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Reduction of dopamine release and synthesis by repeated amphetamine treatment: Role in behavioral sensitization

Assunta Imperato *, M. Carmen Obinu, Giovanna Carta, M. Stefania Mascia, M. Antonietta Casu, Gian Luigi Gessa

Department of Neuroscience 'Bernard B. Brodie', University of Cagliari, Cagliari, Italy

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Abstract

Changes in extracellular dopamine concentration in the ventral striatum during repeated amphetamine administration and over the first 7 days of withdrawal were studied by transversal microdialysis in freely moving rats. 2 days after fiber implantation rats were treated with either amphetamine (1.5 mg/kg i.p.) or saline every 12 h for 14 days. In amphetamine-treated rats, the baseline extracellular dopamine concentration, preceding the morning treatment, increased from 0.43 ± 0.01 on day 1 up to 0.59 ± 0.02 pmol/40 μl sample on day 3 of treatment. Thereafter, dopamine fell rapidly on day 5 (0.16 ± 0.01 pmol/40 μl) and remained at approximately the level reached on day 7 (0.11 ± 0.01 pmol/40 μl) throughout the treatment and also over the 7 days of withdrawal. In contrast, in control rats, the extracellular dopamine concentration (0.40 ± 0.01 pmol/40 μl, on day 1) decreased progressively during the first days of treatment to reach a fairly stable value on day 4 (0.25 ± 0.01 pmol/40 μl sample). Thereafter, dopamine remained stable at this level throughout the remaining period of experimentation. Challenge with amphetamine (1.5 mg/kg i.p.) of animals treated with amphetamine for 10 days or withdrawn for 7 days produced a potentiated motor response compared to that in control rats but much less marked dopamine releasing effects. Dopamine synthesis in the ventral striatum, measured as L-dihydroxyphenylalanine formation after blockade of dihydroxyphenylalanine decarboxylase, was found to be reduced by approximately 60% after 2 weeks of amphetamine treatment and in animals withdrawn for 1 day or 7 days. These results indicate that repeated amphetamine treatment causes persistent inhibition of dopamine synthesis and release in the ventral striatum. Such inhibition may be a compensatory response to the repeated stimulation of postsynaptic dopamine receptors by the endogenously released dopamine and also the cause of postsynaptic sensitization to dopamine action.

Keywords: Microdialysis; Chronic transversal; Amphetamine, repeated; Ventral striatum; Dopamine release; Dopamine synthesis; Behavioral sensitization

1. Introduction

Repeated administration of psychostimulants to rodents results in a progressive increase in the motor stimulant response to a subsequent psychostimulant challenge (for review, see Willner et al., 1993).

This phenomenon, termed behavioral sensitization, has been considered as a model of schizophrenic or manic-like psychotic episodes in animals and in humans following chronic use of psychostimulants (Snyder, 1973; Robinson and Becker, 1986). Vice versa, following discontinuation of chronic use of these drugs, humans may develop a withdrawal syndrome characterized by craving for the drug and by symptoms similar to those of endogenous depression, including lethargy, fatigue and dysphoria (Watson et al., 1972; Waddington et al., 1990). In rats also, withdrawal from chronic administration of these drugs is followed by a behavioral syndrome characterized by hypoactivity, decreased efficacy of intracranial self-stimulation responding, indicative of depression (Leith and Barrett, 1975).

Several studies have shown that dopamine D_1 receptor activation may be critical for the development of behavioral sensitization to indirect dopamine agonists. In fact, dopamine D_1, but not dopamine D_2 receptor antagonists, given systemically or into the ventral tegmental area, have been shown to prevent the development of sensitization to amphetamine (Stewart and Vezina, 1989; Vezina and Stewart, 1989; Drew and Glick, 1990; for review, see Stewart and Badiani, 1993).

* Corresponding author. Current address: CNS Biology, Rhône-Poulenc Rorer Research Center, 13, Quai Jules Guesde, BP 14, 94400 Vitry Sur Seine Cedex, France. Tel.: (33-1) 5571-3413; Fax: (33-1) 5571-3685.

