Basolateral amygdala GABA-A receptors mediate stress-induced memory retrieval impairment in rats

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Abstract

The present study was designed to investigate the involvement of GABA-A receptors of the basolateral amygdala (BLA) in the impairing effect of acute stress on memory retrieval. The BLAs of adult male Wistar rats were bilaterally cannulated and memory retrieval was measured in a step-through type passive avoidance apparatus. Acute stress was evoked by placing the animals on an elevated platform for 10, 20 and 30 min. The results indicated that exposure to 20 and 30 min stress, but not 10 min, before memory retrieval testing (pre-test exposure to stress) decreased the step-through latency, indicating stress-induced memory retrieval impairment. Intra-BLA microinjection of a GABA-A receptor agonist, muscimol (0.005–0.02 μg/rat), 5 min before exposure to an ineffective stress (10 min exposure to stress) induced memory retrieval impairment. It is important to note that pre-test intra-BLA microinjection of the same doses of muscimol had no effect on memory retrieval in the rats unexposed to 10 min stress. The blockade of GABA-A receptors of the BLA by injecting an antagonist, bicuculline (0.4–0.5 μg/rat), 5 min before 20 min exposure to stress, prevented stress-induced memory retrieval. Pre-test intra-BLA microinjection of the same doses of bicuculline (0.4–0.5 μg/rat) in rats unexposed to 20 min stress had no effect on memory retrieval. In addition, pre-treatment with bicuculline (0.1–0.4 μg/rat, intra-BLA) reversed muscimol (0.02 μg/rat, intra-BLA)-induced potentiation on the effect of stress in passive avoidance learning. It can be concluded that pre-test exposure to stress can induce memory retrieval impairment and the BLA GABA-A receptors may be involved in stress-induced memory retrieval impairment.

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Introduction

Exposure to stressful conditions has a significant influence on learning and memory processes (McEwen and Sapolsky, 1995). Although the general outcome of stress is memory impairment (Segev et al., 2012), there are some studies that have reported the neutral (Nijholt et al., 2004; Joëls et al., 2006) or even the facilitative role of stress on memory formation (Beylin and Shors, 1998). These modulatory effects of stress, which may happen by activation of the hypothalamic–pituitary–adrenal axis (HPA), impact hippocampal formation and amygdaloid complex (Vyas et al., 2002; Gill and Grace, 2013). It is well documented that stress can affect the hippocampus-based (Aleisa et al., 2006) or amygdala-based (Kulisch and Albrecth, 2013) memory. Diamond et al. (1996) have shown that exposure to predator stress impairs hippocampal spatial working memory in rats. The amygdala also plays an obvious role in stress-related behaviours (Roozendaal and McGaugh, 1997; Sachs et al., 2013). Interestingly, cerebral microdialysis results have shown that stressful experiments change the extracellular level of neurotransmitters in the amygdala (Kawahara et al., 1993; Reznikov et al., 2007).

The amygdaloid complex comprises almost 13 nuclei which have widely spread efferent and afferent connections with different regions of the brain such as the hippocampus (Sah et al., 2003). One of the important nuclei is the basolateral nucleus (BLA) which is responsible for long-term emotional memory (McGaugh, 2004). Based on previous findings, it seems that the BLA is involved in learning after stress (Waddell et al., 2008). It should be noted that the BLA plays a critical role in the effects of stress on memory consolidation (Roozendaal et al., 2002).
The BLA regulates the effects of glucocorticoid hormones, which are secreted by the adrenal cortex after a stressful event, on both memory consolidation and memory retrieval (Roozendaal, 2003; Roozendaal et al., 2003, 2004). A large body of evidence has also shown that high circulating levels of glucocorticoids during stressful events or pre-test administration of glucocorticoid receptor agonists impairs memory retrieval by their influences on the BLA (for a review see Roozendaal, 2002). The BLA has been shown to regulate hippocampal long term potentiation (LTP) induction during stressful conditions (McIntyre et al., 2005). It has been reported that lesion of the BLA inhibits the memory-enhancement effect of glucocorticoid administration in the dorsal hippocampus (Roozendaal and McGaugh, 1997).

