Amphetamine-induced memory impairment in a discriminative avoidance task is state-dependent in mice

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Abstract

In both humans and laboratory animals, the reports of cognitive effects following acute amphetamine (Amph) administration are mixed and depend, for example, on the timing of administration (e.g. before or after task acquisition) and/or on the memory model used. Besides its cognitive effects, Amph produces other important behavioural effects, including alterations in anxiety and general activity, which could modify the subject’s internal state, thereby facilitating state-dependent learning. Importantly, state-dependency has been linked to drug dependence in humans. This study evaluates the role of state-dependent learning in Amph-induced memory deficits in mice submitted to a discriminative avoidance task. Mice were given Amph (3 mg/kg) before training and/or before testing in the plus-maze discriminative avoidance task, an animal model that concomitantly evaluates learning, memory, anxiety-like behaviour and general activity. Pre-training Amph administration did not affect the ability to learn the discriminative task, but rather induced anxiogenic-like effects and a marked retention deficit in the test session. This memory impairment was completely absent when animals received Amph before both the training and the test sessions. Amph-induced memory impairment of a discriminative avoidance task is state-dependent, such that a response acquired in the ‘Amph state’ cannot be recalled in the normal state. The involvement of anxiety alterations in this ‘Amph state’ is discussed.

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Introduction

Amphetamine (Amph) is highly addictive and can cause individuals to exhibit effects ranging from relatively minor cognitive impairment to severe psychotic symptoms (Wood & Anagnostaras, 2009). In clinical practice, Amph is used in the treatment of attention-deficit hyperactivity disorder as well as excessive daytime sleepiness and narcolepsy (Ahmann et al. 2001). However, its indiscriminate usage is a growing social problem, as Amph has been regarded by the public to be a cognitive enhancer, presumably by promoting mental arousal or wakefulness (Butcher, 2003).

With regard to the acute effects of Amph on the cognitive processes of learning and memory, reports have been mixed and include an absence of effects (Beuzen et al. 1994), memory enhancement (Roozendaal et al. 1996; Ventulani et al. 1993) and memory deficits (Ornstein et al. 2000; Silva et al. 2002a). The nature of the effect seems to depend on several factors, including the timing of administration (e.g. before or after task acquisition) and whether the study uses humans (Soetens et al. 1995) or laboratory animals (Simon & Setlow, 2006; Wood & Anagnostaras, 2009) as well as the memory model.

Previous studies have shown that Amph promotes memory improvement principally when given post-acquisition, supporting the idea that its effects are specifically related to memory consolidation. In
pre-clinical studies, systemic post-training injections of Amph have been shown to enhance the consolidation of spatial learning (Brown et al. 2000; Packard & White, 1989), active avoidance and appetitive (Janak & Martinez, 1992) conditioning tasks (Simon & Setlow, 2006). However, when given pre-training, Amph-induced effects on memory are highly contradictory and include both facilitatory (Beuzen et al. 1994; Ventulani et al. 1993) and inhibitory (Silva et al. 2002a; Wood & Anagnostaras, 2009) effects. The inhibitory pre-training effects of this drug on memory performance can be critically modified by Amph-induced learning impairment and/or the involvement of the state-dependency phenomenon (i.e. the retrieval of a memory engram may require the organism to be in a state that is similar to that in which the engram was initially acquired; Bruins Slot & Colpaert, 1999).

Regarding state-dependency, Amph produces important behavioural effects on both emotional levels (Lin et al. 1999) and general activity (Bernardi et al. 1986; Fukushiro et al. 2007), which could modify the organism’s internal state, thereby facilitating state-dependent learning. From a clinical perspective, this state-dependency could play an important role in Amph abuse, as cues (such as drug intake context and drug-induced interoceptive effects) can become associated with the reinforcement properties of the drug itself (Alvarez et al. 2006; Simon & Setlow, 2006).

