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Anandamide modulation of circadian- and stress-dependent effects on rat short-term memory

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ABSTRACT

The endocannabinoid system plays a key role in the control of emotional responses to environmental challenges. CB1 receptors are highly expressed within cortico-limbic brain areas, where they modulate stress effects on memory processes. Glucocorticoid and endocannabinoid release is influenced by circadian rhythm. Here, we investigated how different stress intensities immediately after encoding influence rat short-term memory in an object recognition task, whether the effects depend on circadian rhythm and if exogenous augmentation of anandamide levels could restore any observed impairment. Two separate cohorts of male adult Sprague-Dawley rats were tested at two different times of the day, morning (inactivity phase) or afternoon (before the onset of the activity phase) in an object recognition task. The anandamide hydrolysis inhibitor URB597 was intraperitoneally administered immediately after the training trial. Rats were thereafter subjected to a forced swim stress under low or high stress conditions and tested 1 h after training. Control rats underwent the same experimental procedure except for the forced swim stress (no stress). We further investigated whether URB597 administration might modulate corticosterone release in rats subjected to the different stress conditions, both in the morning or afternoon. The low stressor elevated plasma corticosterone levels and impaired 1 h recognition memory performance when animals were tested in the morning. Exposure to the higher stress condition elevated plasma corticosterone levels and impaired memory performance, independently of the testing time. These findings show that stress impairing effects on short-term recognition memory are dependent on the intensity of stress and circadian rhythm. URB597 (0.3 mg kg^{-1}) rescued the altered memory performance and decreased corticosterone levels in all the impaired groups yet leaving memory unaltered in the non-impaired groups.

1. Introduction

The endocannabinoid system plays a key regulatory role in many fundamental physiological processes, such as sleep/wake cycles (Lovinger, 2008; Murillo-Rodríguez et al., 2017; Pava et al., 2016), learning and memory (Akirav, 2011; Atsak et al., 2015; Morena and Campolongo, 2014) and central nervous system (CNS) regulation of endocrine functions (Hillard, 2015; Balsevich et al., 2017). The two major endocannabinoids, *N*-arachidonylethanolamide (anandamide, AEA; Devane et al., 1992) and 2-arachidonoyl glycerol (2-AG; Sugiura et al., 1995) are synthesized on demand and travel retrogradely to presynaptic sites to bind cannabinoid type-1 (CB1) receptors (Kano et al., 2009). After being released into the synaptic cleft, AEA and 2-AG are primarily degraded by distinct hydrolytic enzymes, the fatty acid amide hydrolase (FAAH; Cravatt et al., 2001) and monoacylglycerol lipase (MAGL; Dinh et al., 2002), respectively.

Emotion influences memory at multiple levels (McGaugh, 2000), from perceptual recognition and identification (Zeelenberg et al., 2006)

Abbreviations: 2-AG, 2-arachidonoyl glycerol; AEA, anandamide; ANOVA, analysis of variance; SEM, standard error of the mean; CNS, central nervous system; CB1, cannabinoid type-1; CB2, cannabinoid type-2; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; URB597, [(3′-(aminocarbonyl)[1,1′-biphenyl]-3-yl)-cyclohexylcarbamate]; BLA, basolateral complex of the amygdala; mPFC, medial prefrontal cortex; LC, locus coeruleus; HPA, hypothalamic–pituitary–adrenal-axis

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to explicit recognition and recall of emotional stimuli (Kensinger and Schacter, 2008). Compelling evidence indicates that drugs that target the endocannabinoid system induce biphasic effects on cognitive and emotional behavior depending on the level of stress and emotional arousal at the time of encoding and drug consumption (Campolongo et al., 2013; Manduca et al., 2014; Morena et al., 2014, 2015, 2016a). Glucocorticoids are stress response mediators which interact with the endocannabinoid system in the regulation of memory function (Campolongo et al., 2009; Hill et al., 2018; Morena and Campolongo, 2014). Their synthesis is characterized by a circadian release pattern, with peak levels linked to the start of the activity phase and diurnal regulation under control of the circadian clock (Dickmeis, 2009). Literature evidence indicates that the endocannabinoid signaling exhibits a circadian rhythm with variations reported in CB1 receptor expression (Rueda-Orozco et al., 2008), endocannabinoids tissue contents and in the enzymes controlling their synthesis and degradation (Valenti et al., 2004). Extensive research has identified glucocorticoid-endocannabinoid crosstalk as crucial mediator of the glucocorticoid dependent modulation of emotional memories (Atsak et al., 2015; Campolongo et al., 2009), but still it remains uncertain the influence of circadian rhythm on this mediation. Moreover, far less well understood is the relationship between circadian rhythm biology and memory formation (Gerstner and Yin, 2010). Therefore, the main purpose of the present study was to evaluate how different stress intensities may influence short-term recognition memory in rats, investigating whether their action is regulated by circadian rhythm and if AEA has any role on this process. To this aim we investigated the effects of post-training systemic administration of the FAAH inhibitor, URB597, which increases AEA levels at active synapses, on short-term retention of object recognition memory under three different stress conditions (no, low or high forced swim stress), at two different times of the day, morning (inactivity phase) or afternoon (before the onset of the activity phase). Behavioral experiments were paralleled by biochemical analysis aimed at measuring plasma corticosterone levels in all the experimental groups.

