locomotor sensitization (Fig. 2).

### *Elevated Plus-Maze*

The amphetamine-sensitized rats spent more time in open arms 35–40 min after amphetamine challenge compared with rats receiving vehicle ($p < 0.001$; Figs. 3A and 4A) or previously drug-naive rats receiving an acute injection of amphetamine ($p = 0.05$; Figs. 3A and 4A). The amphetamine-sensitized rats also made more entries into open arms after

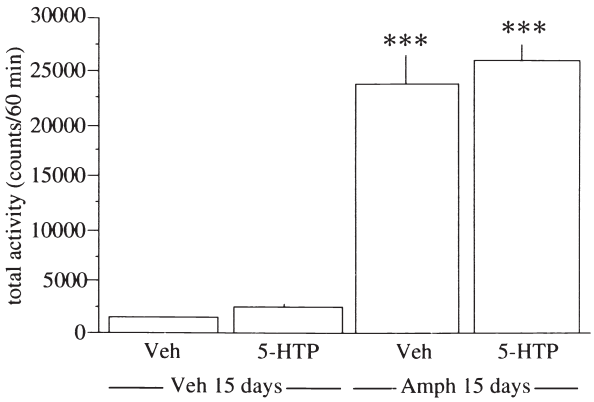


FIG. 2. Effect of acute 5-HTP pretreatment on the expression of amphetamine-sensitization. Rats that had been repeatedly treated with amphetamine (1.0 mg/kg SC) or vehicle (15 days), received 5-HTP (25 mg/kg IP; −1h; with benserazide), or the corresponding vehicle, followed by amphetamine (1.0 mg/kg SC) or vehicle. Shown are the mean + SEM; $n = 8$, all groups. Statistics: Factorial ANOVA followed by the paired t-test. Multiple comparisons were corrected for using Holm's procedure. *** $p < 0.001$ compared with the vehicle treated groups.

amphetamine challenge compared with rats receiving vehicle ($p < 0.01$; Fig. 3B and $p < 0.001$; Fig. 4B). In the 5-HTP ($p < 0.05$; Fig. 4B), but not in the citalopram experiment (Fig. 3B), the amphetamine-sensitized rats made a larger % of entries on open arms than did previously vehicle-treated rats receiving amphetamine for the first time.

Chronic citalopram (5.0 mg/kg SC bid 15 days; $p < 0.05$; Fig. 3A) and acute 5-HTP (25 mg/kg IP; $p < 0.01$; Fig 4A) treatment counteracted the increase in time spent on open arms observed in amphetamine-sensitized rats after amphetamine injection. Acute 5-HTP treatment also counteracted the increased percentage of entries made by the sensitized rats into open arms ($p < 0.001$; Fig 4B), while chronic treatment with citalopram had no statistically significant effect on this measure (Fig. 3B).

The total number of entries made into any arm was increased by acute ($p < 0.05$; Figs. 3C and 4C) and repeated ($p < 0.001$; Figs. 3C and 4C) amphetamine treatment. The increase of total entries, observed after repeated amphetamine treatment, was counteracted by acute 5-HTP ($p < 0.001$; Fig. 4C) and chronic citalopram treatment ($p < 0.01$; Fig 3C).

Acute 5-HTP (Figs. 4A–C) or chronic citalopram (Figs. 3A–C) alone did not affect the behavior in the elevated plus-maze compared with the vehicle-treated controls.

There was no significant correlation between the measures of behavioral inhibition/disinhibition and the total number of entries made in the elevated plus-maze in amphetamine-treated rats (% time vs. total entries; citalopram experiment: $r = 0.128$; n.s.; 5-HTP experiment: $r = 0.420$; n.s.; % entries vs. total entries; citalopram experiment: $r = 0.262$; n.s.; 5-HTP experiment: $r = 0.363$; n.s.). However, there was a strong correlation between the measures of behavioral inhibition in the plus-maze (% time vs. % entries; cit-experiment: $r = 0.689$; $p < 0.01$; 5-HTP experiment: $r = 0.963$; $p < 0.001$).

