Effects of Stress and of Amphetamine on Passive Avoidance Conditioning in Rats

L. Trnečková, S. Hynie, P. Šída, Z. Hliňák, I. Krejčí and V. Klenerová

Institute of Medical Biochemistry, First Medical Faculty, Charles University in Prague, Prague, Czech Republic

Abstract. This study examined the effects of immobilization stress combined with water immersion (ICS) and/or amphetamine (AM) on different memory phases in the passive avoidance task in rats. The performance of rats was evaluated in the retention tests 24 and 48 h after a single acquisition trial. ICS exposure lasting 1 h impaired retention of the learned avoidance response if applied 2 to 4 h before or immediately after training. The stressor did not affect retrieval if presented 5 or 2 h before the retention test. AM was used i.p. at the dose of 8 or 1 mg/kg. Neither 8 mg AM administered 4 h before nor 8 or 1 mg doses given after training did not impair the retention performance in unstressed rats. The 1 mg AM prevented the impairment of retention in animals exposed to the stressor 3 or 4 h before training but had no effect when the stronger impairment was induced by ICS 2 h before training. However, when given 1 h before retention testing, 1 mg AM attenuated even the severe impairment induced by the pre-training stressor exposure. Our results suggest that ICS impairs primarily the early phase of memory consolidation and a low dose of AM can prevent this effect.

Key words: Amphetamine — Immobilization stress — Passive avoidance — Memory — Rat

Introduction

Corticosteroid hormones, secreted in response to stress by adrenal cortex, readily enter the brain and are essential for cognitive performance (de Kloet 2000). Their effect on cognition can turn from adaptive to maladaptive under certain conditions characterized by the type of the stressor and the intensity, duration and chronicity of the stressor application (Lupien and McEwen 1997; de Kloet et al. 1999). Prior exposure of laboratory rodents to an inescapable stressor often impairs their performance in different learning tasks (de Wied and Croiset 1991; Baker and Kim 2002).

Correspondence to: Lenka Trnečková, Institute of Medical Biochemistry, First Medical Faculty, Charles University in Prague, Albertov 4, 128 00 Prague 2, Czech Republic
E-mail: lenka.trneckova@Lf1.cuni.cz

Specifically, restraint and cold stress have been shown to exert deleterious effect on associative or spatial learning and memory (Burešová et al. 1974; Panakhova et al. 1984; Nishimura et al. 1989; Dhabhar et al. 1997; Stillman et al. 1998). In humans, memory dysfunctions were found in patients with chronic posttraumatic stress disorder (Bremner et al. 1996; Korte 2001; Lupien and Lepage 2001; Golier et al. 2002).

In our previous studies we have demonstrated that a high dose of amphetamine (AM) (8 mg/kg) induced similar effects as a restraint stress on corticosterone plasma levels in rats (Klenerova et al. 2001). Also, AM and restraint stress combined with cold (ICS) evoked similar changes in adenylyl cyclase activity in brain (Klenerova et al. 1998, 1999).

In behavioral investigations, we tried to determine the effects of restraint and cold stress ICS on memory for passive avoidance and to examine whether the high dose of amphetamine induces comparable effects. ICS application 2 h before the acquisition trial induced a long-lasting impairment of the avoidance response learning (Klenerova et al. 2003). However, the 8 mg/kg AM dose administered 1 h before training induced marked stereotyped behavior with concomitant sensory and motor disturbances that most probably precluded the correct use of contextual cues decisive for learning the passive avoidance situation (Kaminsky et al. 2001). In the present study we wished to determine whether we could demonstrate the possible deleterious effects of the drug on the performance of rats in passive avoidance paradigm under conditions when the stereotyped behavior does not directly interfere with the acquisition of the experimental situation.

It has been shown that AM also improved performance of laboratory rodents in several models of learning and memory, the effect depending among others on the dose and time of the administration (for review see Grilly and Loveland 2001). Dose- and time-dependent effects were also found in learning the passive avoidance response (Roozendaal and McGaugh 1966; Seliger 1975, 1977; Kowacz and de Wied 1978). Therefore, we can expect that a lower dose of AM may not impair the passive avoidance learning and, on the contrary, it could attenuate the deleterious effects of ICS.

