In this Issue

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

Evaluating Protection Against and Response to Stress

Inappropriate regulation of the brain corticotropin-releasing factor system is associated with anxiety disorders and depression. Using transgenic mice overexpressing urocortin 3, **Neufeld-Cohen *et al.*** (pages 437–447) demonstrate that chronic activation of corticotropin-releasing factor receptor type 2 promotes an anxiety-like state with attenuated behavioral and hormonal responses to stress. This profile may resemble psychiatric syndromes such as posttraumatic stress disorder (PTSD), chronic fatigue and chronic pain states, and suggests a potential role for this receptor in such disorders.

Ghrelin stimulates feeding and metabolism, but may also play a role in the response to stress. **Spencer *et al.*** (pages 457–465) report that ghrelin knockout mice, compared to wild-type mice, showed more anxiety-like behavior and a lower corticosterone response after acute stress, and also displayed increased neuronal activation, which was reversed by exogenous ghrelin. These findings suggest that ghrelin restricts anxiety after acute stress by influencing the hypothalamic-pituitary-adrenal axis and engaging a novel brain circuit involving ghrelin receptor activation of urocortin-1 neurons.

Using an animal model of PTSD, **Rao *et al.*** (pages 466–475) demonstrate that elevated levels of glucocorticoids at the time of acute stress confers protection against the delayed enhancing effect of stress on synaptic connectivity in the basolateral amygdala and anxiety-like behavior. These observations are consistent with clinical reports on the protective effects of glucocorticoids against the development of PTSD symptoms triggered by traumatic stress.

Emotion Regulation and Attention Control

Borderline personality disorder (BPD) is characterized by emotion dysregulation. Using functional magnetic resonance imaging, **Hazlett *et al.*** (pages 448–456) report that, compared with healthy and psychiatric control groups, BPD patients show exaggerated amygdala activation to repeated emotional pictures (unpleasant and pleasant) but a blunted response on self-report valence ratings. BPD patients did not differ in responses to repeated neutral pictures, suggesting a general arousal abnormality characterized by prolonged responses to highly arousing stimuli rather than negative stimuli per se.

Blair *et al.* (pages 476–482) examined emotion regulation and attention control in control subjects and in patients with generalized social phobia and/or generalized anxiety disorder. Control subjects showed increased activation in dorsal anterior cingulate cortex and parietal cortices, brain regions involved in attention control, when regulating their responses. This activation was not present among any of the patient groups, suggesting that a reduced ability to recruit these attention systems might represent a general risk factor for anxiety disorders.

Developmental Influences: Maternal, Hormonal, and Genetic Effects

Data suggest that fetal exposure to maternal mood disorders may influence development. One hypothesized pathway is distress–linked constriction in uterine or umbilical blood flow (UBF). **Monk *et al.*** (pages 483–490) examined the influence of women's depression and anxiety symptoms and medication use on UBF measured at 25 weeks gestation. No associations were found between maternal prenatal mood symptoms and UBF. However, both chronic and acute consumption of bupropion was associated with reduced UBF.

Maternal care influences hippocampal development, synaptic plasticity, and stress regulation in offspring. **Bagot *et al.*** (pages 491–498) examined whether altered *N*-methyl-D-aspartate receptor (NMDAR) function underlies the interaction of maternal and stress effects on hippocampal synaptic plasticity. They found elevated NMDAR function coupled with insensitivity to corticosterone modulation in rats that received low, compared to high, levels of maternal care. These findings are indicative of a chronic alteration of NMDAR function in low-care offspring, which may be responsible for their long-term potentiation deficits.

Hormonal changes are associated with increased risk of anxiety and depression symptoms, and reduced brain-derived neurotrophic factor has been associated with increased affective pathology. **Bath *et al.*** (pages 499–504) now report that female mice homozygous for the *BDNF* Val66Met single nucleotide polymorphism exhibit increased anxiety-like behaviors over the course of early development, show significant fluctuations in anxiety-like behaviors over the estrous cycle, and as adults differ from wild-type mice specifically during the estrus phase of the estrous cycle. These findings have implications regarding the potential role of this variant in contributing to developmental and reproductive hormone-dependent changes in affective disorders in humans.

Research has documented an association between parental and offspring PTSD among persons exposed to extreme stress, but it is unknown whether such an association exists in the general population. **Roberts *et al.*** (pages 505–511) found a dose-response relationship between mothers' PTSD symptoms and risk of PTSD in their adult children in a large population-based sample. Children of women who had PTSD were more likely than children of women without PTSD to experience traumatic events. This pattern suggests that this type of heritability is related to a tendency to engage in risky behaviors rather than an altered pattern of stress response.

Defensive Reactivity in Panic Disorder

Animal models suggest that acute panic and anxious apprehension are distinct emotional states of defensive reactivity. Assessing behavior, anxiety and panic symptoms, heart rate, skin conductance level, and potentiation of the startle reflex during a standardized behavioral avoidance test, **Richter *et al.*** (pages 512–520) demonstrate that defensive reactivity in patients suffering from panic disorder and agoraphobia is dynamically organized, shifting from anxious apprehension to acute panic with increasing imminence of interoceptive threat. This finding provides evidence that defensive reactivity in humans is organized in a comparable way as described in animal models.

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