Brain pathway identified that impairs postpartum social behavior after adolescent stress

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Stress during adolescence can cause postpartum behavioral changes in women and other mammals, including depression and changes in social

behavior after the birth of a child.

However, the neural circuit mechanisms by which adolescent stress leads to later changes in postpartum social behavior are unclear. In a *Nature Communications* study, University of Alabama at Birmingham researcher Minae Niwa, Ph.D., used a mouse model and cutting-edge neurobiological techniques to show how psychological stress during adolescence alters neuronal functions in the brain, resulting in altered postpartum social behavior.

This research builds on her recent finding that mice exposed to social isolation in late adolescence, which alone causes no endocrine or behavioral changes, show long-lasting behavioral changes only when accompanied by pregnancy and delivery. Niwa and colleagues were able to use this behavioral model to probe for postpartum neural circuit differences between mouse dams that were stressed in late adolescence and a control group of mouse dams that remained unstressed in adolescence, due to normal social interactions with other mice.

Niwa focused on the prelimbic cortex, a hub region of the brain that plays a crucial role in social behavior and regulation of stress responses. The UAB researchers used optogenetics—where light signals can selectively activate or inhibit brain circuits—and *in vivo* calcium imaging, which allows researchers to examine neuronal activity of specific neurons in a brain region. These approaches allow investigators to understand how nerve cells communicate in freely-behaving animals.

The UAB Department of Psychiatry and Behavioral Neurobiology researchers found that adolescent psychosocial stress, combined with pregnancy and delivery, caused hypofunction of the glutamatergic pathway that they mapped from the anterior insula region of the brain cortex to the prelimbic cortex. Glutamate is the main excitatory neurotransmitter in the central nervous systems of mammals.

The diminished function of this cortico-cortical pathway altered neuronal activity in the prelimbic cortex and led, in turn, to abnormal social behavior, as seen in a test of how much time a mouse dam spends with a familiar mouse that is confined in one corner of a cage, versus a novel mouse, confined in another corner. In this social novelty trial, the unstressed dams—in contrast to stressed dams—spent more interaction time per visit and more total interaction time with the novel mouse.

Specifically, Niwa and colleagues found that the anterior insula-prelimbic cortex pathway played a crucial role during recognizing the novelty of other mice by modulating what they call "stable neurons" in the prelimbic cortex, which were constantly activated or inhibited by novel mice. A cortico-cortical pathway means that action potential from a neuron in one area of the brain cortex travels to target neurons in another cortical area.

In their first experiments, the UAB researchers found that decreased activity in the anterior insula-prelimbic cortex pathway correlated with reduced preference for social novelty in stressed dams. They then used optogenetics to confirm the functional relevance of this pathway.

Notably, in social novelty trials optogenetic inhibition of the anterior insula-prelimbic pathway in unstressed dams reduced social interaction with novel mice, making their social behavior more like stressed dams. In contrast, optogenetic activation of the anterior insula-prelimbic pathway in stressed dams ameliorated behavioral changes seen in the social novelty trial, making them act more like unstressed dams.

Furthermore, the UAB team was able to restrict the timing of optogenetic modulation in the social novelty trials, so it occurred only during mouse exploration of its cage or only during interaction with the novel or familiar mice that were constrained in two corners of the cage. Results showed that the anterior insula-prelimbic cortex pathway that

modulates the stable neurons in the prelimbic cortex plays a crucial role only during social novelty interactions with other mice, rather than during exploration.

Additionally, they revealed the involvement of a stress-hormone receptor called glucocorticoid receptor, or GR, in the anterior insula-prelimbic pathway. By selectively removing the GR in this pathway, they observed a restoration of the changes in neuronal activity in the prelimbic cortex of stressed dams. "These findings suggest that the prolonged elevation of the stress hormone during the postpartum period plays a crucial role in the observed alterations in neuronal pathway and social behavior," Niwa said.

"Our study has revealed significant findings that demonstrate the involvement of the anterior insula-prelimbic pathway in adolescent stress-induced postpartum alterations related to the recognition of the novelty of other mice, which is a key aspect of social behavior," she said. "Exploring upstream and downstream contributions of the anterior insula-prelimbic pathway would facilitate our understanding of the postpartum social behavioral changes that are induced by social isolation in late adolescence, as well as our understanding of the nature of social behavior."

More information: Kyohei Kin et al, Adolescent stress impairs postpartum social behavior via anterior insula-prelimbic pathway in mice, *Nature Communications* (2023). DOI: 10.1038/s41467-023-38799-6

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