One trial passive avoidance procedure represents a model of learning where the effects of drugs or stressors can be studied by applying them at different stages of the learning and memory process (McGaugh 1966; Baldi et al. 1999; Medina et al. 1999). Thus, we applied ICS or AM at several intervals before or after the acquisition trial, either separately or together. In a similar way we examined the effects of both treatments on the retrieval. While AM in the 8 mg/kg dose was expected to elicit impairment of conditioned passive avoidance, the 1 mg/kg dose was viewed as being able to exert a facilitation of an impaired learning in stressed animals.

In this study we examined the effects of ICS and/or AM on different memory phases in the passive avoidance task in rats.

Materials and Methods

Subjects

The experiments were carried out using male Wistar rats (Velaz, Czech Republic). At the beginning of experiments, the average body weight of rats was 240 ± 20 g. Animals had free access to standard pellet food and water. Rats were housed five *per* cage (42×26 cm) and maintained on a 12 h light/12 h dark cycle (light on at 6.00 o'clock), at a constant temperature (21 ± 1 ℃) and relative humidity (50–70 %). Experiments were carried out in accordance with the Declaration of Helsinki Guiding Principles on Care and Use of Animals (DHEW Publication, NHI 80–23).

Stress

During the exposure to restraint stress combined with water immersion ICS, the rat was immobilized by fixing the front and hind legs with adhesive plaster; then the animal was restrained in a snug-fitting vertical plastic-mesh. This mesh was bent to conform to the size of individual animal and a bandage fixed this shape of mesh. The restrained rat was immersed in the water bath (22 ℃) in such a way that the upper 1/4 of the rat was outside of water (Klenerova et al. 1999). After stressor exposure for 1 h the rat was gently dried, returned to the home cage and left undisturbed until the start of passive avoidance procedure.

Treatment

In the appropriate days AM, 1 or 8 $mg \cdot kg^{-1}$ (AM sulfate, Sigma, USA) was injected intraperitoneally.

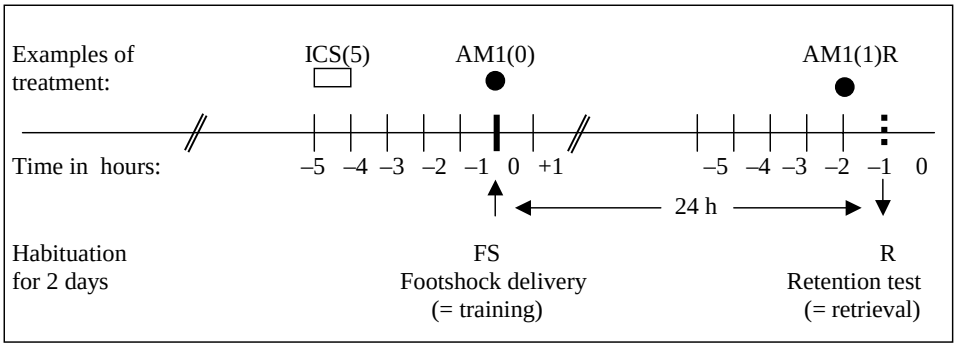
Passive avoidance apparatus and procedure

A shuttle-cage (Coulbourn Instruments Inc., PA, USA) consisting of two compartments of equal size (26×26 cm) separated by a sliding door (8×8 cm) was used. The starting compartment was illuminated while the shock compartment was dark. A stainless steel bar floor was used for delivery of scrambled constant current. Training and testing were performed between 8.00 and 13.00 h. WinLinc software was used for designing passive avoidance testing and to process experimental data.

The algorithm of experiments is shown in Table 1. Each experiment started with two pre-training trials, performed on two consecutive days. Each time, the rat was placed in the illuminated compartment for 50 s. After this interval the sliding door was raised and the latency to enter the dark compartment was recorded. In all experiments, rats were divided at random into experimental groups on the training day. During the single training trial (acquisition) on the third day each rat was placed in the illuminated compartment of the apparatus as in the previous sessions and the latency to enter the shock compartment was recorded. The door was then closed and a footshock (0.3 mA, 3 s) was delivered. The rat was removed from the dark compartment 1 min after termination of the footshock.

