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Effects of dopamine receptor agonist and antagonists on cholestasis-induced anxiolytic-like behaviors in rats

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ABSTRACT

Dysfunctions in the dopamine transmission system have been suggested to contribute to the pathogenesis of hepatic encephalopathy. In an experimental animal model, cholestasis induction through bile duct ligation may present several main pathological features of hepatic encephalopathy. Dopaminergic systems are shown to play pivotal roles in regulation of anxiety-like behaviors. The main bile duct in male Wistar rats, weighing 220–240 g, was ligated using two ligatures plus duct transection in between. Anxiety-like behaviors were measured using the elevated plus maze task. Cholestasis increased the open arm time percentage (%OAT), 13 but not 10 days after bile duct ligation, indicating an anxiolytic-like effect. Sole intraperitoneal injection of apomorphine (dopamine D_1/D_2 receptor agonist, 0.25 mg/kg), SCH23390 (dopamine D_1 receptor antagonist, 0.005, 0.01 and 0.02 mg/kg) or sulpiride (dopamine D_2 receptor antagonist, 0.125, 0.25 and 0.5 mg/kg) did not alter %OAT, open arm entries percentage (%OAE) and locomotor activity in the sham-operated rats. Meanwhile, the higher dose apomorphine (0.5 mg/kg) induced anxiolytic-like behaviors in this group. The subthreshold dose injection of SCH23390 or sulpiride, partially reversed the anxiolytic-like behaviors induced by cholestasis (13 days after bile duct ligation). On the other hand, subthreshold dose of apomorphine in cholestatic rats (10 days post bile duct ligation) induced anxiolytic-like effects which could be blocked by SCH23390 or sulpiride. The effective doses of above drugs did not alter locomotor activity, number of rearings, groomings and defections. These findings suggested that the dopaminergic system may potentially be involved in the modulation of cholestasis-induced anxiolytic-like behaviors in rats.

1. Introduction

Acute and chronic failure in liver function may give rise to cognitive and non-cognitive impairments in the brain, namely; hepatic encephalopathy (Huang et al., 2010; Magen et al., 2010; Zarrindast et al., 2012a). Cholestasis which leads to hepatic encephalopathy (Garcia-Moreno et al., 2005) is potentially associated with liver cirrhosis (Ferenci et al., 2002). The most frequently applied experimental model for induction of cholestasis is common bile duct ligation (Pi-Chieh Wang et al., 2011; Zarrindast et al., 2012a; Zhang et al., 2012). Some investigations have revealed that cholestasis decreases the anxiety-like behaviors (Eslimi et al., 2011), induces memory deficits (Cauli et al., 2009; Huang et al., 2009; Magen et al., 2010; Zarrindast et al., 2012b), tremor (Chung et al., 2005) and alters the sleep pattern (Newton, 2008). It has been made clear that cholestasis alters the activity of all classic neurotransmitter systems such as opioidergic (Roberts et al., 1987; Zhang et al., 2004) and dopaminergic (Glaser et al., 2003, 2006; Zimatkin et al., 2008).

Several studies have also indicated that the two major dopaminergic systems including mesolimbic and mesocortical are involved in anxiogenic- and anxiolytic-like responses induced by some medications or acute stress (Cabib et al., 1988; Deutch et al., 1985; Dunn, 1988; Feenstra et al., 1995; Imperato et al., 1990; Louilot et al., 1986; Nasehi et al., 2011; Puglisi-Allegra et al., 1991; Reinhard et al., 1982). Based on the biochemical and pharmacological properties, two main subfamilies of dopamine

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receptors have been described. These include dopamine D_1-like (D_1 and D_5) and dopamine D_2-like (D_2, D_3 and D_4) subfamilies (Sealfon and Olanow, 2000).

Compelling evidence have shown that cholestasis increases the systemic opioids level (Dehpour et al., 1998; Ebrahimkhani et al., 2006; Ghafourifar et al., 1997; Talaenko et al., 2005) and this phenomenon is involved in the cholestasis-induced anxiolytic-like behaviors (Eslimi et al., 2011). Given the close link between opioidergic and dopaminergic systems with regard to anxiety-like behavior regulation (Radke et al., 2011; Rezayof et al., 2009), it is possible that opioidergic systems induce anxiolytic-like behaviors through their interactions with dopaminergic systems in different brain sites. The above interaction seems to occur within mesolimbic projections. Activation of dopaminergic neurons of nucleus accumbens and ventral tegmental area, in particular, could be mediated by the opioid peptides (Bruijnzeel, 2009; Koob and Le Moal, 2008; Radke et al., 2011).

Referring to the previous studies which have indicated dopaminergic system changes in cholestatic subjects, as well as the involvement of dopaminergic systems in regulation of anxiety-like behaviors, the aim of the present study is to find out the possible involvement of dopamine D_1 and D_2 receptors in cholestasis-induced anxiolytic-like behaviors in rats.

