Biological Psychiatry: Celebrating 50 Years

Commentary

Interneurons in the Prefrontal Cortex: A Role in the Genesis of Anxiety in Adolescence?

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Anxiety and related disorders are some of the most common and disabling disorders, with nearly 30% of the population experiencing anxiety symptoms at some time. The overall cost to the community is enormous, and in the developed world these disorders significantly contribute to the global burden of disease in disability-adjusted life years. In the United States, the lifetime prevalence of panic disorder is 4.7%, with prevalence rates of 12.5% for specific phobia, 12.1% for social anxiety disorder, and 5.7% for generalized anxiety disorder (1). The DSM-5 describes anxiety disorders as those causing recurrent, persistent, and excessive worry.

While anxiety shares many features with fear, the two can be differentiated in that fear is an emotional response to a real or an imminent threat that dissipates when the threat is resolved, whereas anxiety is an anticipatory response to perceived future threats that is long lasting. Fear is a generalized response that arose as a mechanism to protect from us from dangerous situations and that evokes a combination of physiological and behavioral responses that lead to a fight or flight response. The neural circuits and biological mechanisms that mediate fear have long been studied in both humans and animal models using fear conditioning, a Pavlovian learning paradigm in which an emotionally neutral sensory stimulus (the conditioned stimulus [CS]) is contingently paired with an aversive one. After a few pairings, subjects learn that the CS is predictive of danger and develop a defensive response—they form a memory of the dangerous nature of the CS. However, subsequent presentations of the CS with no accompanying aversive stimulus breaks this relationship in a process called extinction, and subjects learn that the CS is no longer dangerous. The neural circuits that underpin fear learning and extinction have been extensively studied, and it is well established that the amygdala, hippocampus, and prefrontal cortex play key roles in both fear learning and extinction.

The physiological and behavioral changes that accompany anxiety have much in common with those evoked by fear, and both fear and anxiety share many of the same neural circuits. This close similarity in the physiological response to fear and anxiety has led to a general understanding that anxiety disorders may arise from the dysfunction of neural circuits that mediate fear. Indeed, extinction forms the basis for many forms of cognitive behavioral therapy that are used to treat some anxiety disorders (2).

The prefrontal cortex, like most cortical areas, contains two types of neurons: excitatory pyramidal neurons and inhibitory gamma-aminobutyric acidergic interneurons. These interneurons comprise <20% of the total interneuron population but maintain tight control over the circuits that are engaged and over the overall activity in this region (3). Two distinct types of interneuron, distinguished by expression of the markers parvalbumin (PV) and somatostatin (SST), form most of the population of interneurons. These two populations have distinct developmental origins and different types of synaptic contacts. Interneurons that express SST are born earlier and innervate distal dendritic regions on local pyramidal neurons, whereas cells that express PV have a delayed development and innervate the soma and proximal dendritic regions (4). As such, these two cell types have different physiological functions.

While the etiology of anxiety disorders is not well understood, a common factor is the early age of onset—the median age of onset of lifetime anxiety disorders is during adolescence (1). First-line treatments for anxiety disorders include pharmacotherapy, such as benzodiazepines and selective serotonin reuptake inhibitors, and behavioral treatments, such as cognitive behavioral therapy—and often a combination of pharmacotherapy and behavioral treatments. A clear understanding of the mechanisms that underpin these disorders is essential to the prevention and management of these disorders. Interestingly, the prefrontal cortex undergoes a prolonged period of development. Extinction forms the basis of many cognitive behavioral therapies, and in both animal (5) and human (6) studies researchers have found a period of extinction suppression during adolescence.

Extinction learning, during which subjects learn that a CS is not dangerous, requires the medial prefrontal cortex (3), and *N*-methyl-D-aspartate receptor–mediated synaptic plasticity in the medial prefrontal cortex (7) is required for the consolidation of extinction memory. Afferents from the prefrontal cortex mediate the expression of extinction, and interneurons in this region are known to play a key role (8). Thus, dysregulation of extinction during adolescence may be a contributing factor to the development of anxiety disorders during this time, and understanding the biology that underpins this difference may provide clues to both the prevention and management of anxiety disorders. In this issue of *Biological Psychiatry*, Koppensteiner *et al.* (9) set out to understand the biological changes that mediate the lack of extinction during adolescence. Using a variety of transgenic mice to label specific interneuron types, Koppensteiner *et al.* (9) study the development of local circuits in the infralimbic prefrontal cortex and the impact of fear learning and extinction. The developmental changes in the prefrontal cortex have been studied before, but this study focuses specifically on the infralimbic prefrontal cortex, a region with a key role in fear extinction (3).

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Using simple behavioral paradigms, Koppensteiner *et al.* (9) first repeated the observation that unlike preadolescent and adults, adolescent animals (postnatal day 29) have a deficit in extinction. They went on to study the development of PV and SST interneurons in the infralimbic prefrontal cortex and the impact of fear learning and extinction on local connections made by these two types of interneurons. The authors found that PV interneurons have a prolonged developmental period, with changes in their electrophysiological properties into adulthood, while SST interneurons are mature at preadolescence. In contrast to the electrophysiological properties, excitatory synaptic input to PV interneurons are mature in the preadolescent, while in SST interneurons, excitatory synaptic input undergoes a delayed maturation. With clear changes in synaptic input to the different types of interneurons, they then tested the impact of fear conditioning and extinction on inhibitory transmission between each interneuron type and local pyramidal neurons. Interestingly, there is a significant increase in inhibition mediated by SST interneurons during adolescence. Moreover, this enhanced inhibition is suppressed by fear learning and does not recover after extinction learning. In contrast, there was little change in these synapses after fear learning or extinction in preadolescent or adult mice.

These results show that in the infralimbic prefrontal cortex, local inhibition is clearly different in adolescent animals compared with preadolescent and adult animals. In particular, inhibition mediated by SST interneurons appears to be much larger during adolescence. These neurons provide shunting inhibition in the dendritic tree and thus modulate synaptic plasticity and learning (10). The finding that these inputs are enhanced during adolescence and then downregulated by fear learning suggests that they are likely involved in fear-related behaviors. While the mechanistic details have not been elucidated, the inability to change these connections after extinction during this critical period suggests that these changes in the SST interneuron network may underpin the inability to extinguish fear during adolescence.

This study raises important questions for the treatment and management of anxiety disorders. For example, benzodiazepines, while effective anxiolytics, are not recommended because of widespread effects on a range of cognitive functions. These effects result from the generalized impact of these compounds on almost all gamma-aminobutyric acid receptors. These receptors are heteromultimers, raising the possibility of finding compounds with more specific biochemical specificity. Interestingly, dendritic synapses made by SST interneurons have been reported to have a specific subunit composition (10), and it may be interesting to test the impact of agents that modulate these receptors on fear learning and extinction. Anxiety disorders are more prevalent in women than in men. Indeed, this distinction is clear at symptom onset, with adolescent girls more likely to show anxiety-like symptoms. Koppensteiner *et al.* (9) used male cohorts to study development. This is a limitation of their study, and a comparison of these findings in female cohorts would shed more light on the mechanisms that underpin these disorders. Whether these dynamic changes in inhibition during adolescence contribute to the genesis of anxiety remains to be studied. Animal models for psychiatric disorders are rare, and these results provide an exciting new model for thinking about the genesis of anxiety disorders.

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