Retention tests were performed 24 and 48 h after the acquisition trial. Each rat was again placed in the illuminated compartment and allowed to step into the

Table 1. A diagram illustrating the algorithm of the experiments



On the third day of the passive avoidance test the footshock (FS) was delivered as an aversive stimulus; application of stress (ICS) or amphetamine (AM) was done in the intervals indicated on the time scale. The abbreviation ICS(5) means that stress started 5 and finished 4 h before application of footshock. AM1(1)R means that amphetamine in a dose 1 mg/kg was given 1 h before retention test (R).

dark compartment. Step-through latencies during all parts of the passive avoidance procedure were recorded with a 240 s ceiling. In all experiments rats were divided at random into experimental groups ($n = 7$–9) on the training day.

Experiment 1. To compare the effects of the stressor and the drug, ICS was applied at 2 and 5 h before or immediately after training. AM at a dose 8 mg/kg was administered 4 h before or immediately after training. Six groups of rats were used as indicated in Table 2.

Experiment 2 (part A and B). Effects of AM (1 mg/kg) on the avoidance learning of unstressed and stressed rats were investigated. AM was administered immediately after the acquisition trial either alone or in combination with ICS presented at four different time intervals before the acquisition trial. Experiment was performed in two parts as shown in Table 2.

Experiment 3 (part A and B). The effects of ICS and AM on the retrieval of the learned avoidance response were studied in stressed and non-stressed rats. AM (1 mg/kg) was administered 1 h before the first retention test in combination with ICS presented before the training or before retention. Experiment was performed in two parts, as described in Table 2.

Data collection and statistical analysis

Experimental data were recorded by WinLinc software (Coulbourn Instruments Inc., PA, USA) that enables both to design experimental protocols for passive avoidance testing and to process experimental data. All statistical tests were conducted using the Systat 9 software (SPSS, Inc., Chicago, USA). The data on the entrance latency in the passive avoidance procedure were evaluated by a two-way ANOVA, the factors were treatment (Experiment 1 = 6 levels; Experiment 2, part

Table 2. Groups of rats used in the experiments presented in this study

Experiment 1 ($n = 54$)	Experiment 2 part A ($n = 52$)	Experiment 2 part B ($n = 45$)	Experiment 3 part A ($n = 21$)	Experiment 3 part B ($n = 35$)
CO	CO	CO	CO	CO
ICS(2)	ICS(2)	ICS(3)	ICS(2)R	ICS(2)
ICS(5)	ICS(2)+AM1(0)	ICS(3)+AM1(0)	ICS(2)R+AM1(1)R	ICS(2)+AM1(1)R
ICS(0)	AM1(0)	ICS(4)	ICS(5)R	
AM8(4)	ICS(5)	ICS(4)+AM1(0)	ICS(5)R+AM1(1)R	
AM8(0)	ICS(5)+AM1(0)			

An experimental design in the passive avoidance task. CO, controls; AM, amphetamine; ICS, stressor exposure lasting 1h; ICS(5), (4), (3), (2), stressor exposure starting 5, 4, 3, 2 h before training or immediately after training (0); ICS(5)R, (2)R, stressor exposure starting 5 or 2 h before retention test; AM8(4), (0), AM in dose 8 mg/kg given 4 h before or immediately after training; AM1(0), AM in dose 1 mg/kg given immediately after training; AM1(1)R, AM in dose 1 mg/kg given 1h before retention test (R).

A = 6 levels; Experiment 2, part B = 5 levels; Experiment 3, part A = 5 levels; Experiment 3, part B = 3 levels) and repeated measurement (3 levels = Days 3, 4 and 5 for all experiments). All *post hoc* comparisons were done using the Bonferroni's multiple test. Statistical significance was set at $p < 0.05$ (two-tailed).

Results

In all experiments, the entrance latencies of control rats were significantly higher in retention tests, when compared to values estimated before the footshock delivery (Day 3 *vs.* Day 4).

