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BRAIN RESEARCH

Research Report

Role of naloxone as an exogenous opioid receptor antagonist in spatial learning and memory of female rats during the estrous cycle

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ARTICLE INFO

Article history:
Accepted 13 December 2008
Available online 25 December 2008

Keywords:
Naloxone
Estrous cycle
Learning and memory
Rat

ABSTRACT

Opioid neurotransmitters play a modulatory role in learning and memory processing. Their levels fluctuate throughout the reproductive cycle. The purpose of this research described herein was to study the effects of an exogenous opioid receptor antagonist, naloxone, on spatial learning and memory during the estrous cycle in female rats. Proestrus and estrus female rats were trained in a Y-maze. After a 4-hour delay, spatial recognition memory was assessed. The rats were administered naloxone (2 mg/kg) or saline before training, after training or before the retention test. The administration of naloxone to the estrus and proestrus rats before and after training had no significant effects on their preference for the novel arm of the Y-maze. Injection of naloxone to estrus rats before the retention test enhanced their preference for the novel arm of the Y-maze, whereas, in the case of the proestrus rats, naloxone decreased their preference for the novel arm. Therefore, it can be concluded that naloxone enhances the retrieval of spatial recognition memory in the estrus phase rat, but that it impairs retrieval in the proestrus phase rat. This finding indicates that there is an interaction between ovarian hormone levels and opioids in cognitive function, so that naloxone prevents the facilitatory role of ovarian hormones in the retrieval of spatial memory.

1. Introduction

Learning and memory are basic mental processes having several stages, namely acquisition, consolidation and retrieval (Okano et al., 2000; Abel and Matthew, 2001; Daumas et al., 2005; De Oliveira Alvares et al., 2008). Several lines of evidence have shown that learning and memory abilities change during the reproductive cycle. The reproductive cycle is called the estrous cycle in the rat, consists of proestrus, estrus, diestrus and metestrus phases, and lasts for 4 days. Each estrous phase takes 1 day (Marcondes et al., 2002). During the reproductive cycle, the proestrus phase is characterized by high estrogen and progestin levels whereas the estrus phase is characterized by low hormone levels (Marcondes et al., 2002). Most previous studies indicated that, in the proestrus phase, the animal had significantly better performance in object placement tasks (Frye et al., 2007; Walf et al., 2006), inhibitory avoidance memory (Rhodes and Frye, 2004), and spatial memory in the water maze (Frick and Berger-Sweeney, 2001), compared to the diestrus/estrus, diestrus and estrus phase animals, respec-

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doi:10.1016/j.brainres.2008.12.043

tively. On the other hand, there are other reports that have indicated that spatial memory is impaired in a water maze during the proestrus phases (Frye and Sturgis, 1995; Warren and Juraska, 1997). In addition, women's cognitive performance fluctuates across phases of the menstrual cycle. For example, high estrogen levels during the menstrual cycle are associated with improved verbal task performance (Hampson, 1990a,b; Rosenberg and Park, 2002), word recall performance (Craig et al., 2008), spatial memory performance (Silverman and Phillips, 1993; Hampson, 1995; Phillips and Silverman, 1997; Hausmann et al., 2000; Hampson et al., 2005) and implicit memory (Maki et al., 2002). Therefore, it is believed that learning and memory processes may be influenced by fluctuations in ovarian hormones.

The effects of estrogen on regions of the brain involved in memory have been well studied. Immediately post-training (but not one, two, or 3-hour post-training), subcutaneous administration of estradiol benzoate (10 μg/0.2 cc) to ovariectomized rats (low ovarian hormones create a condition like the estrus phase) increased memory with a 4-hour or 24-hour intertrial delay (Rhodes and Frye, 2004). The effect was not found with progesterone (500 μg/0.2 cc). Chronic estrogen replacement (minipellets containing 0.18 mg of 17b-estradiol delivered a continuous supply of estrogen for 60 days) in the long-term ovariectomized (4, 8 and 19 months) female mice improves performance in the position discrimination task in the T-maze and reference memory (but not working memory) on the radial arm maze (Heikkinen et al., 2004). Chronic estradiol replacement (subcutaneous implant of capsules containing 25% 17β-estradiol) positively affects working memory in middle-aged rats when initiated immediately after (but not 5 months after) ovariectomy (Daniel et al., 2006). The data from tasks involving hippocampal function (i.e., water and radial arm maze and object recognition task) suggest that the hippocampus is a target of estradiol in enhancing cognitive performance (Walf et al., 2006). Intrahippocampal infusions of 0.5 μM 17β-estradiol 3-sulfate sodium into the ovariectomized rats 48, 24 or 2 h before training enhanced place learning in the Y-maze (Zurkovsky et al., 2007).