2. Material and methods

2.1. Animal care and use

Male adult Sprague-Dawley rats (350–450 g at the time of training and testing, Charles River Laboratories, Calco, Italy) were kept individually in an air-conditioned colony room (temperature: 21 ± 1 °C; lights on from 07:00 AM to 7:00 PM) with pellet food and water available *ad libitum*. Training and testing were performed during the light phase of the cycle between 10:00 AM and 6:00 PM. All procedures involving animal care or treatments were performed in compliance with the ARRIVE guidelines, the Directive 2010/63/EU of the European Parliament, and the D. L. 26/2014 of Italian Ministry of Health.

2.2. Drug treatment

The anandamide hydrolysis inhibitor URB597 [(3′-(aminocarbonyl) [1,1′-biphenyl]-3-yl)-cyclohexylcarbamate] (0.1 or 0.3 mg kg^{-1}; Tocris Bioscience, Bristol UK) was administered intraperitoneally (i.p.) in a volume of 1 ml kg^{-1} immediately after the training trial. Doses were chosen on the basis of pilot experiments performed in our laboratory and on literature data (Kathuria et al., 2003; Campolongo et al., 2013; Morena and Campolongo, 2014), in order to have a maximum augmentation of AEA release in the synaptic cleft. The solutions were freshly prepared on the day of the experiment and dissolved in 5% polyethylene glycol, 5% Tween-80 and 90% saline (vol/vol). The vehicle solution contained 5% polyethylene glycol and 5% Tween-80 in saline only.

2.3. Behavioral procedures

2.3.1. Object recognition task

A slightly modified procedure of that described by Campolongo et al. (2013) was used. The experimental apparatus was a gray open-field box (in cm, 40 wide × 40 deep × 40 high) with the floor covered with sawdust, positioned in a dimly illuminated room. The objects to be discriminated were transparent glass vials (5.5 cm diameter and 5 cm height) and white glass light bulbs (6 cm diameter and 11 cm length). All rats were handled twice per day for 1 min each and extensively habituated to the experimental context twice per day for 3 min each for 7 days preceding the training day. During habituation, rats were allowed to freely explore the apparatus in the absence of objects. The animals were randomly assigned to three different groups: no stress, low stress and high stress conditions and tested either in the morning (rats' inactive phase, 10:00 AM–12:30 PM) or in the afternoon (before the onset of the activity phase, 3:30 PM–6:00 PM). On the training trial, each rat was individually placed in the experimental apparatus at the opposite end from the objects. The rat was allowed to explore two identical objects (A1 and A2) for 6 min, then it was removed from the apparatus and, after drug treatment, if belonging to the low or high stress condition group, it was subjected to a forced swim stress; then, it was returned to its home cage. The no stress group was placed back to its home cage immediately after drug injection. To avoid the presence of olfactory trails, sawdust was stirred, foecal boli were removed and the objects were cleaned with 70% ethanol after each trial. Rat's behavior was recorded by using a video camera positioned above the experimental apparatus and videos were analyzed with Observer XT 12 (Noldus Information Technology BV, Wageningen, The Netherlands) by a trained observer who was unaware of treatment condition. Exploration of an object was defined as pointing the nose to the object at a distance of < 1 cm and/or touching it with the nose. Turning around or sitting on an object was not considered as exploration. During the training trial, the time spent exploring the two objects (total object exploration time, s) was taken as a measure of object exploration, and exploratory behavior of the experimental apparatus was analyzed by the measuring total number of crossings and rearings. For crossings, the floor of the apparatus was divided into four imaginary squares and the total number of crossings between squares was determined. Memory retention was tested 1 h after the training trial. On the retention test trial, one copy of the familiar object (A3) and a new object (B) were placed in the same location as stimuli during the training trial (Fig. 1). All combinations and locations of objects were used to reduce potential biases due to preference for particular locations or objects. Each rat was placed in the apparatus for 6 min, and its behavior was recorded. To analyze cognitive performance, during the retention test, a discrimination index was calculated as the difference in time exploring the novel and the familiar object, expressed as the percentage ratio of the total time spent exploring both objects.

2.3.2. Forced swim stress procedure

Forced swimming was used as the stressor because its neurochemical and hormonal effects are well defined and meet the criteria of a stress-inducing agent (Schneider and Simson, 2007). Immediately after the training trial of the object recognition task rats were forced to swim in a tank (50 cm in height × 20 cm in diameter), filled to a depth of 30 cm with water. At the end of the swimming period, rats were removed from the water and were immediately and gently wiped to dryness with absorbent paper before they were returned to the home cage. Rats in the low and high stress condition groups were subjected to a low or high intensity stressor by using a 1- or 5-min forced swim stress procedure at different water temperatures of 25 ± 1 °C or 19 ± 1 °C, respectively, known to elicit different plasma corticosterone levels (Morena et al., 2015).