2. Materials and methods

2.1. Animals

Male Wistar rats (bred at the institute of cognitive science, Tehran, Iran), weighing 220–240 g at the time of the surgery, were used in this study. Animals were housed in Plexiglas cages in constant temperature (22 ± 2 °C) and automatically controlled light/dark cycle (12:12 h light/dark). They had access to commercial rodent pellets and water ad libitum. Four to five animals were housed in a same cage and eight were used in each experimental group. Each rat was used once only. All experimental procedures and animal use protocols were approved by the Research and Ethics Committee of the Faculty of Science, Tehran University of Medical Sciences.

2.2. Surgical procedure

Two experimental animal groups were used: sham-operated and bile duct ligation. Bile duct ligation was performed under general anesthesia induced by an intraperitoneal injection of ketamine hydrochloride 10% (50 mg/kg) plus xylazine 2% (5 mg/kg). Briefly, the common bile duct was located through a midline abdominal incision, double ligated near the liver, and transected between ligatures. Sham-operated rats underwent the same procedure except that the bile duct was manipulated without ligation or resection (to equalize the possible stress induced by surgery in both sham- and bile duct ligation operated groups). Animals were moved to their cages 5 h post operation to prevent wound dehiscence.

2.3. Elevated plus maze

Elevated plus maze is an anxiety assessment test in rodents that is used as a screening test of all currently available models of both anxiogenic and anxiolytic agents. Elevated plus maze apparatus consisted of two open arms (50×10 cm) and two closed arms (50×10 cm) with 40-cm high walls, extending from a central platform (10×10 cm) to make the shape of a plus sign. The whole apparatus was elevated 50 cm above the floor. The test room was illuminated by two 60-W bulbs located 1.5 m above the apparatus. Animals were placed in the junction of the four arms, after which their entries/duration in each arm as well as their other behavioral patterns (i.e., rearings, head dip) were observed for 5 min. The %OAT and %OAE, reflect the standard anxiety indices. Total arm entries were measured as an index for locomotor activity. A decrease or increase in duration of stay and entries to open arms reflect anxiogenic- and anxiolytic-like behaviors, respectively.

2.4. Other behavioral analysis

Number of rearings (the rat maintains an erect posture which is usually associated with sniffing) and groomings (the rat rubs its face, ears, mouth, vibrissae and eyes with rapid circular movements of its forepaws), as well as the defecation index (the number of boil defection) were considered as the conventional indices for anxiety-like behaviors (Casarrubea et al., 2009; Eslimi et al., 2011; Kalueff et al., 2004). Rearing, grooming and defecation data were thoroughly analyzed, although not shown here. Experiments were performed by someone blinded to the responses and statistical measurements.

2.5. Drugs

The drugs used in this study were ketamine and xylazine (Alfasan Chemical Co, Woerden, Holland), apomorphine (dopamine D_1 and D_2 receptor agonist), SCH23390 (dopamine D_1 receptor antagonist, R(1)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-enzazepine hydrochloride, Tocris, UK) and sulpiride (dopamine D_2 receptor antagonist, Sigma Chemical Co., St Louis, CA, USA). All drugs were dissolved in sterile 0.9% saline just before the experiment, except for sulpiride which was dissolved in one drop glacial acetic acid and sterile 0.9% saline. Control animals received saline or vehicle (for sulpiride). All drugs were administered intraperitoneally.

2.6. Experimental protocol

Ten and 13 days post bile duct ligation, the animals' behaviors were tested in the elevated plus maze. Two groups of animals (i.e. sham-operated and bile duct ligation) groups were considered in each experiment.

2.6.1. Experiment 1: effects of SCH23390 on cholestasis-induced anxiolytic-like behaviors

Eight groups of animals were used in this experiment. The animals (sham-operated or cholestatic rats) received either intraperitoneal injection of saline (1 ml/kg) or different doses of SCH23390 (0.005, 0.01 and 0.02 mg/kg), 30 min prior to testing (13 days post bile duct ligation).

2.6.2. Experiment 2: effects of sulpiride on cholestasis-induced anxiolytic-like behaviors

Ten groups of animals were used in this experiment. Sham-operated or cholestatic rats received intraperitoneal injection of saline (1 ml/kg), vehicle (1 ml/kg) or different doses of sulpiride (0.125, 0.25 and 0.5 mg/kg), 30 min prior to testing (13 days post bile duct ligation).

2.6.3. Experiment 3: effects of apomorphine on cholestasis-induced changes in exploratory behaviors (10 days post bile duct ligation)

Six groups of animals were used in this experiment. Sham-operated and cholestatic rats either received intraperitoneal injections of saline (1 ml/kg) or apomorphine at doses of 0.25 and 0.5 mg/kg, 30 min prior to testing 10 days post bile duct ligation.