Front. Biol. 2018, 13(2): 149–155
https://doi.org/10.1007/s11515-018-1491-5

RESEARCH ARTICLE

Investigating the inhibition of NMDA glutamate receptors in the basolateral nucleus of the amygdala on the pain and inflammation induced by formalin in male Wistar rats

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BACKGROUND: The role of the amygdala in controlling emotional pain has been emphasized in several studies. In this study, the role of the NMDA glutamate receptors in the basolateral nucleus of the amygdala (BLA) in regulating inflammation and emotional pain, induced by formalin, was studied in male rats.
METHODS: Male Wistar rats, weighing 250±20 g, were injected with 20 μL of 2% formalin into the paw of the right hind limb. Memantine, at doses of 1 and 5 μg/rat, was injected bilaterally into the BLA five minutes prior to injecting formalin. Following the injection, the pain and inflammation of the paws were measured using Dubbison-Dennis and mercury immersion methods, respectively. The behavior of the animals, including licking time and foot volume, was assessed.
RESULTS: The results showed that the inactivation of the NMDA receptors in the BLA in the acute phase of pain reduced the licking time (the emotional aspect of pain). However, at a high dose (5 μg/rat), memantine exacerbates the pain induced by formalin in the chronic phase. Additionally, the inhibition of the NMDA receptors in the BLA by memantine enhanced the formalin-induced increase in foot volume (inflammation) in a dose-dependent manner.
CONCLUSION: The study showed that the NMDA glutamate receptors in the BLA are crucial for the emotional pain and inflammation in both chronic and acute phases of formalin-induced pain. However, their roles are more pronounced in the chronic phase than in the acute phase of pain.

Keywords basolateral nucleus of amygdala, formalin test, inflammation, licking time, memantine

Introduction

Pain is an unpleasant sensation, critical for the survival of organisms, which alerts organisms to damage to the different parts of the body (Elman and Borsook, 2016). In addition to tremendous personal suffering arising from the loss of productivity, medical expenditure, and long-term inability, chronic pain imposes heavy costs on the patients, their families, and on society as a whole (Borsook et al., 2016). Several studies have demonstrated that changes in the physical systems in chronic pain can alter psychological processes as well as cognitive and emotional factors that have important effects on the perception of pain. The evaluation and expression of pain in the clinics is challenging, owing to the relationships between emotional and physical pain, and the consequences that alter the psychological status of the expression of pain (Bushnell et al., 2013). Although different parts of the brain are involved in perceiving the agony inflicted by pain, the amygdala is the part of the brain that is mostly associated with the psychological processes and the emotional states of pain (Simons et al., 2014).

The amygdala complex, which is the major component of the limbic system, consists of several nuclei that are located deep in the temporal lobe (Dalooei et al., 2016; Sadeghi-Gharajehdaghi et al., 2017), and plays a role in processing

Received February 19, 2018; accepted April 2, 2018
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pleasure sensations (Fernando et al., 2013), reward, emotional responses, fear, fear conditioning (Mohammadian et al., 2017), and episodic emotional memories (Yonelinas and Ritchey, 2015). It has been shown that the amygdala probably receives nociceptive inputs through the spinoparabrachial–amygdala projections (Bernard et al., 1996). It is believed that the amygdala plays an important role in the emotional-effect dimension of pain (Neugebauer et al., 2004), and contributes to cognitive aspects such as pain-related decision-making damages via interactions with the cortical areas (Ji and Neugebauer, 2010).

