## S E C T I O N

## **ANXIETY AND STRESS DISORDER**

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The chapters in this section reflect the advances that have been made in our understanding of the molecular neurobiology and neural circuits underlying fear and anxiety states and the potential for badly needed advances in the diagnosis, pathophysiology, and treatment of anxiety disorders.

Many readers will be surprised by the data cited in the Kessler and Greenberg chapter on the economic burden of anxiety and stress disorders. Recent surveys demonstrate that anxiety and stress disorders are the most commonly occurring of all mental disorders. Anxiety disorders are temporally the primary disorders in many people with a lifetime history of any mental disorder. Indeed the combined occurrence of high lifetime prevalence with an early age at onset and high chronicity makes anxiety disorders unique.

The chapter by Stein and Lang reviews in detail the course of anxiety and stress disorders over the lifetime. One point they make that is especially important to emphasize is the critical need for further research in childhood anxiety disorders. The presence of an anxiety disorder in childhood or adolescence is a predictor of the persistence into adulthood of not only anxiety disorders but other psychiatric disorders as well, particularly depression. It is not known if early effective treatment of childhood and adolescent anxiety disorders will prevent the development of psychiatric disorders later in life.

Important insights into the pathogenesis of anxiety disorders come from preclinical investigations reviewed by Davis in his chapter. The identification of the brain structures and neural circuits involved in the generation of fear and anxiety-related behaviors are most noteworthy. The delineation of specific neural pathways mediating conditioned and unconditioned fear can logically guide the design and conduct of clinical studies investigating the neurobiological mechanisms of anxiety disorders such as generalized anxiety disorders

der (unconditional fear) and phobic disorders (conditioned fear). Increased knowledge of the neural mechanisms and neurotransmitters involved in extinction may offer novel therapeutic approaches. If we can discover pharmacologic methods to enhance extinction, more effective drug treatments for conditioned fear or anxiety may be found. There is evidence of extinction being mediated by  $\gamma$ -aminobutyric acid (GABA) release. This suggests the possibility of augmenting extinction-based psychotherapy with GABA agonist drug treatment.

Determination of the genetic contribution to anxiety disorders is critically important to progress in understanding etiology and improving treatment.

Merikangas and Pine review the evidence that the major subtypes of the anxiety disorders aggregate in families. However, the magnitude of heritability is relatively moderate, indicating a strong environmental contribution to etiology. Unfortunately, thus far linkage and association studies in anxiety disorders have not been fruitful. Future studies should determine if components of anxiety syndromes are controlled by specific genes. The revolution occurring in genomics research as a consequence of sequencing the human genome and the identification of over 1½ million single nucleotide polymorphisms (SNPs) should make discovery of anxiety-related disease genes a reality. Strategies that are complementary to linkage analyses and utilize data from linkage studies are indicated. Such approaches couple the genotyping of candidate functional SNPs with linkage and equilibrium mapping in chromosomal regions implicated in linkage studies. In parallel with the genetic studies, enhanced efforts to identify endophenotypic biological vulnerability markers are indicated. The studies cited in the chapter on temperament, anxiety sensitivity, autonomic reactivity, psychophysiologic function, ventilatory function, neurochemical, and neuroendocrine factors are good examples of this approach.

Bakshi and Kalin point out in their chapter the advan-

tages of using putative animal endophenotypes of stress and anxiety to identify genetic abnormalities associated with anxiety disorders. Rodent and nonhuman primate studies of mother-infant interactions are particularly compelling, given the important clinical implications if these interactions are found to be a critical factor in future fearful disposition. Targeted mutations leading to anxiety-like endophenotypes in transgenic mice have suggested roles for serotonin receptor subtype 1A (5-HT<sub>1A</sub>), corticotropinreleasing hormone (CRH), GABA, neuropeptide Y, cholecystokinin, and substance P neural systems in the generation on anxiety-fear behaviors. These studies provide clues for the discovery of new medications and pharmacogenomic approaches to treatment. Accelerated drug development efforts focusing on corticotropin-releasing factor 1 (CRF-1) receptor antagonists and benzodiazepine agonists with an anxioselective subunit profile are indicated. The feasibility of pharmacogenomic investigations designed to evaluate the relationships among functional polymorphisms of the 5-HT<sub>1A</sub> receptor, benzodiazepine receptor, and GABA synthesis enzymes and therapeutic responses to specific drugs should be explored.

