In this Issue

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

Susceptibility and Resilience to Stress

Dietz *et al.* (pages 408–414) demonstrate that effects of chronic social stress can be paternally transmitted to both male and female offspring during normal breeding. This depressive-like phenotype was associated with increased plasma levels of corticosterone and decreased levels of vascular endothelial growth factor, both of which have been associated with depression. They also performed in vitro fertilization with sperm from control and defeated mice, but the transmission of depressive-like behaviors was dramatically reduced in these offspring of defeated fathers, compared to natural offspring of defeated fathers, suggesting a limited role of epigenetic factors.

Animal models may elucidate the neurobiological mechanisms that underlie susceptibility or resilience to traumatic stress. **Olson *et al.*** (pages 441–448) describe a mouse model of posttraumatic stress disorder (PTSD) called TERS, or the traumatic experience with reminders of stress, in which some animals show behavioral correlates of PTSD-like symptoms (susceptible mice) whereas others do not (resilient mice). They also provide preclinical evidence for the dysregulation of the noradrenergic system in PTSD.

Chronic mild stress induces anhedonia in some rats, whereas others show resilience to stress. Using magnetic resonance imaging (MRI), diffusion kurtosis imaging and proton MR spectroscopy, **Delgado y Palacios *et al.*** (pages 449–457) now show that the hippocampus is differentially affected by chronic mild stress in anhedonic and resilient subgroups of rats, compared to controls.

The consequences of traumatic stress are determined by both genetic and environmental factors. **Christianson *et al.*** (pages 458–464) demonstrate that providing a safety signal to rats, one that predicts stressor-free periods, in the midst of traumatic stress prevented the development of stressor-induced anxiety. The data suggest that safety signals are detected in the insular cortex, which leads to inhibition of fear circuits in the amygdala and bed nucleus of the stria terminalis.

Biological Responses to Fear and Anxiety

McTeague *et al.* (pages 415–424) measured heart rate acceleration, sweat gland activity, facial expression, and startle reflex reactions in panic disorder patients with and without agoraphobia and healthy controls during fearful mental imagery. Patients with only panic disorder showed heightened defensive reactivity. In contrast, panic disorder patients with agoraphobia showed dampened reactivity, despite reports of intense fear during imagery. This blunted physiological reaction may represent a compromise of the body's fear/defense system secondary to the stress of sustained apprehension and hyperarousal.

Telomeres are cellular structures that index biological age. Individuals with short immune cell telomeres have increased risk for age-related diseases and early death. **O'Donovan *et al.*** (pages 465–471) now report that individuals with PTSD have shorter immune cell telomeres, compared to control subjects, but this association was only significant for those PTSD individuals with a history of multiple childhood traumas. The findings suggest that the aftermath of trauma may be characterized by exaggerated biological responses to stress, which may lead to accelerated biological aging and increased risk for disease.

There is an ongoing debate as to whether threat processing within the amygdala can occur outside of conscious stimulus awareness. Using event-related functional MRI in conjunction with an approach to operationalize awareness, **Lipka *et al.*** (pages 472–478) found stronger amygdalae responses in phobic subjects compared to controls during conscious stimulus processing, but enhanced activation in only the right amygdala during unconscious processing. These findings provide evidence for subliminal threat processing in specific phobia, with the magnitude of amygdala responses specifically potentiated by sustained hypervigilance for threat.

Stress Effects: Potential Treatment Targets and Mechanisms

Kappa-opioid receptor (KOR) blockers have antidepressant- and anxiolytic-like effects in animal models. In this issue, **Knoll *et al.*** (pages 425–433) demonstrate that microinfusion of the KOR antagonist JDTic into the amygdala is sufficient to produce anxiolytic effects. They also provide evidence that exposure to fear-inducing stimuli increases the expression of KORs in the amygdala, and rats that best learn to inhibit their fear responses have lower KOR expression in this region. Together, these findings suggest that fear conditioning and extinction dynamically regulate KOR expression in the amygdala.

Cannabinoid agonists have antinociceptive and anxiolytic-like effects, but potentially adverse effects on memory. **Busquets-Garcia *et al.*** (pages 479–486) evaluated the roles of two specific endocannabinoids using the enzyme inhibitors URB597 and JZL184 in mice. They show that anandamide, but not 2-arachidonoylglycerol, is a central component in the modulation of memory consolidation and that both URB597 and JZL184 induce anxiolytic-like effects through different cannabinoid receptors. The results also suggest that cannabinoid receptor 2 may serve as a novel target for the treatment of anxiety-related disorders.

Early life stress is associated with several neuropsychiatric disorders that do not manifest until adolescence, but the mechanism of these delayed effects is unclear. **Brenhouse and Andersen** (pages 434–440) investigated in rats whether the inflammatory enzyme cyclooxygenase-2 plays a role in the effects of early life maternal separation stress on parvalbumin-expressing interneurons in the prefrontal cortex. Prophylactic cyclooxygenase-2 inhibition during preadolescence prevented parvalbumin loss and improved working memory deficits seen in adolescence after maternal separation.

The *fosB* gene encodes FosB and ΔFosB proteins. ΔFosB is highly stable and accumulates in brain after stress or antidepressant treatments. Using two types of new *fosB* mutant mice, **Ohnishi *et al.*** (pages 487–495) found that mice with accumulated ΔFosB showed increased locomotor activity and elevated Akt phosphorylation independent of FosB. ΔFosB+ mice also showed antidepressive-like behaviors and increased E-cadherin expression in striatum, but these effects were only detected while in the presence of FosB. These data highlight the importance of *fosB* in regulating stress and mood disorders.

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