The basolateral nuclei of the amygdala (BLA) are predominantly composed of glutamatergic projection neurons and preferentially form the input region for sensory information, including nociceptive information, from the midline and posterior nuclei of the thalamus, and cortical regions such as the anterior cingulate cortex, insula, and other medial prefrontal cortical areas (Neugebauer, 2015, Motahari et al., 2016). Studies showed that this information is transferred by glutamatergic BLA neurons that establish excitatory synapses with the target neurons, which in turn generate excitation. In comparison to this projection, synaptic connections to the intercalated GABAergic neurons provide an inhibitory interface capable of generating feed-forward inhibition (Zeitler et al., 2016). It has been shown that the BLA contains neurons that respond preferentially to noxious stimuli, and damages to the BLA could prevent the development of chronic pain states (Li et al., 2013). According to these studies, it seems that the nuclei of the BLA play an important role in modulating the effects of pain, and controlling the activity of the glutamatergic neurons of the BLA could offer a desirable therapeutic strategy for chronic pain. However, there is little information about the role of the glutamatergic neurons of the BLA in pain. In this study, we therefore investigated the role of the glutamatergic receptors of the BLA in the behavioral and inflammatory aspects of pain, by inhibiting the glutamatergic NMDA receptors in the BLA.

Material and methods

Animals used

Male Wistar rats, weighing 250±20 g, purchased from Pasteur Institute, Tehran, Iran, were used for all the experiments in this study (n = 8 rats for each group). The animals were housed in groups of three per cage in a 12 h light-dark cycle at a constant ambient temperature of 23± 1°C, and were allowed free access to food and water. All the experiments were conducted in accordance with standard ethical guidelines and were approved by the Medical Committee on the Use and Care of Animals of Baqiyatallah University (approval number: 81/021). All the experiments were performed in a manner so as to reduce the number of animals used and to decrease their pain and suffering.

Drugs

Memantine hydrobromide (Darupakhsh, Iran), lidocaine hydrochloride (Sigma-Aldrich, CA, USA), ketamine hydrochloride, (Sigma-Aldrich, CA, USA), diazepam (Sigma-Aldrich, CA, USA), and 2% formalin (Sigma-Aldrich, CA, USA) were used in this study. The drugs were dissolved in sterile saline. Ketamine and diazepam were injected subcutaneously at a dose of 1 mL/kg. Memantine was administered by intra-BLA infusions at doses of 1 and 5 μg/rat. The control groups were administered with saline.

Experimental groups

The animals were randomly divided into four groups, containing eight rats per group. One of the groups served as the control (intact) group. The animals of the vehicle group underwent surgery (as described in the next section) and were bilaterally administered with 1 μl normal saline, which served as a vehicle for memantine, followed by injections of 20 μL of 2% formalin to the paw of the right foot. The animals of the other two groups received memantine at doses of 1 or 5 μg/rat in both the left and right sides of the BLA, five minutes prior to administration of 2% formalin injection. The response of the animals to the pain induced by the 2% formalin injection was determined at different intervals of time.

Surgical procedures

The animals were anesthetized with ketamine hydrochloride (70 mg/kg, intraperitoneal (IP) + diazepam (5-7 mg/kg, IP)) (Ghobadi et al., 2016; Ehteram et al., 2017; Hassantash et al., 2017). Two stainless steel cannula (23 gauge) were bilaterally implanted using stereotaxic surgery, into the BLA. The stereotaxic coordinates for BLA, according to the Paxinos and Watson atlas (2006), were: AP = –2.9 mm, ML = ±4.8 mm, DV = 8.1 mm. The guide cannula was fixed to the skull using two anchoring screws and dental acrylic. All the animals were allowed one week for recovering from the surgery and anesthesia. During the intra-BLA injections, each animal received an injection of memantine dissolved in saline at a dose of 1 or 5 μg/rat, administered with a 30 gauge blunt tapered needle, at a rate of 1 μL/min. After the injection, the needle was left in the guide cannula for an additional minute and subsequently removed. After five minutes, the animals were subjected to the formalin test, described in the next section.

Following the formalin test, the animals were anesthetized. For histological verification of the location of the injection cannulas in the BLA, Golgi staining was performed. The animals received a transcardiac perfusion of 0.9% normal saline followed by perfusion with 10% buffered formalin. The brains were removed, blocked, and cut coronally through the cannula placements (Fig. 1).