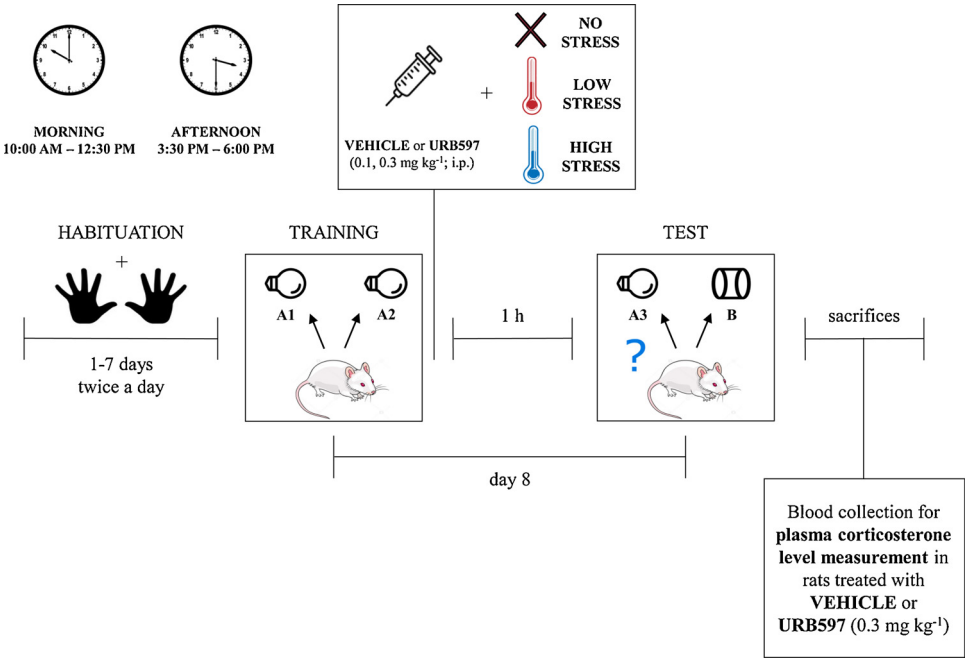

Fig. 1. Diagram of the experimental procedure.

2.4. Plasma corticosterone levels

Corticosterone levels were determined in rats in the no stress, low stress and high stress conditions that were tested in the morning or afternoon and in rats that were handled (twice per day for 7 days) but not trained (home cage), at the two different times of the day. As novelty stimulation triggers an HPA-axis response that leads to a corticosterone plasma peak at 30 min and normalizes within 90 min after stress exposure (de Kloet et al., 2005), rats were killed immediately after the test trial, 60 min after the URB597 administration. Trunk blood was collected after decapitation in tubes containing 200 µl of 0.1 M EDTA and samples were centrifuged at 1000 × *g* for 15 min at 4 °C. Plasma was stored at −20 °C and analyzed for corticosterone levels using a DetectX ELISA kit (Arbor Assays, Ann Arbor, MI, USA) according to the manufacturer's instructions as previously described (Fletcher et al., 2018). In compliance with EU animal legislation (3R principle: reduction) corticosterone levels were measured in vehicle-treated and in URB 0.3 mg kg^{-1} (effective dose in rescuing stress-dependent memory impairments) treated rats.

2.5. Data and statistical analysis

One-sample t-tests were used to determine whether the discrimination index was different from zero. Object recognition data and plasma corticosterone levels were analyzed by two-way ANOVAs. Tukey-Kramer *post hoc* tests were used to determine the source of the detected significances. P values of < 0.05 were considered statistically significant. To be included in the statistical analysis rats had to reach a minimum criterion of total object exploration time > 10 s on either training or testing. Prior findings indicate that such rats adequately acquire the task (Okuda et al., 2004; Roozendaal et al., 2008; Winters et al., 2009; Campolongo et al., 2013; Barsegyan et al., 2019). All data are expressed as mean ± standard error of the mean (SEM).

3. Results

3.1. Effects of different stress intensities and circadian rhythm on short-term recognition memory retention performance and plasma corticosterone levels

To determine whether different stress intensities modulate short-term memory retention performance and whether these effects are dependent on circadian rhythm, we first analyzed the behavioral performance of all vehicle-treated rats, used in the subsequent URB597 experiments, at different times of the day (e.g. morning and afternoon), in order to unveil any possible influence of stress or time on memory and corticosterone levels.

One-sample t-tests revealed that the discrimination indexes of vehicle-treated rats were significantly different from zero for both the no stress groups tested either in the morning or in the afternoon ($t_{(7)} = 4.654$, $P = 0.002$ and $t_{(9)} = 4.384$, $P = 0.002$, respectively; Fig. 2a) and for the low stress condition group tested in the afternoon ($t_{(10)} = 3.715$, $P = 0.004$; Fig. 2a), thus indicating that these three animal groups discriminated the novel object. In contrast, rats in the remaining low and high stress conditions morning groups and the high stress condition afternoon group did not express memory retention for the familiar object. Two-way ANOVA for discrimination index revealed a significant stress condition effect ($F_{(2.50)} = 4.313$, $P = 0.019$) and a tendency toward significance for the time of the testing ($F_{(1.50)} = 3.082$, $P = 0.085$) and for the interaction between these two factors ($F_{(2.50)} = 2.493$, $P = 0.093$). *Post hoc* analysis showed that the low stress condition significantly decreased the discrimination index of rats tested in the morning as compared to the no stress group tested at the same time of the day and the corresponding low stress condition group tested in the afternoon ($P < 0.05$ for both comparisons; Fig. 2a).

Regarding the total object exploration time on the testing trial, two-way ANOVA revealed a significant stress condition effect ($F_{(2.50)} = 12.693$, $P < 0.0001$), but no significant time of testing or stress condition x time of testing interaction effects. Finally, rats' exploratory behavior of the apparatus during the test trial did not differ among the different experimental groups. Two-way ANOVAs for number of crossings or rearings revealed no significant stress condition, no time of testing or stress condition x time of testing interaction effects (Table 1).