Experiment 1

Fig. 1 presents the effects of different timing of stress exposure and AM at a dose of 8 mg/kg (AM8) on the entrance latency estimated during training and retention testing.

A two-way analysis of variance (ANOVA) conducted on the entrance latencies revealed significant effects of the factor treatment [$F(5,47) = 8.6$, $p < 0.001$], repeated measurements [$F(2,94) = 117.2$, $p < 0.001$] and treatment x repeated measurement interaction [$F(10,94) = 10.1$, $p < 0.001$]. On Day 3 longer entrance latencies were found in the rats exposed to ICS(2) compared to the control. Post-shock entrance latencies (Days 4 and 5) showed that the rats exposed to the stressor 2 h before [ICS(2)] or immediately after footshock delivery [ICS(0)] exhibited shorter latencies than control animals, while no impairment of learning was recorded when the stressor exposure preceded training by 5 h [ICS(5)]. Latencies of rats treated with AM 4 h before or immediately after training [AM8(4), AM8(0)] did not differ from the control ones.

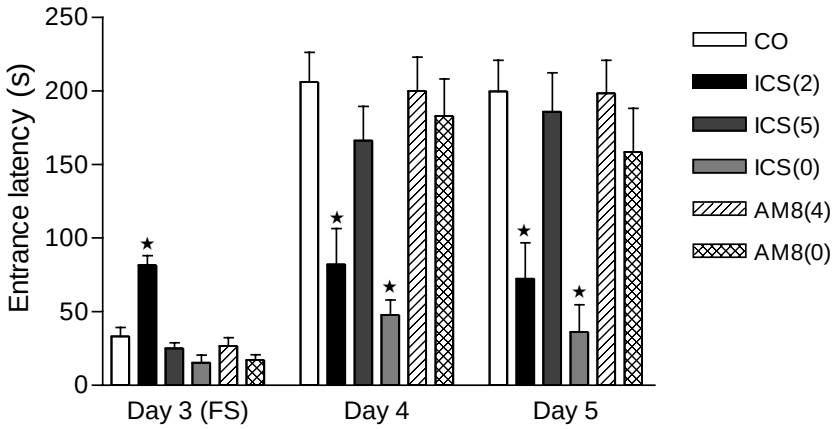


Figure 1. Effects of ICS or AM8 on retention performance of rats in step-through passive avoidance task (Experiment 1). Animals were exposed to ICS or treated with AM8 at different times before or immediately after training. Data are expressed as training (Day 3) and retention test (Day 4 and 5) entrance latencies (mean ± S.E.M.) in seconds. Design of experiments are depicted in Table 1 and 2. FS, footshock; $\star$ $p < 0.05$ *vs.* controls (CO).

Experiment 2, part A

Fig. 2A demonstrates the effect of 1 mg/kg amphetamine given immediately after training [AM1(0)] on retention performance of not stressed rats, and of rats exposed to ICS at 5 and 2 before training [ICS(5) + AM1(0), ICS(2) + AM1(0)].

A two-way ANOVA conducted on the entrance latencies showed significant effects of the factor treatment [$F(5,46) = 3.4$, $p = 0.011$], repeated measurements [$F(2,9) = 82.55$, $p < 0.001$] and treatment x repeated measurement interaction [$F(10,92) = 8.1$, $p < 0.001$]. On Day 3 a significant difference between the control and ICS(2) was found. The critical finding on Days 4 and 5 was that AM did not affect the retention latencies of non-stressed and stressed rats. As in Experiment 1, ICS(2) but not ICS(5) decreased retention latencies.

Experiment 2, part B

Fig. 2B shows the effect of 1 mg/kg AM administered after training [AM1(0)] on the retention impairment induced by the stressor exposure introduced 5 or 4 h before the acquisition [ICS(5), ICS(4)].

A two-way ANOVA conducted on the entrance latencies revealed significant effects of the factor treatment [$F(4,40) = 5.2$, $p = 0.002$], repeated measurements [$F(2,80) = 178.6$, $p < 0.001$] and treatment x repeated measurement interaction [$F(8,80) = 4.0$, $p = 0.001$]. No difference among the groups was found on Day 3. Post shock (Day 4) avoidance latencies in both stressed groups [ICS(4), ICS(3)] were shorter than those observed in the control. [AM 1(0)] restored retention avoidances

of rats exposed to both used stressors. Despite the similarities of results from Day 4 and 5, on Day 5 the only statistical difference was between ICS(4) and the control.

