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Involvement of the nucleus accumbens shell dopaminergic system in prelimbic NMDA-induced anxiolytic-like behaviors

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ABSTRACT

Background: Nucleus accumbens (NAc) and prefrontal cortex (PFC) dopaminergic and glutamatergic systems are involved in fear/anxiety-related behaviors; meanwhile NAc dopaminergic system activity is mediated by PFC via NAc glutamatergic projections. This study has investigated the involvement of NAc shell dopaminergic system in prelimbic NMDA-induced anxiolytic-like behaviors.
Method: Elevated plus-maze apparatus was employed to test parameters of anxiety-like behaviors in male Wistar rats.
Results: Unilateral intra-prelimbic injection of NMDA (0.9 μg/μl) but not D-AP7 (NMDA receptor antagonist; 0.25, 0.5 and 1 μg/μl) induced anxiolytic-like behaviors which was blocked by D-AP7. Moreover, unilateral infusion of SCH23390 (dopamine D1 receptor antagonist; 0.25, 0.5 and 1 μg/μl) and quinpirole (dopamine D2 receptor agonist; 0.125, 0.25 and 0.5 μg/μl) into the left NAc shell, did not alter anxiety-like behaviors. However, injection of SKF38393 (dopamine D1 receptor agonist; 3 μg/μl) and sulpiride (dopamine D2 receptor antagonist; 0.4 and 0.6 μg/μl) into the left NAc shell, likewise induced anxiolytic-like behaviors which were blocked by SCH23390 (0.25 μg/μl) and SKF96365 (Ca-channel blocker; 0.125 μg/μl)/SCH23390 (0.25 μg/μl), respectively. Furthermore, infusion of the subthreshold dose of SCH23390 (0.25 μg/μl) or quinpirole (0.25 μg/μl) into the left NAc shell, reduced while did not alter intra-prelimbic NMDA-induced anxiolytic-like behaviors, respectively. In addition, intra-NAc shell administration of the subthreshold dose of SKF38393 (1 μg/μl) or sulpiride (0.2 μg/μl), potentiated the lower dose response, while decreased the higher dose intra-left prelimbic NMDA response.
Conclusion: Our results suggested a modulatory effect of the NAc shell dopaminergic system on prelimbic NMDA-induced anxiolytic-like behaviors.

1. Introduction

Several investigations have elaborated on the neurobiology of anxiety and the drugs inducing anxiety-like behaviors in different brain regions (Nasehi et al., 2011; Zarrindast et al., 2010, 2011c). Different neuronal regulatory mechanism(s) have also been involved in anxiety-related behaviors (Bergink et al., 2004). Glutamatergic and dopaminergic systems are shown to play a critical role in anxiety-like behaviors both in humans and animals (Cortese and Phan, 2005; Mathew et al., 1981; Nasehi et al., 2011; Robinson et al., 2006; Zarrindast et al., 2011c). It has been demonstrated that, up to 40% of all brain neuronal terminals have glutamatergic synaptic elements (Simon and Gorman, 2006). Likewise, several studies have indicated that dopaminergic system modulates the neuronal activities involved in fear or anxiety-like behaviors (Garpenstrand et al., 2001; Pezze and Feldon, 2004). Dopamine exerts its effects via two dopamine receptor subfamilies known as D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptors (Sealfon and Olanow, 2000).

The anxiety-like behaviors are regulated by various brain regions and neuronal pathways such as dopaminergic outputs from

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ventral tegmental area (VTA) to nucleus accumbens (da Cunha et al., 2008; Pezze and Feldon, 2004). Furthermore, VTA and NAc are shown to have close interactions with regard to anxiety-like behaviors' regulatory processes (Doherty and Gratton, 2007; Murase et al., 1993; Taber and Fibiger, 1995).