Attempts to explain the mechanisms underlying behavioral sensitization and withdrawal symptomatology have focused on possible changes in dopamine neurotransmission, since evidence from various sources suggests that dopamine systems play a critical role in the action of psychostimulants and in the reward processes (Di Chiara and Imperato, 1988; Kalivas et al., 1993). Accordingly, it has been suggested that behavioral sensitization to psychostimulants is mediated by increased dopamine neurotransmission in limbic areas (Kalivas et al., 1993) whereas decreased dopamine output is a common neurobiological substrate of the withdrawal symptomatology of these drugs, both in animals (Robertson et al., 1991; Rossetti et al., 1992) and in humans (McDougle et al., 1992).

However, while investigators have reported that behavioral sensitization to amphetamine is associated with enhanced dopamine release in limbic areas (Robinson et al., 1988; Patrick et al., 1991), other have failed to find such effects (Kolta et al., 1985; Wolf et al., 1992). Some investigators have observed a reduction in dopamine release in response to an amphetamine challenge under conditions of behavioral sensitization (Segal and Kuczenski, 1992).

Regarding withdrawal conditions, a number of studies have shown a decrease in extracellular dopamine concentration in limbic areas following withdrawal from chronic ethanol (Diana et al., 1993), morphine (Acquas et al., 1991), cocaine (Imperato et al., 1992) or amphetamine (Rossetti et al., 1992), suggesting that decreased dopamine neurotransmission may be responsible for the subjective adversive symptoms associated with withdrawal from these drugs.

However, other studies have reported that amphetamine withdrawal is not associated with a decreased extracellular dopamine concentration in the ventral striatum (Crippens and Robinson, 1994).

Recently, Imperato et al. (1992), using a chronic, implanted transversal dialysis probe, have found that repeated administration of cocaine produces a marked reduction in dopamine release in the ventral striatum that persists for over 7 days after withdrawal. Since transversal dialysis has been shown to allow reliable measurements of extracellular dopamine concentration for several weeks after probe implantation (Imperato et al., 1992, 1994), we used this technique to study the changes in extracellular dopamine in the ventral striatum during and after chronic amphetamine treatment. The relationship of these changes with the behavioral responses to amphetamine was also studied.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (Charles River) weighing 250–300 g were housed in groups of three per cage for at least 10 days before use. Food and water were freely available and the animals were kept under an artificial 12/12 h light/dark cycle (lights on from 7 a.m. to 7 p.m.) at a temperature of 22°C. Experiments were carried out between 8.30 a.m. and 5 p.m.

2.2. Microdialysis implantation, experimental procedure and treatment

The rats were anesthetized with chloralhydrate (0.4 g/kg i.p.) and implanted with a dialysis tube (AN 69-HF, wet tube o.d., 320 μm; Hospal-Dasco, Bologna, Italy) at the level of the ventral striata according to the Paxinos atlas (Paxinos and Watson, 1986) (A +1.5 from bregma; V −6.5 from the skull). At the end of the experiments, the localization of the dialysis probe was verified using a microtome cryostat. Transversal dialysis probes were implanted according to the technique revised by Imperato et al. (1992). These chronic probes have been shown to remain for weeks reliably efficient as assessed by limited glial reaction, stable dialysate dopamine concentrations over time, Ca^{2+} dependence of dialysate dopamine and reproducible response to pharmacological interventions (Imperato et al., 1992, 1994).

Ringer solution containing (mM) KCl 3, NaCl 125, $CaCl_2$ 1.3, $MgCl_2$ 1.0, $NaHCO_3$ 23, and a potassium phosphate buffer 1.5, pH 7.3 was pumped through the dialysis probe at a constant rate of 2 μl/min. Samples, 40 μl, were collected every 20 min. Each sample was injected in a high-performance liquid chromatograph (HPLC) with electrochemical detection according to the technique described by Imperato et al. (1992) for the evaluation of dopamine. The detection limit for dopamine was 0.002 pmol/injection.

Experiments started 48 h after implantation of the dialysis probe.

The rats were injected i.p. either with *d*-amphetamine (1.5 mg/kg i.p.) or saline (3 ml/kg) every 12 h for 14 days. Basal dopamine values were determined (mean of three or four values differing from each other by no more than 10%) before the morning treatment. Gentle injection of saline did not alter dopamine release significantly.

Because of the strong difference in the basal and in the amphetamine-induced dopamine release between the saline- and the amphetamine-treated groups, we wanted to test whether these diversities could be due simply to different recovery through the dialysis tube. We observed that a non-dopaminergic agent like atropine 10 μg/kg i.p. enhanced acetylcholine release 5-fold with a duration of more than 3 h in both groups. These results suggest that the differences observed are linked to selective alterations at the dopaminergic level and not to recovery through the dialysis tube. The enhancement of acetylcholine release after atropine is in agreement with previously published data (Imperato et al., 1991).

