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Modulation of muscimol state-dependent memory by α_2-adrenoceptors of the dorsal hippocampal area

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ABSTRACT

In the present study, the effects of bilateral intra-dorsal hippocampal (intra-CA1) injections of α_2-adrenoceptor agonist and antagonist, on muscimol state-dependent memory were examined in mice. A single-trial step-down passive avoidance task was used for the assessment of memory retention in adult male NMRI mice. Administration of muscimol (0.1 μg/mouse, intra-CA1) 15 min before training or testing induced impairment of memory retention. Injection of the same dose of the drug 15 min before testing restored memory retention impaired under pre-training muscimol influence. Pre-test intra-CA1 administration of the α_2-adrenoceptor agonist clonidine (0.5 and 1 μg/mouse) impaired memory retention, although the low dose of the drug (0.25 μg/mouse) did not affect memory retention. Pre-test intra-CA1 administration of the α_2-adrenoceptor antagonist yohimbine (1 and 2 μg/mouse) improved memory retention, although the low dose of the drug (0.5 μg/mouse) did not affect memory retention. In other series of experiments, pre-test co-administration of certain doses of clonidine (0.125 and 0.25 μg/mouse, intra-CA1), doses which were ineffective when given alone, and muscimol (0.1 μg/mouse, intra-CA1) significantly inhibited muscimol state-dependent memory. Pre-test intra-CA1 administration of certain doses of yohimbine (0.25 and 0.5 μg/mouse), doses which were ineffective when given alone, improved pre-training muscimol (0.1 μg/mouse)-induced retrieval impairment. Moreover, pre-test co-administration of yohimbine (0.25 and 0.5 μg/mouse, intra-CA1) and muscimol (0.025 μg/mouse, intra-CA1), an ineffective dose, significantly restored the retrieval and induced muscimol state-dependent memory. It may be concluded that the α_2-adrenoceptors of the dorsal hippocampal area play an important role in muscimol state-dependent memory.

1. Introduction

α_2-adrenoceptors in the central nervous system are involved in the modulation of memory process (Galeotti et al., 2004a, b; Mondaca et al., 2004; Ji et al., 2008).

These receptors are widely distributed in the brain, and is localized both pre- and postsynaptically, with high densities in the cortex, on locus coeruleus dendrites and in area CA1 of the hippocampus (Verhage et al., 1992; Nicholas et al., 1996; McDonald et al., 1997; Boehm, 1999; Galeotti et al., 2004a).

Many clinical and experimental studies have shown that systemic administration of α_2-adrenoceptor agonists impairs memory, while their antagonists facilitate memory storage and retrieval in variety of tasks (Haapalinna et al., 1998; Riekkinen et al., 1999; Hall et al., 2001; Chopin et al., 2002; Galeotti et al., 2004a, b; Mondaca et al., 2004).

γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system and plays a controlling role on the balance of excitability and inhibitory states in the cortex, hippocampus and the interneurons and is involved in information processing in the hippocampus (Paulsen and Moser, 1998; Vargas-Caballero et al., 2010).

It is a well known fact that administration of $GABA_A$ receptor agonists or antagonists impairs or improves memory storage and retrieval in inhibitory avoidance tasks respectively (Castellano and McGaugh, 1990; Farr et al., 2000; Chapouthier, 2004; Amaral et al., 2007; Jafari-Sabet, 2011).

GABA exerts its action by binding to specific membrane receptors that are divided into two major groups: ionotropic $GABA_A$/$GABA_C$ receptors and metabotropic $GABA_B$ receptors (Bormann, 2000; Semyanov and Kullmann, 2002; Emson, 2007; Olsen and Sieghart, 2009).

Our previous studies have shown that pre-training intra-dorsal hippocampal (intra-CA1) administration of a $GABA_A$ receptor agonist, muscimol induced memory impairment which was restored when the same dose of the drug was administered 24 h later in a pre-test session (Jafari-Sabet and Jannat-Dastjerdi, 2009; Jafari-Sabet, 2011). Thus the retrieval of an event from memory

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may require that the organism be in a state that is similar to that in which the event was initially acquired. This phenomenon has been named state-dependent learning (Izquierdo, 1980; Bruins Slot and Colpaert, 1999; Jafari-Sabet et al., 2005; Zarrindast et al., 2006; Jafari-Sabet, 2011).

One of the most well-known and important physiological actions of α_2-adrenoceptor activation are modulation the release of other neurotransmitters in other areas of the brain (Zhang and Ordway, 2003; Alachkar et al., 2006).

Extensive evidence indicates that α_2-adrenoceptors activation increases the basal release of GABA in rat hippocampus, cerebral cortex and striatum (Pittaluga and Raiteri, 1987; Maura et al., 1988; Ciranna et al., 2000; Zhang and Ordway, 2003; Alachkar et al., 2006).

Several experimental studies in animals and transgenic approaches suggested that the hippocampal formation plays a crucial role in various types of memory including inhibitory avoidance (Lorenzini et al., 1996; Moser and Moser, 1998; Minichiello et al., 1999; Zola and Squire, 2001; Jafari-Sabet, 2006a; Jafari-Sabet and Jannat-Dastjerdi, 2009). It is well known that the hippocampus receives information from the entorhinal cortex and is connected through it to the amygdale and other cortical areas. Some of these areas have also been involved in memory processing (Izquierdo and McGaugh, 2000; Szapiro et al., 2002; Jafari-Sabet, 2006b; Ferry and McGaugh, 2008).