In a previous study (Silva et al. 2002a), we investigated the effects of Amph on the plus-maze discriminative avoidance task (PM-DAT), an animal model that evaluated learning, memory, anxiety and general activity concomitantly (Gulick & Gould, 2011; Silva & Frussa-Filho, 2000). We demonstrated that when 3 mg/kg Amph was given acutely before training, it significantly decreased anxiety and impaired memory in the test session. When the drug was administered acutely after the training session, no cognitive effects were found. After repeated treatment (daily injections for 10 d), the anxiogenic effect was abolished while the amnestic effect remained. In order to extend these findings, the aim of the present study was to investigate the role of state-dependency on the effects of the same pre-training amnestic dose of Amph (3 mg/kg; Silva et al. 2002a) in mice subjected to the PM-DAT.

Methods

Subjects
Swiss EPM-M1 male mice (aged 3 months; outbred, raised and maintained in the Centre for Development of Experimental Models in Medicine and Biology of Universidade Federal de São Paulo) were used. Animals weighing 30–35 g were housed under controlled temperatures (22–23 °C) and lighting (12-h light/dark cycle, lights on 06:45 hours). Food and water were available ad libitum. Animals used in this study were maintained in accordance with the National Institute of Health Guide for the care and use of laboratory animals (NIH Publications No. 80-23), revised 1996 and the Brazilian Law for Procedures for Animal Scientific Use (#11794/2008). The experimental procedures were approved by the Institutional Animal Care and Use Committee under the protocol #0960/09.

Drugs
damphetamine sulfate (3 mg Amph/kg body weight; Sigma Chemical Co., USA) was diluted in saline (Sal) to a total volume of 10 ml/kg and was injected i.p. For control mice, Sal was injected.

PM-DAT
The apparatus employed in the PM-DAT was a modified wooden elevated plus-maze containing two enclosed arms with sidewalls and no top (length x width x height = 28.5 x 18.5 x 18.5 cm) opposite from two open arms (length x width = 28.5 x 7 cm). The aversive enclosed arm was an enclosed arm with a 100-W lamp (which was turned on only during the aversive stimulus) placed over the exact centre and a sound generator placed under the arm. In the 10-min training session, the mouse was placed at the centre of the apparatus; when the animal entered the aversive enclosed arm, continuous aversive stimuli were delivered and were continued until the animal left the arm. The aversive stimuli consisted of both illuminating the 100-W light and generating an 80-dB sound. In the test session (performed in the same room 24 h after the training session), the mouse was again placed in the centre of the apparatus and was observed for 3 min. However, no aversive stimuli were applied when the mouse entered the aversive enclosed arm (although the non-illuminated lamp remained in the middle of this arm to provide a visual spatial cue for identifying the aversive arm).

It is important to mention that the duration of the training session was 10 min while the duration of the test session was only 3 min. In fact the test session was shorter to avoid the possibility that animals re-interpreted the aversively enclosed arm as a neutral/safe place in the testing (when the aversive stimuli is
absent), preventing the influence of a new learning that would impair the measurement of memory in the test session.

During both sessions, the experimenter was blind to the mouse’s treatment group, and the apparatus was cleaned with 5% alcohol after each session. The time spent in each arm of the apparatus (aversive, non-aversive and open arms) as well as numbers of entries (an entry is defined as the placement of all four paws in one arm) in each of these arms was recorded. Based on them, we calculated the total number of entries into any of the arms; percent time spent in the aversive enclosed arm (time spent in aversive enclosed arm/time spent in both the enclosed arms × 100) and percent time spent in the open arms (time spent in open arms/sum of the time spent in both open and both the enclosed arms × 100).

In the present study, we considered the following:

- **Learning**: the progressive avoidance to the aversive enclosed arm represented by the decrease in percent time spent in the aversive enclosed arm throughout the training session, when the aversive stimuli are present.
- **Memory**: the discrimination of the time spent in the aversive vs. non-aversive enclosed arms during the test session. Among the groups, the percent time spent in the aversive enclosed arm, which represents retention of the task in the test session, was compared to test for quantitative differences.
- **Anxiety**: the percent time spent in the open arms of the apparatus.
- **Locomotion**: number of entries into any of the arms.

### Statistical analysis

The total number of entries into any arm, the percent time spent in the open arms and the percent time spent in the aversive enclosed arm were calculated and compared using the t test for independent samples in the training session and two-way analysis of variance (ANOVA) followed by Duncan’s test in the testing session. The ANOVA with repeated measures was employed to analyse the decrease in percent time spent in the aversive enclosed arm throughout the training and test sessions. Two-way ANOVA followed by Duncan’s test was used to analyse the time spent in the aversive vs. non-aversive enclosed arms during the training session and three-way ANOVA was used in the test session to analyse the same parameter. A probability of p < 0.05 was considered significant for all comparisons made.