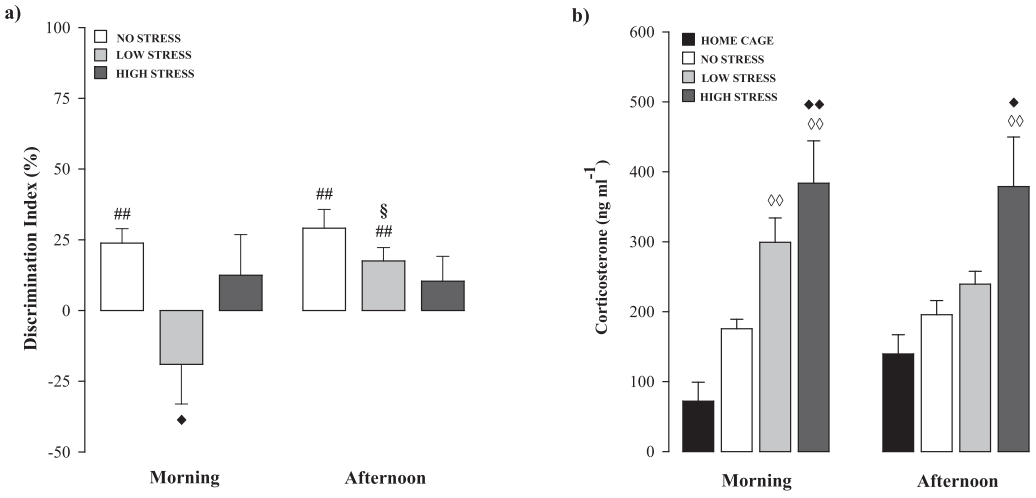

Fig. 2. Circadian-dependent effects of different stress conditions on short-term memory.
a) Discrimination index on the testing trial for vehicle-treated rats that were subjected to no, low or high stress conditions immediately after the training trial performed in the morning or afternoon. *Post hoc* comparisons reported significant differences between groups as follows: ◆ $P < 0.05$ vs the corresponding no stress group. § $P < 0.05$ vs the corresponding low stress group trained in the morning. ## $P < 0.01$, one-sample t-tests significantly different from zero. Data are expressed as mean ± SEM (n = 8–11 per group). **b)** Plasma corticosterone levels of home cage and vehicle-treated rats subjected to no, low or high stress condition immediately after the training trial that were euthanized, in the morning or in the afternoon, 60 min after stress exposure, immediately after test. *Post hoc* comparisons reported significant differences between groups as follows: ◊◊ $P < 0.01$ vs the corresponding home cage group. ◆ $P < 0.05$; ◆◆ $P < 0.01$ vs the corresponding no stress group. Data are expressed as mean ± SEM (n = 7–9 per group).

Furthermore, we evaluated whether plasma corticosterone levels were differentially modulated by the different stress conditions, at two times of the day.

Two-way ANOVA for plasma corticosterone levels immediately after test, revealed a significant stress condition effect ($F_{(3.54)} = 17.836$, $P < 0.0001$), but no significant time or stress condition x time effects. *Post hoc* analysis showed that rats that were subjected to low stress condition had higher corticosterone levels than home cage control rats only in the morning ($P < 0.01$; Fig. 2b). Moreover, rats subjected to the high stress condition presented significant higher corticosterone levels than home cage control rats and no stress groups both in the morning ($P < 0.01$, for both comparisons; Fig. 2b) and in the afternoon ($P < 0.01$ and $P < 0.05$; for home cage and no stress groups, respectively; Fig. 2b).

3.2. Effects of the AEA hydrolysis inhibitor URB597 on short-term object recognition memory performance and plasma corticosterone levels in the no, low and high stress condition groups tested in the morning

This experiment investigated whether immediate post-training injection of the AEA hydrolysis inhibitor URB597 modulates short-term performance on an object recognition task and plasma corticosterone levels and whether these effects are influenced by different stress conditions in animals tested in the morning.

As shown in Fig. 3a, one-sample t-tests revealed that the discrimination indexes were significantly different from zero for all no stress treatment groups ($t_{(7)} = 4.654$, $P = 0.002$; $t_{(7)} = 2.741$, $P = 0.029$ and $t_{(7)} = 4.745$, $P = 0.002$; vehicle, URB597 0.1 and URB597 0.3 mg kg^{-1}, respectively), while, for the low and high stress groups, only URB597 0.3 mg kg^{-1}treated rats discriminated the new object ($t_{(7)} = 3.206$, $P = 0.015$, $t_{(7)} = 5.533$, $P = 0.001$, for the low and high stress conditions URB597 0.3 mg kg^{-1} groups, respectively). In contrast, low and high stressed rats in the remaining vehicle and URB597 0.1 mg kg^{-1} groups did not express memory retention for the familiar object. Two-way ANOVA for the discrimination index revealed significant stress condition ($F_{(2.63)} = 3.838$, $P = 0.027$) and treatment ($F_{(2.63)} = 7.257$, $P = 0.002$) effects as well as a tendency toward significance for the interaction between these two factors ($F_{(4.63)} = 2.112$, $P = 0.090$). *Post hoc* analysis showed that URB597 0.3 mg kg^{-1} treated rats subjected to low or high stress presented a better discrimination index relative to their corresponding vehicle groups ($P < 0.05$, for both comparisons; Fig. 3a). Moreover, rats that were treated with URB597 0.3 mg kg^{-1} and then subjected to the high stress condition showed a high discrimination index as compared to those administered the same dose of URB597 but subjected to the no or low stress procedure ($P < 0.05$, for both comparisons; Fig. 3a). Concerning the total

Table 1
Exploratory behavior on the testing trial for vehicle- and URB597-treated rats that were subjected to no, low or high stress conditions immediately after the training trial, in the morning and in the afternoon sessions.

