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Adult forebrain NMDA receptors gate social motivation and social memory

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ABSTRACT

Motivation to engage in social interaction is critical to ensure normal social behaviors, whereas dysregulation in social motivation can contribute to psychiatric diseases such as schizophrenia, autism, social anxiety disorders and post-traumatic stress disorder (PTSD). While dopamine is well known to regulate motivation, its downstream targets are poorly understood. Given the fact that the dopamine 1 (D1) receptors are often physically coupled with the NMDA receptors, we hypothesize that the NMDA receptor activity in the adult forebrain principal neurons are crucial not only for learning and memory, but also for the proper gating of social motivation. Here, we tested this hypothesis by examining sociability and social memory in inducible forebrain-specific NR1 knockout mice. These mice are ideal for exploring the role of the NR1 subunit in social behavior because the NR1 subunit can be selectively knocked out after the critical developmental period, in which NR1 is required for normal development. We found that the inducible deletion of the NMDA receptors prior to behavioral assays impaired, not only object and social recognition memory tests, but also resulted in profound deficits in social motivation. Mice with ablated NR1 subunits in the forebrain demonstrated significant decreases in sociability compared to their wild type counterparts. These results suggest that in addition to its crucial role in learning and memory, the NMDA receptors in the adult forebrain principal neurons gate social motivation, independent of neuronal development.

1. Introduction

Social interactions are complex behaviors requiring multiple cognitive processes and interpretation of multifaceted social stimuli. A key aspect of a social interaction is the motivation of each organism to initiate and respond to the other. Social interaction is thought to produce an internal reward state which will, in turn, reinforce and promote approach behaviors (Ikemoto, Yang, & Tan, 2015). Impaired or abnormal social behaviors have been known to exacerbate many psychiatric conditions including schizophrenia (Lai et al., 2014; Vaskinn, Ventura, Andreassen, Melle, & Sundet, 2015; Witten et al., 2014), autism (Bambini-Junior et al., 2014; Devine, 2014; Enter, Colzato, & Roelofs ,2012; Lin, Rangel, & Adolphs, 2012; Wang et al., 2013), depression (Iniguez et al., 2014; Zanier-Gomes et al., 2015), and post-traumatic stress disorder (Eagle, Fitzpatrick, & Perrine, 2013; Sripada, Lamp, Defever, Venners, & Rauch, 2016; Sripada, Pfeiffer, Rauch, & Bohnert, 2015). Many of these conditions have also been found to be affected by dopamine activity in the brain. Dopamine has been widely studied for its roles in reward and motivational behaviors. For example, DA neurons showed a marked increase in calcium transients during social interactions (Gunaydin et al., 2014), whereas decreased dopamine activity in the prefrontal cortex has been indicated in the altered social behaviors following social defeat stress (Jin et al., 2015; Novick et al., 2015; Watt et al., 2014). Further, when the DA neurons in the VTA were optogenetically stimulated, the mice significantly increased the investigation of a novel conspecific while the investigation of a novel object remained unchanged (Gunaydin and Deisseroth, 2014).

Largely missing thus far from the field of social cognition, is the analysis of downstream molecules that participate in regulation of social motivation during adulthood. It has been shown that the dopamine receptors interact closely with the N-methyl-d-aspartate (NMDA) receptor in the forebrain neurons in the cortex, hippocampus, striatum, etc. (Fiorentini, Gardoni, Spano, Di Luca, & Missale, 2003; Hu, Liu, Li, Gao, & Huang, 2010; Lee et al., 2002; Sarantis, Matsokis, & Angelatou, 2009; Varela, Hirsch, Chapman, Leverich, & Greene, 2009; Vastagh et al., 2012). Consistent with this rationale, several studies showed that a genetic knockdown of the NMDA receptors throughout development in whole body resulted in altered social behavior (Mohn, Gainetdinov, Caron, &

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Koller, 1999). Deletion of the NMDA receptors in the GABAergic interneurons during development also caused deficits in social memories (Belforte et al., 2010). Similarly, social behaviors were impaired when NR1 was knocked out in parvalbumin (PV)-positive interneurons during development. These PV NR1 knockout mice displayed lower levels of approach to a novel mouse indicating reduced social motivation, as well as lower levels of exploration of the novel mouse, relative to the wild-type mice (Saunders et al., 2013). These observations added to the notion that impaired neural development may be the main cause for social impairment. However, the NMDA receptor is known for its role in regulating cognitive functions that are independent of neural development (Cui et al., 2004; Tsien et al., 1996). The question is whether the NMDA receptors in adult principal excitatory neurons gate cognitive computational signals for social motivation and social interactions. Here we seek to determine, and differentiate, if the NMDA receptor in the forebrain neurons regulates social motivation vs. social memory in the adult brain. We examined this question by analyzing the inducible and forebrain-specific NMDAR1 knockout mice (iFB-KO) (Cui et al., 2004; Tsien et al., 1996) in a sociability test, social recognition memory tests and non-social recognition test.