### Experimental design

#### Role of state-dependency in memory impairment induced by acute administration of Amph in mice tested in the PM-DAT

Mice were randomly assigned to one of four experimental groups containing 10 mice each. The groups were based on whether they were to receive either Sal or Amph (3 mg/kg body weight) before the training and/or test session: pre-training/pre-test injection of Sal (Sal–Sal); pre-test injection of Amph (Sal–Amph); pre-training administration of Amph (Amph–Sal); or pre-training/pre-test administration of Amph (Amph–Amph). The animals were subjected to a training session in the PM-DAT 15 min after the relevant injection and the behavioural parameters described above were registered minute by minute. The mice received their second injection of Sal or Amph 24 h after the training session and a test session was performed 15 min later.

#### Results

#### Role of state-dependency in memory impairment induced by acute administration of Amph in mice tested in the PM-DAT

The Sal–Sal and Sal–Amph groups performed the training session after a Sal injection, whereas the Amph–Sal and Amph–Amph groups performed this session after an Amph injection. Therefore, for the training session, data from animals of the Sal–Sal and Sal–Amph groups were pooled into the Sal group; similarly, training session data from the Amph–Sal and Amph–Amph groups were pooled into the Amph group. Two-way ANOVA for time spent in both enclosed arms revealed that only the arm type factor (aversive vs. non-aversive) had a significant effect \((F_{1,76} = 496.35; p < 0.001)\). No significant effects of treatment factor (Sal × Amph; \(F_{1,76} = 0.56; p = 0.45\)) or interaction \((F_{1,76} = 0.73; p = 0.39\)) were found. The post-hoc analysis by Duncan’s test revealed that the mice treated with either Sal or Amph spent significantly less time in the aversive arm than in the non-aversive enclosed arm during the training session (Fig. 1a), confirming the effectiveness of the aversive stimuli. The t test for independent samples showed no significant difference between groups concerning the percent time spent in the aversive enclosed arm in the training session as a whole \((t_{38} = 0.92; p = 0.36\); Fig. 1b). ANOVA for the percent time spent in the aversive arm with treatment as the between-subject factor and time (minutes of observation) as the repeated-measure
the within-subject factor was applied. The analysis revealed a significant effect of arm type ($F_{1,72} = 700.48; \ p < 0.001$), as well as significant pre-training treatment $\times$ arm type ($F_{1,72} = 11.04; \ p = 0.001$), pre-test treatment $\times$ arm type ($F_{1,72} = 34.42; \ p < 0.001$) and pre-training $\times$ pre-test $\times$ arm type ($F_{1,72} = 12.63; \ p = 0.001$) interaction effects. On the other hand, no significant effects were found for pre-training ($F_{1,72} = 0.001; \ p = 0.98$) or pre-test ($F_{1,72} = 2.73; \ p = 0.10$) factors. The post-hoc analysis by Duncan’s test revealed that animals from all four experimental groups spent significantly less time in the aversive enclosed arm than in the non-aversive enclosed arm (Fig. 2a). Since all mice retained the task, the percent time spent in the aversive enclosed arm was analysed to explore possible differences in the magnitude of this retention. Accordingly, two-way ANOVA followed by Duncan’s test revealed significant effects of pre-training ($F_{1,34} = 5.10; \ p < 0.05$) and pre-test ($F_{1,34} = 9.88; \ p < 0.005$) treatments and pre-training $\times$ pre-test interaction ($F_{1,34} = 5.06; \ p < 0.05$). This finding shows that this parameter (i.e. memory impairment) was enhanced in the animals treated with Amph before training (Amph–Sal) relative to the other three groups. Taken together, these data demonstrate that pre-training Amph treatment causes state-dependent memory impairment, inasmuch as the pre-test administration of this drug (Amph–Amph) abolishes such memory deficit (Fig. 2b).