## DISCUSSION

Daily administration of a moderate dose of amphetamine (1.0 mg/kg SC) for 15 consecutive days significantly enhanced the stimulatory effect of the drug, and, thus, the amphetamine-treated animals were behaviorally sensitized. This observation is supported by numerous reports (13,15,21,73), and according to previous studies, this behavioral enhancement probably derives from drug-induced alterations of several different neurochemical mechanisms, including an augmented amphetamine-induced elevation of extracellular mesocorticolimbic DA levels and increased post-synaptic DA receptor function (52,63,74).

Serotonin and serotonergic drugs have been observed to modify some of the behavioral and neurochemical responses to amphetamine (14,29,42,47,57). In the present study, acute 5-HTP or chronic citalopram treatment did not influence locomotor activity per se, although acute citalopram pretreatment reduced the locomotor activating effects of amphetamine in previously drug-naive animals. However, neither citalopram nor 5-HTP significantly altered the amphetamine-induced response in amphetamine-sensitized rats. These observations differ from previous findings (3), demonstrating that acute administration of similar doses of citalopram did not influence the locomotor stimulatory properties of acute amphetamine, and that chronic dietary citalopram treatment (10 or 40 mg/kg/day) potentiated the amphetamine-induced locomotor activity in Wistar rats (3). This enhancement was attributed to pharmacokinetic effects, as the amphetamine concentrations were elevated in the blood and brain of chronically citalopram-treated rats. Since the amphetamine levels were not determined in the present study, citalopram-induced changes of amphetamine uptake or metabolism can not be excluded. However, chronic citalopram injections for 15 days did not influence the locomotor stimulatory effect of acute amphetamine in the present study, suggesting that the amphetamine levels were not altered by chronic citalopram using the present treatment paradigm. The differences between the effects of chronic citalopram in the previous and the present reports are not easily explained, but since different rat strains and routes of citalopram administration were used in the two experiments we can not exclude that these factors may be important. Moreover, since the present study, but not the former, evaluated the effects of citalopram on amphetamine-induced locomotor stimulation in habituated animals, this difference may also be of utter importance. However, it should be noted that if pharmacokinetic alterations were involved (see above), the behavioral consequences of the elevated amphetamine levels must have been counteracted by the chronic citalopram treatment. If so, the antagonism of the sensitized amphetamine-induced locomotor response observed after chronic citalopram treatment would be in line with the previously reported effect of citalopram on nicotine sensitization (54).

The present study further demonstrates that amphetamine-sensitized rats spend more time and make more entries on the open arms in the elevated plus-maze when challenged with amphetamine (1.0 mg/kg SC; −35 min), compared with vehicle-treated rats receiving acute amphetamine or vehicle-treated rats receiving vehicle only. Since the open arm exploration in the elevated plus-maze normally is inhibited (see Materials and methods), the increase in time spent on and entries made on open arms reflects amphetamine-induced behavioral disinhibition in the amphetamine-sensitized animals (see also Methods). Acute pretreatment with 5-HTP or chronic treatment with citalopram counteracted the disinhibitory response to amphetamine in the sensitized rats in the elevated plus-maze. Although 5-HTP pretreatment antagonized the amphetamine-induced increase both in time spent on and