	Morning			Afternoon		
	Total object exploration time (s)	Number of crossings	Number of rearings	Total object exploration time (s)	Number of crossings	Number of rearings
NO STRESS						
VEHICLE	58.2 ± 8.2	21.4 ± 4.2	26.4 ± 5.8	46.3 ± 7.5	17.6 ± 4.1	26.6 ± 4.8
URB 0.1	50.6 ± 9.4	20.8 ± 4.1	34.6 ± 6.7	68.5 ± 18.3	24.0 ± 4.9	31.1 ± 5.4
URB 0.3	47.0 ± 5.7	23.6 ± 3.6	30.5 ± 4.9	48.4 ± 7.0	20.0 ± 4.0	26.4 ± 4.4
LOW STRESS						
VEHICLE	33.4 ± 5.9 *	23.0 ± 3.7	39.1 ± 4.6	32.8 ± 4.0	16.9 ± 2.3	28.7 ± 3.7
URB 0.1	32.4 ± 6.4	16.8 ± 2.1	32.0 ± 4.3	31.5 ± 5.7 *	13.8 ± 3.1	24.6 ± 4.3
URB 0.3	20.9 ± 3.9 **	16.9 ± 2.3	31.8 ± 5.8	35.6 ± 5.0	19.8 ± 2.5	26.1 ± 3.8
HIGH STRESS						
VEHICLE	17.0 ± 4.8 **	15.6 ± 3.4	43.0 ± 6.8	30.9 ± 3.0	15.9 ± 2.0	34.6 ± 8.6
URB 0.1	17.3 ± 4.0 *	13.6 ± 3.5	33.6 ± 9.0	29.9 ± 3.4 *	10.9 ± 1.1	39.1 ± 4.7
URB 0.3	15.5 ± 3.6 **	17.3 ± 2.5	37.8 ± 4.0	28.1 ± 4.8 *	10.5 ± 1.3	30.0 ± 7.6

Total time spent exploring the two objects (in seconds) and the number of crossings and rearings of all groups tested in the morning and in the afternoon. * $P < 0.05$; ** $P < 0.01$ vs the corresponding no stress group. Data are expressed as mean ± SEM (n = 8–12 per group).

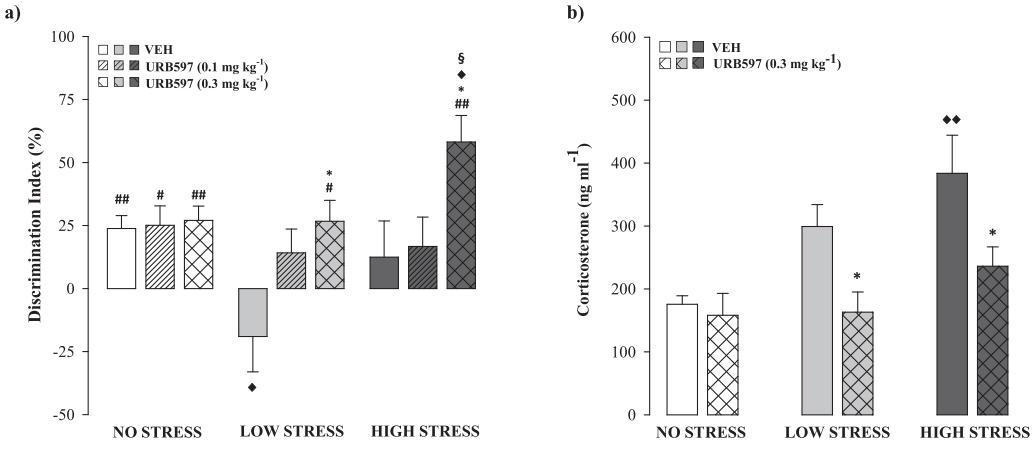

Fig. 3. URB597 modulation of stress-dependent effects on short-term memory in the morning.
a) Discrimination index on the testing trial for vehicle- and URB597-treated rats that were subjected to no, low or high stress conditions immediately after the training trial performed in the morning. *Post hoc* comparisons reported significant differences between groups as follows: * $P < 0.05$ vs the corresponding vehicle group. ◆ $P < 0.05$ vs the corresponding no stress group. § $P < 0.05$ vs the corresponding low stress group. # $P < 0.05$; ## $P < 0.01$, one-sample t-tests significantly different from zero. Data are expressed as mean ± SEM (n = 8–9 per group). **b)** Plasma corticosterone levels of vehicle and URB597 0.3 mg kg^{-1} treated rats subjected to no, low or high stress condition immediately after the training trial that were euthanized in the morning, 60 min after stress exposure, immediately after test. *Post hoc* comparisons reported significant differences between groups as follows: * $P < 0.05$ vs the corresponding vehicle group. ◆◆ $P < 0.01$ vs the corresponding no stress group. Data are expressed as mean ± SEM (n = 6–9 per group).

exploration time of the two objects on the testing trial, two-way ANOVA revealed a significant stress condition effect ($F_{(2.63)} = 24.885$, $P < 0.0001$), but no significant treatment or stress condition x treatment effects. Finally, rats' exploratory behavior of the apparatus during the test trial did not differ among the different experimental groups. Two-way ANOVAs for number of crossings and rearings revealed no significant stress condition, treatment or stress condition x treatment interaction effects (Table 1).

Two-way ANOVA for plasma corticosterone levels revealed significant stress condition ($F_{(2.41)} = 6.969$, $P = 0.003$) and treatment ($F_{(1.41)} = 10.634$, $P = 0.002$) effects, but no significant interaction between these two factors. *Post hoc* analysis showed that URB597 0.3 mg kg^{-1} treated rats subjected to low or high stress presented lower corticosterone levels than their corresponding vehicle groups ($P < 0.05$, for both comparisons; Fig. 3b), suggesting that URB597 0.3 mg kg^{-1} counteracted the stress-induced increase on plasma corticosterone levels, in both the low and high stress conditions.