Experiment 3, part A

Fig. 3A demonstrates: firstly, the effects of the stressor applied at 2 or 5 h before the retention test [ICS(2)R, ICS(5)R] on the retrieval of the avoidance response; secondly, the combination of the stressor with the low dose of the drug administered 1 h before retention [ICS(2)R + AM1(1)R, ICS(5)R + AM1(1)R].

A two-way ANOVA conducted on the entrance latencies showed no significant effects of the factor treatment [$F(4,30) = 1.9$, $p = 0.135$], repeated measurements [$F(2,60) = 667.9$, $p < 0.001$] and treatment x repeated measurement interaction [$F(8,60) = 1.6$, $p < 0.15$]. No differences among the groups were found on Day 3. The main finding on the post-shock (Day 4 and 5) was the absence of deteriorating effect in both groups exposed to the stressor [ICS(2)R, ICS(5)R]. Not surprisingly, AM did not influence these high avoidance responses.

Experiment 3, part B

Fig. 3B shows the antagonizing effect of AM at 1 mg dose administered 1 h before the retention test [AM1(1)R] on retrieval of avoidance response impaired by the stressor presented 2 h before training [ICS(2)]. A two-way ANOVA conducted on the entrance latencies showed significant effects of the factor treatment [$F(2,18) = 5.5$, $p = 0.013$], repeated measurements [$F(2,36) = 4.0$, $p = 0.029$] and treatment x repeated measurement interaction [$F(4,36) = 8.7$, $p < 0.001$]. At Day 3 there were no differences among the groups. On Day 4, AM significantly enhanced latencies decreased by the stressor; there was no difference between ICS(2) + AM1(1)R and the control. This effect persisted also on Day 5.

Discussion

In the present study we investigated the effects of ICS and AM and their combination on acquisition, consolidation and retrieval phases of memory in the passive avoidance paradigm in rats. ICS impaired learning of passive avoidance task, when applied 2 h before the acquisition trial (Fig. 1). When longer intervals, namely 3 to 5 h, were used between the stressor exposure and acquisition, the learning deficit decreased and finally disappeared. Stressor exposure after training also impaired retention. Previously, we found that the rats displayed unimpaired retention when the stressor presentation was introduced 3 h after training (Klenerova et al. 2003). In comparable experiments on DBA mice, the immediate post-training application of restraint stress impaired retention of an inhibitory response examined after 24 h; stress application 2 h after training did not affect retention performance (Cabib and Castellano 1997).

When 8 mg/kg dose of AM was administered 4 h before the learning trial, there were no signs of stereotypy observed, although it is highly probable that the locomotor augmentation still persisted (Segal and Kuczenski 1994). Rats entered