In addition, several main regions of animals' and humans' brain such as medial prefrontal cortex (MPFC), NAc, amygdale and hippocampus are clearly shown to be involved in regulation of anxiety-like behaviors (Davis, 1992; Del Arco and Mora, 2008; Hajizadeh Moghaddam et al., 2008; Rostami et al., 2006; Zarrindast et al., 2008a, 2005).

NAc in particular, is a deep-seated nucleus modulating some cognitive and non-cognitive functions such as anxiety-like behaviors (Gray, 1995; Inoue et al., 1994; Salamone et al., 1997), emotion (Davidson and Irwin, 1999), defensive behaviors (da Cunha et al., 2008), locomotion (Gargiulo, 1996; Martinez et al., 2002), depression (Shirayama and Chaki, 2006) and reward responses (Martinez et al., 2002; Salamone et al., 1997).

On the other hand, some behavioral assays have revealed that two parts of the PFC including ventral prelimbic (PL) and infralimbic (IL) regions play a critical role in the modulation of anxiety-like behaviors (Espejo, 1997; Wall et al., 2003), emotion (Del Arco and Mora, 2008; Mora and Cobo, 1990), depression (Rogers et al., 2004) and reward responses (Robbins and Everitt, 1996). The rats' brain MPFC region as well as the orbitofrontal cortex of primates possess both pyramidal neuronal systems, i.e. glutamatergic and GABAergic interneurons (Harte and O'Connor, 2005; Somogyi et al., 1998).

It has been shown that PFC extends direct and indirect interconnections to other regions of the brain such as basal forebrain and brain stem nuclei (Uylings et al., 2003). Moreover, The ventral PFC projects fibers to the dorsal and medial parts of NAc Shell regulating the activity of this site upon cognitive and non-cognitive functions (Ding et al., 2001). While PFC glutamatergic system regulates the emotional behaviors directly through the NAc (Fuller et al., 1987; Ongur and Price, 2000; Robbins, 2000; Sesack and Pickel, 1992) it exerts the same effect indirectly via innervation of amygdala, hippocampus and VTA connections (Del Arco and Mora, 2009; Forster and Blaha, 2000). Besides, there is 'feedback' circuit comprising ventral pallido-thalamo-cortical pathways relaying the NAc shell to the MPFC (Groenewegen et al., 1999). The interaction between PFC glutamatergic and NAc dopaminergic systems (both in shell and core subregions) has been shown to modulate motor and cognitive functions via different pathways (Brady and O'Donnell, 2004; Jentsch and Roth, 1999; Kelley and Throne, 1992; Murase et al., 1993; Taber and Fibiger, 1995; Wu et al., 1993).

Given the insights from earlier works, the aim of the present study was to evaluate firstly, the possible involvement of the NAc Shell dopaminergic and prelimbic glutamatergic systems in regulation of anxiety-like behaviors and secondly, the possible interaction(s) between these systems for the same, in male Wistar rats.

2. Materials and method

2.1. Subjects

Male Wistar rats weighing 240–280 g (2 months old, bred at the Institute for Cognitive Science Studies, Tehran, Iran), at the time of surgery, were used. Animals were housed in groups of 5–6/cage having free access to food and water in a room with a 12:12 h light/dark cycle (lights on at 07.00 h), and controlled temperature (23 ± 1 °C). Animal handling was limited to the time of weighing, drug administration and cage cleaning. All experiments were performed between 09:00 h and 14:00 h, and each rat was tested only once. Each experimental and control group comprised eight rats (Table 1).

2.2. Surgery

Animals were anaesthetized using a ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg) solution. They were then positioned in a stereotaxic frame (Stoelting Co, Illinois, USA) in flat-skull position. A midline incision was made in the skin of the skull, and the underlying periosteum was retracted. A stainless steel guide cannulae (22 gauge) was implanted (unilaterally) 1.5 mm above the left prelimbic and 2 mm above the left NAc Shell region according to the respective coordinates in rats' brain stereotaxic atlas (Paxinos and Watson, 2007).