3.3. Effects of the AEA hydrolysis inhibitor URB597 on short-term object recognition memory performance and plasma corticosterone levels in the no, low and high stress condition groups tested in the afternoon

This experiment investigated whether immediate post-training injection of the AEA hydrolysis inhibitor URB597 altered short-term performance on an object recognition task and plasma corticosterone levels and whether these effects were influenced by different stress conditions (no, low and high stress) when animals were tested in the afternoon.

As shown in Fig. 4a, one-sample t-tests revealed that the discrimination indexes were significantly different from zero for the no stress and low stress vehicle, URB597 0.1 mg kg^{-1} and URB597 0.3 mg kg^{-1} groups ($t_{(9)} = 4.384$, $P = 0.002$; $t_{(8)} = 2.658$, $P = 0.029$ and $t_{(7)} = 2.805$, $P = 0.026$, respectively for no stress groups; $t_{(10)} = 3.715$, $P = 0.004$; $t_{(10)} = 2.435$, $P = 0.035$ and $t_{(10)} = 4.412$, $P = 0.001$, respectively for low stress condition groups) and the high stress condition URB597 (0.1 and 0.3 mg kg^{-1}) groups ($t_{(11)} = 3.266$, $P = 0.008$; $t_{(11)} = 7.987$, $P < 0.0001$), thus indicating that these animals discriminated the novel object with respect to the familiar one. Rats in the remaining high stress vehicle group did not express memory retention for the familiar object (Fig. 4a). Two-way ANOVA for discrimination index revealed no significant stress condition or treatment effects, but a significant interaction between these two factors ($F_{(4.86)} = 2.593$, $P = 0.042$). *Post hoc* comparisons showed that, among rats tested under the high stress condition, URB597 0.3 mg kg^{-1} significantly increased the discrimination index as compared to vehicle treated rats ($P < 0.01$; Fig. 4a). Moreover, rats treated with the high dose of URB597 and subjected to the high stress condition presented a significant high discrimination index as compared to their corresponding low stress group ($P < 0.05$; Fig. 4a). Concerning the total exploration time of the two objects on the testing trial, two-way ANOVA revealed a significant stress condition effect ($F_{(2.86)} = 9.794$, $P = 0.0001$), but no significant treatment or stress condition x treatment effect (Table 1). Two-way ANOVA for number of crossings revealed a significant stress condition effect ($F_{(2.86)} = 5.902$, $P = 0.004$), but no significant treatment or stress condition x treatment interaction effects (Table 1). Concerning the number of rearings, two-way ANOVA revealed no significant stress condition effect, no treatment effect or any interaction between these two factors (Table 1).

Two-way ANOVA for plasma corticosterone levels revealed significant treatment ($F_{(1.37)} = 6.169$, $P = 0.018$) and stress condition x treatment interaction ($F_{(2.37)} = 6.289$, $P = 0.005$) effects, but no significant effect of the stress condition. *Post hoc* analysis showed that only URB597 0.3 mg kg^{-1} treated rats subjected to high stress presented lower corticosterone levels than their corresponding vehicle group ($P < 0.01$; Fig. 4b), suggesting that URB597 0.3 mg kg^{-1} counteracted the stress-induced increase on plasma corticosterone levels in the high stress condition.

4. Discussion

The present findings show that systemic administration of the AEA hydrolysis inhibitor URB597 counteracts the stress impairing effects on short-term object recognition memory, in a stress intensity- and circadian-dependent fashion. We have previously shown that activation of CB1 receptors differentially modulates short-term recognition memory in rats depending on environmental aversiveness and on the level of stress the animal experienced at the time of drug administration and memory encoding (Campolongo et al., 2013, 2012). In particular, post-training administration of the CB1 receptor agonist WIN55,212-2 enhanced object recognition performance (tested 24 h later) exclusively in animals training under a high arousal state (Campolongo et al., 2013). Literature data suggested that low versus high doses of THC and synthetic cannabinoid agonists provoke opposite stress-induced corticosterone release through CB1-mediated mechanisms (Mayer et al., 2014; Patel et al., 2004; Sano et al., 2009). Evidence has indicated that endocannabinoid augmentation approaches via FAAH or MAGL inhibitors generally produce dose-related decreases in the regulation of HPA-axis function and anxiety, whereas THC and exogenous cannabinoids