GABA is the main inhibitory neurotransmitter in the brain (Young and Chu, 1990) which has two distinctive receptors, namely ionotropic GABA-A/C receptors and metabotropic GABA-B receptors (Watanabe et al., 2002). GABA-A receptors are involved in different physiological behaviours like modulating learning and memory (Izquierdo and Medina, 1991; Paulsen and Moser, 1998), anxiety (Sanders and Shekhar, 1995) and fear (Crestani et al., 2002). There is a large distribution of GABA-A receptors in the BLA (Niehoff and Kuhar, 1983). Previous studies have indicated that the activation of GABA-A receptors in the BLA attenuates memory retrieval (Zarrindast et al., 2004). Exposure to stress has also been suggested to change the extracellular concentration of GABA in the BLA (Reznikov et al., 2009) and enhances the activity of the GABA-A receptors in the brain (Schwartz et al., 1987). In view of the fact that acute stress affects memory formation, and that the BLA GABA-A receptors play a key role in emotional learning (Lin et al., 2011), the aim of the present study was to investigate whether the BLA GABA-A receptors are involved in the effects of acute inescapable stress (placing on an elevated platform) on memory retrieval of rats in a passive avoidance task. The passive avoidance learning task (with a 24 h testing interval) used in the present study is an accepted model to test long-term memory in rats (Izquierdo and Medina, 1991; Izquierdo et al., 1999). On the other hand, an elevated platform can be used to evaluate the changes in neurophysiological parameters in response to stress-like conditions in rats (Degroot et al., 2004). Rocher et al. (2004) have also shown that 30 min exposure to the elevated platform stress inhibited the hippocampal-prefrontal cortex long-term potentiation (LTP) in rats.

Materials and methods

Animals

The experiments were conducted using adult male Wistar rats (Pasteur Institute, Iran) with the weight range of, 220−250 g. The animals were housed four per cage in a temperature-controlled environment (22 °C) under a 12 h light/12 h dark cycle (lights on at 07:00 hours) and had free access to food and water. Each animal was used once only and seven animals were used per group. The experiments were performed during the light phase of the cycle between 08:00 hours and 14:00 hours. Behavioural tests and animal care were conducted in accordance with the standard ethical guidelines (DHEW Publications, NIH, 80–23) and were approved by the local ethical committee.

Surgery

The animals were anaesthetized with ketamine–xylazine (100 mg/kg ketamine–4 mg/kg xylazine) mixture. During the surgery, the animals were cannulated by two 22-gauge guide steel cannulae, which were placed 1 mm above the target site. The cannulae were implanted bilaterally in the basolateral amygdala (BLA; AP: −2.4; ML: ±5; DV: −7) according to the Paxinos and Watson (2007) atlas by stereotaxic instrument. They were allowed 7 d for recovery before starting the experiments.

Passive avoidance apparatus

To test the memory retrieval, a two-compartment step through inhibitory avoidance apparatus was used. Two compartments had the same size (20 cm × 20 cm × 30 cm) and were separated by a guillotine door (7 cm × 9 cm) in the middle of the dividing wall. The walls and the floor of one compartment consisted of white opaque resin (light compartment) and the walls of the other compartment were dark but its floor was a stainless steel grid (2.5 mm in diameter, separated by a distance of 1 cm) and was connected to an insulated stimulator so that an intermittent electric shock (50 Hz, 1 mA, 3 s) could be delivered when a rat entered the compartment.

