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Research report

Effects of immobilization stress on emotional behaviors in dopamine D3 receptor knockout mice

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HIGHLIGHTS

- The D3KO mice show regular basal emotional behaviors.
- The anxiety-like behaviors are unchanged in D3KO mice under stress.
- D3KO mice show a resistance to the former immobilization stress in the TST.

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ABSTRACT

A central problem in understanding the dopamine system in anxiety and depression is to specify functions of different members of the dopamine receptor family. Recent studies have reported that the dopamine D2/D3 receptor agonist pramipexole exerts an antidepressant-like effect in the chronic mild stress model and in the behavioral despair model, suggesting dopamine D3 receptor may be an important target for antidepressant actions. The aim of the present study was to examine the role of dopamine D3 receptor on the anxiety-like and depression-like behaviors induced by immobilization stress. We subjected D3 receptor knockout (D3KO) mice to a series of behavioral paradigms after acute (1 h) or chronic (1 h a day for 14 days) immobilization stress. The results showed that immobilization stress significantly altered the anxiety-like behaviors (open field test and elevated plus maze) and depression-like behaviors (tail suspension test) in both D3KO mice and their wild-type littermates. Moreover, further analysis of the data indicated that the D3KO mice, but not their littermates, failed to show a change in immobility time in the tail suspension test after the acute and chronic stress as compared to intact controls, suggesting an increased resistance to the immobilization stress given before behavioral tests. Although our study did not suggest a significant role of D3 receptor in regulating basal anxiety-like and depression-like behaviors, it demonstrated the mice lacking D3 receptor might be more resistant to stressful procedure than their WT littermates.

1. Introduction

The pervasiveness of anxiety and depression has enormous costs for modern society. With a prevalence rate of approximately 5% worldwide, major depressive disorder (MDD) is the most common mood disorder [1]. MDD occurs in up to 60% of people with anxiety disorders [2]. Comorbid anxiety and depression is associated with more severe symptoms, greater functional impairment and persistent course of illness than either depression or anxiety alone [3]. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed drugs for the treatment of MDD and several anxiety disorders [4]. With regards to the poor prognosis of a large proportion of patients, further understanding of the neurobiology of depression and anxiety at the molecular and cellular level is necessary so that more effective treatments can be developed.

Stressful events appear to play a role in the onset, progression and treatment outcomes of several psychiatric disorders, including anxiety disorders and MDD [5–8]. Stress that induces

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alterations in neuroendocrine systems and brain activity promotes the changes in physiological and behavioral responses [9,10]. The hypothalamus–pituitary–adrenal (HPA) axis has been most frequently discussed as one of the major pathways through which the central nervous system exerts its influence on neural functions under stressful conditions [11,12]. Increasing amounts of evidence implicated a putative role of dopamine system in the regulation of the HPA axis response to stress [13,14]. The fact that exposure to stress results in enhanced dopamine release in limbic areas [15], and the observation that dopamine D1 and D2 receptor agonists activate the HPA axis [16] supports the assumption that dopamine plays a stimulatory role in the control of the neuroendocrine stress axis. A central issue in understanding the dopamine system in the stress-related process is to link various dopaminergic functions to different members of the two DA receptor classes, the D1 class (D1 and D5) and the D2 class (D2, D3, and D4) receptors [17].

The dopamine D3 receptor has recently been associated with anxiety-like behaviors in rats [18] and was postulated as a potential therapeutic target for depression [19]. Unlike the dopamine D2 receptor, which is widely distributed throughout the brain, the D3 receptor has a specific distribution to limbic areas, such as the nucleus accumbens (NAc), the olfactory tubercle, the islands of Calleja, and to a lesser extent, the dorsal striatum and hippocampus [17,20]. Chronic antidepressant treatment has been reported to enhance D3 receptor binding in the rat brain [21]. Lammers et al. have shown a selective increase in dopamine D3 receptor gene expression after chronic treatment with fluoxetine and tranylcypromine, as well as chronic electroconvulsive therapy (ECT) [22]. Although these studies have focused on the potential role of D3 receptor in depression-like behaviors, the results from Chourbaji et al. do not indicate an evident involvement of the D3 receptor in the development of a depression-like phenotype in knockout studies [23].

Whereas the activation of the HPA axis is associated with dopamine release in limbic areas, the role of dopamine receptors, particular D3 receptor, in the control of the emotional behaviors under stress conditions is less clear. In this study, we used the immobilization stress model in different genotypes of mice, including D3 receptor knockout (D3KO) mice and their wild-type (WT) littermates, to examine the changes in anxiety-like and depression-like behaviors.

2. Materials and methods

2.1. Animal

The D3KO mice were previously generated by Xu et al. as described [20]. Homozygous mutant and WT littermates were produced from heterozygous breeding. The genetic background of the D3KO mice was initially 50% 129SvJ and 50% C57BL/6J, and was bred with C57BL/6J mice for three generations [24–26]. Mice 10–12 weeks of age were group housed in a temperature-controlled environment under a 12 h dark/light cycle and allowed to acclimate to new housing for at least 5 days before experimental manipulation. Only male mice were used in this study. All experimental procedures were approved by the Animal Care and Use Committee of Xi'an Jiaotong University.

