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Differential mechanisms of opioidergic and dopaminergic systems of the ventral hippocampus (CA_3) in anxiolytic-like behaviors induced by cholestasis in mice

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ABSTRACT

There are several studies carried out to test the effect of cholestasis on memory impairment and anxiolytic-like behaviors. Some previous studies have shown that cholestasis alters the activity of opioidergic and dopaminergic systems. The aim of the present study is however to investigate the role of mu opioid, D_1 and D_2 dopamine ventral hippocampal (CA_3) receptors upon cholestasis-induced anxiolytic-like behaviors in hole-board task. Male mice weighing 25–30 g were used. Cholestasis was induced by ligation of the main bile duct. Our data indicated that cholestasis can induce anxiolytic-like response. Furthermore, the results showed that the intra-CA_3 injection of naloxone, a mu receptor antagonist at 0.25 and 0.5 μg/mouse, SCH_{23390}, a D_1 dopamine receptor antagonist or sulpiride, as a D_2 dopamine receptor antagonist, 5 min before testing, reversed the cholestasis-induced anxiolytic-like behaviors seven days after bile duct ligation (BDL). Unlike the higher dose of SCH_{23390} (0.5 μg/mouse) which induced anxiogenic-like behaviors, other doses of the above drugs did not alter the exploratory behaviors in examined mice. Based on our findings, co-administration of the subthreshold dose of naloxone (0.125 μg/mouse), SCH_{23390} or sulpiride, and SCH_{23390} with sulpiride, neither altered exploratory behaviors in animals nor reversed the cholestasis-induced anxiolytic-like behaviors, seven days post BDL. Current results demonstrated firstly, the anxiolytic-like behaviors are evident in cholestatic mice seven days post BDL; secondly, there are plausible mechanisms governing the involvement of the CA3 opioidergic and dopaminergic systems in this phenomenon and thirdly, there seem to be no interaction between these systems.

1. Introduction

Hepatic encephalopathy is a critical liver-related disorder which may potentially alter various cognitive and non-cognitive functions. This disorder may impair learning and memory (Nasehi et al., 2013a, 2013b; Zarrindast et al., 2012), induce anxiolytic-like behaviors (Eslimi et al., 2011; Zarrindast et al., 2013), cause alterations in sleep pattern (Newton, 2008) and result in tremor (Chung et al., 2005). Evidence has suggested that these behavioral presentations are linked to the altered neurotransmission and neural communication systems which involve opioids (met-enkephalin), dopamine, serotonin, noradrenaline GABA, glutamate and acetylcholine (Cauli et al., 2006b, 2007a, 2007b). These potential changes correspond to the release of neurotransmitters, activity of synaptic cleft enzymes, and the receptors in post synaptic membrane (Cauli et al., 2009). Among these lines, cholestasis is shown to alter the activity of opioidergic (Zhang et al., 2004) and dopaminergic (Glaser et al., 2006; Zimatkin et al., 2008) systems.

Some investigations have substantiated that the opioid receptor system may play a key role in the pathophysiology of cholestasis (Gholipour et al., 2008; Jones and Bergasa, 2000). This system has three super-family of G-protein-coupled receptors including mu, delta and kappa of which, mu receptor is involved in major opioid actions, such as anxiety-related behaviors (Saxe et al., 2006; Voronina et al., 1994) and impairment of memory

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formation (Nasehi et al., 2010). In addition, accumulating evidences have suggested interactions between the opioidergic and dopaminergic systems in the modulation of anxiety-like behaviors (Rezayof et al., 2009; Tenore, 2008), memory (Zarrindast et al., 2006a, 2006b) and reward (Ma et al., 2009).

Moreover, it has been postulated that the two major dopaminergic systems known as mesolimbic and mesocortical pathways, play a key part in regulation of the anxiety-related behaviors induced by anxiogenic- or anxiolytic drugs (Ahmadi et al., 2013; Nasehi et al., 2011). Two main subfamilies of dopamine receptors including D_1-like (D_1 and D_5) and D_2-like (D_2, D_3 and D_4) have been discovered (Sealfon and Olanow, 2000).

As pointed out in our recently done studies, both opioidergic and dopaminergic systems are involved in cholestasis-induced anxiolytic-like behaviors, inasmuch as peripheral but not local injection of naloxone and dopamine D_1 or D_2 receptors antagonist reversed this phenomenon (Eslimi et al., 2011; Zarrindast et al., 2013). Given the cardinal role of the hippocampal formation in learning, memory processing and the anxiety-like behaviors (Nasehi et al., 2011, 2009) and the involvement of the ventral hippocampus in the modulation of the anxiety-like behaviors (Zarrindast et al., 2010), the aim of the present study was to investigate the possible involvement of mu opioid, D_1 and D_2 dopaminergic receptors and the interactions of the ventral hippocampal opioidergic and dopaminergic systems (CA_3) in cholestasis-induced anxiolytic-like effects.

