Brain Research 1644 (2016) 79–87

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres

Research report

Serotonin$_7$ receptors in the lateral habenular nucleus regulate depressive-like behaviors in the hemiparkinsonian rats

Ling Na Han [a], Li Zhang [b], Yi Na Sun [b], Cheng Xue Du [b], Yu Ming Zhang [b], Tao Wang [b], Jin Zhang [b], Jian Liu [b,*]

[a] Department of Physiology, Changzhi Medical College, Changzhi 046000, China
[b] Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Xi'an Jiaotong University Health Science Center, Xi'an 710061, China

ARTICLE INFO

Article history:
Received 26 January 2016
Received in revised form
7 May 2016
Accepted 9 May 2016
Available online 10 May 2016

Keywords:
Lateral habenular nucleus
Depression
5-HT$_7$ receptors
Parkinson's disease
Rat

ABSTRACT

Preclinical studies indicate that serotonin$_7$ (5-HT$_7$) receptors may regulate depressive-like behaviors. Depression is a common symptom in Parkinson's disease (PD); however, its pathophysiology is unclear. Here we examined whether 5-HT$_7$ receptors in the lateral habenular nucleus (LHb) involve in the regulation of PD-related depression. Unilateral 6-hydroxydopamine lesions of the substantia nigra pars compacta in rats induced depressive-like responses as measured by the sucrose preference and forced swim tests when compared to sham-operated rats. Intra-LHb injection of 5-HT$_7$ receptor agonist AS19 (1, 2 and 4 μg/rat) induced or increased the expression of depressive-like behaviors in sham-operated and the lesioned rats. Further, intra-LHb injection of 5-HT$_7$ receptor antagonist SB269970 (1.5, 3 and 6 μg/rat) produced antidepressant effects in the two groups of rats. However, the doses producing these effects in the lesioned rats were higher than those in sham-operated rats. Neurochemical results showed that intra-LHb injection of AS19 (4 μg/rat) decreased dopamine and 5-HT levels in the medial prefrontal cortex, habenula and hippocampus in sham-operated and the lesioned rats; whereas SB269970 (6 μg/rat) increased dopamine and 5-HT levels in these structures. In addition, noradrenaline levels in these structures were not changed after intra-LHb injection of AS19 or SB269970 in the two groups of rats. These findings suggest that activation or blockade of 5-HT$_7$ receptors in the LHb may change the activity of LHb glutamate neurons, and then decreases or increases dopamine and 5-HT levels in the limbic and limbic-related brain regions, which are involved in the regulation of depressive-like behaviors.

1. Introduction

The central serotonin (5-HT) system is involved in the regulation of various brain functions, and the pathophysiology of neuropsychiatric disorders, such as depression. 5-HT mediates its effect via an interaction with 14 identified 5-HT receptor subtypes (Barnes and Sharp, 1999), but the role of each subtype in the pathophysiology and treatment of the neuropsychiatric disorders is still not completely clear. The 5-HT$_7$ receptor is a G-protein-coupled receptor, and activation of the receptor increases neuronal excitability. Further, several studies have found that the 5-HT$_7$ receptors are expressed in multiple brain regions (Gustafson et al., 1996; Barnes and Sharp, 1999; Neumaier et al., 2001).

Concerning the role of 5-HT$_7$ receptors in depression, several studies have proved that blockade and inactivation of the 5-HT$_7$ receptor lead to an antidepressant-like effect (Guscott et al., 2005; Hedlund et al., 2005; Bonaventure et al., 2007). It has even been shown that there is a synergistic interaction between individually ineffective doses of the selective 5-HT$_7$ receptor antagonist SB269970 and antidepressants (Bonaventure et al., 2007; Wesolowska et al., 2007). Further, some antidepressant drugs (e.g., amisulpride) have high affinity for 5-HT$_7$ receptor and reduce immobility time in the forced swim test (FST) in 5-HT$_7{}^{+/+}$ mice but not in 5-HT$_7{}^{-/-}$ mice (Abbas et al., 2009). These findings have led to the implication of a role for 5-HT$_7$ receptor in the treatment of depression.