Fig 3a

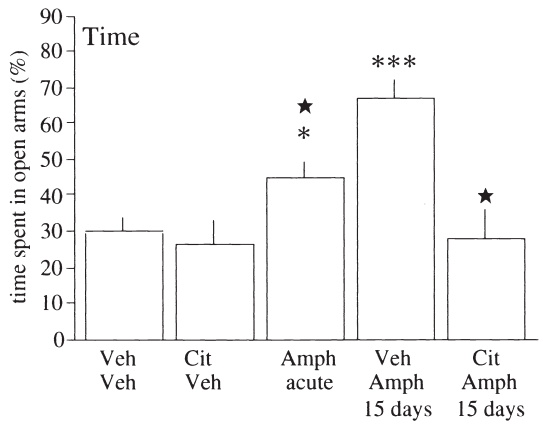


Fig 3b

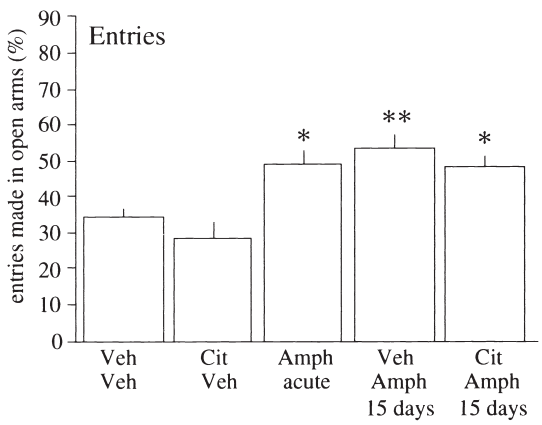


Fig 3c

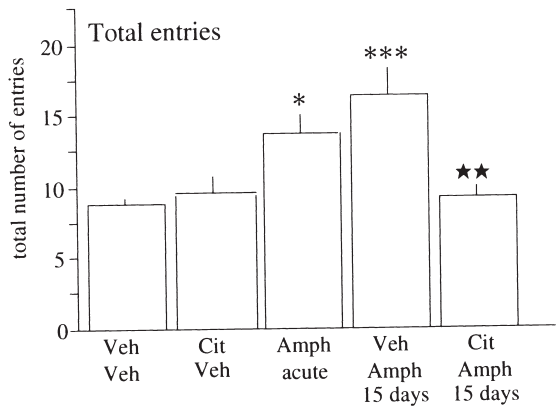


FIG. 3. (A) Effect of amphetamine (1.0 mg/kg SC) and citalopram (5.0 mg/kg SC), alone or in combination, on the percent time (open time/total time) spent on open arms in the elevated plus-maze. Shown are the means + SEM; $n = 8$, all groups. Statistics: Factorial ANOVA followed by Fisher's PLSD test. Multiple comparisons were corrected for using Holm's procedure. * $p < 0.05$ and *** $p < 0.001$ compared with veh + veh, ★ $p < 0.05$ compared with veh + amph 15 days. (B) Effect of amphetamine (1.0 mg/kg SC) and citalopram (5.0 mg/kg SC), alone or in combination, on the percent entries (open entries /total entries) spent on open arms in the elevated plus-maze. Shown are the means + SEM; $n = 8$, all groups. Statistics: Factorial ANOVA followed by Fisher's PLSD test. Multiple comparisons were corrected for using Holm's procedure. * $p < 0.05$ and ** $p < 0.01$ compared with veh + veh. (C) Effect of amphetamine (1.0 mg/kg SC) and citalopram (5.0 mg/kg SC), alone or in combination, on the total number of entries made on any arm in the elevated plus-maze. Shown are the means + SEM; $n = 8$, all groups. Statistics: Factorial ANOVA followed by Fisher's PLSD test. Multiple comparisons were corrected for using Holm's procedure. * $p < 0.01$ and *** $p < 0.001$ compared with veh + veh, ★★ $p < 0.01$ compared with veh + amph 15 days.

entries made into open arms, chronic citalopram significantly reduced the open arm time only. Behavioral disinhibition in the elevated plus-maze is ordinarily interpreted to reflect an alleviation of anxiety (60,61). However, there is compelling evidence suggesting that disinhibited behavior in various animal conflict models could also reflect a loss of impulse control (78), especially when observed in animals with low serotonergic activity (78,84). Thus, manipulations which attenuate or enhance brain 5-HT neurotransmission disinhibit or inhibit, respectively, the behavior in rat anxiety models invoking aversive stimuli, such as the elevated plus-maze (12,78,81,84). Because amphetamine increases impulsive behavior in rats (18) the present observations of an amphetamine-induced disinhibition in the elevated plus-maze after subchronic treatment may argue in favour of this outcome reflecting a loss of impulse control rather than anxiolysis; amphetamine reduces impulse control, but not anxiety, also in humans (86). Thus, even though the elevated plus-maze is not a validated experimental impulsivity model, the present results could indicate that 5-HTP and citalopram may restore an amphetamine-induced loss of inhibitory control which may be related to impulsivity.

