The Neural Basis of Early Life Stress-induced Social Dysfunction

*Sora Shin, Horia Pribiag, Varoth Lilascharoen, Daniel Knowland, Xiao-Yun Wang, Byung Kook Lim**

Early life stress (ELS), such as childhood adversity, is a core component in over 30% of all psychiatric illnesses such as schizophrenia, autism spectrum disorder and major depression. Especially, social impairment is highly associated with these ELS-induced mental illnesses and can occur later in life as a major symptom of these diseases. Despite the continued investment into identifying effective treatment, most approaches are merely alleviating or masking small subsets of symptoms. This is largely due to the lack of knowledge of the neural circuitry underlying ELS-induced social impairment. Here, we examine the neural adaptation underlying ELS-induced social abnormalities.

Methods: In rodents, early social deprivation (ESD) during first two weeks after birth induces pervasive and long-lasting abnormality in social interaction, lack of ultrasonic vocalization and so on. Thus, in this animal model of ELS, we anatomically and functionally dissect the neural circuitry mediating ELS-induced social impairment in combination with various techniques including optogenetic, viral mediated tracing, electrophysiology, molecular profiling and real time micro-endoscopic calcium imaging in freely moving animal.

Results: We found that ELS-induced downregulation of dopamine receptor 3 (Drd3) signaling and its corresponding effects on neural activity in the lateral septum (LS) are both necessary and sufficient to cause social abnormalities in adulthood. Using *in vivo* Ca^{2+} imaging, we found that Drd3-expressing-LS ($Drd3^{LS}$) neurons show blunted neuronal activity in response to social stimuli in animals exposed to ELS, while the optogenetic activation of $Drd3^{LS}$ neurons rescues ELS-induced social impairments. Furthermore, pharmacological treatment with the Drd3 agonist, which increases $Drd3^{LS}$ neuronal activity, normalizes the social dysfunctions of ELS mice. Thus, we identify Drd3 in the LS as a critical mediator and potential therapeutic target of social abnormalities caused by ELS.

Discussion: Our findings reveal a novel role of Drd3LS neuronal signaling and its corresponding neuronal activity in mediating ELS-induced social dysfunction. This is a significant advance in our understanding of the neural mechanisms by which adverse events in early life can alter specific neuronal activity and cause behavioral dysfunction in adult life. Therefore, our results may provide promising information for the development of novel therapeutic strategies that target adverse childhood experience-related symptomatology associated with numerous neuropsychiatric disorders.

Reference:

Drd3 Signaling in the Lateral Septum Mediates Early Life Stress-Induced Social Dysfunction. (2018) Shin S, Pribiag H, Lilascharoen V, Knowland D, Wang XY, Lim BK.Neuron. 97(1):195-20

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