Behavioural protocol

Training phase

The animals were allowed to habituate in the experimental room for 1 h prior to the experiments. Then, each animal was gently placed in the brightly lit compartment of the apparatus; after 5 s, the guillotine door was opened and the animal was allowed to enter the dark compartment. The latency with which the animal crossed into the dark compartment was recorded. Animals that waited more than 100 s to cross to the dark compartment were discarded from the experiments. Once the animal crossed with all four paws to the next compartment, the guillotine door was closed and the rat was taken into its home cage. The trial was repeated after 30 min as in the acquisition trial where after 5 s the guillotine door was opened and as soon as the animal crossed to the dark (shock) compartment the door was closed and a foot shock
(50 Hz, 1 mA, 3 s) was immediately delivered to the grid floor of the dark room. After 20 s, the rat was removed from the apparatus and placed temporarily into its home cage. After 2 min the animal was retested in the same way as the previous trials; if the rat did not enter the dark compartment during 120 s, successful acquisition of passive avoidance response was recorded. Otherwise, when the rat entered the dark compartment (before 120 s) for a second time, the door was closed and the animal received the same shock again. After retesting, if the rat acquired the acquisition of passive avoidance, the training was finished successfully.

Retrieval test

Twenty-four hours after training, a retrieval test was performed to measure long-term memory. Each animal was placed in the light compartment for 20 s, the door was opened, and the step-through latency for entering into the dark compartment was measured. The test session ended when the animal entered the dark compartment or remained in the light compartment for 300 s (criterion for retrieval). During these sessions, no electric shock was applied. All training and test sessions were carried out during the light phase between 08:00 and 14:00 hours.

Stress protocol

In the present study, the elevated platform was used to induce stress. Animals were picked up and placed on an elevated platform for different time periods (10, 20 and 30 min). After 10 min, the animals showed the behavioural signs of stress such as urination and defecation (Xu et al., 1998). It should be noted that the animals were exposed to inescapable stress on the test day (pre-test exposure to stress).

Drug treatment and microinjection

The drugs used in this study included bicuculline (UK) and muscimol (UK). Bicuculline was dissolved in a drop of glacial acetic acid with a Hamilton microsyringe, and was made up to a volume of 5 ml with sterile 0.9% saline (which was also used as vehicle) and was then diluted to the required volume which was also used as vehicle. Muscimol was dissolved just in sterile 0.9% saline immediately before each experiment. Both drugs were injected bilaterally into the BLA (intra-BLA) in a volume of 0.3 μl in each side (0.6 μl/rat). The injections were given by two 27-gauge injector cannulae which were 1 mm taller than the implanted cannulae to reach the target site. The injection needle was attached with a polyethylene tube to a 2 μl Hamilton syringe. Time for the microinjection of drugs was 60 s. For better diffusion of the drug into the target site, the injectors were left in place for an additional 60 s. The time intervals between drug administrations (Coleman-Mesches and McGaugh, 1995; Spanis et al., 1999) and the drug doses (Rassouli et al., 2010) were based on our pilot experiments and previous studies.

Experimental design

Experiment 1

In this experiment, three groups of animals were used for evaluating the influence of acute stress exposure on memory retrieval. On the training day, each animal was trained in a passive avoidance task. On the test day, acute stress was induced by placing the rat on the elevated platform for 10, 20 and 30 min before the test session. A control group was trained and tested without stress. Each value represents mean±S.E.M. of seven animals per group. ***p<0.001 compared to the control group.

Experiment 2

In this experiment, the effects of bilateral microinjection of different doses of GABA-A receptor agonist, muscimol into the basolateral amygdala (intra-BLA) on memory retrieval were investigated in rats unexposed or exposed to stress. Four groups of animals were trained and followed by pre-test intra-BLA microinjection of muscimol (0, 0.005, 0.01 and 0.02 μg/rat). Memory retrieval was measured 5 min after muscimol injection (Fig. 2, left panel). The other four groups were trained and received intra-BLA microinjection of the same doses of muscimol after successful training. After 5 min, they were placed on the elevated platform for 10 min (an ineffective time of stress), and then the step-through latency on the passive avoidance task was measured (Fig. 2, right panel).
In this experiment, the effects of bilateral intra-BLA microinjection of different doses of bicuculline, a GABA-A receptor antagonist, on memory retrieval were investigated in rats unexposed or exposed to stress. 24 h after successful training in the passive avoidance task, four groups of animals received intra-BLA microinjection of the same doses of muscimol and after 5 min they were placed on the elevated platform for 10 min. After stress exposure, they were tested for evaluating step-through latency. Each value represents mean±S.E.M. of seven animals per group. **p<0.01, ***p<0.001 compared with the saline/stress groups.