2. Results

2.1. Novel object recognition

2.1.1. Short-term novel object recognition

The novel object paradigm was utilized to determine the non-social object recognition memory in the iFB-KO mice. In all our experiments, we temporally inactivated the NMDA receptors in the forebrain principal neurons of adult mice five days prior to behavioral tests by feeding these mice tetracycline (Cui et al., 2004; Shimizu, Tang, Rampon, & Tsien, 2000). First, the iFB-KO mice were tested in their ability to learn and remember an object for a short period of time - namely, a one-hour novel recognition test. These mutant mice, as well as littermate control mice, were first allowed to investigate two identical objects in the training phase and, after the delay time, were allowed to investigate one of the familiar objects from the training phase and one novel object (Fig. 1a). A preference for the novel object over the familiar object indicated a memory for the familiar object as rodents are more likely to spend more time investigating an unfamiliar object. Both the iFB-KO mice and their wild-type littermates spent approximately equal amounts of time investigating the objects in the training phase (Wt: 32.02 ± 4.14 s; iFB-KO: 36.19 ± 4.47 s; $p < 0.05$; Fig. 1b), spending an approximately equal percentage of time with both objects (Wt: 50.55 ± 1.73%; iFB-KO: 49.41 ± 2.20%; Fig. 1c). When the distance that the animals travelled while investigating the two objects was measured, it was found that the iFB-KO mice travelled significantly less than the wild-type mice during the training phase (Wt: 2128.28 ± 176.20 cm; iFB-KO: 1577.59 ± 155.67 cm; $p < 0.05$; Fig. 1d).

After one hour the iFB-KO mice showed only a slight preference for the novel object (39.70 ± 4.39 s), spending significantly more time with the familiar object (35.26 ± 4.27 s) than their wild-type littermates (22.16 ± 3.65 s; $p < 0.05$). Conversely, the wild-type mice spent a significantly greater percentage of time with the novel object (37.92 ± 4.98 s; 62.15 ± 4.43%, $p < 0.05$; Fig. 1c) than the iFB-KO mice (54.17 ± 2.74%). The wild-type animals spent significantly more time investigating the novel object in the recall session, than the familiar object in the training session ($p < 0.05$) indicating the wild-type mouse's memory of the object from the training phase. Interestingly, there were no significant differences between the distanced travelled between the two groups while exploring the objects (Wt: 1588.46 ± 225.46 cm; iFB-KO: 1285.4 ± 110.30 cm).

2.1.2. Long-term novel object recognition

Similarly, we tested the iFB-KO mice in a 24-h novel object recognition paradigm, where the delay between the training session and the recall session was 24 h (Fig. 2a). In the training session, the iFB-KO mice investigated a novel object as much as their wild-type littermates (Wt: 38.83 ± 4.19 s; iFB-KO: 37.75 ± 37.75 s; Fig. 2b). Over the course of the training round, the iFB-KO animals spent nearly the same amount of time investigating each object, as did their wild-type littermates (Wt: 50.90 ± 3.17%; iFB-KO: 51.59 ± 5.11%; Fig. 2c). Both groups of animals also ambulated similar distances while exploring both objects (Wt: 1908.20 ± 205.16 cm; iFB-KO: 1515.49 ± 177.76 cm; Fig. 2d). This demonstrates that the iFB-KO mice show similar motivation to explore a novel object as their wild-type littermates.

After a 24-h delay, each mouse was placed into the novel object arena with one of the, now familiar, objects from the training session, and a novel object (Fig. 2a). The mice were allowed to explore for five minutes. The iFB-KO mice spent equal amounts of time investigating each object (familiar: 35.63 ± 4.58 s; novel: 35.82 ± 4.50 s). Their wild-type littermates, however, spent significantly more time investigating the novel object than the familiar object (familiar: 23.64 ± 3.43 s; novel: 38.64 ± 5.33 s; $p < 0.05$). The wild-type mice spend a significantly greater percentage of time investigating the novel object in the recall session than the object in the training session (61.67 ± 3.04%; $p < 0.01$) indicating their memory of the familiar object. Interestingly, the wild-type mice spent a significantly larger percentage of time investigating the novel object in the recall session than the iFB-KO mice ($p < 0.05$). These data indicate that the iFB-KO mice are unable to form a long-term memory of the object. Interestingly, when the distance travelled by the animals was plotted, the iFB-KO mice were found to travel significantly shorter distances than the wild-type animals (Wt: 1830.09 ± 182.02 cm; iFB-KO: 1264.06 ± 195.91 cm; $p < 0.05$). Taken together, the above experiments suggest that the mutant mice exhibited normal motivation to explore non-social objects, yet they were significantly impaired in the formation of long-term novel object recognition memories.

2.2. Social discrimination

To investigate the social recognition memory of the iFB-KO mice, we utilized a social discrimination paradigm consisting of a training session in which the subject mouse is presented with a novel juvenile mouse, and a recall session in which the subject animal is allowed to investigate the familiar animal from the training session and a novel juvenile (Fig. 3a). A preference for the novel stimulus animal over the familiar animal indicates a memory for the familiar conspecific. The social discrimination paradigm is advantageous due to the ability for each animal to act as its own control. For these tasks, we enclosed the stimulus juvenile males in wire mesh enclosures so that the interaction time is that of the subject animals and not influenced by the interest of the stimulus mouse.

2.2.1. Short-term social discrimination

To determine the short-term social recognition memory of the iFB-KO mice, we tested them in a one-hour social discrimination paradigm. In the training session, the iFB-KO mice spent significant less time exploring the novel juvenile conspecific than their wild-type littermate (Wt: 80.43 ± 4.92 s; iFB-KO: 57.13 ± 7.66 s; $p < 0.05$; Fig. 3b). These data indicate a reduced motivation for exploring a conspecific. When the distance that the mice travelled in the experimental arena was measured no significant differences