Pharmacology, Biochemistry and Behavior 143 (2016) 57–64

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Additive effect of BLA $GABA_A$ receptor mechanism and (+)-MK-801 on memory retention deficit, an isobologram analysis

Mitra Khakpoor [a], Mohammad Nasehi [b,*], Akbar Vahdati [a], Seyed-Ebrahim Hoseyni [a], Mohammad-Reza Zarrindast [b,c,d,e,f,g,**]

[a] Department of Biology, Shiraz Branch, Islamic Azad University, Shiraz, Iran
[b] Cognitive and Neuroscience Research Center, CNRC, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran
[c] Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[d] Iranian National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran
[e] School of Cognitive Sciences, Institute for Research in Fundamental Sciences (IPM), Tehran, Iran
[f] Substance Abuse and Dependence Research Center, University of School Welfare and Rehabilitation Sciences, Tehran, Iran
[g] Medical Genomics Research Center, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran

ARTICLE INFO

Article history:
Received 11 September 2015
Received in revised form 2 February 2016
Accepted 3 February 2016
Available online 4 February 2016

Keywords:
(+)-MK-801
Muscimol
Bicuculline
BLA
Step-through

ABSTRACT

There is a near correlation between N-methyl-D-aspartate (NMDA) and γ-aminobutyric acid (GABA) receptors in the modulation of learning and memory in the basolateral amygdala (BLA). In this study, we investigated the involvement of $GABA_A$ receptors in the BLA in amnesia induced by (+)-MK-801, a noncompetitive antagonist of NMDA receptors, in male Wistar rats. After guide cannulae were bilaterally placed in the BLA, animals were trained in a step-through type passive avoidance task and then tested 24 h after training to measure memory retrieval and locomotor activity. Post-training intra-BLA microinjection of (+)-MK-801 (0.5 μg/rat) and $GABA_A$ receptor agonists (muscimol at doses 0.05 and 0.1 μg/rat) or antagonist (bicuculline at doses 0.05 and 0.1 μg/rat) decreased step-through latency during retrieval but did not alter locomotor activity. Results also showed that a subthreshold dose of muscimol (0.025 μg/rat) potentiated impairment induced by (+)-MK-801, whereas bicuculline (0.025 μg/rat) restored it. Furthermore, the highest dose of muscimol (0.5 μg/rat) increased locomotor activity induced by (+)-MK-801. Isobologram analysis showed that there was an additive but not synergistic effect between muscimol and (+)-MK-801 on memory retention deficits in the BLA. In conclusion, muscimol and bicuculline decreased retention of memory formation in the BLA, and $GABA_A$ receptors in the BLA may be involved in the additive effect on (+)-MK-801-induced memory retention deficits.

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1. Introduction

Glutamate is the main excitatory neurotransmitter in the brain and is associated with two types of receptors: N-methyl-D-aspartate (NMDA) non-NMDA (e.g., AMPA and kainate) ionotropic receptors and G-protein-coupled metabotropic receptors (Nasehi et al., 2015a; Zarrindast et al., 2012). NMDA receptors are an important mediator of synaptic plasticity involved in fast excitatory synaptic transmission underlying neurobiological processes, particularly emotional activities of learning and memory (Barkus et al., 2010; Riaza Bermudo-Soriano et al., 2012). Calcium flow via NMDA receptors can activate protein kinases, phosphatases, and relevant signaling enzymes that regulate several cellular mechanisms, such as ion channel transmission, cytoskeletal activity, and gene expression (Garner et al., 2000; Kennedy, 2000). These effects can regulate mechanisms related to learning and memory, neuronal survival, and diverse development in the adult mammalian central nervous system (CNS) (Elgersma and Silva, 1999).