Experiment 3

In this experiment, the effects of bilateral intra-BLA microinjection of different doses of bicuculline on memory retrieval in rats unexposed or exposed to 10 min inescapable stress. The animals were trained in a passive avoidance task. On the test day, four groups received intra-BLA microinjection of muscimol (0.005–0.02µg/rat) and were tested after 5 min (left panel). The other four groups received intra-BLA microinjection of the same doses of muscimol and after 5 min they were placed on the elevated platform for 10 min. After stress exposure, they were tested for evaluating step-through latency. Each value represents mean±S.E.M. of seven animals per group. **p<0.01, ***p<0.001 compared with the saline/stress groups.

Experiment 4

In this experiment, the effect of intra-BLA microinjection of bicuculline on muscimol-induced response in the rats exposed to 10-min inescapable stress was examined. Four groups of animals were trained in the passive avoidance task. On the test day, they received intra-BLA microinjection of bicuculline (0, 0.1, 0.3 and 0.4µg/rat) plus muscimol (0.02µg/rat, intra-BLA) with 5 min interval; after 5 min they were placed on the elevated platform for 10 min. After stress exposure, step-through latency of each animal was measured on the passive avoidance task (Fig. 3, right panel).

Histological verification of cannula placements

After the test sessions, each animal was killed by carbon dioxide. The animals received bilateral microinjection of 1% methylene-blue solution which was injected into the BLA (0.3 µl/each side), as described in the drug section. Then, the animal was decapitated and its brain was removed and fixed in 10% formalin solution. Sectioning was done after 1 wk by Campden Microtome Vibroslice. The sites of injections were verified according to the atlas of Paxinos and Watson (2007). Data from the animals with injection sites located outside the BLA regions were not used in the analysis.

Data analysis

The data are expressed as means±S.E.M. The statistical analyses were performed using one- and two-way
Pre-test intra-BLA microinjection of bicuculline on memory retrieval in rats unexposed or exposed to stress

Figure 4. The effect of pre-test intra-BLA microinjection of bicuculline on muscimol-induced response in rats exposed to stress. Six groups of animals were trained in a passive avoidance task. On the test day, four groups of animals received intra-BLA microinjection of bicuculline (0.1–0.4 μg/rat) plus muscimol (0.02 μg/rat, intra-BLA) with 5 min interval, and after 5 min they were placed on the elevated platform for 10 min. After stress exposure, they were tested for measuring step-through latency. Two control groups received two intra-BLA injections of vehicle (0.6 μl/rat) plus saline (0.6 μl/rat, a 5 min interval) with or without stress. Step-through latency of each animal was also tested for the two control groups. Each value represents mean±S.E.M. of seven animals per group. **p<0.001 compared with the vehicle/saline/stress group. +++p<0.001 compared with the vehicle/muscimol/stress group.

analysis of variance (ANOVA). Post-hoc comparison of means was carried out with the Tukey test for multiple comparisons, when appropriate. The level of statistical significance was set at p<0.05. Calculations were performed using SPSS statistical package.

Results

The effect of the elevated platform stress on memory retrieval

Figure 1 shows the effect of pre-test exposure to stress on step-through latency. One-way ANOVA revealed that 20 and 30 min exposure to stress, but not 10 min, reduced the step-through latency in the passive avoidance task (F3,24 = 23.4, p<0.001), indicating stress-induced memory impairment.

