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ScienceDirect
Behavioural Brain Research 189 (2008) 170–179
BEHAVIOURAL BRAIN RESEARCH
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Research report

A sensitizing regimen of amphetamine that disrupts attentional set-shifting does not disrupt working or long-term memory

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Received 18 September 2007; received in revised form 11 December 2007; accepted 27 December 2007
Available online 20 January 2008

Abstract

Exposure to an intermittent, escalating dose of amphetamine induces a sensitized state that, both behaviourally and neurochemically, mirrors several features linked to the positive symptoms of schizophrenia. Increasingly it is being realized that cognitive deficits are a core component of schizophrenia; therefore we sought to assess the effects of inducing an amphetamine-sensitized state on memory (working and long-term) and cognitive flexibility, two cognitive domains impaired in schizophrenia. Rats were exposed to a sensitizing regimen of amphetamine (1–5 mg/kg; three times per week for 5 weeks; escalating at 1 mg/kg per week) or saline. In experiment 1, animals were tested on an operant delayed non-match to position task (working memory). Experiment 2 used a standard fixed-platform location water maze task (long-term memory), while experiment 3 used a variable-platform location water maze task (long-term memory and working memory). Amphetamine-sensitized animals were not impaired on any of these tasks. In experiment 4, animals were assessed on a strategy selection task in which they were first required to learn to locate a food reward using a particular learning strategy (place or response) then to learn to shift to an alternate learning strategy (response or place). Amphetamine-sensitized animals were not impaired on this task. In the final experiment animals were found to be impaired in performance of the extra-dimensional shift component of an attentional set-shifting task. These results suggest that while amphetamine sensitization does not produce memory impairments similar to those seen in schizophrenia, it does produce strong impairments in set-shifting, suggesting changes in prefrontal function similar to those seen in schizophrenia.

Keywords: Animal model; Schizophrenia; Dopamine; Cognition; Amphetamine sensitization; Morris water maze; Delayed non-matching to position; Attentional set-shifting

1. Introduction

Amphetamine sensitization has been suggested to model some aspects of schizophrenia [30,31,40,42,51–53]. Briefly, amphetamine sensitization refers to a process whereby responses to amphetamine increase through repeated exposure to the drug [40]. This increased responsiveness is maintained during withdrawal from the drug, and has been shown to last up to 1-year post drug exposure in rats [35]. Following the induction of sensitization, animals show impaired performance on a number of tasks thought to involve psychological processes similar to those disrupted in schizophrenia, such as pre-pulse inhibition [44,51–53] although see [31,43], latent inhibition [30,31,43,53], attentional vigilance [8], sustained attention [18] and attentional set-shifting [13,16]. In the latter task, amphetamine-sensitized animals displayed an impairment in making an extra-dimensional attentional shift, as well as difficulties in reversal learning, similar to what has been found in animals with prefrontal lesions [1,28], schizophrenic patients [34] and human amphetamine abusers [32].

These findings suggest that amphetamine sensitization reproduces many of the attentional and pre-attentional deficits associated with schizophrenia. What is less well known, however, is the extent to which amphetamine sensitization can model other areas of cognitive impairment in schizophrenia. Schizophrenia is associated with impairments in both working [20] and long-term

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doi:10.1016/j.bbr.2007.12.032

memory [7,24]. In non-human primates, exposure to a sensitizing regimen of amphetamine produced short-term deficits in performance of a delayed response task, a measure of working memory. In contrast, a brief exposure regimen of amphetamine (2.5 mg/kg for 5 days) did not disrupt performance of a radial maze based delayed alternation task in rats [50]. Regarding long-term memory, one study found that amphetamine sensitization (1–5 mg/kg, three injections per day for 6 days) failed to disrupt acquisition or retention of a fixed platform position water maze task in rats [41]. In contrast, animals exposed to a repeated single dose of amphetamine (3 mg/kg, five injections over 10 days) showed deficits in an object recognition memory task which required the retention of information about objects encountered 2 or 4 h earlier [2], suggesting that some forms of long-term memory may be impaired in sensitized animals. Thus, there are conflicting results from animal studies on the impact of the amphetamine-sensitized state on memory and it is possible that this could relate to differences between the various procedures used to induce the sensitized state.

In our work an intermittent schedule of amphetamine, where the drug is given three times per week over 5 weeks, with the dose escalating at a rate of 1 mg/kg per week, induces a variety of behavioural deficits when animals are tested several weeks after drug treatment [18,51–53]. These deficits include poor attentional set-shifting and sustained visual attention. The present studies extended these findings to examine the impact of this regimen of amphetamine on working and long-term memory. Working memory was assessed on an operant delayed non-match to position (DNMTP) task [12]. Three experiments were conducted that assessed long-term memory. The first of these examined the effect of amphetamine sensitization on long-term memory in a standard fixed platform position water maze task. The second experiment used a more demanding variable platform position water maze task, in which animals were required to locate a hidden platform in a novel position each day. In the final experiment, animals were tested on a strategy shifting task which required learning to locate a food reward on a plus maze using a particular type of memory (place or response) followed by a shift to a different type of memory (response or place). Interference with the prefrontal cortex produces a selective deficit in the ability to switch memory strategies [37] and performance of this and similar tasks is dependent upon prefrontal dopamine function [19,37–39]. This task was included in order to assess the impact of amphetamine sensitization on prefrontal control over learning and memory processes. Finally, experiment 5 assessed the effects of amphetamine sensitization on an attentional set-shifting task [1,28] since we have previously found impaired attentional set-shifting in the amphetamine-induced sensitized state [16].