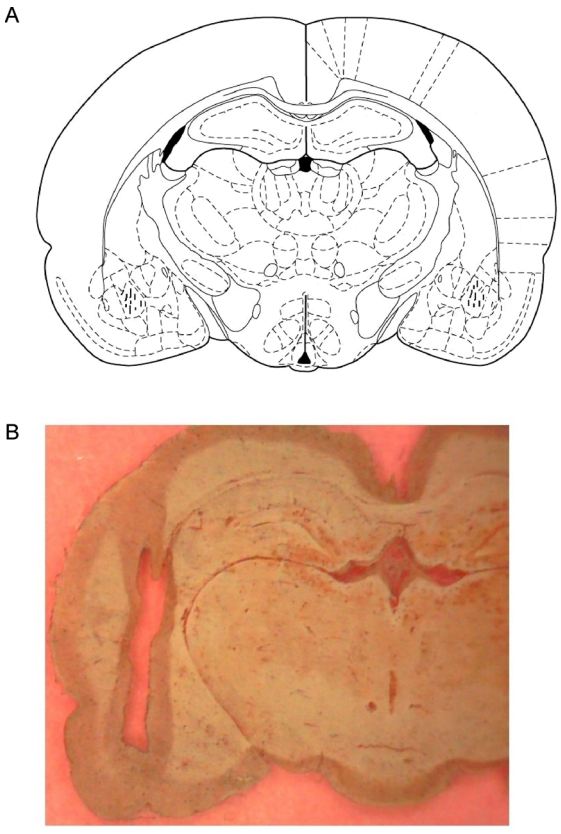

Figure 1 (A) Location of the cannula tips in the BLA, according to the atlas of Paxinos and Watson. The lines indicate where the cannula tips were placed. (B) Actual histological verification of the cannula placements.

Formalin test

The formalin test was performed according to the modified method of Dubuisson and Dennis (1977). Each animal was placed inside a Plexiglas box having dimensions of 30 cm × 30 cm × 30 cm (length × width × height) following the formalin injection into the plantar surface of the paw of the right hind limb. The position of the foot and the way the animals responded to the 20 µL injection of 2% formalin were evaluated by the observers. In this study, the time spent on nociceptive behavior, defined by the licking of the injected paw, was recorded at 5 min intervals for one hour immediately following the formalin injection into the paw. Each animal was injected with saline, followed by mementine injection at a dose of 1 or 5 µg/rat into the BLA, 5 min prior to injecting 2% formalin.

Determining the degree of inflammation

For determining the degree of inflammation induced by formalin (Ahmadiani et al., 2000; Husseini et al., 2016), the left foot of each animal was considered as the control, into which saline was injected. The right and left feet were separately placed in a container containing mercury, and the exact weight of each foot was determined by calculating the change in the weight of mercury after immersing the left (control) foot and the right (test) foot. The change in the weight of the test foot was determined after the formalin injection. The change in volume was deduced by dividing the change in weight by the density of mercury (13.6). The anti-inflammatory effect of memantine, injected into the BLA, was assessed one hour after the 2% formalin injection.

Statistical analyses

All the data are represented as the mean ± SEM for 8 animals. One-way analysis of variance (ANOVA) followed by Tukey test was performed to compare the specific groups. Differences were considered statistically significant at $p < 0.05$.

Results

Effect of bilateral injections of memantine into the BLA on the licking time in the formalin test