Abundant evidence indicates that NMDA receptors in the amygdala play a critical role in learning and memory (Hegoburu et al., 2014; Schmidt et al., 2015). The amygdaloid complex is a heterogeneous structure in the mid temporal lobe consisting of several different cortical areas and nuclei (Pitkanen et al., 1997), including the central amygdala (CeA), basolateral amygdala (BLA), basomedial amygdala (BMA), and medial amygdaloid (MeA) nuclei (LeDoux, 1992). These areas as well as other brain regions, are connected via specific pathways (Pitkanen et al., 1997). The amygdaloid structures, particularly the BLA, play a critical role in learning and memory processing mechanisms (Chegini et al., 2014; Mohammadi et al., 2015). Memories are not always equivalent; for example, recall tends to be better with feelings of fear, rage, or satisfaction (LeDoux, 1992). The amygdala, particularly the BLA, like many other components of the limbic system, plays a key role in emotional and motivational memory and learning (LeDoux, 2000; McDonald, 2003).

* Corresponding authors.
** Correspondence to: M.R. Zarrindast, Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
E-mail addresses: Nasehi@iricss.org (M. Nasehi), zarinmr@ams.ac.ir (M.-R. Zarrindast).

http://dx.doi.org/10.1016/j.pbb.2016.02.001
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Much evidence indicates that memory consolidation occurs within hours (Cammarota et al., 2008; McGaugh, 2000), and others have demonstrated that consolidated memories can remain for many days (Medina et al., 2008), months, or even years as long-term memory (Medina et al., 2008). The BLA can impact synaptic plasticity, which facilitates consolidation (Johnson et al., 1996). Emotional arousal induces memory consolidation via the BLA (Paz et al., 2006; Pelletier et al., 2005). According to most accounts, the BLA plays a key role in the formation of inhibitory avoidance memory (Gruart et al., 2006; Izquierdo et al., 2006). Synchronous activation of inputs into the BLA induces long-term potentiation that leads to glutamate release. Afterward, NMDA receptors are activated in postsynaptic neurons, followed by calcium entry which initiates a signal transduction cascade associated with the activation of long-term potentiation (Rodrigues et al., 2001). Previous studies have shown that post-training injection of NMDA receptors antagonists into the BLA of animal models causes amnesia (Izquierdo et al., 1992; Kim and McGaugh, 1992).

Notably, 50%–60% of all neurons in the brain are glutamatergic, and the residual 40%–50% are GABAergic (Storm-Mathisen and Iversen, 1979; Winfield et al., 1981); <10% of neurons release other monoamines, neuropeptides, and/or neuroendocrine neuromodulators (Altamura et al., 1993; Yildiz-Yesiloglu and Ankerst, 2006). Appropriate functioning of the CNS is dependent on the physiological balance of excitatory/inhibitory signals (Naseri et al., 2014; Zarrabian et al., 2016). The BLA is the principal input nucleus of the amygdala and includes two important types of neurons (Woodruff et al., 2006): glutamatergic neurons (80%) (Woodruff et al., 2006) with multipolar dendritic trees covered with spines and axons which provide parallels to neighboring BLA cells, amygdaloid nuclei, or other regions of the brain (McDonald, 1992) and GABAergic interneurons (20%) with aspiny to thin spinose dendrites and short axons (McDonald, 1992).

The GABAergic system plays a conclusive role in the regulation of many cognitive and noncognitive behaviors, such as memory and anxiety (Naseri et al., 2014; Yousefi et al., 2013). GABA binds to three kinds of receptors: ionotropic $GABA_A$ and $GABA_C$ receptors and metabotropic $GABA_B$ receptors (Olsen and Sieghart, 2009). $GABA_A$ receptors show effective inhibition through fast-acting, ligand-gated chloride channels (Olsen and Sieghart, 2009). It has been reported that the activation of NMDA receptor complexes regulates the expression of GABA receptors (Harris et al., 1994). It showed that GABA vesicle capacity is in kinetic balance with terminal glutamate condensation (Mathews and Diamond, 2003). Glutamate in GABAergic neurons has two origins. First, glutamate transporters (excitatory amino acid carrier 1) in the presynaptic terminals of GABAergic neurons allow glutamate entry into these interneurons (Kanai and Hediger, 1992; Nakayama et al., 1996). Second, glutamate enters astrocytes via astrocyte-specific glutamate transporter-1 and is converted to glutamine by glutamine synthases and then released from astrocytes (Arriza et al., 1994; Pines et al., 1992). In both GABA and glutamatergic neurons, glutamine is converted to glutamate by phosphate-activated glutamine dehydrogenase after transferred into these neurons. In GABAergic neurons, glutamate decarboxylase converts glutamate into GABA (Kim et al., 2015; Liang et al., 2006). Considering this evidence, the aim of the present study was to investigate the possible involvement of BLA $GABA_A$ receptors in the amnestic-like effects of (+)-MK-801 (NMDA receptor antagonist) in the step-through passive avoidance task.