The ANOVA for the percent time spent in the aversive arm with treatment as the between-subject factor and time as the repeated-measure factor revealed only significant effect of pre-test factor ($F_{3,38} = 4.50; \ p = 0.04$) and pre-training $\times$ pre-test ($F_{1,38} = 6.17; \ p = 0.02$) interaction. No significant effects were found for time ($F_{2,32} = 0.40; \ p = 0.67$), time $\times$ pre-training ($F_{2,32} = 0.89; \ p = 0.92$), time $\times$ pre-test ($F_{2,32} = 0.38; \ p = 0.69$), time $\times$ pre-training $\times$ pre-test ($F_{2,32} = 0.08; \ p = 0.92$) or pre-training ($F_{1,38} = 1.39; \ p = 0.25$). Indeed, all groups displayed a linear percent time spent in the aversive arm throughout the session, demonstrating that the cognitive effects are related to drug-induced impairment and not to a possible new learning that the aversive is no longer threatening (Fig. 2c).

Concerning anxiety-like behaviour and locomotor activity, with regard to the percent time spent in the open arms during the training session, t test for independent samples revealed that the animals treated with Amph spent significantly less time in these arms, consistent with an anxiogenic effect ($t_{38} = 2.11; \ p < 0.05$; Fig. 3a). Conversely, no significant difference was found when the total number of entries was analysed ($t_{38} = 0.24; \ p = 0.81$; Fig. 3b).
With regard to the percent time spent in the open arms during the test session, two-way ANOVA revealed no significant effects of pre-training (F_{1,36} = 0.37; p = 0.55), pre-test (F_{1,36} = 2.46; p = 0.13) or pre-training × pre-test (F_{1,36} = 0.00; p = 0.99; Fig. 3c). Finally, two-way ANOVA for the total number of entries showed significant effects of pre-test treatment (F_{1,36} = 7.56; p = 0.009), but not for pre-training (F_{1,36} = 0.41; p = 0.52) or pre-training × pre-test (F_{1,36} = 0.09; p = 0.77). Hence, the mice injected with Amph prior to the test session (the Sal–Amph and Amp–Amph groups) exhibited decreased motor activity compared to their respective control groups that were treated with Sal (Sal–Sal and Amph–Sal; Fig. 3d).

Discussion

Whereas there are many reports describing the effect of post-training Amph administration in facilitating memory tasks (Packard & White, 1989; Simon & Setlow, 2006), the pre-training effects of this psycho-stimulant on memory are highly controversial (Ventulani et al. 1993; Wood & Anagnostaras, 2009). Thus, although Amph seems to improve memory consolidation, pre-training administration can impair cognitive performance by either inhibiting the learning process or producing state-dependent memory deficits. Using the PM-DAT, we found that pre-training Amph administration produced memory deficits in the absence of a learning impairment. However, these deficits were completely abolished by a subsequent pre-test Amph injection, revealing a critical role of state-dependency in the cognitive effects of Amph.

In the PM-DAT, learning is defined as progressively decreased exploration of the aversive enclosed arm where light and sound (the aversive stimuli) are presented during the training session. Since learning is quantified as a change in performance within a specific period of time, the progressive learned avoidance of this arm is measured as the percent time spent in the arm throughout the training session (Alvarenga et al. 2008; Niigaki et al. 2010; Patti et al. 2006). With regard to the experimental validation of this parameter as a learning index, we have demonstrated that, for example, sleep deprivation produces learning deficits in rats (Alvarenga et al. 2008), which is in agreement with clinical data (Dinges et al. 1997). In the present study, the pre-training acute administration of Amph did not alter the animals' ability to progressively avoid the aversive enclosed arm in the training session, suggesting that learning remained intact (Fig. 1c). In contrast, Amph administration led
to a decreased percent time spent in the open arms during the training session (Fig. 3a). Quantifying this parameter provides an effective measure of anxiety levels, as it is decreased by classic anxiogenic drugs, such as caffeine (Silva & Frussa-Filho, 2000), and is increased by classic anxiolytic agents, such as chlor-diazepoxide and ethanol (Gulick & Gould, 2009a, b, 2011; Kameda et al. 2007; Silva & Frussa-Filho, 2000, 2002). In this vein, the anxiogenic effect of Amph has been extensively demonstrated with mice and rats, both in the traditional elevated plus-maze (Biala & Kruk, 2009; Biala et al. 2009; Lapin, 1993) and in the PM-DAT (Silva et al. 2002a).

