Pharmacology, Biochemistry and Behavior 100 (2011) 180–184

Contents lists available at SciVerse ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Withdrawal from repeated treatment with amphetamine reduces novelty-seeking behavior and enhances environmental habituation in mice ☆

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ARTICLE INFO

Article history:
Received 12 May 2011
Received in revised form 29 July 2011
Accepted 13 August 2011
Available online 22 August 2011

Keywords:
Amphetamine
Anxiety
Dopamine
Environmental habituation
Novelty-seeking
Withdrawal

ABSTRACT

Anhedonia associated with a dysphoric state is an important feature of amphetamine withdrawal in humans. We aimed to investigate the effects of amphetamine withdrawal on two motivation-related behaviors in mice: novelty seeking and environmental habituation. Because anxiety can interfere with the behavioral outcome of other tasks, amphetamine-withdrawn mice were also evaluated in the elevated plus maze. Swiss male mice (three months old) were treated with 2.0 mg/kg amphetamine for 13 days, every other day, in their home cages (a total of seven injections). Twenty-four hours after withdrawal from drug treatment, mice were tested in a free-choice novelty apparatus containing one familiar and one novel compartment or in the elevated plus maze. Novelty-seeking behavior was assessed by comparing the time spent in the novel compartment vs. the familiar compartment, whereas environmental habituation was concomitantly evaluated by the time–response curve of total locomotion (novel + familiar). Novelty seeking was decreased during amphetamine withdrawal, and this result was not associated with changes in the anxiety-like behavior of mice. Additionally, amphetamine withdrawal enhanced environmental habituation. The concomitant decrease in novelty seeking and the increase in environmental habituation seem to be related to amphetamine withdrawal-induced anhedonia. Thus, the model proposed here could be used as a tool for the study of mechanisms and potential treatment of the anhedonic behavioral consequences of psychostimulant withdrawal.

1. Introduction

Drug withdrawal syndrome is a common problem among addicts. For example, approximately 87% of the amphetamine (Amp) users report withdrawal symptoms (Srisurapanont et al., 2001). For this reason, understanding the mechanisms that underlie drug withdrawal, as well as the behavioral alterations that occur during this state, is relevant, particularly because the intense craving related to this process may be a critical factor leading to relapse.

Amp withdrawal has been much less studied than cocaine, ethanol and opiate withdrawal, but an increasing interest on the part of clinicians and researchers in characterizing Amp withdrawal has been observed in recent decades (Kitanaka et al., 2008; McGregor et al., 2005). In humans, Amp increases arousal, reduces fatigue and appetite and induces hyperactivity, mood elevation as well as euphoria when taken acutely (Drevets et al., 2001; D'Souza and Markou, 2010). With repeated use, tolerance to those effects develops and increasing amounts of the drug must be taken to maintain the individual's mood (Brauer et al., 1996; Schenk and Partridge, 1997). Consequently, compulsive and uncontrolled drug intake occurs (Everitt and Robbins, 2005; Koob and Le Moal, 1997; Robinson and Berridge, 2008). Eventually, drug intake ceases, and the individual experiences the effects of psychostimulant withdrawal (Koob et al., 1997). The DSM-IV description of stimulant withdrawal requires cessation of cocaine or Amp followed by a dysphoric mood, typified by sadness or anhedonia, and at least two of the physiological changes, such as fatigue, sleep alteration, psychomotor agitation, drug craving, increased appetite, psychomotor retardation and vivid, unpleasant dreams (American Psychiatric Association, 2000). Amp withdrawal, particularly, has been reported to peak within a few days, with the most characteristic symptom being depression with occasional suicidal ideation (Lago and Kosten, 1994). In this regard, anhedonia is a core symptom of this depressive state (Barr et al., 2002; D'Souza and Markou, 2010) and is defined as a markedly diminished interest or pleasure in all or most activities, even those which are rewarding (Gardner, 2000; Kitanaka et al., 2008).