After injecting 20 µL of 2% formalin into the paw of the right hind limb, the pain response evoked (licking time) by formalin was investigated. The results showed that a two-phase response was observed following formalin injection: (1) a first phase or neurogenic phase, which lasted for up to 5 min following formalin injection, and (2) a secondary phase or inflammatory phase, which lasted for 20–40 min after formalin injection. The first and second phases corresponded to the acute and chronic phases of formalin administration, respectively. According to these results, the first 5 min was the peak of the acute phase, while the 20–40 min following formalin injections was the peak of the chronic phase. The results showed that in the acute phase, memantine at both doses of 1 and 5 µg/rat, could antagonize the effect of formalin on the licking time. The inhibition was more pronounced at a dose of 1 µg/rat. Additionally, the inhibitory effect of memantine at both doses on the acute phase of the pain evoked by formalin was significant. However, the licking time in the chronic phase for the animals receiving intra-BLA memantine at a dose of 5 µg/rat was higher than that of the animals receiving saline and memantine at a dose of 1 µg/rat. Thus, the intra-BLA administration of memantine at a higher dose (5 µg/rat) could not attenuate the chronic phase of pain. Therefore, these data suggest that the NMDA glutamate receptors play a critical role in the first phase of pain in the formalin test (Fig. 2).

Infusion of the NMDA glutamate receptor antagonist into the BLA increased the inflammation of the paw of the hind limb

As shown in Fig. 2, intra-BLA administration of memantine at doses of 1 and 5 µg/rat, significantly ($p < 0.01$) increased

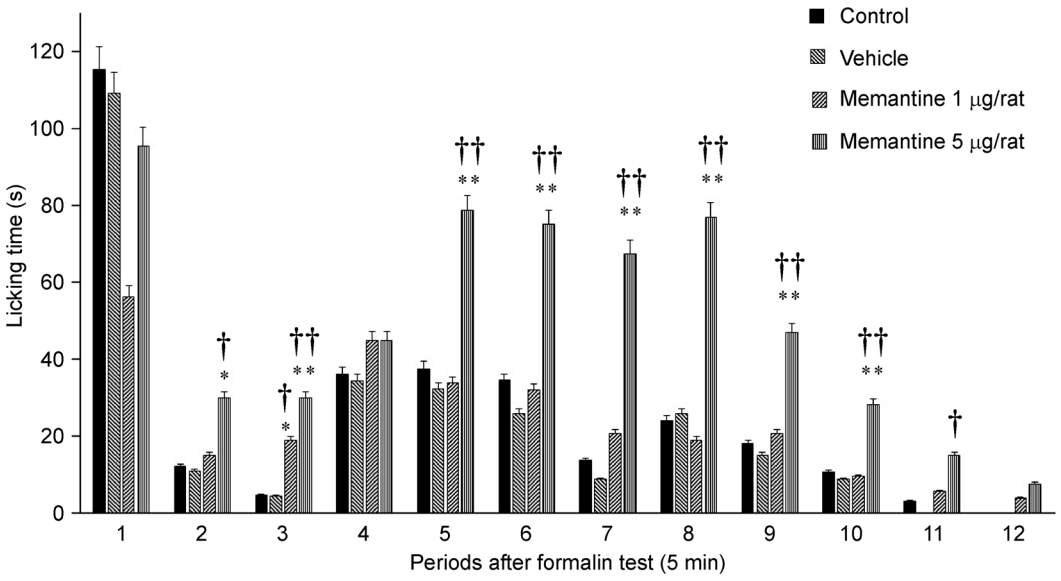

Figure 2 The effect of bilateral intra-BLA administration of memantine at different doses of 1 or 5 μg/rat, during the formalin test, on licking time. A two-phase response was observed after injecting formalin, where the first phase (acute phase) lasted for up to 5 min and the secondary phase (chronic phase) occurred 20–40 min following formalin injection. Bilateral intra-BLA administration of memantine at both doses, 5 min prior to injecting formalin, inhibited the effect of formalin on the licking time in the acute phase. However, the licking time in the animals receiving intra-BLA memantine at a dose of 5 μg/rat was higher in the chronic phase than in the animals receiving saline and memantine at a dose of 1 μg/rat. The data are represented as the mean±SEM, for eight rats, $*P < 0.05$, $**P < 0.01$ compared to the control group. $\dagger P < 0.05$, $\dagger\dagger P < 0.01$, compared to the vehicle group.

the inflammation (foot volume) caused by formalin injections into the paw of the right hind limb of the animals. This inflammatory effect was much higher at a dose of 5 μg/rat than at 1 μg/rat of memantine. The increase in foot volumes were 0.23±0.1, 0.19±0.1, 0.32±0.1, and 0.35±0.1 mm^3 in the control, vehicle, 1 μg/rat memantine, and 5 μg/rat memantine groups, respectively (Fig. 3).