2. Materials and methods

2.1. Ethics

All experimental procedures and methods in animal use were approved by the Research and Ethics Committee of the School of Advanced Medical Technology, Tehran University of Medical Sciences.

2.2. Animals

Male albino NMRI mice (Institute of Cognitive Science, Tehran, Iran) weighing 25–30 g upon surgery were used. Animals were kept in an animal house with a 12 h light: dark cycle (lights on at 07:00 AM) at a controlled temperature ($22 \pm 2^{\circ}C$). Animals were housed in groups of seven in Plexiglas cages where food and water were available ad libitum. A total of ten animals were used in each group and each animal was used once only. All behavioral experiments were performed during the light phase of the light: dark cycle.

2.3. Bile Duct Ligation (BDL) surgery and the induction cholestasis

There were two experimental groups, sham-operated and bile duct-ligated (BDL) mice. BDL surgery was performed under intraperitoneal anesthesia with a mixture of ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg). Following laparotomy, the common bile duct was double-ligated with silk threads and excised between the ligatures to prevent regeneration. In each sham-operated control group, the bile duct was identified, manipulated, and left in situ (Bergasa et al., 1994). Sterile 0.9% NaCl solution (1 ml/mouse) was injected intraperitoneally immediately after the surgery (to prevent the possible drop in the blood pressure due to the bloodshed in belly operation). All surgeries were performed under the aseptic condition. Immediately after operation, each animal was placed in a cage by itself to prevent wound dehiscence and then moved to its original home cage 4 h later (Rastegar et al., 2002; Zarrindast et al., 2012). Surgery-related mortality was 10.94%.

2.4. Guide cannula implantation

Mice were anesthetized using the intraperitoneal (i.p.) injections 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. The 22-gauge guide cannulae were placed (bilaterally) 1 mm above the intended injection site according to the Paxinos and Franklin atlas of rodents' brain (Paxinos and Franklin, 2001). Stereotaxic coordinates for the CA_3 regions of the ventral hippocampus were: AP -2.18 mm from the bregma; L ± 2.3 mm from the sagittal suture and V -2.1 mm from the skull surface. The cannulae were secured with dental acrylic. Stainless steel stylets (27-gauge) were inserted into the guide cannulae to keep them free from debris. All animals were allowed for one week recovery period from surgery and the effects of the anesthetic agents before being used in the experiments.

2.5. Intra-CA_3 injections

For drug infusion, animals were gently restrained in hand; the stylets were removed from the guide cannulae and replaced by 27-gauge injection needles (1 mm below the tip of the guide cannulae). Animals received a total volume of 1 μl/mouse (0.5 μl/side) of the infused drugs over 60 s. Injection needles were then left in place for an additional 60 s to facilitate diffusion.

2.6. Drugs

The following drugs were used in the experiments: ketamine and xylazine (for surgical procedure; Alfasan Chemical Co, Woerden, and Holland), naloxone hydrochloride (Tocris, UK), SCH_{23390} (Tocris, UK) and sulpiride (Sigma Chemical Co., St Louis, CA, USA). Naloxone and SCH_{23390} were dissolved in sterile 0.9% physiological saline. Sulpiride was dissolved in a minimal volume of diluted acetic acid (1 drop of 5 μl; pH 6.3), subsequently increased to a volume of 5 ml with 0.9% physiological saline and then diluted to the required volume using 0.9% NaCl solution. The drugs were injected at a volume of 0.5 μl/side into the CA_3 region (1 μl/mouse). Drug doses were selected based on pilot and previous studies (Nasehi et al., 2013a, 2011; Zarrindast et al., 2012).

2.7. Apparatus and the behavioral test

The hole-board test, as a simple method for examining the animal's response to an unfamiliar environment, was first introduced by Boissier and Simon (Boissier and Simon, 1962). This test has been used to evaluate the emotional responses, anxiety and/or stress reactions in animals (Rodriguez Echandia et al., 1987). Various behavioral outputs observed and measured in this test allow for a comprehensive description of the animal's behavior. We employed the hole-board apparatus (Borj Sanat Co, Tehran, Iran) consisting of gray Perspex panels (40 cm × 40 cm, 2.2 cm thick) with 16 equidistant floor holes, 3 cm in diameter (Vinade et al., 2003; Zarrindast et al., 2012). The board was positioned 15 cm above at a table. Animals were placed singly at the center of the board away from the observer. The numbers of head-dips were recorded by photocells arranged below the holes over a 5 min period of animal's exploration. Furthermore, the locomotor activity was measured by an observer blinded to the treatments given during the testing phase. For this purpose, the hole-board arena was divided into four equal sized squares. Locomotion was measured as the number of crossings from one square to another. Other behavioral performances such as latency to the first head-dip, rearing, grooming and defecation were manually recorded by the observer during the test period. Rearing, grooming and defecation data have not been shown in all experiments here.