In This Issue

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

Mechanisms of Depression-Related Behavior and Biology

Evidence suggests that sirtuins play a role in cognition and synaptic plasticity, but their role in mood regulation remains unclarified. Using a depression model of mice subjected to chronic stress, **Abe-Higuchi *et al.*** (pages 815–826) report that pharmacologic and genetic inhibition of hippocampal SIRT1 increased depression-like behaviors, whereas SIRT1 activation blocked the development of depression-like behaviors and increased phosphorylation of ERK1/2. These data suggest that dysfunction of the hippocampal SIRT1-ERK1/2 pathway may be a mechanism underlying the development of depression-related behavior elicited by chronic stress and may thus represent a novel therapeutic target for depression.

Depression is associated with disturbances in circadian rhythms, but most prior studies investigating this relationship have been unable to exclude the effects of noncircadian mechanisms. **Landgraf *et al.*** (pages 827–835) present a mouse model in which the CLOCK gene was functionally inactivated by a short hairpin Bmal1 RNA. Bmal1 is a protein that dimerizes with the CLOCK gene. Inactivation of *Clock* in the suprachiasmatic nucleus (SCN), the brain region responsible for the control of circadian rhythms, suppressed circadian rhythms. Their data reveal that this selective disruption of *Clock* in the SCN causes depression-like behavior and increases sensitivity to stress, establishing SCN-*Bmal1*-knockdown mice as a novel animal model of depression from which noncircadian effects can be excluded.

ADCY3, which codes for type III adenylyl cyclase (AC3), has recently been implicated in major depressive disorder in humans. Here, **Chen *et al.*** (pages 836–848) employed multiple approaches in *Adcy3* knockout mouse models to evaluate the role of AC3 in depression. They found that loss of AC3 leads to reduced neuronal activity, altered sleep patterns and depression-like behaviors, providing evidence that supports AC3 as a risk factor for depression.

Brain Development in Children at Risk for Depression

Depression is associated with abnormal functional connectivity in multiple brain networks, but whether this reflects the state of or risk for depression is unknown. Using resting-state functional magnetic resonance imaging, **Chai *et al.*** (pages 849–858) report that unaffected children of parents with a history of depression exhibit altered functional connectivity in default mode, cognitive control, and affective networks, compared to children of parents with no history of depression. These results identify functional brain measures that could potentially be used in early intervention efforts for at-risk children to reduce their likelihood of developing depression.

Maternal depression during and following pregnancy is linked to numerous negative outcomes in children, but few studies have examined the association between maternal depression and children's brain structure. Using magnetic resonance imaging, **Lebel *et al.*** (pages 859–868) report that higher maternal depressive symptoms in the second trimester of pregnancy and postpartum are associated with altered brain structure in their preschool-aged children, including reduced cortical thickness in right frontal and middle temporal regions and lower diffusivity. These results suggest that brain development may be abnormal in children exposed to higher levels of maternal depression.

Early Life Stress × *FKBP5* Polymorphisms = Depression

Polymorphisms in *FKBP5*, which is involved in the regulation of the hypothalamic-pituitary-adrenal axis stress response, have been linked to self-reported early life stress. Analyzing data from a prospective birth cohort study, **Lahti *et al.*** (pages 869–877) found an association between depressive symptoms in midlife and early life stress in individuals with specific *FKBP5* variants. These moderating effects of *FKBP5* were present for both self-reported and objectively recorded experiences of early life stress, but not for stressful events in adulthood.

Neuromedin U and Drug Reward

Neuromedin U, a neuropeptide enriched in the nucleus accumbens, has been linked to the regulation of food reward, but whether it also plays a role in the regulation of drug-related reward or behavior has been unclear. **Kasper *et al.*** (pages 878–887) characterize a gamma-aminobutyric acid (GABA) ergic pathway from the dorsal raphe nucleus to the nucleus accumbens, demonstrating that neuromedin U signaling regulates the release of GABA into the nucleus accumbens, which leads to the suppression of cocaine-driven behavior in rats. These findings suggest the overlap of food and drug-related mechanisms on circuitry underlying motivated behaviors.

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