It is imperative that these findings from the preclinical studies of anxiety and fear states be translated into increased knowledge of the neural circuits and associated neural mechanisms that can account for the signs and symptoms in patients with anxiety disorders. Rauch and Shin reviewed the neuroimaging findings relevant to anxiety and stress disorders. Their chapter emphasizes the areas of congruence between animal studies and clinical neuroimaging investigations. For example, imaging studies in healthy subjects support a role for the amygdala in fear conditioning and the frontal cortex in extinction. In the imaging studies of patients with anxiety disorders, progress has been made in identifying specific neural circuits. Functional relationships among the amygdala, hippocampus, and medial prefrontal cortex have been reported in patients with posttraumatic stress disorder (PTSD). The imaging findings in patients with obsessive-compulsive disorder (OCD) are consistent with "pathology" in cortico-striatal-thalamo-cortical circuitry. Unfortunately, a critical gap in knowledge exists regarding the relevant neural circuits involved in panic disorder, social anxiety disorder, and generalized anxiety disorder. The neurochemical systems associated with anxiety and fear circuits are reviewed in the chapter by Charney and Drevets. As predicted from the preclinical studies, abnormalities in norepinephrine, benzodiazepine, glucocorticoid, and CRH systems have been identified in patients with anxiety disorders. However, most of the findings reviewed should be deemed preliminary, and they require replication. None of the reported neurobiological distinctions between patients and controls is robust enough to be of diagnostic relevance.

Tallman, Cassella, and Kehne review the mechanism of action of anxiolytic drugs and the status of new and novel therapeutic agents. They highlight the therapeutic potential and current status of CRH antagonist drug development. They also note the potential of developing targets for the CRF-2 receptor and other peptides, such as vasoactive intestinal peptide (VIP), involved in the regulation of stress. In regard to benzodiazepine drug development, they note an ideal drug might have limited effects on the  $\alpha_1$  subtype with increased responsiveness at  $\alpha_2$  and  $\alpha_3$  subunits. Glutamate receptor agonists and modulators are proposed as viable targets for anxiety disorders. For example, point mutations in the glycine-binding site of the NR1 subunit result in mice that have reduced glycine affinity and an anxiolytic profile. Group II metabotrophic glutamate agonists are in early clinical development for the treatment of anxiety disorders. Other novel drug targets include antagonists of AMPA receptors and antagonists of strychnine-sensitive glycine site, both of which show anxiolytic profiles in animal models.

Ultimately, the goal of research on the neurobiological underpinnings of anxiety disorders is to lead to more effective, more rapidly acting treatments, to achieve a more complete response, and to be able to predict responses to specific treatments. In their review, Gorman, Kent, and Coplan highlight the extremely broad spectrum of action of norepinephrine and serotonin transport inhibitors in anxiety disorders. These drugs are limited by a delayed onset and incomplete response in many patients. This suggests that norepinephrine and serotonin have broad modulatory effects on other neuronal systems, which are more primarily related to the pathogenesis of anxiety disorders.

In summary, a reading of these chapters reveals that there have not been fundamental advances in our ability to diagnose anxiety disorders based on known etiology. The mainstay of medication treatment continues to be classes of medications that have existed for decades. There are major gaps in our knowledge of anxiety disorders in children. The mechanisms responsible for the occurrence of anxiety disorders in childhood and adolescence leading to increased risk for other psychiatric disorders in adulthood are unknown. However, the potential for progress is great. A multidisciplinary team approach utilizing the findings from preclinical investigations on neural circuitry, neurochemistry, and genetics to inform clinical investigations of genetic vulnerability, environmental risk factors, neuroimaging, pharmacogenomics, and novel drug design and testing will be a pathway to discovery.