Discussion

In this study we investigated whether the pharmacological inactivation of the NMDA glutamate receptors in the BLA could modulate inflammation and the emotional effects of acute and/or chronic pain, using the formalin test. On the other hand, this study also tested the hypothesis that the pain-related activity of the BLA contributes to the emotional-affective and inflammatory aspects of pain. The licking time and foot volume were used as indicators of inflammation and emotional effects of pain. In our experiments, intra-BLA injections of memantine, the antagonist of NMDA glutamate receptors, altered the behavioral response, indicated by the licking time, in a dose-dependent manner, in formalin-induced pain. In the acute phase, memantine, at both doses reduced the effect of formalin on the licking time. However, intra-BLA microinjection of memantine at a higher dose (5 μg/rat) increased the licking time in the chronic phase more effectively than at the lower dose (1 μg/rat). Therefore, according to the results of the formalin test, it seems that the NMDA glutamate receptors have a pivotal role in the first phase of pain. Also, the intra-BLA administration of memantine at doses of 1 and 5 μg/rat, increased the inflammation during the formalin test in a dose-dependent manner.

The amygdala is considered a neural region for the interactions between pain and emotion (Neugebauer et al., 2004). We observed abnormal behavioral responses, indicated by the licking time, following treatment with NMDA glutamate receptor antagonists, which demonstrated that these receptors may be involved in the emotive behavioral responses to pain in the present study.

Several studies showed that decreasing the activity of the amygdala by inducing lesions or by pharmacological intervention suppresses pain-related behaviors in different pain models (Palazzo et al., 2008; Ren et al., 2013). It is well documented that increasing the activity of the amygdala exogenously can exacerbate or generate pain responses under normal conditions in the absence of any tissue damages (Han et al., 2010; Bahari et al., 2014; Bahari et al., 2015).

Studies revealed that the pain-related elevation of excitatory transmission and outputs from the amygdala can develop, because the suppressive control mechanisms are damaged. Feed-forward suppression of the central nucleus of the amygdala neurons involves the glutamatergic projections from the BLA and the medial prefrontal cortex, to a cluster of GABAergic neurons in the intercalated cell masses. The