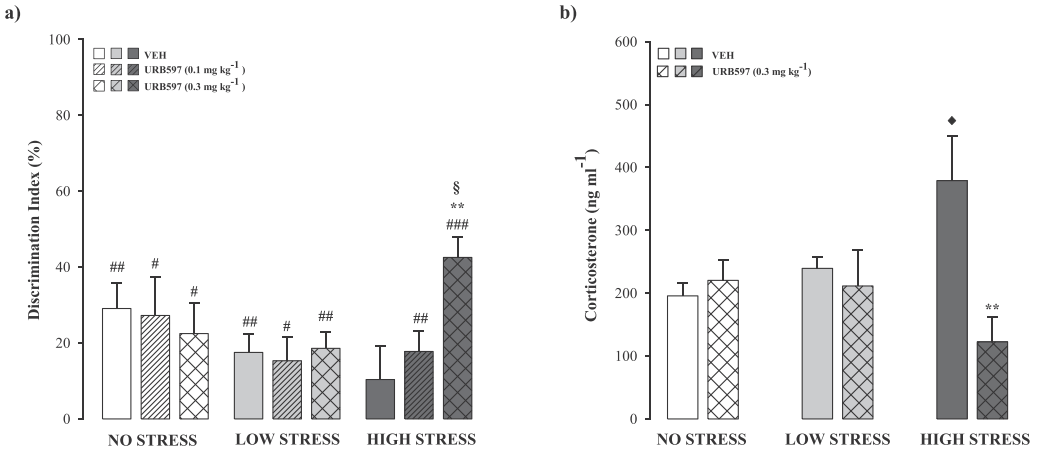

Fig. 4. URB597 modulation of stress-dependent effects on short-term memory in the afternoon.
a) Discrimination index on the testing trial for vehicle- and URB597-treated rats that were subjected to no, low or high stress conditions immediately after the training trial, in the afternoon session. *Post hoc* comparisons reported significant differences between groups as follows: ** $P < 0.01$ vs the corresponding vehicle group. § $P < 0.05$ vs the corresponding low stress group. # $P < 0.05$; ## $P < 0.01$; ### $P < 0.0001$, one-sample t-tests significantly different from zero. Data are expressed as mean ± SEM (n = 8–12 per group). **b)** Plasma corticosterone levels of vehicle and URB597 0.3 mg kg^{-1} treated rats subjected to no, low or high stress condition immediately after the training trial that were euthanized in the afternoon, 60 min after stress exposure, immediately after test. *Post hoc* comparisons reported significant differences between groups as follows: ** $P < 0.01$ vs the corresponding vehicle group. ♦ $P < 0.05$ vs the corresponding no stress group. Data are expressed as mean ± SEM (n = 6–8 per group).

produce biphasic effects with low doses mimicking endocannabinoid augmentation effects (Hill et al., 2018). Although there is one report showing that systemic administration of the FAAH inhibitor URB597 impairs the acquisition and early consolidation of contextual fear conditioning (Burman et al., 2016), other studies investigating the AEA signaling indicated that URB597 treatment enhanced consolidation (Morena et al., 2014) and impaired retrieval of aversive memories throughout indirect CB1 activation (Ratano et al., 2014). CB1 receptors are abundantly expressed in cortico-limbic regions, including the basolateral complex of the amygdala (BLA), hippocampus and medial prefrontal cortex (mPFC), where they modulate emotional arousal effects on memory (Akirav, 2013; Morena et al., 2015, 2014; Tasker et al., 2015) and regulate HPA-axis activity (Morena et al., 2016b). Extensive research has demonstrated that not only CB1 receptors, but also glucocorticoid receptors are located within this brain circuitry (Herkenham et al., 1990; Hill et al., 2010; Myers et al., 2014). Numerous evidence shows that glucocorticoids enhance memory consolidation of emotionally arousing experiences, but impair memory retrieval and working memory (de Quervain et al., 2017; McIntyre and Roozendaal, 2007). These different glucocorticoids effects are dependent on a non-genomically mediated interaction with noradrenergic transmission within the BLA and the hippocampus, wherein the endocannabinoid system has been shown to play an important role in mediating such effects (Atsak et al., 2015, 2012a; Jiang et al., 2014). Specifically, glucocorticoids or a stressor, administered shortly before or immediately after training, impair short-term memory performances in an object recognition task (Okuda et al., 2004; Roozendaal et al., 2006b), likely by negatively interfering with memory retrieval. Similarly, intrahippocampal infusions of the cannabinoid agonist WIN55,212–2 impair the retrieval of memory (Morena et al., 2015); however, antagonism of hippocampal β-adrenoceptor activity blocks the memory retrieval impairment induced by WIN55,212–2 (Atsak et al., 2012a), supporting the evidence that glucocorticoid and endocannabinoid signaling interact to impair the retrieval of emotional memory through their influence on downstream noradrenergic activity (Balsevich et al., 2017). The locus coeruleus (LC), the main source of norepinephrine in the mammalian forebrain, provides norepinephrine to different brain regions, including the BLA (McCall et al., 2017) and mPFC (Sara, 2009), wherein activation of CB1 receptors results in decreased cortical norepinephrine release (Reyes et al., 2012), when it is normally potentiated by acute swim stress exposure (Morilak et al., 2005). Evidence suggests that under high levels of stress the LC promotes fear learning by enhancing BLA function, while simultaneously blunting prefrontal function. Conversely, low levels of arousal are sufficient for the LC to facilitate mPFC function and promote downstream inhibition of the amygdala (Giustino and Maren, 2018). Herein we demonstrated that exposure to a low stress immediately after the training trial selectively impairs short-term memory retention/retrieval when animals are tested in the morning while exposure to high stress impairs short-term performance independently of the testing time. Interestingly, the stressed groups that were unable to discriminate between the 2 objects were those presenting increased levels of corticosterone. This is in accordance with extensive human and animal research showing that glucocorticoids impair memory retrieval (Roozendaal et al., 2006a; Wolf et al., 2016; de Quervain et al., 2019). Interestingly, our findings showed that post-training treatment with the AEA hydrolysis inhibitor URB597 counteracts these impairing effects of stress on memory performance, both in the morning and afternoon testing sessions. Specifically, systemic URB597 injection, at the dose of 0.3 mg kg^{-1}, enhances short-term memory retention in the low stress condition group tested in the morning, as well as in both the high stress groups tested either in the morning or in the afternoon, maintaining unaltered the performances of rats that did not show any cognitive impairment. Extensive evidence indicates that cannabinoids, either administered exogenously or released from endogenous sites, have pronounced effects on learning and memory (Hill et al., 2018; Marsicano and Lafenêtre, 2009; Morena and Campolongo, 2014; Ratano et al., 2017). Moreover, previous evidence has shown that AEA and 2-AG modulate emotional memory processes by interacting with glucocorticoids and other stress-activated neuromodulatory systems such as norepinephrine, in brain limbic regions (Atsak et al., 2015, 2012b; Campolongo et al., 2009; Morena et al., 2016a, 2015, 2014; Morena and Campolongo, 2014). Our finding that URB597 treatment has no effects in animals tested under no stress condition but selectively affects memory in the presence of a stressor, is in line with this evidence and has a high impact potential. On the light of this evidence it is tentative to speculate that stress of different intensities at two times of the day differentially regulated LC-NE action on the mPFC, since such interaction might be described by an inverted-U function that can either enhance or hinder learning depending on different arousal states (Giustino and Maren, 2018). The exact mechanisms underlying cannabinoid modulation of norepinephrine has yet to be determined, but evidence indicated that it may involve direct influences of CB1 receptors that are localized to noradrenergic axon terminals in the mPFC (Oropeza et al., 2007), which contribute to regulating norepinephrine release. In particular, microdialysis data supported a mechanism whereby administration of WIN55,212–2 prior to swim stress exposure decreased cortical norepinephrine efflux by inhibiting presynaptic inhibitory α2-adrenergic autoreceptors (Reyes et al., 2012), and such evidence is supported by predominant presynaptic distribution of α2-