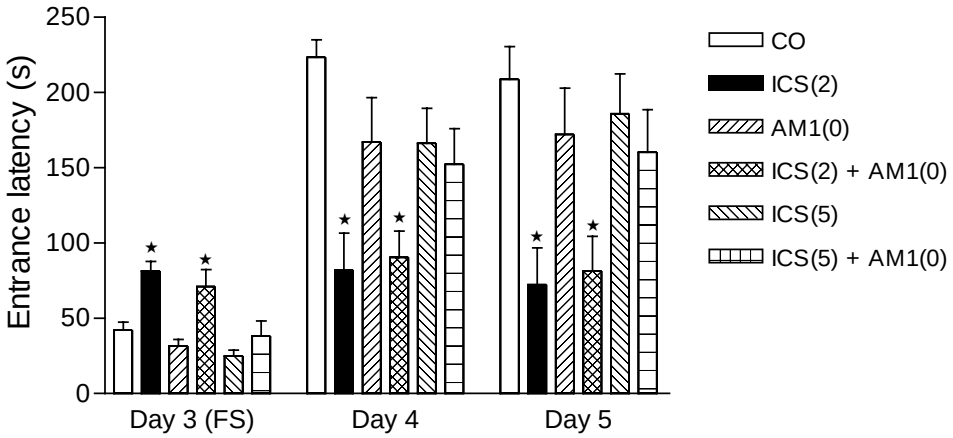


Figure 2A. Effects of ICS and AM1 applied separately or in combination, on retention performance of rats in step-through passive avoidance task (Experiment 2, part A). Animals were exposed to ICS at 5 and 2 h before training, AM was administered immediately after footshock (FS) delivery. Data are expressed as training (Day 3) and retention test (Day 4 and 5) entrance latencies (mean ± S.E.M.) in seconds. ⋆ $p < 0.05$ *vs.* controls (CO).

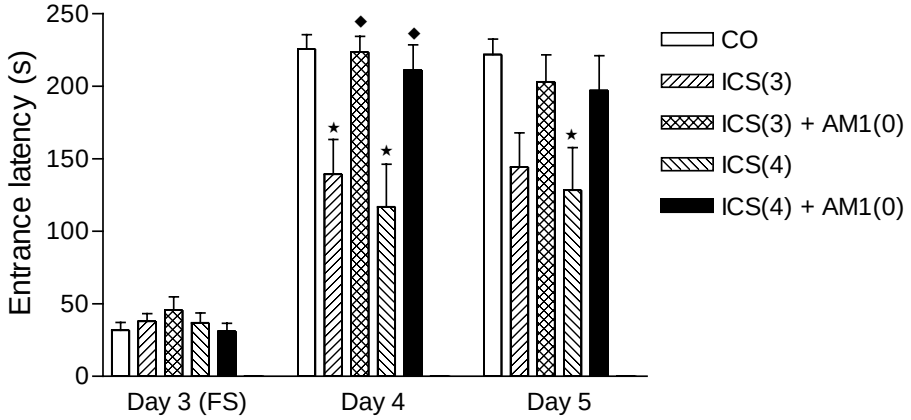


Figure 2B. Effects of ICS and AM1 applied separately or in combination, on retention performance of rats in step-through passive avoidance task (Experiment 2, part B). Animals were exposed to ICS at 4 and 3 h before training, AM was administered immediately after footshock (FS) delivery. Data are expressed as training (Day 3) and retention test (Day 4 and 5) entrance latencies (mean ± S.E.M.) in seconds. ⋆ $p < 0.05$ *vs.* controls (CO); ◆ $p < 0.05$ *vs.* appropriate ICS group.

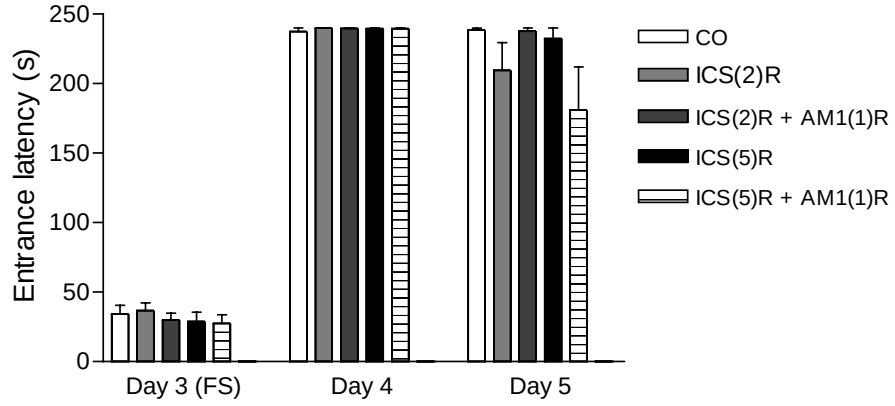


Figure 3A. Effects of ICS and AM1 applied separately or in combination, on retrieval of acquired avoidance response in step-through passive avoidance task (Experiment 3, part A). Animals were exposed to ICS at 5 and 2 h before retention testing, AM was administered 1 h before retention test. Data are expressed as training (Day 3) and retention test (Day 4 and 5) entrance latencies (mean ± S.E.M.) in seconds. FS, footshock; CO, controls.