Acute and repeated amphetamine treatment also increased the total number of entries made in the elevated plus-

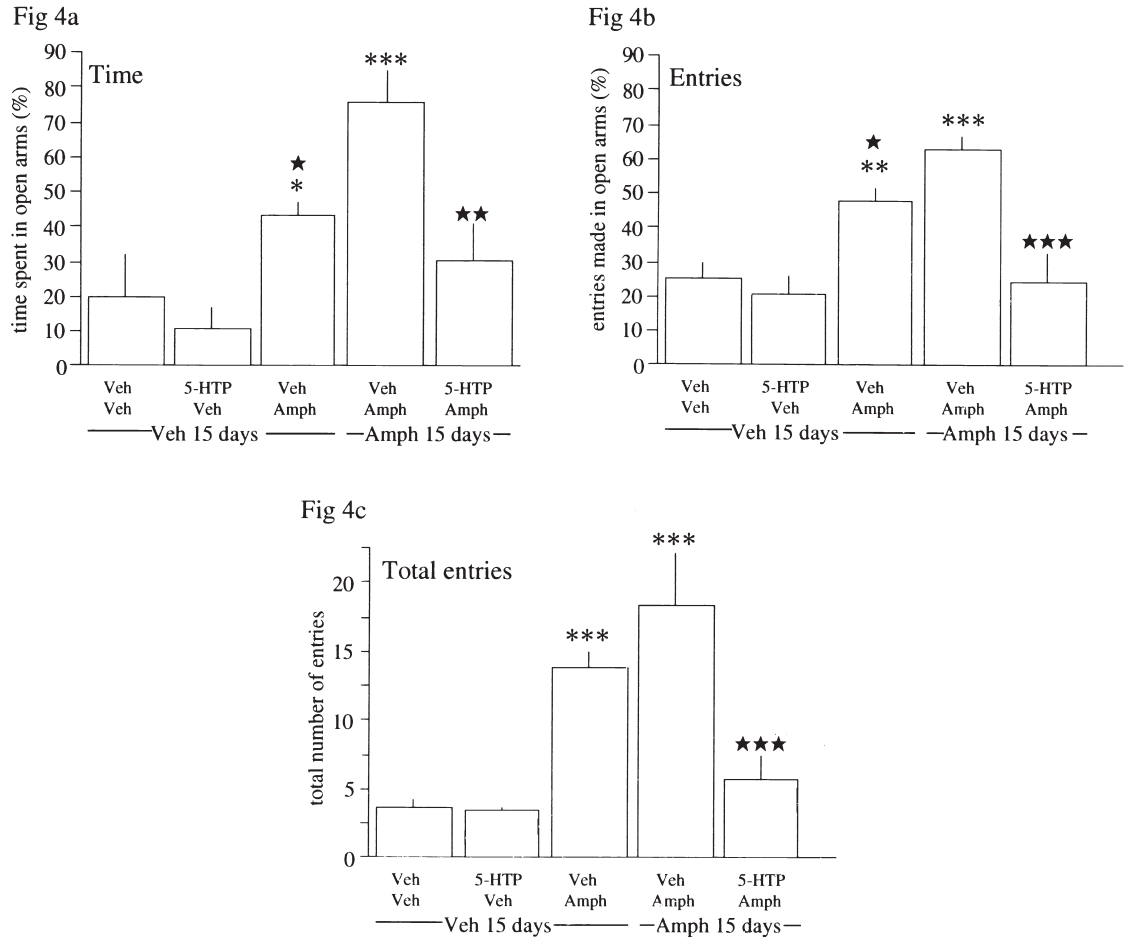


FIG. 4. (A) Effect of amphetamine (1.0 mg/kg SC) and acute 5-HTP (25 mg/kg IP; with benserazide pretreatment) on the percent of time (open time/total time) on open arms observed in the elevated plus-maze. Shown are the means + SEM; $n = 8$, all groups. Statistics: Factorial ANOVA followed by Fisher's PLSD test. Multiple comparisons were corrected for using Holm's procedure. * $p < 0.05$ and *** $p < 0.001$ compared with veh + veh, ★ $p < 0.05$ and ★★ $p < 0.01$ compared with veh + amph 15 days. (B) Effect of amphetamine (1.0 mg/kg SC) and acute 5-HTP (25 mg/kg IP; with benserazide pretreatment) on the percent of entries (open entries/total entries) made into open arms in the elevated plus-maze. Shown are the means + SEM; $n = 8$, all groups. Statistics: Factorial ANOVA followed by Fisher's PLSD test. Multiple comparisons were corrected for using Holm's procedure. ** $p < 0.01$ and *** $p < 0.001$ compared with veh + veh, ★ $p < 0.05$ and ★★★ $p < 0.001$ compared with veh + amph 15 days. (C) Effect of amphetamine (1.0 mg/kg SC) and acute 5-HTP (25 mg/kg IP; with benserazide pretreatment) on the total number of entries made into any arm in the elevated plus-maze in amphetamine-sensitized rats. Shown are the means + SEM; $n = 8$, all groups. Statistics: Factorial ANOVA followed by Fisher's PLSD test. Multiple comparisons were corrected for using Holm's procedure. *** $p < 0.001$ compared with veh + veh, ★★★ $p < 0.001$ compared with veh + amph 15 days.

maze. It has been argued that such drug-evoked locomotor stimulation may influence the behavior in the elevated plus-maze, possibly resulting in a nonspecific disinhibition towards the aversive stimulus (i.e., open arms). Thus since 5-HTP and citalopram decreased both the measures of behavioral disinhibition and the total number of entries in the amphetamine-treated rats, it may be claimed that their effects on behavioral disinhibition is but a secondary consequence of the decreased locomotor activity. The relationship between general activity and behavioral inhibition