The behavioral response to amphetamine was evaluated in the same rats as used for microdialysis studies by

summing the % of time spent (mean ± S.E.M.) by rats in the performance of several behavioral items (locomotion, rearing, confined sniffing and licking) during the 2 h following amphetamine injection.

Dopamine synthesis was measured as L-dihydroxyphenylalanine accumulation after inhibition of dihydroxyphenylalanine decarboxylase with NSD 1015 (3-hydroxybenzylhydrazine dihydrochloride α-hydrazino-*m*-cresol) (100 mg/kg i.p.) 60 min before killing. These experiments were carried out in a separate group of rats (not implanted with the dialysis probe) that were treated with amphetamine or saline in the same way as were the operated rats.

For quantification of L-dihydroxyphenylalanine in the ventral striatum, rats were injected 1 h before killing with NSD 1015 100 mg/kg i.p.. These rats were decapitated and the brain was rapidly removed and the ventral part of the striatum was quickly dissected on ice. The two striata of each rat were homogenized in approximately 400 μl of perchloric acid 0.2 M (1 mg of tissue in 20 μl of perchloric acid). After centrifugation at 5000 × *g* for 40 min, the supernatants were removed and 20 μl was injected in the high pressure liquid chromatograph. The high pressure liquid chromatography for evaluation of L-dihydroxyphenylalanine was the same as that used for dopamine except that the buffer was a KH_2PO_4 buffer at pH 4.3.

Samples from animals not treated with NSD 1015 showed no quantifiable L-dihydroxyphenylalanine peak.

2.3. Drugs

d-Amphetamine sulphate and NSD 1015 were dissolved in distilled water and administered intraperitoneally in a volume of 0.3 ml/100 g. Dosages refer to the amphetamine salt.

2.4. Statistical analysis

Between-group comparisons were performed using a two-way analysis of variance for repeated measures, the factors being pretreatment (3 levels = vehicle compared to amphetamine-treated and withdrawn rats as in Fig. 3), treatment (2 levels = vehicle compared to chronic-amphetamine 1.5 mg/kg as in Fig. 1) and time point (21 levels = 1–21 days as Fig. 1, 7 levels = 0–120 in as in Fig. 3).

The data presented in Fig. 2 and Fig. 4 were analyzed by one-way analysis of variance.

Post-hoc analysis was performed by means of Student's *t* test for paired and unpaired data.

3. Results

Fig. 1 shows the changes in baseline concentrations of extracellular dopamine in the ventral striatum during 14 consecutive days of amphetamine treatment (1.5 mg/kg i.p. every 12 h) and during the first 7 days following treatment discontinuation. The baseline dopamine concentration was defined as the mean value for the samples collected during the 2 h preceding the morning treatment. In saline-treated rats, the baseline dopamine concentrations decreased progressively. On day 1 of the experiment (2 days after surgery) they were 0.40 ± 0.01 and declined to 0.25 ± 0.01 pmol/40 μl on day 4 (about 40% decrease). Thereafter, the baseline concentrations remained stable at this level throughout the remaining period of experimentation. This is in agreement with our previously published data (Imperato et al., 1992, 1994).