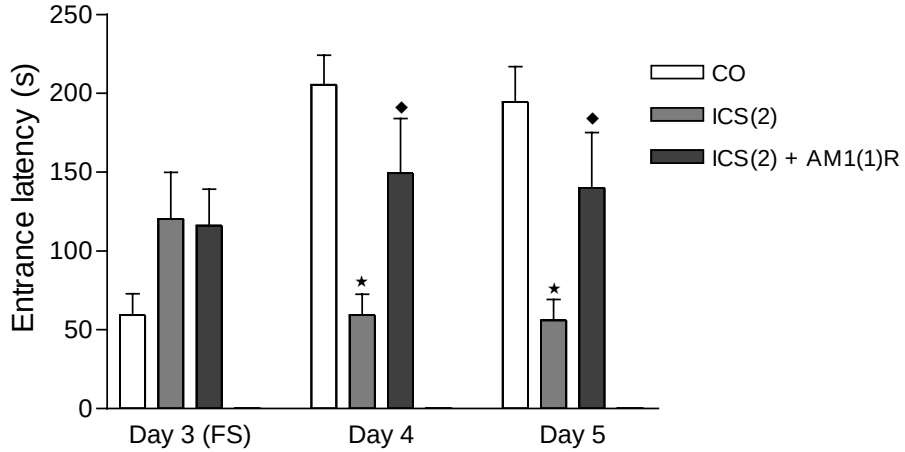


Figure 3B. Effects of AM1 on impaired memory of ICS exposed rats, in step-through passive avoidance task (Experiment 3, part B). Stressed animals were exposed to ICS 2 h before training, AM was administered immediately after footshock (FS) delivery. Data are expressed as training (Day 3) and retention test (Day 4 and 5) entrance latencies (mean ± S.E.M.) in seconds. ⋆ $p < 0.05$ *vs.* controls (CO); ◆ $p < 0.05$ *vs.* appropriate ICS group.

the dark compartment with latencies comparable to those of controls and retention performance was not impaired. This finding, together with the absence of learning deterioration when 8 mg/kg AM was injected immediately after acquisition trial, indicates that AM did not interfere with learning of the task. As expected, 1 mg/kg AM, considered a low dose of the drug (Grilly and Loveland 2001; Maes et al. 2001), did not cause any signs of stereotyped behavior and did not affect retention when administered shortly after learning trial.

While the presentation of ICS before or immediately after acquisition impaired retention performance, exposure either 2 or 5 h before retention test did not influence the acquired avoidance response. This finding indicates that in the stressed rats, states of arousal and attention to the perceptual cues of the apparatus were not altered to the degree hampering retrieval of information from the long-term memory that were relevant to the situation.

The present results support the notion that ICS impaired learning of the inhibitory response primarily by acting on the consolidation phase of memory formation. On the contrary, even a high dose of AM failed to affect consolidation and most probably also acquisition phases of learning and memory processing.

It has been well established that hormones and neuromodulatory factors released by the reaction of hypothalamic-pituitary-adrenal (HPA) axis to stress stimuli influence neurobiological mechanisms underlying learning and memory formation. Corticosteroid hormones secreted by the adrenal cortex are considered to be essential for cognitive performance (de Kloet 2000; Lupien and Lepage 2001). In laboratory rodents, corticosterone has been shown to induce positive or negative cognitive changes depending on several variables, like the dose, time and context of application (de Wied and Croiset 1991; de Kloet et al. 1999). Stressors such as restraint, cold or combination of both, have been shown to impair performance of rats in several appetitively or aversively motivated learning tasks (Burešová et al. 1974; Panakhova et al. 1984; Cabib and Castellano 1997; Stillman et al. 1998; Klenerova et al. 2003). In previous experiments on rats, ICS significantly increased plasma corticosterone measured 1 h after exposure cessation and this elevation returned to pre-stress values within 4 h (Klenerova et al. 2003). These results were obtained in experiments performed according to the same protocol as the present ones and can thus refer to rats exposed to the stressor 2 to 5 h before training. It appears conceivable to assume that it was the high elevation of corticosterone, which contributed to the observed learning deficit.