The small number of studies on Amp withdrawal along with the absence of clear-cut physical withdrawal symptoms makes it difficult

☆ Financial support: CNPq, FAPESP, CAPES, FADA, AFIP.
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doi:10.1016/j.pbb.2011.08.015

to demonstrate conclusively the presence of Amp withdrawal as seen with other drugs. Clinical results on Amp withdrawal are conflicting, most likely due to differences between inpatient and outpatient samples (for example, outpatients may have used the drug and been exposed to drug-related stimuli) (Lago and Kosten, 1994). Therefore, there has been growing concern over the relevance of valid and reliable animal models that express the behavioral consequences of Amp withdrawal. It has proven very difficult to model all symptoms of withdrawal from not only Amp but all drugs of abuse in humans using one animal model (Kokkinidis et al., 1986; Murphy et al., 2001; Russig et al., 2003).

Animal models of Amp withdrawal focus on the dysphoric state associated with it, which is most commonly evaluated in rodents by a reduction in response to reward brain stimulation (Cassens et al., 1981; Kokkinidis et al., 1980; Leith and Barrett, 1976, 1980; Lin et al., 1999; Markou and Koob, 1991; Wise and Munn, 1995) or natural rewards (Barr and Phillips, 1999, 2002; Barr et al., 1999, 2002). Previous reports have also demonstrated decreases in several motivational components of sexual behavior after withdrawal from repeated treatment with Amp in rats (see D'Souza and Markou, 2010 and Kitanaka et al., 2008 for recent reviews). Importantly, few reports are available regarding the behavioral aspects of Amp withdrawal in mice (Cryan et al., 2003; Kokkinidis et al., 1986), an animal species particularly useful for the study of gene expression.

More recently, novelty reward has been proposed as a putative measure of anhedonia in rats (Besheer and Bevins, 2003; Bevins and Besheer, 2005) because withdrawal from nicotine blocked the acquisition of conditioned place preference for novel objects (Besheer and Bevins, 2003). As for Amp, there are some indirect evidence of decreased novelty reward in Amp-withdrawn rats. Indeed, Amp withdrawal impaired novel object recognition (Bisagno et al., 2005; Schreiber et al., 1976) and decreased spontaneous locomotion in a novel experimental context (Russig et al., 2005). However, Amp withdrawal has also been reported to decrease spontaneous locomotion in previously habituated experimental contexts (Paulson et al., 1991), which could cause both decreased locomotion in novel environments and decreased novel object recognition. Within this context, it would be relevant to investigate the behavior of Amp-withdrawn rodents in more specific tasks related to novelty responses, such as within-session locomotor habituation and novelty-induced place preference, which have not been previously investigated in rats or mice. This study was aimed to evaluate the effects of withdrawal from Amp on these two tasks concomitantly in mice. Because enhanced anxiety has already been linked controversially to Amp withdrawal (see Lago and Kosten, 1994) and can interfere with the behavioral readout of other tasks, elevated plus-maze performance was also investigated during Amp withdrawal.

2. Methods

2.1. Subjects

Three-month-old Swiss EPM-M1 male mice (40–45 g) from our own colony were used. The animals were housed, 10–13 per cage, in polypropylene cages (32 cm × 42 cm × 18 cm) under conditions of controlled temperature (22–23 °C) and lighting (12/12 h light/dark, lights on at 06:45 h). Food and water were available ad libitum throughout the experiment.

The experimental protocol was approved by the committee for the use of animal subjects from our Institution (Universidade Federal de São Paulo, UNIFESP, CEP No. 0122/07). In addition, the experiment was performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, revised 1996).

2.2. Drug

D-amphetamine (SIGMA®) was freshly diluted in saline solution. Saline was used as the control solution. The solutions were administered intraperitoneally at a volume of 10 ml/kg body weight. Repeated treatment and testing were performed between 8:00 and 11:00 h.

2.3. Behavioral tests

2.3.1. Novelty place preference test

The free-choice novelty apparatus consisted of two compartments (one black with a white grid floor and one white with a black smooth floor) of equal size (18 × 16 × 40 cm) that were both accessible from a central choice compartment (10 × 10 × 40 cm).