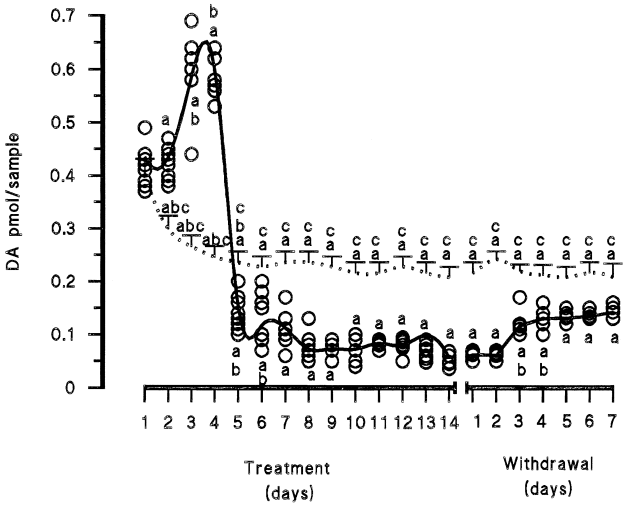

Fig. 1. Time-course of the changes in baseline extracellular dopamine concentrations in the ventral striatum during chronic amphetamine treatment (1.5 mg/kg i.p. every 12 h for 14 days) and during 1 week of withdrawal. Dotted line indicates control values. Data are expressed as means (± S.E.M.) pmol in 40 μl samples. For more details see Section 2. Analysis of variance revealed a significant main effect of treatment ($F(1,419) = 196.564$; $P < 0.001$), a significant main effect of repeated measures ($F(20,419) = 267.146$; $P < 0.001$) and significant interaction between factors ($F(20,419) = 60.137$; $P < 0.001$). $n = 5$ control rats. $n = 15$ amphetamine-treated rats. a = $P < 0.01$ versus basal values; b = $P < 0.01$ versus previous day; c = $P < 0.01$ versus amphetamine-treated rats on the same day.

In contrast, during the first 3 days of amphetamine administration, the baseline dopamine concentrations increased progressively from an initial value of 0.43 ± 0.01 on day 1 up to 0.59 ± 0.02 pmol/40 μl sample on day 3 of treatment. Subsequently, the extracellular dopamine concentrations fell rapidly. On day 5 they became 0.16 ± 0.01 and on day 7 0.11 ± 0.01 pmol/40 μl sample, an about 65% and 75% decrease, respectively, compared to day 1, and an about 35% and 55% decrease compared, respectively, to days 5 and 7 for the controls. Thereafter, the dopamine concentration remained reduced at approximately this level throughout the remaining period of treatment and also over the 7 days of withdrawal.

Fig. 2 compares the effect of a challenge dose of amphetamine (1.5 mg/kg i.p.) on dopamine release in

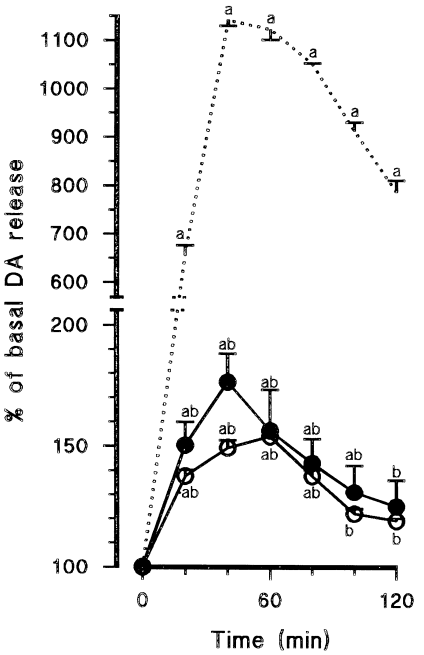

Fig. 2. Effect of a challenge dose of amphetamine (1.5 mg/kg i.p.) on extracellular dopamine concentrations in the ventral striatum of control rats (dotted line), of rats chronically treated with amphetamine (●) and of rats chronically treated for 2 weeks and then withdrawn for 1 week (○). Data expressed as the mean (±S.E.M.) percent variation from basal values. For more details see Section 2. Analysis of variance revealed a significant mean effect of pretreatment ($F(2,83) = 1000.00$; $P < 0.001$), a significant mean effect of repeated measures ($F(6,83) = 73.721$; $P < 0.001$) and significant interaction between factors ($F(12,83) = 68.471$); $P < 0.001$). $n = 4$ for each group. a = $P < 0.01$ versus basal values; b = $P < 0.01$ versus controls.

control rats, in a group of rats that had received amphetamine for 10 days (last dose 12 h beforehand) and in a group of rats withdrawn from chronic treatment for 7 days. For the second group of rats, the amphetamine challenge represented the morning treatment.

It appears that amphetamine challenge increased the baseline dopamine release more than 10-fold in saline-treated rats, but only by 90 and 50% in amphetamine-treated and in amphetamine-withdrawn rats, respectively.

