NEUROPSYCHIATRIC DISORDERS

Elucidating the neurobiology of sociability

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Autism spectrum disorders (ASD) are characterized by severe deficits in sociability for which no FDA-approved treatments are available. Several studies are underway to elucidate the brain circuits and signaling pathways that regulate sociability, as these efforts might enhance our understanding of ASD pathophysiology and guide the development of therapies.

In a new study published in the *Journal of Clinical Investigation*, investigators from Vanderbilt University School of Medicine identify the basolateral amygdala-nucleus accumbens (BLA-NAc) circuit as a critical neural regulator of social function. Using optogenetic and pharmacological interventions, they show that reduction of BLA-NAc circuitry activity improves social behavior in a mouse model of ASD. These findings suggest that the BLA-NAc circuit is a promising pharmacological target for the treatment of ASD-associated symptoms.

The nucleus accumbens (NAc) is a striatal region classically linked to rewarding experiences. Studies have shown that basolateral amygdala (BLA) input is required for dopamine to enhance the cue-evoked firing of NAc neurons, which promotes reward-seeking behavior. “Because the BLA-NAc circuit underlies decision-making in response to rewarding cues and subsequent behavioral responses, we hypothesize that activity in the BLA-NAc circuit may regulate multiple aspects of sociability under physiological conditions and perhaps under conditions of impaired social function,” explain the investigators in the introduction of their report.

To examine the role of BLA-NAc circuit on social function, the investigators used an optogenetic approach. They introduced blue-light activated cation channel Channelrhodopsin-2 (ChR2) into the BLA of C57BL/6J mice via viral transduction and a few weeks later, delivered blue light into the NAc via fiber optic cannulas to activate the BLA-NAc circuit; social function was then tested in the three-chamber social

Credit: Brain light/ Alamy Stock Photo.

interaction (SI) task, the juvenile reciprocal test and the conditioned place preference (CPP) test.

Behavioral analysis of ChR2-expressing mice versus control mice revealed that BLA-NAc circuit activation reduces social behavior and induces social avoidance. Light-dark and elevated plus maze tests—commonly used to assess anxiety-like behavior—were also performed, which revealed that the social avoidance observed during BLA-NAc stimulation was not secondary to increased anxiety-like behavior.

To assess the role of BLA-NAc in social deficits associated with ASD, the investigators applied another optogenetic approach to inhibit BLA-NAc activity via orange-light activation of a transgene encoding the chloride pump Halorhodopsin (NpHR) in *Shank3B^{-/-}* mice, a mouse model of ASD. *Shank3B^{-/-}* mice are characterized by an excision of exons 13–16 in the *SHANK3* gene that has been implicated in multiple neurodevelopmental and psychiatric disorders, including ASD. Previous studies have shown that *Shank3B^{-/-}*

mice display a strong ASD-like phenotype with impaired social interactions in the three-chamber SI task, lack of social novelty preference and repetitive behavior.

Here, inhibition of the BLA-NAc circuit in *Shank3B^{-/-}* mice via orange-light activation normalized the time the mice spent in the mouse chamber in the three-chamber SI test, which supports the hypothesis that reducing BLA-NAc activity can enhance sociability under pathological conditions.

Next, the team hypothesized that the endocannabinoid system, which regulates several central nervous system functions, might be involved in the regulation of BLA-NAc activity and therefore affect social behavior. Studies have shown that increasing the level of 2-arachidonoylglycerol (2-AG) increases social play in juvenile rats, while decreasing 2-AG decreases acquisition of social CPP in mice. Here the investigators show that pharmacological augmentation of 2-AG with JZL184—an inhibitor for monoacylglycerol lipase, the primary enzyme responsible for degrading 2-AG—could counteract the social impairment observed in the three-chamber SI task in wild-type mice after optogenetic BLA-NAc circuit activation and in *Shank3B^{-/-}* mice.

“These data reveal the BLA-NAc circuit as a critical regulator of social function and suggest pharmacological 2-AG augmentation could represent a promising approach to the treatment of social domain symptoms in ASDs,” conclude the investigators. The team also proposes a working model in which 2-AG augmentation reduces social deficits in *Shank3B^{-/-}* mice via normalization of hyperactive GABAergic and glutamatergic signaling in the NAc and reduction of BLA-NAc-elicited feed-forward inhibition.

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