In contrast to estrogen, much less is known about the effects of progesterone on hippocampal physiology and memory. Mice were trained in spontaneous alternation, object recognition, object placement, water maze, or fear conditioning tasks, and were subcutaneously injected with progesterone (10 mg/kg) 1 h before training or immediately post-training. They were then tested 1, 4, or 24 h later. Progesterone treatment to ovariectomized mice can improve cognitive performance across these tasks (Frye and Walf, 2008). Acute post-training intraperitoneal administration of progesterone (5, 10, or 20 mg/kg) into the ovariectomized mice dose dependently enhances hippocampal-dependent memory in the water maze and object recognition task (Lewis et al., 2008; Harburger et al., 2008). Ovariectomized rats were administered with progesterone (4 mg/kg, subcutaneously) immediately after training in the object placement task, and were tested 4 h later. They performed significantly better when tested 4 h later than did the control group (Frye et al., 2007).

In addition to the ovarian hormones, a number of neurotransmitter systems such as cholinergic, glutamatergic, GABAergic, serotonergic, histaminergic and opioid peptides are involved in the formation and retrieval of memory traces (Brown et al., 1988; Paulsen and Moser, 1998; Buhot et al., 2000; Bacciottini et al., 2001; White and Ruske, 2002, Power et al., 2003; Kilgard, 2003; Harvey, 2003; Miranda et al., 2003; Myhrer, 2003; Simonyi et al., 2005; Dringenberg and Kuo, 2006). It is known that opioid neuronal systems play an important role during the acquisition, consolidation and retrieval of the learning and memory processes (Izquierdo et al., 1980; Introini-Collison and Baratti, 1986; Ukai et al., 1993a,b, 1995, 1997; Ilyutchenok and Dubrovina, 1995; Dubrovina and Ilyutchenok, 1996; Hiramatsu and Kameyama, 1998; Sher, 1998; Trujillo, 2000; Zarrindast et al., 2002; Jang et al., 2003; Yang et al., 2003; Meilandt et al., 2004; Kamei et al., 2005; Cole and McNally, 2007). For example, two endogenous, potent and selective μ-opioid receptor agonists named endomorphin-1 and endomorphin-2 impair passive avoidance learning in mice (Ukai et al., 2001). In mice, immediate post-training administration of naloxone (an opiate receptor antagonist) causes improvement in retention test results in the following week (Flood et al., 1987). In male animals, it has been shown that the dentate gyrus of the hippocampus contains two major opioid peptides, enkephalins and dynorphins (Drake et al., 2007, McQuiston, 2007). The presence of both opioids (Olson et al., 1993) and their delta, kappa and mu receptors (Crain et al., 1986; Unterwald et al., 1991; Commons and Milner, 1996; Ding et al., 1996; Drake and Milner, 1999) in the hippocampus suggests that they could play a role in function (McLean et al., 1987; Hiller et al., 1994; Mansour et al., 1994; Arvidson et al., 1995; Simmons and Chavkin, 1996; Halasy et al., 2000), but the exact role of opioids and their receptors on learning and memory is complicated. For example, in male animals, activation of the hippocampal kappa opioid receptor impairs spatial learning (Sandin et al., 1998; Daumas et al., 2005) or plays no role (Jamot et al., 2003). The mu opioid receptor plays a positive role in learning and memory by increasing long-term potentiation (LTP) in CA3 neurons of the hippocampus (Jamot et al., 2003). On the other hand, microinjection of the endogenous mu-selective opioid peptide endomorphin-2 (but not the delta opioid receptor) into the CA3 region of the rat hippocampus significantly impairs spatial ability (Sandin et al., 2000).

Endorphin levels fluctuate during human menstrual cycles and animal estrous cycles (Wehrenberg et al., 1982; Vrbicky et al., 1982; Forman et al., 1983; Veith et al., 1984; Laatikainen et al., 1985; Martyn et al., 1987; Babu et al., 1987; Hamilton and Gallant, 1988; Chuong et al., 1989; Saad et al., 1992; Meczekalski and Warenik-Szymankiewicz, 1995; De Lourdes Figuerola et al., 1997; Ferrer et al., 1997; Roman et al., 2006) and it is thought that gonadal hormones and opioid systems interact, where estrogen can change the density of the opioid receptors in the hippocampus. For example, mu opioid receptors were increased in the hippocampus of ovariectomized rats (Piva et al., 1995). On the other hand, the mu opioid receptors in the hippocampus of the ovariectomized rat were decreased 48 h after a single subcutaneous injection of 3 μg/0.1 ml/rat estradiol benzoate (Slamberová et al., 2003), or were unchanged 48 h after a single subcutaneous injection of 10 mg of 17-b-estradiol-3-benzoate (Quiñones-Jenab et al., 1997). To our knowledge, there is no report about interaction