2. Methods

2.1. Subjects

184 male Wistar rats (Institute of Cognitive Science, Tehran, Iran) weighing 240–270 g and aging 4 months at the time of surgery were housed four per in plexiglas cages, under a 12 h light:12 h dark cycle (lights on 07:00 h) and controlled temperature (23 ± 1 °C). They had free access to food and water and were allowed to adapt to the laboratory conditions for at least 1 week prior to surgery. Animals were handled approximately 3 min each day prior to behavioral testing and all experiments were done during the light phase between 9:00 and 14:00 h and each animal was tasted once only. Eight animals were used in each group of experiments. All protocols in this study were performed in agreement with the guide for the Care and Use of Laboratory Animals as adopted by the Ethics Committee of Faculty of Science, Tehran University (357: November 2000).

2.2. Drugs

The drugs used in the study were (+)-MK801 (NMDA receptor antagonist; Sigma, Poole, Dorset, UK), muscimol (agonist of $GABA_A$ receptor) (Tocris, Bristol, UK) and bicuculline (antagonist of $GABA_A$ receptor) (Tocris, Bristol, UK). (+)-MK801 and muscimol were dissolved in the sterile 0.9% saline; bicuculline was dissolved in a drop of glacial acetic acid and made up to volume of 5 ml with sterile 0.9% saline (as vehicle). All drugs were injected intra BLA in a volume of 0.6 μl (3 μl/site) (Chegini et al., 2014; Mohammadi et al., 2015).

2.3. Surgery and microinjections

The animals were anesthetized with intraperitoneal injection of a solution containing ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg) and then placed in a stereotaxic frame (Stoelting Co, Illinois, USA) with flat-skull position. A midline incision was made in the skin of the skull, and then the underlying periosteum was retracted. Two 22-gauge stainless steel guide cannulae were implanted (bilaterally) 2 mm above the BLA region according to according to the atlas of Paxinos and Watson (Paxinos and Watson, 2007). Stereotaxic coordinates for the BLA region were anteroposterior (AP) = −2.2 mm from bregma, mediolateral (ML) ± 5.1 from the sagital suture and Dorsoventral (DV) = −8.4 mm from the skull surface. The cannulae were secured to the bone with dental acrylic cement. Stainless steel stylets (27 gauge) were implanted in the guide cannulas in order to prevent clogging when drug was injected into BLA. All animals were allowed about 5–7 days recovery period from surgery and from the effect of the anesthetic agents (Valizadegan et al., 2013; Zarrindast et al., 2011a).

For drug injection, the animals were gently handled; the stylets were removed from the guide cannulae and replaced substituted with dental 27-gauge injection needles (2 mm below the tip of the guide cannula). The needle was linked to a 1 μl Hamilton microsyringes by means of polyethylene tube and the injection were performed by hand. The forward motion of a small air bubble within the polyethylene tubing interposed between the superior end of the needle and the microsyringe was taken as a proof for the drug flow. Bilateral intra-BLA microinjections of drugs were done by 0.3 μl solution on each site over a 60-s period. Drugs were injected immediately after training (Ahmadi et al., 2013; Zarrindast et al., 2012).

2.4. Inhibitory avoidance task

Rats were trained and tested in a step-through type passive avoidance apparatus which consisted of two compartments, one light (white opaque resin, 20 cm × 20 cm × 30 cm) and the other dark (black opaque resin, 20 cm × 20 cm × 30 cm). In the middle of a dividing wall, a guillotine door (7.9 cm2) could be lifted manually. The floor of the light side of the compartment was made of plastic. The floor of the dark compartment was made of stainless steel rods (2.5 mm in diameter) separated by a distance of 1 cm (distance between the centers of grids) on the floor of the dark compartment to produce foot shock. Intermittent electric shocks (50 Hz, 3 s, and 1 mA intensity) were delivered to the grid floor of the dark compartment by an isolated stimulator.

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