Since amphetamine is known to release newly synthesized dopamine from nerve terminals, we checked whether

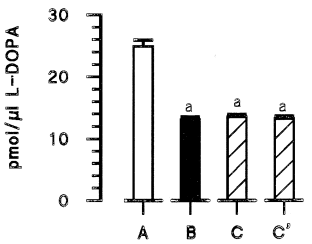

Fig. 3. L-Dihydroxyphenylalanine (L-DOPA) formation (pmol/sample) in control rats (A), in rats treated with amphetamine (1.5 mg/kg i.p. every 12 h) for 2 weeks (B), in 1 day withdrawn rats (C) and in 1 week withdrawn rats (C′). For more details see Section 2. $n = 4$ for each group; a = $P < 0.01$ versus controls.

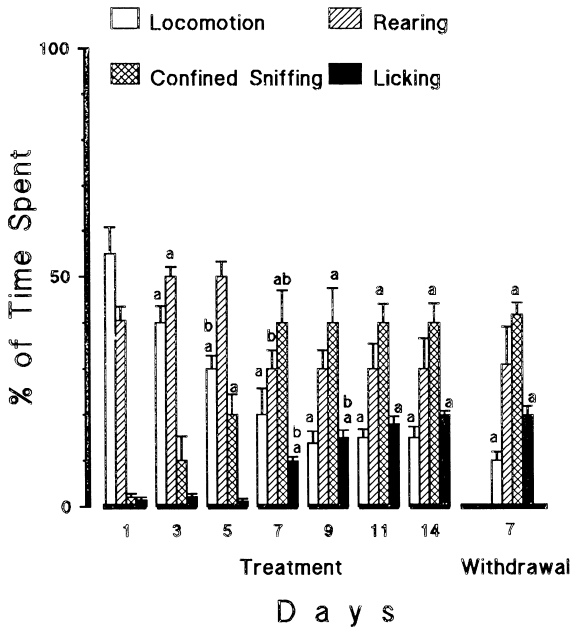

Fig. 4. Behavioral response to amphetamine during treatment and one week after its discontinuation. Behavior was evaluated as % of time spent (mean ± S.E.M.) by rats in the performance of several behavioral items (locomotion, rearing, confined sniffing and licking) in 20-min periods. The % of time spent on each behavioral item in 6 consecutive periods (2 h) were added up in order to quantify the behavioral effects of amphetamine during the microdialysis experiment. $n = 15$ a = $P < 0.01$ versus the first day of treatment; b = $P < 0.01$ versus the previous day.

or not the reduced effectiveness of the drug was due to suppression of dopamine synthesis. The latter was measured as L-dihydroxyphenylalanine accumulation after inhibition of dihydroxyphenylalanine decarboxylase with NSD 1015. As shown in Fig. 3, L-dihydroxyphenylalanine formation in the ventral striatum was found to be reduced by about 60% at 2 h, 24 h and 7 days after the last chronic amphetamine administration.

Fig. 4 shows the behavioral response of the animals to the first daily amphetamine dose over the 14 days of treatment and the response to challenge with amphetamine (1.5 mg/kg i.p.) at day 7 after withdrawal. It appears that amphetamine-induced motor activity decreased gradually during treatment, whereas amphetamine-induced stereotypy, consisting of confined sniffing and licking, increased gradually.

The behavioral sensitization persisted throughout the chronic treatment and also during the 7 days of withdrawal.

4. Discussion

The results of the present study confirm and extend the observation of Rossetti et al. (1992) that the basal extracellular concentrations of dopamine in the ventral striatum are markedly reduced after both one and seven days from discontinuation of chronic amphetamine treatment.

However, our results also show that the reduction in dopamine concentrations starts early during chronic treatment and is a lasting phenomenon. Thus, basal dopamine release after an initial increase during the first three days of treatment remained reduced throughout the treatment period (except for the relatively short periods following each amphetamine treatment). This decrease in extracellular dopamine concentration was associated with a marked reduction both in dopamine synthesis, as indicated by the reduction of L-dihydroxyphenylalanine formation, and in the dopamine releasing effect of amphetamine.

However, despite the reduced dopamine releasing effect, we found that, in agreement with previous observations (see Kalivas et al., 1993), amphetamine-induced behavioral stimulation was potentiated.

Our results are in agreement with a previous observation by Segal and Kuczenski (1992) showing that behavioral sensitization in response to challenge with amphetamine was associated with a significant reduction in the dopamine releasing effect of the drug in animals repeatedly injected with amphetamine.

However, our results contrast with the observation of Robinson and Becker (1986) showing that amphetamine challenge produced a greater dopamine release in animals withdrawn from chronic amphetamine treatment. Our results also contrast with those of Crippens and Robinson (1994) who found no decrease in the extracellular concentration of dopamine in the ventral striatum 24 h after withdrawal from chronic amphetamine treatment.