In the present study, the pre-training acute administration of 3 mg/kg Amph did not modify locomotor activity (as measured by the total number of entries into any of the arms) during the training session (Fig. 3b). This result contradicts findings from our own laboratory showing that a similar dose of Amph significantly enhanced the mouse’s locomotor activity in the open-field test (Calzavara et al. 2008; Carvalho et al. 2009). This discrepancy between the PM-DAT and open-field tests might suggest that measuring the total number of entries in the former test may not be a sufficiently sensitive index of locomotor activity.

However, this seems not to be the case because the total number of entries in the PM-DAT has been shown to be as sensitive as the open-field model in evaluating hypolocomotion induced by the catecholamine-depleting agent reserpine (Carvalho et al. 2003; Silva et al. 2002b), as well as the classic biphasic pattern of ethanol-derived changes in motor activity (Araujo et al. 2005, 2006, 2009; Gulick & Gould, 2009a, b, 2011; Kameda et al. 2007). In addition, we previously demonstrated that hyperlocomotion induced by non-pharmacological methods such as continuous exposure to light (Abilio et al. 1999) or paradoxical sleep deprivation (Frussa-Filho et al. 2004) can be accurately detected by the total number of entries in the PM-DAT (Patti et al. 2010).

An alternative explanation for the discrepancy between the PM-DAT and open-field test findings with regard to Amph’s effect on motor activity may lie in the experimental design, as there are qualitative environmental differences between these two tests. Indeed, whereas the open-field arena can be a neutral environment, the PM-DAT contains two open arms simulating a condition naturally avoided by rodents and one aversive enclosed arm that can be actively avoided, making this apparatus more anxiogenic than

Fig. 3. The effect of amphetamine (Amph) on the plus-maze discriminative avoidance task in the training or testing performance. Mice were treated with saline (Sal) or 3 mg/kg Amph 15 min before training session and tested 24 h later, 15 min after an injection of Sal or 3 mg/kg Amph. Results are presented as means ± S.E. of percent time spent in the open arms during the training (a) and test (c) sessions and total number of entries during the training (b) and test (d) sessions. * p < 0.05 compared to the Sal-treated group (independent samples t test); + p < 0.05 compared to the respective Sal pre-test-treated group (two-way analysis of variance and Duncan’s test).
an open-field arena. This fact is supported by recent reports that brightly illuminating (thereby making more aversive) the open-field arena decreases both spontaneous (Bouwknecht et al. 2007) and Amphetamine-induced (Fukushiro & Frussa-Filho, 2010) locomotor activity. Thus, the apparent absence of a hyperlocomotor effect of Amphetamine in the PM-DAT could be explained by increased anxiety-like behaviour induced by the drug combined with an aversive environment. Within this context, our group has demonstrated that the anxiogenic effect of acute Amphetamine administration can mask its hyperlocomotor effect (Zanlorenzi et al. unpublished data). Indeed, when Amphetamine was administered together with the anxiolytic benzodiazepine chlordiazepoxide, the latter inhibited Amphetamine-induced anxiogenic effects and enhanced Amphetamine-induced hyperlocomotor effects in mice subjected to the open-field arena. Additionally, we demonstrated that the PM-DAT was not sensitive enough to detect the well-known stimulant effect of caffeine unless chlordiazepoxide was also administered (Silva & Frussa-Filho, 2000).

Using the PM-DAT, our group and others have reported that impaired memory can be identified as reduced avoidance of the aversive enclosed arm in the test session (Fig. 2a), namely, when the time spent in this arm is the same as that spent in the non-aversive enclosed arm. A similar effect has been reported for the pre-training administration of scopolamine (Claro et al. 1999; Silva et al. 1999), chlordiazepoxide (Silva & Frussa-Filho, 2000), morphine (Patti et al. 2006), ethanol (Gulick & Gould, 2009a, b, 2011; Kameda et al. 2007) and cocaine (Niigaki et al. 2010). Alternatively, impaired memory can be demonstrated by an increase in the percent time spent in the aversive enclosed arm in the test session, even under conditions in which the animal is able to avoid this arm. This effect has been reported for pre-training administration of caffeine (Silva & Frussa-Filho, 2000) and Amphetamine (Silva et al. 2002a), and for paradoxical sleep deprivation (Alvarenga et al. 2008). In this regard, our study corroborates the findings of Silva et al. (2002a), who reported that the pre-training acute administration of 1 or 3 mg/kg Amphetamine induced amnestic effects seen as an increase in the percent time spent in the aversive enclosed arm during the test session (Fig. 2b).