Mice were individually confined to one of the main compartments using an unbiased design for three 20-min sessions, 24 h apart. The main compartment where animals were confined during these three days was designated as the "familiar" compartment. An unbiased design was used because pilot studies from our laboratory have shown that mice present no initial preference for any of the main compartments. On the test day, the sliding doors were removed, and mice were placed individually in the central compartment, from which they could freely access the familiar and the novel compartments. Time spent in each compartment of the apparatus was quantified for 10 min. In addition, the locomotion frequency in each compartment of the apparatus was quantified in the first and last two-minute intervals of the 10-min session.

Novelty-seeking behavior was evaluated by comparing the time spent in the familiar and the novel compartments, with an increase in the time spent in the novel compartment indicating enhanced novelty-seeking behavior. Environmental habituation was evaluated using the time–response curve of total locomotion (locomotion in the novel compartment + locomotion in the familiar compartment during the first and the last two-minute intervals of observation), with a stronger decrease in the values of this curve revealing enhanced habituation.

2.3.2. Elevated plus-maze test

The plus maze consisted of two open (28.5 × 7 cm) and two closed (28.5 × 7 × 14 cm) arms, arranged perpendicularly, and was elevated 50 cm above the floor. In the behavioral trial, each mouse was placed on the central platform of the apparatus. Over a period of 5 min, the time spent in open and enclosed arms was recorded. Percent time in open arms (time spent in open arms/time spent in open + enclosed arms) was calculated.

3. Experimental procedures

3.1. Experiment 1. Effects of withdrawal from repeated treatment with Amp on novelty-seeking behavior and environmental habituation in mice

Mice were randomly allocated to two groups: Sal (N = 11) and Amp (N = 12). All animals were individually confined to one of the main compartments of the free-choice novelty apparatus ("familiar" compartment) for 20 min a day on three consecutive days. After 24 h, repeated treatment with saline or 2.0 mg/kg Amp commenced. Animals received an intraperitoneal (i.p.) injection of saline (Sal) or 2.0 mg/kg Amp (Amp) for 13 days, every other day, in their home cages (a total of seven injections of Sal or Amp). Twenty-four hours after the last injection, the animals were tested for novelty-seeking behavior and environmental habituation during withdrawal.

3.2. Experiment 2. Effects of withdrawal from repeated treatment with Amp on anxiety levels, as evaluated by the elevated plus maze test in mice

The same protocol from the previous experiment was followed, except that 24 h after the last injection, 23 other mice (Sal: N = 10 and Amp: N = 13) were tested in the elevated plus maze.

An intermittent treatment with Amp was used because, as reviewed by Russig et al. (2005), continuous Amp can lead to neurotoxic effects, whereas intermittent injections are associated with sensitization of locomotor activity in response to an Amp challenge. We have chosen a paradigm of repeated treatment with Amp and a dose of Amp that effectively induce behavioral sensitization under the conditions of our laboratory (Araujo et al., 2006; Costa et al., 2001, 2007; Fukushiro and Frussa-Filho, 2011). Within this context, sensitization-related changes in the brain appear to be important for the transition from casual to compulsive drug use that characterizes the addiction process (Robinson and Berridge, 2008).

4. Data analysis

ANOVAs with repeated measures (compartment vs. drug treatment and time vs. drug treatment) were used. Multiple comparisons were performed using the *t*-test for paired samples, Student's *t*-test or Duncan's post hoc test. A p-value less than 0.05 was considered as a statistically significant difference.

5. Results

5.1. Experiment 1. Withdrawal from repeated treatment with Amp reduces novelty-seeking behavior and enhances environmental habituation in mice

Fig. 1 shows the time mice spent in the familiar and the novel compartments 24 h after withdrawal from repeated treatment with saline or Amp. ANOVA with repeated measures revealed significant effects due to the compartment (familiar vs. novel) [$F(1,21)=6.7$, $p<0.05$] as well as a significant interaction between compartment (familiar vs. novel) and drug treatment (Sal vs. Amp) [$F(1,21)=4.7$, $p<0.05$]. The *t*-test for paired samples showed that the Amp (but not the Sal) group presented a significant decrease in the time spent in the novel compartment compared to the time spent in the familiar compartment. These data indicate that novelty-seeking behavior is reduced in mice withdrawn from repeated treatment with Amp.