has been thoroughly examined by several investigators, and in particular by File and colleagues (20,56,61). These studies have concluded that the measures of behavioral inhibition (% time and % entries in open arms) and the total number of entries during the first exposure to the elevated plus-maze are independent variables. Furthermore, an analysis of the behavior in the present amphetamine-treated groups did not disclose a correlation between the total number of entries and the measures of behavioral inhibition/disinhibition (see Results). Other studies also have failed to observe a clear correlation between the total number to entries made and the confinement to open arms (82,83). In addition, since the present results are expressed as a ratio between open and open + closed arms, nonspecific effects of drug-induced locomotion, which ought to increase the entries into both open and closed arms, should be minor.

Indeed, even though the total arm entries after amphetamine were reduced by the same treatments that decreased the open arm confinement in the present study, this is by no means

the rule in the present model. For instance, in our previous study only the nicotine-induced disinhibition, but not the increase in total arm entries, was counteracted by chronic citalopram treatment (54). Interestingly, the drug-induced locomotor activity recorded in the activity boxes in habituated animals appears to derive from yet other neurochemical processes. Thus, while amphetamine-induced stimulation of total activity in the elevated plus-maze was reduced both by 5-HTP and citalopram, none of these treatments altered the amphetamine-induced locomotor stimulation observed in the activity boxes. Exactly the opposite was observed in our previous study (54) in which citalopram counteracted the stimulant action of nicotine in the activity boxes but not in the elevated plus-maze. Taken together, the experimental results obtained so far in a number of studies, including the present, thus suggest that the open arms visits/time spent in open arms and the total number of entries in this novel environment are separate entities which may be governed by different neurochemical mechanisms.

