In This Issue

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

Stress and the Amygdala: Circuitry and Drug Mechanisms

Stress is associated with synaptic remodeling in basolateral amygdala (BLA) projection neurons (PNs), but whether chronic stress differentially impacts the distinct functional output circuits of BLA PNs remains unclear. Using a mouse model of chronic restraint stress, **Zhang *et al.*** (pages 189–201) found that stress increases the density of mature mushroom-shaped spines and augments glutamatergic transmission in BLA PNs targeting the ventral hippocampus, a brain region implicated in establishing emotional contexts, but not in those targeting the medial prefrontal cortex or nucleus accumbens. These stress effects in BLA to ventral hippocampus PNs correlated with anxiety-like behavior, suggesting that chronic stress may shape the glutamatergic synapses of amygdala neurons in a circuit-specific manner.

Benzodiazepines, a class of drugs used to treat anxiety, modulate the gamma-aminobutyric acid A receptor ($GABA_AR$), although the precise mechanisms of action remain unclear. Here, **Shen *et al.*** (pages 202–213) report that deficits in palmitoylation of gephyrin, a scaffold protein for $GABA_AR$, in the BLA was associated with increased anxiety behavior in rats. Benzodiazepine administration increased BLA gephyrin palmitoylation, which was shown to be dependent on $GABA_AR$ postsynaptic stabilization. These data provide a mechanistic link between gephyrin palmitoylation in the BLA and the anxiolytic effects of benzodiazepines.

Autophagy, which helps maintain cellular homeostasis, plays a role in memory processes. SAR405 is a novel compound that selectively inhibits vacuolar sorting protein 34 (Vps34) and thus prevents autophagy. **Li *et al.*** (pages 214–225) used an animal model of auditory fear conditioning to investigate the effects of SAR405 on fear memories. They report that SAR405 pretreatment in the BLA prevented fear memory consolidation via autophagy inhibition and disruption of the autophagic degradation of $GABA_A$ receptors. These findings suggest that SAR405 may have value as a potential therapeutic approach for disorders characterized by exaggerated fear memories.

Role of Adrenergic Receptors in Resilience and Arousal

Recent evidence suggests that noradrenergic locus coeruleus neurons projecting to ventral tegmental area (VTA) dopamine neurons are implicated in stress resilience. Using a chronic social defeat stress mouse model of depression, **Zhang *et al.*** (pages 226–236) investigated the mechanisms underlying the promotion of resilience by this circuitry. They found that locus coeruleus modulation of VTA neuronal firing is increased in resilient, but not susceptible, mice. Optogenetic activation of this circuitry in susceptible mice reversed depression-like behaviors and stress-induced cellular changes. Further, they identified α_1- and β_3-adrenergic receptors in VTA dopamine neurons as necessary for these proresilience effects. These data provide insight into the mechanisms underlying the neural circuitry of stress resilience.

The regulation of wakefulness is critical for normal behavioral function. Dopamine neurons in the ventral periaqueductal gray (vPAG) promote arousal, but the underlying mechanisms remain unclear. Here, **Porter-Stransky *et al.*** (pages 237–247) used multiple techniques in mice to show that α_1-adrenergic receptors in the vPAG increase arousal, promote glutamatergic input onto vPAG dopamine neurons, and are enriched on vPAG astrocytes. These data suggest that noradrenergic mechanisms control the wake-promoting effects of vPAG dopamine neurons.

Reversing Influences of Intergenerational Stress

There is growing evidence for transgenerational negative effects of stress conveyed via epigenetic mechanisms, which raises questions about how to prevent negative effects of stress in parents from affecting their children. For example, it is not clear whether extinction-based cognitive behavioral treatments for posttraumatic stress disorder will prevent negative effects in offspring. **Aoued *et al.*** (pages 248–256) used an olfactory fear conditioning model to test this hypothesis in animals and found that extinction training in adult male mice reversed behavioral sensitivity and enhancements in olfactory neuroanatomy in their offspring. Further, extinction training restored DNA methylation at the promoters of odorant receptor genes in the parental sperm. Taken together, these data suggest that behavioral interventions have the potential to reverse behavioral, neuroanatomical, and germline influences of intergenerational stress.

Cell-Dependent Cortical Microcircuit Aging

Age-related behavioral and cognitive changes are mediated by changes in cortical microcircuits. Here, **Shukla *et al.*** (pages 257–267) assessed the long-term behavioral and cell-specific gene expression changes associated with aging in mice. They found distinct age-related transcriptomic profiles across the four cell types that form cortical microcircuits. Excitatory pyramidal cells showed high age-related vulnerability, while inhibitory neurons that express parvalbumin, somatostatin, and vasoactive intestinal peptide varied in the degree of adaptation to aging. Also, age-associated changes in cognition and anxiety correlated with normal age-related gene expression changes. These data provide insight into the cell-specific molecular changes associated with aging.

Adversity and Biological Aging in Youths

Recent conceptual models argue that early life adversity (ELA) accelerates development, which may contribute to poor health outcomes, but whether this pattern is present across all ELA or emerges following only specific adversity types is unclear. **Sumner *et al.*** (pages 268–278) assessed two metrics of biological aging in children and adolescents exposed to ELA characterized by threat (e.g., violence) or deprivation (e.g., neglect, food insecurity). They found that exposure to threat-related, but not deprivation-related, ELA is associated with advanced DNA methylation age and pubertal stage relative to chronological age. Accelerated DNA methylation age was related to greater depressive symptoms. These data suggest that early threat-related experiences may accelerate biological aging.

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