Changes in neuronal excitability and histone modifications within the LHb may underlie anxiety and depression following early life stresses

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Traumatic early life stressors (i.e. child abuse) increase the prevalence of stress-related psychiatric disorders later in life, such as depression and addiction. In particular, early life stress can induce epigenetic changes that potentially contribute to dopaminergic (DA) synaptic dysfunction, which provide targets for therapeutic intervention. Thus, we turned our attention to the lateral habenula (LHb), an epithalamic structure of primarily glutamatergic neurons that controls DA signaling via intermediate GABAergic structures. We investigated whether maternal deprivation (MD) induces changes in neuronal excitability and anxiety-like behavior along with epigenetic modifications, specifically histone acetylation, in the LHb. Using whole cell patch clamp, we show increased LHb excitability in response to a single 24-hr episode of MD. In addition, we show decreased acetylation at two epigenetic marks, H3K9 and H3K14 in response to MD using quantitative western blot. Lastly, through use of the Forced Swim Test (FST), we show that pre-adolescent rats (P21-P30) exhibit increased climbing behavior (active coping behavior) and decreased immobility (passive coping behavior). Interestingly, we similarly examined adolescent rats (P41-P50). Although we observed an increase in LHb excitability, there was a drastic shift in behavioral phenotype. Adolescent MD rats exhibit increased immobility time and decreased climbing behavior. This suggests that, if involved, the LHb could play a role in the shift from a panic-like to a depressive-like phenotype. Future research will determine whether LHb hyperexcitability truly underlies these MD-induced behavioral abnormalities and whether they can be reversed through the use of histone deacetylase inhibiton.
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