adrenergic receptors in the mPFC (Cerrito and Preziosi, 1985; Dennis et al., 1987; Pudovkina et al., 2001).

It is well known that stress effects on memory performance follow an inverted U-shaped relationship; very low or very high levels of stress have detrimental effects, while intermediate levels lead to optimal memory performances (Baldi and Bucherelli, 2005). In mammals, an important feature of glucocorticoid regulation is a diurnal release pattern, with serum cortisol/corticosterone concentration peak in the morning and lowest at night (Dickmeis, 2009). Since rats are nocturnal animals, under laboratory circumstances of a regular light/dark cycle, the peak of HPA rhythm occurs in the afternoon, just before the onset of the activity phase; the nadir occurs during sleep, when corticosterone levels reach their lowest serum concentration, whereas in the morning (during the rats' inactive phase) the HPA-axis activity begins to increase (Bertani et al., 2010; Gong et al., 2015). Although different studies have demonstrated that circadian clocks can influence learning and memory function (Tapp and Holloway, 1981; Gerstner and Yin, 2010; Smarr et al., 2014), no circadian effect has been documented on short-term memory recognition performances yet. Our results show that vehicle-treated animals tested in the morning session have impaired memory retention when exposed to both low and high stressors. These groups of rats also presented higher plasma corticosterone levels than no stress group. However, when vehicle-treated rats were tested in the afternoon, memory retention was only negatively affected by the exposure to the high stressor, which in parallel increased rats' plasma corticosterone levels. It is tentative to speculate that when animals are tested during the low activity phase of the HPA-axis (i.e. morning session), both low and high stressor exposures induce a severe deviation from homeostasis which negatively affects memory retention performance. Our finding that exposure to low and high stress conditions elevated plasma corticosterone levels in rats that were trained in the morning, is in line with this evidence. Conversely, when animals are tested at the beginning of their active phase (i.e. afternoon), at their plasma corticosterone concentration peak, the high, but not the low, stress exposure might induce a more robust deflection from homeostasis, thus only the high stress condition group presents impairments in memory retention performance and higher plasma corticosterone levels. Our results indicate that maximal memory strength requires an intermediate level of stress, thus are in line with the Yerkes-Dodson law. Of note, boosting AEA levels with systemic URB597 injections is capable to specifically counteract these stress detrimental effects on short-term memory performance, decreasing plasma corticosterone levels in impaired memory groups. Previous findings indicated that WIN55,212-2 inhibited stress-induced elevation in corticosterone levels (Campolongo et al., 2013; Ganon-Elazar and Akirav, 2012, 2009), ameliorating the detrimental effects of stress on memory. Nevertheless, evidence demonstrated that the effects of cannabinoid drugs such as WIN55,212-2 on plasma corticosterone levels strictly depend on the level of arousal at the moment of administration. Previous findings demonstrated that URB597 is capable to reduce plasma corticosterone levels in response to repeated stress exposures (Hill et al., 2010). Whether this URB597 effect is due to an interaction with the HPA axis activity or to a direct effect on memory performance, or both, needs to be further investigated, but the current data strongly indicate that URB597 is able to reduce plasma corticosterone levels in short-term memory impaired-groups. Taken together, our findings indicate that stress impairing effects on short-term recognition memory seem to be dependent on the intensity of stress and HPA axis circadian rhythm and that treatment with URB597 is capable of specifically counteracting these detrimental effects. These results suggest that FAAH inhibition may be a potential therapeutic target for stress-inducing memory alterations highlighting the need for clinical studies to examine this possible cannabinoid mechanism of restoring memory impairments.

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Author contributions

All authors contributed to and have approved the final manuscript. Alessia Santori, Paola Colucci and Maria Morena contributed to the design of the experiments, performed the experiments, analyzed data and wrote the manuscript. Giulia Federica Mancini performed the experiments and analyzed data. Viviana Trezza, Maura Palmery, Stefano Puglisi-Allegra and Matthew Hill analyzed data and contributed to the design of the experiments. Patrizia Campolongo supervised the project, designed the experiments and wrote the manuscript. All authors read and approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.06.018.

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