One-trial step-down inhibitory ('passive') avoidance in rodents, has long been a favorite model for biochemical and pharmacological studies of memory (Izquierdo et al., 2006) and induces long-term potentiation (LTP) in CA1 region of the hippocampus (Bliss and Collingridge, 1993; Malenka, 2003; Whitlock and Heynen, 2006).

In this one-trial learning task, animals are placed on a platform and receive a footshock after stepping down from the platform to a grid. When the animals are tested, they are exposed to the training apparatus, but no footshock is administered, which is in fact the method of choice for initiating memory extinction. Animals learn to remain longer on the platform than they do on the training session (Szapiro et al., 2002).

Since the role of CA1 α_2-adrenoceptors on muscimol state-dependent memory has not been shown previously, the aim of the present study was to investigate the effects of bilateral intradorsal hippocampal (intra-CA1) injections of α_2-adrenoceptor agonist and antagonist on muscimol induced state-dependent memory retrieval in a passive avoidance task in mice.

2. Materials and methods

2.1. Animals

Male albino NMRI mice (Razi Institute, Iran), weighing 25–35 g at the time of the surgery were used. The animals were kept in an animal house with a 12-h light/12-h dark cycle and controlled temperature (22 ± 2 °C). Food and water were available ad libitum. Animals were housed in groups of 10 in Plexiglas animal cages. Each animal was used once only. Ten animals were used in each group. Training and testing were done during the light phase of the cycle. All procedures were carried out in accordance with institutional guidelines for animal care and use.

2.2. Surgical and infusion procedures

Mice were anesthetized with intraperitoneal injection of ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg) and placed in a stereotaxic apparatus. The skin was incised and the skull was cleaned. Two 23-gauge guide cannulae were placed (bilaterally) 1 mm above the intended site of injection according to the atlas of Paxinos and Franklin (2001). Stereotaxic coordinates for the CA1 regions of the dorsal hippocampi were AP: −2 mm from bregma, L: ±1.6 from the sagittal suture and V: −1.5 mm from the skull surface. The cannulae were secured to anchor jewelers' screws with dental acrylic. Stainless steel stylets (30-gauge) were inserted into the guide cannulae to keep them free of debris. All animals were allowed 1 week to recover from surgery and clear anesthetic.

For drug infusion, the animals were gently restrained by hand; the stylets were removed from the guide cannulae and replaced by 30-gauge injection needles (1 mm below the tip of the guide cannulae). The injector cannula was attached to a polyethylene tube fitted to a 1-μl Hamilton syringe. The injection solutions were administered in a total volume of 1 μl/mouse (0.5 μl in each side, intra-CA1) over a 60 s period. Injection needles were left in place for an additional 60 s to facilitate the diffusion of the drugs.

2.3. Passive avoidance apparatus

Animals were submitted to the behavioral procedure 7 days after surgery. The apparatus was a (30 cm × 30 cm × 40 cm high) wooden box the floor of which consisted of parallel stainless steel bars (0.3 cm diameter spaced 1 cm apart). A wooden platform (4 cm × 4 cm × 4 cm) was placed on the center of the grid floor. In the training session the animals were placed on the platform and their latency to step down on the grid with all four paws was measured. Immediately after stepping down on the grid, animals received electric shocks (1 Hz, 0.5 s, 45 V DC) continuously for 15 s. The shocks were delivered to the grid floor by an isolated (Harvard Stimulator 6002, England) stimulator. If any animal stayed on the platform more than 20 s or stepped up to the platform before the end of 15 s of electric shocks, it was omitted from the experiments. Retention test session was carried out 24 h after training and was procedurally identical to training, except that no shock was delivered to the animals. Step-down latency was used as a measure of memory retention. An upper cut-off time of 300 s was set (Jafari-Sabet et al., 2005; Jafari-Sabet and Jannat-Dastjerdi, 2009; Jafari-Sabet, 2011). The retention test was carried out between 8:00 a.m. and 3:00 p.m.

2.4. Drugs

The drugs used in the present study were muscimol (Tocris Cookson Ltd, UK), clonidine (Tolid Daru Company Tehran, Iran), yohimbine (Nuova-Linnea, Switzerland). All drugs were dissolved in sterile 0.9% saline and were injected into the dorsal hippocampal CA1 regions (intra-CA1) 1 μl/mouse. Control animals received saline.

2.5. Experimental design

Ten animals were used in each experimental group. In experiments where the animals received one or two injections, the control groups also received one or two saline injections.

2.5.1. Experiment 1

This experiment examined muscimol state-dependent memory. In this experiment, four groups of animals were used. Two groups of animals received saline (1 μl/mouse, intra-CA1) 15 min before training and were tested 15 min after pre-test saline (1 μl/mouse, intra-CA1) or muscimol (0.1 μg/mouse, intra-CA1) injection. Two other groups of animals in this experiment were trained 15 min after pre-training muscimol (0.1 μg/mouse, intra-CA1) and were tested 24 h later, 15 min after pre-test saline (1 μl/mouse, intra-CA1) or muscimol (0.1 μg/mouse, intra-CA1) injection (Fig. 2).