The reason for the discrepancy between results of the present study and those just mentioned might possibly be that a different microdialysis technique was used (for review, see Westerink et al., 1987).

Indeed, these authors used monolateral, concentric vertical probes via a previously fixed guide cannula and collected dialysates only once for 2 h from each animal, 24 h after the insertion of the dialysis probe.

On the other hand, we used chronically implanted transversal dialysis probes and collected dialysate samples daily from the same animals, starting 2 days after the operation throughout the 3 weeks of the experimental period. Changes in dialysate dopamine were assessed in the same animal and the mean values for amphetamine-treated animals were compared with values obtained from saline-treated animals at the same time interval after probe implantation.

A number of possible explanations could be offered for the various findings now presented.

The initial increase in baseline dopamine concentration might be correlated with a transient reduction in the sensitivity of dopamine autoreceptors controlling dopamine synthesis, release and dopaminergic firing, which was observed during the first days of amphetamine treatment (White and Wang, 1984).

Conversely, the suppression of dopamine synthesis may well explain the marked reduction in the dopamine releasing effect of amphetamine, since this drug is known to preferentially release newly synthetized dopamine from nerve terminals (Chiueh and Moore, 1975). Moreover, in view of recent findings showing that the dopamine transporter is an obligatory target for psychostimulants (Giros et al., 1996), it can also be proposed that a possible alteration in the dopamine transporter system in the amphetamine-treated animals could be responsible for the reduced effects of amphetamine.

The reduction in dopamine synthesis and release, the decreased dopamine releasing effect of amphetamine and the behavioral sensitization might be interdependent effects which could be explained as follows. The repeated stimulation of postsynaptic dopamine receptors elicited by dopamine released by amphetamine could result in a compensatory reduction in dopaminergic activity which persists longer than the acute effect of the drug.

Conversely, the reduction in dopaminergic activity might be responsible for the development of postsynaptic dopamine receptor supersensitivity. The latter may, in turn, be responsible for behavioral sensitization and for further maintenance, via a feedback inhibitory mechanism, of the reduction in dopamine release and synthesis.

Some considerations support our hypothesis.

The finding that the time course of the reduction in dopamine release paralleled that of behavioral sensitization supports the possibility that the reduction in nerve activity may play a role in the development of behavioral sensitization.

The hypothesis that repeated suppression of dopaminergic neurotransmission is needed in order to allow the behavioral sensitization to develop is consistent with the fact that behavioral sensitization can be produced by intermittent treatment with psychostimulants, but not by their continuous administration, e.g., by minipump infusion or pellet implantation (Inada et al., 1991; Zeigler et al., 1991; King et al., 1994).

In conclusion, our results argue against the hypothesis that the potentiated behavioral response to amphetamine after repeated treatment is due to potentiation of the dopamine releasing effect of the drug. On the contrary, our results indicate that the potentiated behavioral effect of amphetamine is associated with a markedly reduced dopamine release. On the other hand, our results are consistent with the hypothesis that sensitization to amphetamine behavioral effects is dependent on postsynaptic events. Accordingly, recent findings show that chronic cocaine as well as morphine and unlike haloperidol, increase the cyclic AMP system and decrease G-protein selectively in limbic areas (Guitar and Nestler, 1989; Terwilliger et al., 1991).

We have suggested that reduction of the dopaminergic output might be the cause of behavioral sensitization, and that the supersensitivity to dopamine at the postsynaptic level might further sustain the reduction of dopaminergic activity. Moreover, as mentioned in the Introduction, a

recent report by Imperato et al. (1992) indicates that repeated administration of cocaine causes a marked reduction in extracellular baseline dopamine concentration in the ventral striatum both during chronic treatment and during withdrawal, suggesting that the ability to cause a reduction in dopamine output is a general property of chronically administered psychostimulants.

Although, alteration regarding other neurotransmitters cannot be excluded, our results may have clinical relevance, suggesting that a fall in dopamine output following a 'binge' on a psychostimulant might be responsible for the rebound dysphoria, depression, fatigue and lethargy which are observed in chronic users of psychostimulants, whereas the supersensitivity to dopamine might be responsible for the craving and the compulsive use of these drugs (Watson et al., 1972; Waddington et al., 1990).

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