Although Parkinson's disease (PD) is characterized by a movement disorder, a variety of evidence suggest that PD is associated with a range of non-motor symptoms such as depression, anxiety and cognitive deficits, and depression is the most common encountered non-motor symptom of PD (Zesiewicz and Hauser, 2002; Lohle et al., 2009). Studies have proved that degeneration of the nigrostriatal pathway leads to an impairment of central 5-HT system, including the loss of 5-HT neurons, reduction of brain 5-HT content, hyperactivity of 5-HT neurons and alterations in

* Correspondence to: Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Xi'an Jiaotong University Health Science Center, Yan Ta Xi Lu 76, Xi'an 710061, China.
E-mail address: liujian@mail.xjtu.edu.cn (J. Liu).

http://dx.doi.org/10.1016/j.brainres.2016.05.016
0006-8993/

various types of 5-HT receptors (Scholtissen et al., 2006; Wang et al., 2009; Huot et al., 2011; Hui et al., 2015). In addition, we have shown that unilateral lesions of the substantia nigra pars compacta (SNc) in rats induce depressive-like behaviors, and activation of 5-HT_{2C} receptors by Ro60-0175 in the lateral habenular nucleus (LHb) induces or enhances depressive-like behaviors (Han et al., 2015). As been mentioned above, the 5-HT system plays an important role in the regulation of PD-related depression.

The LHb is a nucleus of the epithalamus, which mainly contains glutamate neurons (Vincent et al., 1980; Kiss et al., 2002). The LHb receives limbic and motor signals from diverse forebrain regions and projects mainly to brain monoamine cell groups (Herkenham and Nauta, 1977, 1979; Hikosaka et al., 2008; Hong and Hikosaka, 2008). Several studies have shown that the LHb closely associates with depression. Previous studies have found hyperactivity of the LHb during depressed states (Caldecott-Hazard et al., 1988; Morris et al., 1999; Shumake et al., 2003; Roiser et al., 2009; Li et al., 2011, 2013), whereas reduction of LHb activity by electrolytic lesions (Amat et al., 2001; Yang et al., 2008), deep brain stimulation (Sartorius et al., 2010; Li et al., 2011, 2013) and pharmacological inhibition using the γ-aminobutyric acid-A ($GABA_A$) receptor agonist muscimol (Winter et al., 2011) have shown antidepressant effects in depressed patients and rat models of depression. The LHb receives 5-HT innervation from the median raphe nucleus (MRN; Vertes et al., 1999), and expresses a moderate level of 5-HT_7 receptors (Neumaier et al., 2001). Based on these studies, we speculate that 5-HT_7 receptors in the LHb may be involved in the regulation of depression in PD.

Therefore, the present study was designed to (i) clarify the effects of 5-HT_7 receptors agonist AS19 and antagonist SB269970 injected into the LHb on depression behaviors by commonly used paradigms the sucrose preference test and FST in rat with unilateral SNc lesion; (ii) investigate changes in monoamine levels in the limbic and limbic-related brain regions after intra-LHb injection of the agonist and antagonist in this lesion model. In this study, the sequence in the experimental procedures is described in Fig. 1.

2. Results

2.1. The location of injection sites, tyrosine hydroxylase immunohistochemistry and neurochemistry

The photomicrograph in Fig. 2A illustrates injection site in the LHb of the 6-hydroxydopamine (6-OHDA)-lesioned rat. In sham-operated rats, the number of tyrosine hydroxylase immunoreactive (TH-ir) neurons in the SNc and ventral tegmental area (VTA) on the injected side decreased slightly to 94 ± 2% and 95 ± 1% when compared to the uninjected side, respectively ($n=8$; Fig. 2B). In the lesioned rats, the SNc of the injected side showed a total loss of TH-ir neurons when compared to the uninjected side, and the amount of TH-ir neurons in the VTA on the lesioned side decreased significantly to 54 ± 5% ($n=8$, $P<0.001$; unpaired Student's *t*-test; Fig. 2B′). Compared to sham-operated rats, the unilateral 6-OHDA lesions of the SNc in rats significantly decreased dopamine (DA) level in the ipsilateral striatum ($P<0.001$; unpaired Student's *t*-test; Fig. 2C).