The effects of pre-test bilateral intra-BLA microinjection of muscimol on memory retrieval in rats unexposed or exposed to stress

Figure 2 shows the effects of bilateral microinjection of muscimol on memory retrieval in rats unexposed or exposed to 10 min inescapable stress (an ineffective time of stress). Two-way ANOVA revealed a significant difference in memory retrieval between the groups of animals that received pre-test intra-BLA microinjection of muscimol (0.005, 0.01 and 0.02 μg/rat) without stress and those that received pre-test intra-BLA microinjection of the same doses of muscimol with 10 min inescapable stress (within group comparison: treatment effect: F1,48 = 28.85, p<0.001; dose effect: F3,48 = 26.63, p<0.001; treatment×dose interaction: F3,48 = 11.83, p<0.001) in the passive avoidance task. In addition, post-hoc analysis revealed that pre-test intra-BLA microinjection of muscimol (0.005, 0.01 and 0.02 μg/rat) in the rats without stress had no effect on memory retrieval (F3,24 = 2.06, p>0.05). Further analysis also showed that pre-test intra-BLA microinjection of the same doses of muscimol, 5 min before exposure to stress (10 min) inhibited memory retrieval (F3,24 = 29.26, p<0.001, indicating a potentiating effect for muscimol on stress-induced memory impairment.

The effects of pre-test bilateral intra-BLA microinjection of bicuculline on memory retrieval in rats unexposed or exposed to stress

Figure 3 shows the effects of pre-test microinjection of different doses of bicuculline into the BLA on memory retrieval in rats unexposed or exposed to 20 min inescapable stress. Two-way ANOVA revealed a significant difference in memory retrieval between the groups of animals that received pre-test intra-BLA microinjection of bicuculline (0, 0.4, 0.45 and 0.5 μg/rat) without stress and those that received pre-test intra-BLA microinjection of the same doses of bicuculline with 20 min inescapable stress (within group comparison: treatment effect: F1,48 = 246.8, p<0.001; dose effect: F3,48 = 29.5, p<0.001; treatment×dose interaction: F3,48 = 25.7, p<0.001). In addition, post-hoc analysis revealed that pre-test intra-BLA microinjection of bicuculline (0, 0.4, 0.45 and 0.5 μg/rat) plus saline in the rats without stress exposure had no effect on memory retrieval (F3,24 = 0.43, p>0.05). Further analysis also showed that pre-test intra-BLA microinjection of the same doses of bicuculline, 5 min before stress exposure (20 min) improved memory retrieval (F3,24 = 26.94, p<0.001), indicating the inhibitory effect of bicuculline on stress-induced memory impairment.

The effect of pre-test intra-BLA microinjection of bicuculline on muscimol-induced response in rats exposed to stress

Figure 4 shows the effect of the blockade of GABA-A receptors by bilateral microinjection of bicuculline into the BLA on muscimol-induced response in rats exposed to 10 min inescapable stress. One-way ANOVA indicated that pre-test intra-BLA microinjection of different doses of bicuculline (0.1, 0.3 and 0.4 μg/rat) altered the response induced by the administration of muscimol (0.02 μg/rat, intra-BLA) in rats exposed to 10 min inescapable stress.
Post-hoc analysis showed that bicuculline (0.3 and 0.4 \mu g/rat) reversed muscimol-induced potentiation on the effect of stress in passive avoidance learning.