As mentioned in the Introduction, Amphetamine can produce memory enhancement (Roozendaal et al. 1996; Ventulani et al. 1993) dependent on the time of administration (i.e. before or after the task training). In this context, the cognitive effect observed in the test session could have been produced by a deleterious effect of Amphetamine on memory or by a facilitatory effect of learning that the entry in the aversive arm is no longer followed by the presentation of aversive stimuli. In the present study, we have verified that all the groups spent similar percent time in the aversive enclosed arm throughout the test session (Fig. 2c), demonstrating that there were no alterations in their exploratory pattern, thus discarding the possible occurrence of a new learning in the test session.

Given the close relationship between memory and anxiety in behavioural tasks (Mathews, 1990; Silva & Frussa-Filho, 2000), the anxiogenic effect of Amphetamine demonstrated in this study may have contributed to the appearance of the Amphetamine-induced retention deficit in the Amphetamine–Saline group during the test session. In support of this scenario, Silva & Frussa-Filho (2000) demonstrated that altered (either increased or decreased) anxiety levels during the plus-maze discriminative avoidance conditioning task led to retention deficits during testing. In that study, pre-training caffeine administration decreased the percentage of time spent in the open arms in the training session but did not modify acquisition performance. Pre-training caffeine treatment did, however, lead to performance deficits during the test session that were rescued by simultaneous pre-training chlordiazepoxide administration, as with the anxiogenic effect. In addition, the biochemical events involved in memory formation are regulated by hormonal and neurohormonal mechanisms related to stress and anxiety (Korneyev, 1997). Within this context, one could argue that the cognitive effects of Amphetamine are derived from the alterations in anxiety levels instead of being mnemonic in nature. However, this does not seem to be the case since we have demonstrated in a previous series of experiments (Silva et al. 2002a) that the acute pre-training administration of 1 mg/kg Amphetamine also induced amnesia (likewise the administration of 3 mg/kg) in the PM-DAT, without altering anxiety or locomotion. Still in this concern, when we administered 3 mg/kg for 10 consecutive days before the training session in the same model, the anxiogenic effect was tolerated, but the memory deficit remained.

The amnestic effect produced by pre-training Amphetamine administration (in the Amphetamine–Saline group) was completely abolished by pre-test Amphetamine administration (in the Amphetamine–Amphetamine group) and this result suggests a preponderant involvement of the state-dependency phenomenon on memory impairment induced by the pre-training Amphetamine administration (Fig. 2b).

State-dependent learning is often considered to be bidirectional. Thus, animals that are trained after a Sal injection should develop retention deficits
when Amph is administered before the test session. However, in our study, mice given pre-training Sal and pre-testing Amph (the Sal–Amph group) showed retention levels similar to the control (Sal–Sal) group. In this respect, it has been shown that drug-to-vehicle changes often exert greater state-dependent effects than vehicle-to-drug changes (Colpaert, 1990; Jackson et al. 1992; Patti et al. 2006).

From a clinical perspective, as recently noted by Young & Colpaert (2009), the state-dependency of stimulants such as Amph may dramatically influence drug use, learning permanence and the ability to use information in new conditions. According to the authors, individuals who use Amph to enhance learning may indeed learn slightly faster and/or with less effort than those who do not use Amph. Later, however, they may need to retake Amph to recall or use the learned information. Our experimental data seem in excellent agreement with this view. In addition, state-dependency has been linked to both anxiety and drug dependence in humans (Colpaert, 1990).

Taken together, these results corroborate our previous work (Silva et al. 2002a) describing decreased retention of a discriminative avoidance task induced by acute pre-training Amph administration. Importantly, the present study demonstrates that this memory impairment is state-dependent. These findings reinforce the importance of considering the participation of state-dependent learning when interpreting the cognitive effects of Amph.

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Statement of Interest

None.

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