Stereotaxic coordinates for the left PL region were 3.4 mm anterior to bregma, 0.9 mm lateral to the midline and −3 mm ventral to the dorsal surface of the skull. For the left shell of the NAc, the coordinates were 1.2 mm posterior to bregma, 0.9 mm lateral to the midline and −5.3 mm ventral to the dorsal surface of the skull. Inserted cannulae were secured to the bone using dental acrylic cement. A styled was introduced into the guide cannula to prevent possible obstruction. All animals were allowed about 5–7 days to recover from surgery and the effect of the anesthetic agents.

2.3. Drug microinjections

Microinjections were given through the indwelled cannula (27-gauge, Supa; Iran), terminating 2 mm below the ventral tip of the guide cannulae, connected to a

Table 1
Summarizes all experiments, experimental animal groups, drugs injection and their applied doses.

Figures	% OAT	% OAE	Locomotor activity	First injection intra-NAc shell (0.3 μl/rat)	Second injection intra-NAc shell (0.3 μl/rat)	First injection in prelimbic (0.5 μl/rat)	Second injection in prelimbic (0.5 μl/rat)
1	A (Panel 1)	B (Panel 1)	C (Panel 1)	–	–	Saline (0.5 μl/rat)	NMDA (0.3, 0.6, 0.9 and 1.2 μg/μl)
	A (Panel 2)	B (Panel 2)	C (Panel 2)	–	–	Saline (0.5 μl/rat)	D-AP7 (0.25, 0.5 and 1 μg/rat)
	A (Panel 3)	B (Panel 3)	C (Panel 3)	–	–	D-AP7 (0.25 μg/μl)	NMDA (0.3, 0.6 and 0.9 μg/μl)
2	A (Panel 1)	B (Panel 1)	C (Panel 1)	Saline (0.3 μl/rat)	SKF38393 (1, 3 and 4 μg/μl)	–	–
	A (Panel 2)	B (Panel 2)	C (Panel 2)	SCH23390 (0.25, 0.5 and 1 μg/μl)	Saline (0.3 μl/rat)	–	–
	A (Panel 3)	B (Panel 3)	C (Panel 3)	SCH23390 (0.25 μg/μl)	SKF38393 (1, 3 and 4 μg/μl)	–	–
3	A (Panel 1)	B (Panel 1)	C (Panel 1)	Saline (0.3 μl/rat)	Quinpirole (0.125, 0.25 and 0.5 μg/μl)	–	–
	A (Panel 2)	B (Panel 2)	C (Panel 2)	Saline (0.3 μl/rat)	Sulpiride (0.2, 0.4 and 0.6 μg/μl)	–	–
	A (Panel 3)	B (Panel 3)	C (Panel 3)	SKF96365 (0.125 μg/μl)	Sulpiride (0.4 μg/μl)	–	–
	A (Panel 4)	B (Panel 4)	C (Panel 4)	SCH23390 (0.25 μg/μl)	Sulpiride (0.4 μg/μl)	–	–
4	A (Panel 1)	B (Panel 1)	C (Panel 1)	Saline (0.3 μl/rat)	–	NMDA (0.3, 0.6 and 0.9 μg/μl)	–
	A (Panel 2)	B (Panel 2)	C (Panel 2)	SKF38393 (1 μg/μl)	–	NMDA (0.3, 0.6 and 0.9 μg/μl)	–
	A (Panel 3)	B (Panel 3)	C (Panel 3)	SCH23390 (0.25 μg/μl)	–	NMDA (0.3, 0.6 and 0.9 μg/μl)	–
	A (Panel 4)	B (Panel 4)	C (Panel 4)	Quinpirole (0.25 μg/μl)	–	NMDA (0.3, 0.6 and 0.9 μg/μl)	–
	A (Panel 5)	B (Panel 5)	C (Panel 5)	Sulpiride (0.2 μg/μl)	–	NMDA (0.3, 0.6 and 0.9 μg/μl)	–