2.2. Genotyping

To confirm the genotypes of D3KO and WT mice at the time of weaning, genomic DNA extracted from the tail was analyzed by PCR as described [20,24]. The sequences of four oligonucleotide primers are: 5′-GCT CAC CAC TAG GTA GTT G-3′, 5′-ACC TCT GAG CCA GAT AAG C-3′, 5′-CAT TCT GCA CGC TTC AAA AGC G-3′, and 5′-TTT CTC GGC AGG AGC AAG GTG-3′.

2.3. Immobilization stress

To create a reproducible animal model of stress-induced anxiety-like and depression-like behaviors, we administrated a 1-day or 14-day immobilization stress to mice and subsequently performed behavioral assessments.

D3KO and WT mice were subjected to immobilization stress by restraint using a plastic cylinder with a diameter of 3 cm and height of 12 cm. For the acute immobilization stress (AIS) groups (2 groups/genotype for all behavioral testing), only one 1-h immobilization stress was applied, each behavioral test (mentioned in the 2.4 behavioral testing) was conducted 30 min after the immobilization. For the chronic immobilization stress (CIS) groups (2 groups/genotype for all behavioral testing), 1-h immobilization stress was applied once daily for 14 days, each behavioral test (mentioned in the behavioral testing) was conducted 23 h after the last immobilization. Control mice were handled as the stressed animal but without any stress.

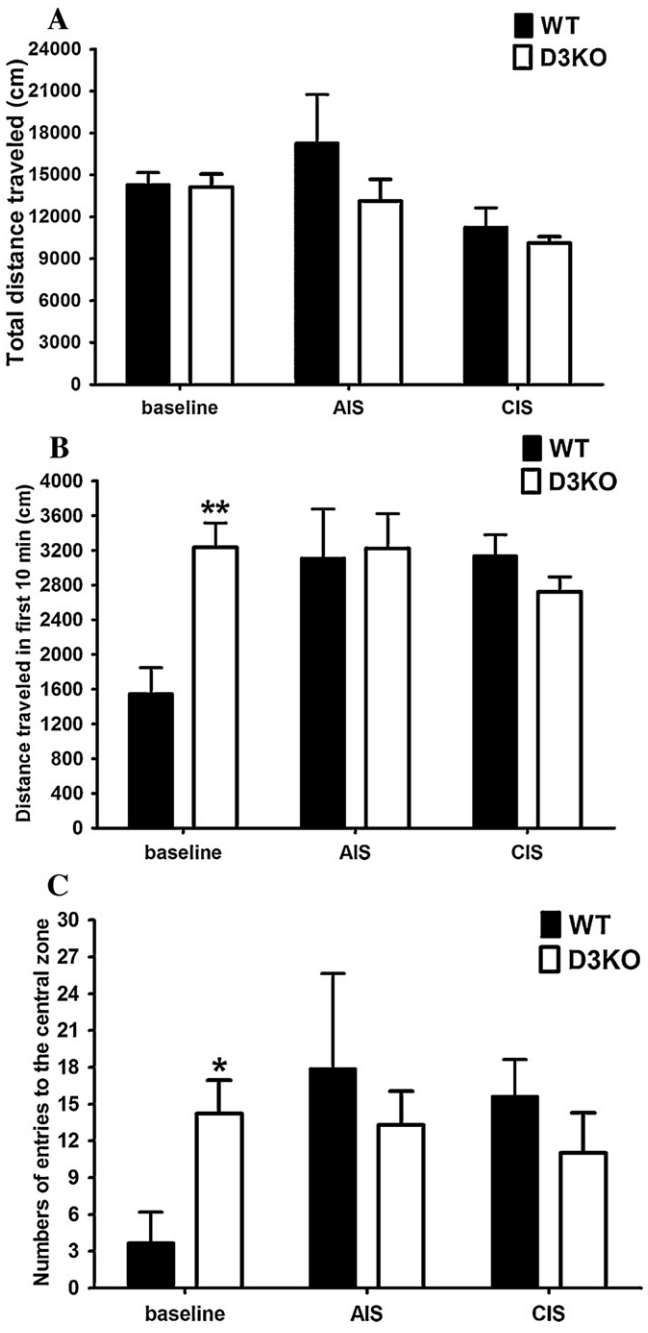

Fig. 1. The locomotor and exploratory behaviors of D3KO mice under basal, AIS and CIS conditions in the Open field test. (A) The total distance in 60 min, (B) The distance traveled in first 10 min and (C) the numbers of entries to the central zone in the first 10 min were measured. All data are expressed as the mean ± SEM (n = 8–10 for each group). $^{*}p < 0.05$ and $^{**}p < 0.01$, D3KO baseline versus WT baseline.

2.4. Behavioral testing

Prior to each experiment, the animals were brought to the testing room for at least 30 min. Tests were conducted during the light cycle between 8:00 am and 3:00 pm. For all paradigms, 8–10 D3KO mice/experiment were used with a matched number of WT littermates. In the acute paradigm, behavioral tests were conducted