Discussion

Our findings indicated that pre-test 20 and 30 min exposure to inescapable stress effectively decreased the step-through latency, suggesting stress-induced memory impairment. In agreement with our results, exposure to a forced swimming stress (Rezvanfard et al., 2011) or acute immobilization stress (Rashidy-Four et al., 2004) have been reported to impair memory retention or retrieval in the avoidance learning task. In addition, exposure to a stressful experience has been found to impair memory consolidation and retrieval of a hippocampal-dependent non-aversive object location task in rats that were habituated to exposure to elevated platform stress (Maroun and Akirav, 2008; Segev et al., 2012). Our results also revealed that exposure to 10 min stress had no effect on memory retrieval, suggesting that this duration of stress exposure is lower than the minimum time required to affect memory retrieval. de Quervain et al. (1998) reported that time-dependent effect of stress on memory retrieval in a water-maze spatial task depended on the circulating corticosterone levels at the time of testing, suggesting that increased adrenocortical function induced by the stressor may disrupt memory retrieval. Interestingly, it has been shown that 10 min acute stress maximally and rapidly increased plasma corticosterone concentrations in rats (Goto et al., 1995). Acute stress caused by brief (10 min) neck restraint also increased LTP, which is a cellular model for learning and memory formation, in the dentate gyrus by increasing corticosterone plasma concentration and activating glucoorticoid receptors (Spyrka et al., 2011). Since hippocampal LTP is reinforced in the animals that are exposed to 10 min swimming stress, it has been suggested that the LTP enhancement may be dependent on stress-induced corticosterone release from the adrenal glands (Ahmed et al., 2006). In contrast, Xu et al. (1997) showed that exposure to 30 min acute stress increased corticosterone plasma levels and blocked the LTP induction in the animals. Other studies have also confirmed that the exposure to 20, 30 and 60 min acute stress can significantly increase the plasma corticosterone level in rats (Degroot et al., 2004; Kavushansky and Richter-Levin, 2006; Yuen et al., 2009). It seems that the duration and intensity of the stressors are significant factors which modulate the effect of stress on memory formation (Sandi and Pinelo-Nava, 2007). On the other hand, Maroun and Richter-Levins (2003) showed that LTP induction in the hippocampus and the basolateral amygdala (BLA)-medial prefrontal cortex pathway was simultaneously blocked by acute elevated platform stress. Stress-induced plasticity including dendritic elongation and spine formation in the BLA can also be induced by acute or chronic immobilization stress (Mitra et al., 2005; Vyas et al., 2006). Considering that the BLA plays a critical role in mediating stress-related effects on memory formation and that the BLA GABA-A receptors are involved in passive avoidance learning (Roozendaal et al., 2009), the present study was actually designed to examine the effects of pre-test bilateral intra-BLA microinjections of muscimol and/or bicuculline on memory retrieval in rats exposed or unexposed to acute elevated platform stress.

Our findings showed that pre-test bilateral intra-BLA microinjection of muscimol by itself had no effect on the retention latencies in rats unexposed to stress. Although it has been shown that the activation of the BLA’s GABA-A receptors impairs memory consolidation (Nazari-Serenjeh and Rezayof, 2013) and intra-BLA injection of bicuculline GABA-A receptor antagonist enhances memory retrieval (Wilensky et al., 2000), the results obtained in this study revealed that intra-BLA administration of muscimol at the doses used does not influence memory retrieval. Interestingly, our results also showed that pre-test intra-BLA microinjection of the same doses of muscimol, 5 min before exposure to 10 min stress (an ineffective stress) decreased step-through latency, suggesting stress-induced memory impairment. Since the activation of the BLA GABA-A receptors potentiates the response of an ineffective stress on memory retrieval, one may suggest that the GABA-A receptors of BLA may play a critical role in stress-induced memory impairment. According to the fact that GABAergic synaptic transmission has a strong inhibitory control on the activity of the BLA projection neurons (Royer et al., 1999; Szinyei et al., 2000), it has been suggested that changes of this neurotransmission can affect stress-induced behaviours. Reznikov et al. (2009), using an in vivo microdialysis technique, showed that acute restraint stress increased GABA efflux in the BLA, while the same type of stress had no effect on central amygdala efflux. Several investigations have also reported that stressful conditions may change the GABA transmission in different regions of the brain. For example, de Groote and Linthorst (2007) reported that exposure to a novel cage or to forced swimming increased GABA release in rats’ hippocampus. The release of GABA in the nucleus accumbens has also been shown to increase during stressful situations (Saulskaya and Marsden, 1995). It is important to note that GABAergic system via GABA-A receptors regulates the hypothalamic-pituitary-adrenal (HPA) axis which mediates body’s physiological response to stress (Sarkar et al., 2011). The HPA system is in turn controlled by corticotropin releasing hormone (CRH) neurons in the paraventricular nucleus (PVN), which are under GABAergic inhibition (Herman et al., 2004). Bhatnagar et al. (2004) reported that intra-BLA injection of muscimol enhanced the HPA response to acute restraint in the rats previously exposed to a different repeated stressor, suggesting that the amygdala GABA-A receptors may be involved in
regulating HPA activity. In addition, exposure to the predator stress increased GABA in the amygdala and also corticotropin-releasing factor (CRF) in the PVN and the amygdala (Cook, 2004). Interestingly, glucocorticoids enhance muscimol binding to GABA receptors in different brain regions including the cortex, the hippocampus, the thalamus and the cerebellum, indicating the inhibitory effect of glucocorticoids on neuronal firing (Majewska et al., 1985). Moreover, an acutely administered corticosterone increased the expression of GABA-A receptor alpha-2 subunits in the BLA and the dentate gyrus of high anxiety rats (Wislowska-Stanek et al., 2012). The uptake of GABA also increased in hippocampal neurons of adrenalectomized rats, and treatment with corticosterone reversed this increase (Miller et al., 1978). Therefore, it could be suggested that glucocorticoids have an important role in modulating GABA-A receptors and regulating GABAergic neurotransmission. On the other hand, some evidence suggests that glucocorticoids enhance memory consolidation of passive avoidance training but impair memory retrieval of fear conditioning through a nongenomically mediated interaction with the endocannabinoid system which in turn affects the GABAergic neurotransmission (Campolongo et al., 2009; Atsak et al., 2012a, b). Based on all the above evidence, it seems that the functional interaction between the BLA GABAergic system and other brain sites is probably important for the effect of stress on memory retrieval.