Fig. 2 shows the total locomotion (locomotion in the familiar compartment + locomotion in the novel compartment) of the same mice. ANOVA with repeated measures revealed significant effects due to the factors of time (0–2 min vs. 8–10 min) [$F(1,21)=67.3$, $p<0.001$] and drug treatment (Sal vs. Amp) [$F(1,21)=7.1$, $p<0.05$], as well as a significant interaction between these two factors [$F(1,21)=6.7$, $p<0.05$]. Duncan's post-hoc test showed that both the Sal and Amp groups exhibited decreased locomotion throughout the session (8–10 min vs. 0–2 min), indicating that both groups habituated to the apparatus. In addition, at the 8–10 min interval, the Amp group presented significantly less locomotion counts than the Sal group, indicating enhanced environmental habituation during Amp withdrawal.

5.2. Experiment 2. Withdrawal from repeated treatment with Amp does not modify anxiety-like behavior in mice

Panels a and b of Fig. 3 show, respectively, the time spent in the closed and open arms and the percent time spent in open arms in the plus-maze apparatus, 24 h after withdrawal from repeated treatment with saline or Amp. All of the animals spent more time in the closed arms compared to the open arms, as revealed by a significant effect of arm (closed vs. open) using ANOVA with repeated measures [$F(1,21)=96.7$, $p<0.001$]. The *t*-test for paired samples confirmed this result (Fig. 3a). For the percent time on open arms (Fig. 3b), Student's *t*-test showed no significant differences between the Sal and the Amp groups. These data indicate that withdrawal from repeated treatment with Amp did not modify anxiety-like behavior in mice.

6. Discussion

In the present study, we demonstrated that withdrawal from repeated treatment with Amp decreased novelty-seeking behavior and increased environmental habituation in mice, without concurrent changes in anxiety-like behavior.

Importantly, we have previously shown that the dose and protocol of repeated treatment with Amp used in the present paper are effective in inducing behavioral sensitization in mice (Araujo et al., 2006; Costa et al., 2001; Fukushiro and Frussa-Filho, 2011). The neuroadaptations underlying behavioral sensitization are thought to be the same as those that develop during the process of addiction (Robinson and Berridge, 2008).

Although, in the present paper, the control mice showed neither preference nor aversion towards the novel compartment, the novelty-induced place aversion (i.e., the decrease in novelty-seeking behavior) that developed in Amp-withdrawn mice suggests decreased sensitivity to brain reward (anhedonia) during withdrawal from this drug. These data are in agreement with those obtained previously by Besheer

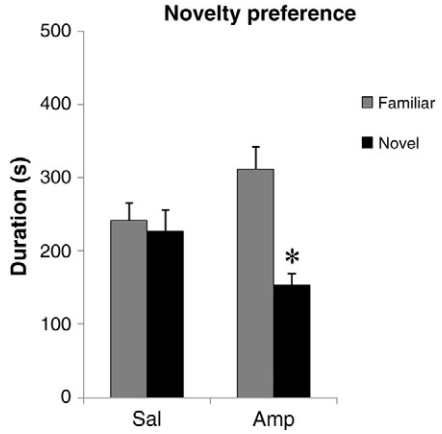

Fig. 1. Time spent in the familiar and novel compartments of the free-choice novelty apparatus 24 h after withdrawal from repeated treatment with saline (Sal) or amphetamine (Amp). Novelty-seeking behavior was reduced in Amp-withdrawn mice. Data are reported as mean ± SEM. *$p<0.05$ compared to the familiar compartment. ANOVA with repeated measures and *t*-test for paired samples.

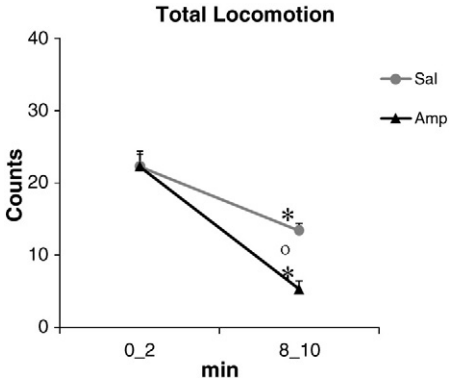

Fig. 2. Total locomotion (familiar + novel compartments) in the free-choice novelty apparatus 24 h after withdrawal from repeated treatment with saline (Sal) or amphetamine (Amp). Environmental habituation was increased in Amp-withdrawn mice. Data are reported as mean ± SEM. *$p<0.05$ compared to the same group at the 0–2 min interval. °$p<0.05$ compared to the Sal group at the same time interval. ANOVA with repeated measures and Duncan's test.