Stress and psychostimulants, such as AM or cocaine, share the property of increasing extracellular dopamine levels in limbic brain regions and of enhancing the release of pituitary-adrenal hormones, adrenocorticotropic hormone and corticosterone (Swerdlow et al. 1992; Weiss et al. 1997; Klenerova et al. 2001). The increase in plasma levels of both pituitary-adrenal hormones due to AM is dose- and time-dependent and appears to be comparable to HPA axis activation in animals exposed to an inescapable stress; e.g. restraint lasting 15 or 30 min induced comparable enhancement of plasma corticosterone as 8 mg/kg AM, estimated at the same time intervals (Klenerova et al. 2001). However, AM at dose 8 mg/kg administered

after training, did not influence learning in the similar way as did ICS. Obviously, other effects of AM on behavior are responsible for the observed difference. There exists an extensive literature describing the levels of stress hormones and various neurotransmitters after application of stress and psychostimulants. Certainly, dopamine plays an important role, however, it depends on its localization in the brain and the length of its elevation after stress or AM (e.g. Cabib and Castellano 1997). Our data do not provide any direct evidence for the effect of AM, which is responsible for the differential effect of AM and stress.

Several authors reported that low doses of AM administered before or after the learning trial facilitated passive avoidance responding (Seliger 1975, 1977; Kovacz and de Wied 1978; Roozendaal et al. 1996). The present study was aimed primarily at investigating the deleterious effects of ICS or of the high dose of AM; it is to say that the employed footshock intensity increased avoidance latency close to the chosen criterion, leaving thus no space for detection of possible improvement. Therefore, we could not expect improved learning unless the stressor had impaired it. In keeping with this notion, the 1 mg/kg dose of AM injected before or after acquisition to non-stressed rats did not change retention latencies. Post-learning application of AM also did not ameliorate the strong impairment induced by ICS, presented 2 h before training. Only when the stressor application preceded acquisition at longer intervals (4 or 3 h), causing thus less pronounced learning impairment, AM facilitated retention performance. When the stress-acquisition interval was yet prolonged (5 h), retention latency of the stressed animals did not differ from those of the controls and no effect of the drug was observed.

The 1 mg/kg dose was reported to enhance significantly plasma corticosterone in rats (Swerdlow et al. 1992). However, it is highly probable that other actions of AM contributed to the ameliorating effect. It has been shown that in the passive avoidance paradigm, the release of catecholamines from the peripheral storage sites, like adrenaline from adrenal medulla, are responsible, at least in part, for the AM-induced improvement of memory formation (Bohus et al. 1993; Mabry et al. 1995; Roozendaal et al. 1996). Systemically administered AM readily enters the brain and can modulate acquisition performance by a direct activation of central dopaminergic or noradrenergic systems (Prasad et al. 1995; Halladay et al. 2000). The involvement of dopamine dependent mechanisms in passive avoidance learning task has been supported by findings in mice, where administration of selective D1 and D2 antagonists prevented AM effects on memory formation (Cabib et al. 1996; Cabib and Castellano 1997).

In experiments exploring the effects of the stressor on retrieval of the acquired inhibitory response, the rats exposed to the stressor 5 or 2 h before retention testing exhibited unimpaired performance. This was not affected by 1 mg/kg dose of AM injected 1 h before the test (Fig. 3A).

However, retention deficit induced by pre-training stressor exposure applied 2 h before footshock was attenuated by the pre-retention application of AM (Fig. 3B). Also in this phase of memory processing facilitation of avoidance behavior has been shown to be induced by adrenaline and vasopressin treatment shortly before the

retention test (de Wied 1977; McGaugh 1981; de Wied and Croiset 1991; Bohus et al. 1993).

The release of adrenomedullary hormones could thus be at least partly responsible for the observed AM effect. Also, the enhanced states of arousal and attention could facilitate the reception of external cues relevant for the retrieved response.

In conclusion, the present behavioral data demonstrate that in the passive avoidance paradigm, ICS induces amnesia by acting primarily on the early phase of memory consolidation; low doses of AM, applied after training or before the retention test, can prevent this effect. Observed effects of ICS and AM suggest that these two insults activate different stressor effector systems related to cognitive functions.

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