In order to show the involvement of GABA-A receptors of the BLA in stress-induced memory impairment, different doses of bicuculline, a competitive antagonist of GABA-A receptors, alone or in combination with stress, was injected into the BLA before the testing phase. The obtained results showed that pre-test intra-BLA microinjections of bicuculline by itself had no effect on memory retrieval while pre-test microinjections of the same doses of bicuculline, 5 min before 20 min stress exposure, inhibited the impairment effect of stress on memory retrieval. Ample evidence suggests that The BLA GABAergic neurotransmission has a critical role in the control of the emotional consequences of stress (Isaardi et al., 2004). Using contextual fear conditioning, Berlau and McGaugh (2006) reported that intra-BLA microinjection of bicuculline enhanced the consolidation of the extinction memory trace. It has also been claimed that the facilitation of fear conditioning may be related to increased neuronal excitability attributable to depressed GABAergic inhibition in the BLA, but not in the central amygdala (Rodriguez Manzanares et al., 2005). It should be considered that Reznikov et al. (2007, 2009) showed, by using in vivo microdialysis, that an acute restraint stress increases both extracellular glutamate levels and GABA efflux in the BLA. There is evidence that the reduction of the BLA GABAergic inhibition may lead to long-term changes in synaptic plasticity and facilitation of memory formation via the potentiation of NMDA receptor-mediated transmission (Rodriguez Manzanares et al., 2005). Considering that amygdala may be involved in both inhibitory and excitatory regulation of the stress axis (Herman et al., 2002), it seems that in the current study, intra-BLA injection of bicuculline may change the balance of inhibitory GABA and excitatory glutamate which can inhibit stress-induced memory retrieval impairment. To further verify the hypothesis that GABA-A receptors of the BLA may directly be involved in stress-induced memory impairment, we examined the effect of pre-test intra-BLA microinjections of bicuculline on memory retrieval by co-administration of muscimol and an ineffective inescapable stress. The results revealed that bicuculline reduced muscimol response induced by pre-test administration of muscimol plus 10 min stress exposure. Therefore, it can be concluded that acute stress modulates the GABAergic transmission in the BLA and that there is a link between the GABA-A receptors of the BLA and the impairment effect of stress on memory retrieval in passive avoidance learning.

Statement of Interest
None.

References


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