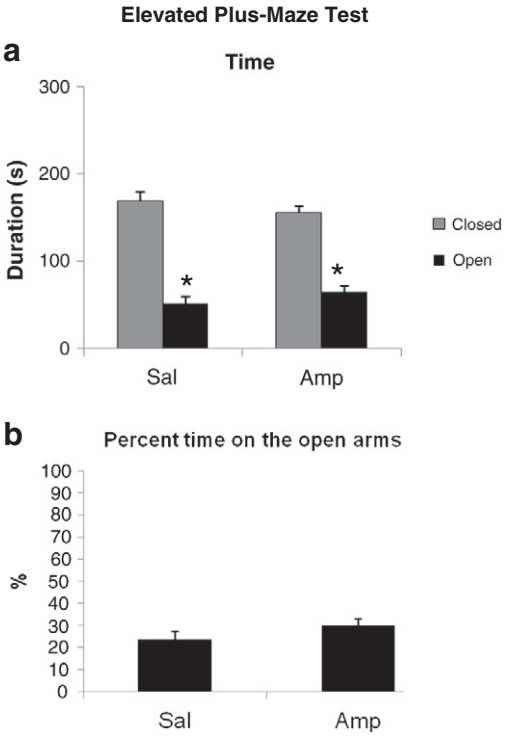

Fig. 3. Time spent in the closed and open arms (a) and percent time on the open arms (b) in the elevated plus maze, 24 h after withdrawal from repeated treatment with saline (Sal) or amphetamine (Amp). Anxiety-like behavior was not modified during Amp withdrawal. Data are reported as mean ± SEM. *$p<0.05$ compared to the closed arms. ANOVA with repeated measures and *t*-test for paired samples (a) and Student's *t*-test (b).

and Bevins (2003) for nicotine withdrawal, using a similar model of novelty-seeking behavior: novel object-place conditioning. These authors verified that 1- and 2-day (but not 4-day) withdrawal from chronic nicotine treatment prevented the establishment of an appetitive place preference conditioned by access to a familiar compartment with novel objects in rats. As suggested by Bevins and Besheer (2005), the novelty-seeking behavior evaluated by the free-choice novelty test might be an effective measure for assessing drug withdrawal-induced anhedonia. Importantly, all of the novel object place conditioning research to date has used rats as experimental subjects and nicotine as the drug of abuse. The present data extend in some way the effects of drug withdrawal on novelty seeking to mice and Amp. Further, this model adds within-session locomotor habituation to an environment as another measure of anhedonia induced by Amp withdrawal that can be evaluated concomitantly in the free-choice novelty apparatus. As demonstrated in Fig. 2, Amp withdrawal also potentiated locomotor habituation to the free-choice novelty apparatus.

Previous studies on drug withdrawal have investigated spontaneous locomotion in rodents withdrawn from repeated treatment with Amp. Those studies have generally demonstrated decreased spontaneous locomotion after several periods of withdrawal (Paulson et al., 1991; Robinson and Camp, 1987; Russig et al., 2005). Although several studies to date have investigated spontaneous locomotion, there have been no reports on the effects of drug withdrawal on habituation to an environment, which would evaluate animal motivation more precisely. Indeed, enhanced within-session habituation of open-field locomotor activity among rodents has been proposed to reflect decreased motivational effects of novelty, which has been observed, for example, after neuroleptic treatment (Carey, 1987). Accordingly, the impairment of within-session habituation of open-field locomotion has been observed after an Amp challenge injection in mice previously "sensitized" by repeated intermittent administration of this psychostimulant (Fukushiro and Frussa-Filho, 2011).