2. Methods

2.1. Subjects

Male, Spraque–Dawley (Charles Rivers, Saint-Constant, Quebec) rats weighing between 275 and 300 g at the beginning of each experiment were used. Animals were housed in a room maintained at 22 (±2) °C and were kept on a 12:12 light/dark cycle (lights on at 08:00). Eighty-three animals were used (experiment 1: saline $n = 12$ and amphetamine $n = 12$; experiment 2: saline $n = 10$ and amphetamine $n = 10$; experiment 3: saline $n = 10$ and amphetamine $n = 10$. A single group of animals (saline $n = 9$ and amphetamine $n = 10$) were run on the strategy-shifting (experiment 4) and attentional set-shifting tasks (experiment 5).

2.2. Amphetamine sensitization

Amphetamine injections (IP) took place three times a week (Monday, Wednesday and Friday) for 5 weeks. During week 1, amphetamine treated animals received a dose of 1 mg/kg (from salt), with the dose being escalated by 1 mg/kg each subsequent week (dose during the final week was 5 mg/kg). Control animals received saline. All injections were administered in a 1 ml/kg volume.

2.3. Experiment 1: delayed non-match to position

DNMTP training took place in standard operant conditioning chambers (Med Associates, St. Albans, Vermont). Each chamber was equipped with a pellet dispenser, two retractable response levers, a pellet magazine, two stimulus lights and an infrared photobeam located in the pellet magazine on the front wall. The pellet magazine was located in the lower centre of the chamber and the response levers were located to the left and right of the magazine. One stimulus light was located above each response lever. Additionally, two opaque barriers (5 cm deep × 0.5 cm wide), running the height of the chamber were positioned perpendicular to the front wall, separating each response lever from the magazine.

Animals were first trained to respond on a FR1 schedule of reinforcement, with both response levers available during these sessions. Each session lasted for 30 min or until 100 responses on either lever had been made. This training lasted for four sessions. Animals were then trained to respond to signalled presentations of the response lever. At the start of each trial, a stimulus light was illuminated and the response lever immediately below that stimulus light was extended into the chamber. Animals were required to press the lever within 20 s in order to receive reinforcement. Once a response had occurred, the stimulus light was turned off and the response lever was retracted. If no response occurred, the stimulus light was turned off and the lever was retracted, followed by a 20 s time-out period. Each session consisted of 50 presentations of each lever, for 100 trials, and training on this phase lasted for three to five sessions. Animals were then trained on the DNMTP task. Each DNMTP trial consisted of a sample phase and a choice phase. The sample phase was initiated by the extension of a response lever into the chamber, along with illumination of the corresponding stimulus light. A response on this lever caused the stimulus light to extinguish, the lever to retract, and the delay period to begin. During the delay period animals were required to nose-poke in the food magazine. The first nose-poke response after the delay period had timed out triggered the start of the choice phase. Here, both response levers were extended into the chamber, and both of the stimulus lights were illuminated. To receive reinforcement, animals were required to respond on the lever that was not present during the sample phase. All DNMTP sessions consisted of 100 trials. Accuracy, defined as the percentage of trials with a correct response, was the primary measure of performance and was calculated separately for each delay value. Both the barriers and the nose-poke requirement during the delay periods were used to minimize the use mediating strategies that rats could use to solve the task.

Animals were initially trained only at the shortest delay (100 trials at 1 s delay). Once performance had reached a level of 85% accuracy, the next delay was introduced (i.e. 1 s and 4 s delay, 50 trials each). Further delays were gradually phased in until rats were being tested with delays of 1, 4, 8, 16 and 24 s, with 20 trials at each delay period per session. Once behaviour had stabilized, animals were given a further 10 sessions of training prior to the start of drug treatment (Baseline phase). Based on average performance on this baseline phase rats were matched to two groups to receive amphetamine or saline injections. During the 5 weeks amphetamine sensitization period, animals were given DNMTP sessions on non-injection days (Tuesday and Thursday) (sensitization phase). After the sensitization phase had finished testing was conducted three times per week (Monday, Wednesday and Friday) for 5 weeks (withdrawal phase).

2.4. Experiment 2: fixed platform location water maze

The water maze was constructed from a circular, white plastic tub, 1.5 m in diameter and 79 cm deep. The platform was made from clear Plexiglas (15 cm