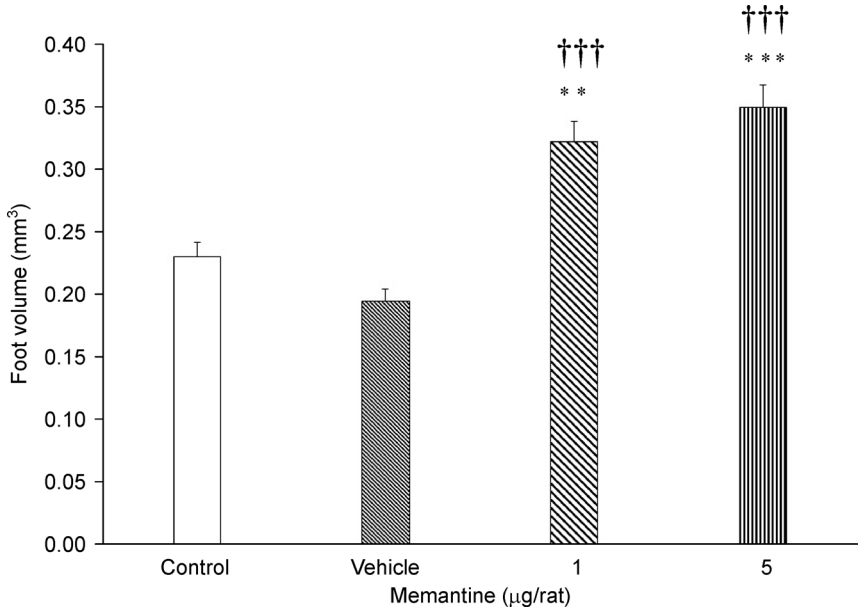

Figure 3 Effects of injecting the NMDA glutamate receptor antagonist, memantine, into the BLA on inflammation. The intra-BLA administration of memantine, at doses of 1 and 5 μg/rat, increased the volume of the foot (foot volume), caused by injecting formalin into the paw of the right hind limb. The data are represented as the mean±SEM, for eight rats, $^{**}p < 0.01$, $^{***}p < 0.001$ compared to the control group. $\dagger\dagger\dagger p < 0.001$ compared to the vehicle group.

reduced activation of this inhibitory gating mechanism in pain allows the development of glutamate and neuropeptide, which drives synaptic plasticity in the central nucleus of the amygdala (Ren et al., 2013). One of the mechanisms behind this damaged suppression is the loss of cortical output, resulting from BLA hyperactivity that leads to abnormally increased feed-forward inhibition of the principal cells in the medial prefrontal cortex (Ji and Neugebauer, 2010; Ji and Neugebauer, 2011). The abnormal persistence of emotional-affective states in pain occurs due to the damage to engage cortically-driven intercalated cell masses, which mediate the inhibitory control of the processing activities of the amygdala (Dalley et al., 2011; Apkarian et al., 2013). Neugebauer and coworkers (2009) showed that the output from the amygdala is elevated due to neuroplasticity in the BLA and the central nucleus of the amygdala, which has emerged as an important contributor to emotional-affective behaviors in animal pain models.

Electrophysiological and behavioral studies suggest that the NMDA receptors are more important for the induction rather than the maintenance of inflammation, in models of inflammatory pain. For example, Ansah and coworkers (2010) showed that the bilateral intra-CeA injection of an NMDA receptor antagonist, MK-801, inhibited nocifensive (hind limb withdrawal reflex) and affective (place avoidance test) behaviors in the spared nerve injury model of neuropathic pain. Also, Li and Neugebauer (2004) demonstrated using the arthritis pain model, that activation of NMDA and non-NMDA receptors are necessary for generating hyperactivity in the central nucleus of the neurons of the amygdala.

Studies have shown that glutamate activates GABAergic transmission onto pyramidal cells via non-NMDA receptors. Di-synaptic feed-forward inhibition is found to occur in many regions of the brain and involves the activation of inhibitory interneurons and their target cells by the same excitatory input (Silberberg and Markram, 2007; Ferrante et al., 2009). Ren and coworkers (2007) showed that the ionotropic glutamate receptors mediate the excitation of the nerve endings of inhibitory interneurons, and cause subsequent synaptic inhibition of the nearby pyramidal cells. Such mechanisms may have contributed to the results of the present study. On the other hand, a high dose of memantine may have inhibited the NMDA receptors on the GABAergic neurons, which reduced the inhibitory tone in the BLA and consequently increased the emotional state in response to the formalin test. According to our results, it seems that the NMDA glutamate receptors in the BLA could have more prominent roles in chronic pain than in the acute phase of pain induced by formalin in male Wistar rats.

Conclusion

Our results confirm and extend the previous findings, which demonstrated that NMDA glutamate receptors are involved in the chronic and acute phases of pain. We have also shown that these receptors could have anti-inflammatory effects. Additionally, the results showed that the NMDA glutamate receptors in the BLA have a prominent role in the chronic phase, rather than in the acute phase of pain.

Acknowledgements

This study was supported by the Neuroscience Sciences Research Center at Baqiyatallah University of Medical Sciences, Tehran, Iran.

Compliance with ethics guidelines

The authors declare that they have no conflicts of interest.

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