Overall, the present data suggest the development of anhedonia in mice withdrawn from repeated treatment with Amp. Psychostimulant withdrawal-induced anhedonia has been modeled in experimental animals as a failure to maintain responses to natural or artificial reward stimuli (see Vacca et al., 2007). We should emphasize that we are not suggesting that other measures of reward function such as intracranial self-stimulation and sucrose intake, for instance, might be replaced by the models proposed here. Instead, we are suggesting that the novelty-seeking behavior and environmental habituation could be used in addition to these other measures. Testing the effects of withdrawal from a range of doses of Amp and other drugs of abuse in these models would also be interesting approaches for the future.

Alternatively, the novelty-induced place aversion and increased within-session environmental habituation observed during Amp withdrawal in the present study might be associated with increased levels of anxiety. An anxiogenic-like response during Amp withdrawal could contribute to elevate the anxiogenic potential of the novel compartment (see Fukushiro and Frussa-Filho, 2011 for a discussion on this issue), resulting in the avoidance of such an environment and in increased locomotor habituation. Therefore, an elevated plus-maze test was performed 24 h after repeated Amp treatment (Experiment 2). Amp-withdrawn mice did not show evidence of enhanced anxiety when compared to saline-withdrawn controls.

In disagreement with our data, Cancela et al. (2001) have reported increased anxiety-like behavior in the elevated plus maze during withdrawal from an intermittent Amp administration schedule in rats. In contrast, we have previously verified in our laboratory that mice withdrawn from repeated treatment with Amp presented no modification in the percent time spent on the open arms of the plus-maze discriminative avoidance task (an animal model that simultaneously evaluates learning/memory, anxiety and motor activity) when compared to saline-treated control mice (Silva et al., 2002). Likewise, none of the different protocols of Amp administration used by Russig et al. (2005) produced modifications in the levels of anxiety-like behavior among rats tested in the elevated plus maze during withdrawal. These conflicting results may be due to different administration schedules, withdrawal time points, or strain and species differences. Russig et al. (2005) have demonstrated that the behavioral consequences of Amp withdrawal depend critically on the administration schedule, the dose and the duration of withdrawal.

The results of Experiment 2 suggest that the protocol of Amp treatment used in the present paper appears to produce more effects on motivation than on anxiety-like behavior of animals during abstinence. It is possible that repeated treatment with Amp for longer periods would affect not only motivation but also anxiety-like behavior of rodents. From a clinical point of view, although anxiety may be present in psychostimulant withdrawal, anhedonia is the core symptom of this syndrome (D'Souza and Markou, 2010). Thus, the lack of modifications on the anxiety-like levels of Amp-withdrawn mice was not completely unexpected.

From a clinical perspective, our findings provide some additional information regarding alterations in responses to novelty during acute Amp withdrawal. This could provide new insights on how to manage Amp withdrawal during early stages. It should be acknowledged, however, that although acute psychostimulant withdrawal should be better understood and treated correctly, treatment of the protracted abstinence syndrome should also be studied because it may help in preventing relapse to psychostimulants.

7. Conclusions

In conclusion, by using novelty-seeking behavior and environmental habituation we could concomitantly evaluate the anhedonia that develops during Amp withdrawal. From a clinical point of view, as pointed out by Kitanaka et al. (2008), medication for treatment

of the dysphoric state is important for Amp abusers to avoid impulsive self-injurious acts that are committed with unconscious on uncontrolled suicidal ideation. However, successful treatments for anhedonia induced by Amp withdrawal remain elusive, because its exact molecular basis has not yet been fully elucidated. Simple and practical animal models such as the ones proposed in the present study may represent important tools in this direction.

Acknowledgements

This research was supported by fellowships from Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP), from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), from Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), from Fundo de Apoio ao Docente e Aluno (FADA) and from Associação Fundo de Pesquisa em Psicobiologia (AFIP). This manuscript was edited for English language by American Journal Experts (AJE), but we are entirely responsible for the scientific content of the paper. The authors would like to thank Ms. Teotila R. R. Amaral, Mr. Cleomar S. Ferreira and Mr. Antônio R. Santos for capable technical support.

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