It is possible that the citalopram- and 5-HTP-induced reversals of behavioral disinhibition after amphetamine challenge result from the restoration of a disturbed neurochemical situation in the behaviorally sensitized animals, or derive from a strengthening of the normal 5-HT system to a point at which it outweighs the influence of enhanced dopaminergic activity. Because manipulations which decrease 5-HT neurotransmission enhance the locomotor stimulatory effects of DA activating drugs, like amphetamine (11,14,47), the enhanced locomotor activity observed after repeated amphetamine treatment could partly derive from a relative reduction of 5-HT neurotransmission. Arguing against this latter hypothesis is, however, the fact that in amphetamine-sensitized rats chronic citalopram or acute 5-HTP did not modify the expression of locomotor sensitization, a result contrary to the observations previously made in nicotine-sensitized rats (54). It should also be noted, however, that although only one dose of citalopram and 5-HTP was applied in the present experiments, it is possible that higher doses of these substances may be required in order to counteract the expression of amphetamine-induced locomotor sensitization, as compared with that of amphetamine-induced disinhibition.

The rationale for studying the relation between locomotor sensitization (related to incentive motivation) and behavioral inhibition (related to inhibitory control) is supported by a current review (30). Interestingly, different neurochemical mechanisms appear to be involved in the behaviors studied in the experimental models used here, one studying locomotor activity in habituated animals and one studying locomotor activity/exploratory behavior in a novel conflict situation. Nevertheless, repeated daily treatment with amphetamine (present study) or nicotine (54) in a manner producing sensitization to the locomotor stimulatory effects of the drugs, simultaneously induces an amphetamine- or nicotine-induced disinhibitory behavior. In this context it should be noted that there are convincing evidence demonstrating that animals with low 5-HT activity, in addition to being generally disinhibited (78,81), enhance their consumption of various drugs of abuse, especially ethanol (17,44,45,70). Moreover, ibotenic acid depletions of neurons in the N Acc, but not the septum, increase alcohol consumption as well as disinhibited behavior in conflict tasks (31). Indeed, the propensity of rats to consume ethanol appears to be positively correlated with their impulsivity (67). Therefore, the ability of repeated treatment with amphetamine and nicotine to increase ethanol consumption in the rat (9,19) may be related to the behavioral disinhibition that develops in association with such treatments.

Disinhibitory behavior in the elevated plus-maze after repeated amphetamine treatment could be compatible with the induction of a low-serotonergic state (for refs, see above; see also 4), at least in relation to the activity of transmitters associated with forward locomotion/incentive motivation such as DA (49). Thus, an imbalance between the drug-induced elevation of 5-HT and DA could occur which may be responsible for the present effects. Supporting this hypothesis, cocaine-induced elevations of 5-HT and DA levels show distinct patterns in sensitized animals, i.e. the increase in 5-HT concentrations was greater in the cell-body (dorsal raphe nucleus) than in the terminal region (N Acc), whereas the DA-elevation was more pronounced in the terminal (N Acc) than in the cell-body (VTA) area (58). This observation may suggest a relative decrease in 5-HT activity but an increase in DA activity in N Acc after chronic cocaine treatment.

In conclusion, the present findings demonstrate that repeated treatment with amphetamine in a manner producing behavioral sensitization to its locomotor stimulatory effects, results in disinhibited behavior in the elevated plus-maze in rats tested during amphetamine exposure. The expression of the behavioral disinhibiton, but not locomotor sensitization, was counteracted by acute 5-HTP and chronic citalopram treatment. The present findings suggest that these behaviors are distinct entities, and that the neurochemical alterations which result in locomotor sensitization and behavioral disinhibition may be parallel, but separate. Whereas alterations both of brain DA and 5-HT activity could be involved in the development of these amphetamine-induced behaviors, the attenuating effects of 5-HTP and citalopram are likely to involve increased 5-HT neurotransmission. However, since the present study did not include neurochemical measures, further studies are required to elucidate the neurochemical alterations associated with the presently observed behavioral effects. Considering that both behavioral sensitization and disinhibition may contribute to, and predict, behaviors related to substance abuse, drugs that counteract the expression of these phenomena could prove helpful in the clinical treatment of drug abuse.

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