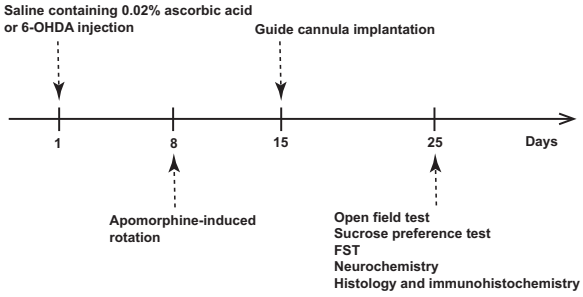

Fig. 1. Timeline and summary of 6-OHDA injection, apomorphine-induced rotation, guide cannula implantation, behavior tests, neurochemistry, histology and immunohistochemistry.

2.2. The effects of DA lesion and activation and blockade of LHb 5-HT_7 receptors on locomotor activity in the open field test

Fig. 3 shows the effects of unilateral 6-OHDA lesioning and intra-LHb injection of potent, selective 5-HT_7 receptor agonist AS19 or the selective antagonist SB269970 on horizontal and vertical activities. A two-way ANOVA analysis (lesion × drug) showed a significant effect on locomotor activity for lesion ($F_{1,82}=129.51$, $P<0.001$, Fig. 3A; $F_{1,82}=106.88$, $P<0.001$, Fig. 3B; $F_{1,82}=38.22$, $P<0.001$, Fig. 3C; $F_{1,82}=15.09$, $P<0.001$, Fig. 3D), but not for the drugs. Subsequent pairwise analysis showed that intra-LHb injection of the drugs did not affect locomotor activity when compared to vehicle injection into the LHb in the same group (Fig. 3).

2.3. The effects of DA lesion and activation and blockade of LHb 5-HT_7 receptors on depressive-like behaviors in the sucrose preference test and FST

As shown in Fig. 4A and B, unilateral 6-OHDA lesioning and intra-LHb injection of AS19 or SB269970 affected sucrose consumption in the sucrose preference test. A two-way ANOVA analysis (lesion × drug) showed significant differences on sucrose consumption both for lesion ($F_{1,72}=55.18$, $P<0.001$, Fig. 4A; $F_{1,72}=144.76$, $P<0.001$, Fig. 4B) and for the drugs ($F_{3,72}=6.81$, $P<0.001$ for AS19, Fig. 4A; $F_{3,72}=7.11$, $P<0.001$ for SB269970, Fig. 4B). Pairwise analysis showed that treatment with AS19 in sham-operated rats significantly decreased sucrose consumption at doses of 2 and 4 μg when compared to rats treated with vehicle in the same group ($P<0.05$ for 2 μg, $P<0.01$ for 4 μg, Bonferroni's test, Fig. 4A). In the lesioned rats, the decrease reached statistical significance at a dose of 4 μg ($P<0.05$, Bonferroni's test, Fig. 4A). In contrast to the effect of AS19, treatment with SB269970 significantly increased sucrose consumption in both sham-operated and the lesioned rats. The doses producing statistical significance were at 3 and 6 μg in sham-operated rats (both $P<0.05$, Bonferroni's test, Fig. 4B) and 6 μg in the lesioned rats ($P<0.01$, Bonferroni's test, Fig. 4B), respectively.

As illustrated in Fig. 4C and D, unilateral 6-OHDA lesioning and intra-LHb injection of AS19 or SB269970 affected immobility time in the FST. A two-way ANOVA analysis (lesion × drug) showed significant differences on immobility time both for lesion ($F_{1,74}=65.69$, $P<0.001$, Fig. 4C; $F_{1,74}=178.56$, $P<0.001$, Fig. 4D) and for the drugs ($F_{3,74}=6.92$, $P<0.001$ for AS19, Fig. 4C; $F_{3,74}=14.66$, $P<0.001$ for SB269970, Fig. 4D). Pairwise analysis showed that treatment with AS19 in sham-operated rats significantly increased immobility time at doses of 2 and 4 μg when compared to rats treated with vehicle in the same group (both $P<0.05$, Bonferroni's test, Fig. 4C). In the lesioned rats, the increase reached statistical significance at a dose of 4 μg ($P<0.01$, Bonferroni's test, Fig. 4C). In contrast to the effect of AS19, treatment with SB269970 significantly decreased immobility time in both sham-operated and the lesioned rats. The doses producing statistical significance were at 3 and 6 μg in sham-operated rats (both $P<0.05$, Bonferroni's test, Fig. 4D) and 6 μg in the lesioned rats ($P<0.001$, Bonferroni's test, Fig. 4D), respectively.