In This Issue

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A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Stress-Related Epigenetic Mechanisms of Histone Modifications

Cdk5 (cyclin-dependent kinase 5) has been implicated in fear memory and stress behavior in male mice, but mechanisms in females are less understood. **Sase *et al.*** (pages 623–634) applied *Cdk5*-targeted epigenetic editing of both male and female mice. *Cdk5* expression and acetylation was increased in male, but not female, mice after fear memory retrieval. Further, histone acetylation in the hippocampus of female, but not male, mice attenuated fear memory retrieval and increased tau phosphorylation. These findings contribute to our understanding of sex-specific mechanisms in the epigenetic regulation of *Cdk5* and provide insight into the sex differences associated with stress-related disorders.

Stress may alter epigenetic regulation of transcriptional programming, leading to depression, but the underlying mechanisms remain unclear. Using a model of chronic social defeat stress, **Liu *et al.*** (pages 635–649) report that susceptible rodents show lower histone crotonylation and increased chromodomain Y-like protein (CDYL) in the prelimbic cortex, which was associated with depression-like behaviors. CDYL knockdown prevented stress-induced depression-like behaviors. Further, the authors show that CDYL-mediated histone crotonylation regulates structural plasticity of dendritic spines in prelimbic cortex through the control of VGF expression, suggesting that it plays a critical role in stress-induced depression and should be investigated as a potential therapeutic target.

Hippocampal SIK2 Plays a Role in Depression

Both CREB (cyclic adenosine monophosphate response element binding protein) and BDNF (brain-derived neurotrophic factor) are implicated in stress and depression. Salt-inducible kinases (SIKs) phosphorylate the CREB-regulated transcription coactivators (CRTCs). Here, **Jiang *et al.*** (pages 650–666) show that chronic stress in mice increases the expression of hippocampal SIK2, leading to decreased CRTC1-CREB binding and BDNF signaling in the hippocampus and depressive-like behaviors. Hippocampal SIK2 blockade exerted antidepressant-like effects mediated via the CRTC1-CREB-BDNF pathway. Lastly, the antidepressant actions of fluoxetine, venlafaxine, and mirtazapine were all found to involve hippocampal SIK2-CRTC1 signaling. Collectively, these findings suggest that hippocampal SIK2 may be a potential target for antidepressant development.

Immune Cells and Stress

Chronic stress causes long-lasting changes in microglia and neurons, which is associated with increased behavioral reactivity to later acute stressors and immune challenge. **Weber *et al.*** (pages 667–678) depleted and repopulated microglia after mice were exposed to chronic stress, and they report that this prevented heightened immune reactivity to a peripheral immune challenge but did not prevent anxiety following acute stress. These data provide evidence that microglia and neurons remain stress-sensitized weeks after chronic stress and are essential for stress-induced immune reactivity but not recurrence of anxiety behaviors.

Interleukin (IL)-6, an inflammatory cytokine, is elevated in animals and humans exposed to chronic stress, but its functional role remains unclear. Here, **Niraula *et al.*** (pages 679–689) demonstrate that social defeat stress in wild-type mice increased IL-6, which in turn primed circulating monocytes that were then recruited to the brain and took on an inflammatory phenotype, including increased IL-1β expression. Conversely, IL-6 knockout mice showed an attenuated inflammatory profile in monocytes, reduced inflammatory signaling in the brain, and an absence of anxiety-like behavior. These data reveal an IL-6–dependent transcriptional monocyte signature that promotes anxiety.

Brain Network Differences of Susceptibility Versus Resilience

Individuals with a history of maltreatment show multiple brain abnormalities regardless of the presence or absence of psychopathology. **Ohashi *et al.*** (pages 690–702) constructed network models using diffusion tensor imaging data from young adults in an effort to identify compensatory brain alterations associated with resilience. The authors found that maltreated participants with and without psychopathology show the same abnormalities in global network architecture when compared with unexposed control participants. However, asymptomatic (resilient) participants showed reduced nodal efficiency, including in the right amygdala, relative to symptomatic (susceptible) participants. These findings suggest that specific differences in brain network architecture may moderate the relationship between maltreatment and psychopathology.

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