Commentary

Small-Conductance, Calcium-Activated Potassium Channels: A Key Circuit Determinant for Stress-Induced Amygdala Dysfunction

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Anxiety disorders are one of the most common mental illnesses, encompassing general anxiety disorder, social phobia, posttraumatic stress disorder, and obsessive-compulsive disorder, among other illnesses. Decades of research have significantly improved our understanding of the neural dysfunctions associated with anxiety disorders, in both human studies and reclinical models. However, numerous patients remain treatment resistant owing to the limitations of current therapies (1). Future studies focused on the neurobiological substrate underlying anxiety disorders and, more specifically, neural circuit function and dysfunction will allow for the establishment of new treatment options.

Anxiety disorders are multifactorial. Among multiple hereditary and environmental factors, stress exposure has emerged as a major risk factor for the development of mood disorders, resulting in an increasing number of preclinical studies using stress-induced models for anxiety. Adaptive or anticipatory responses to a stressful environment are initiated through the comparison of environmental stimuli to either innate program or memory and thus rely heavily on limbic and associated circuits in brain structures, such as cortical brain areas, the thalamus, the hippocampus (HPC), the striatum, and the amygdala complex (AMG) (2). The dysfunctional connectivity between these brain areas has been suggested by clinical imaging studies to support pathological behaviors such as anxiety.

Although the AMG is involved in processing positive emotions and reward, it is also well known for playing a crucial role in fear conditioning and for regulating stress-induced adaptive and pathological behaviors, including anxiety. Clinical imaging studies show that patients with anxiety disorders display altered AMG activity, morphology, and connectivity (3). In addition, preclinical studies consistently show that AMG lesions reduce fear, emotional responses, and anxiety-like behaviors, positioning the AMG as a major structure in the expression of anxiety behaviors (2).

The AMG is part of the limbic system and is composed of multiple highly interconnected nuclei situated in the temporal lobe. The AMG can be broken down into three main groups: the basomedial AMG, the central AMG, and the basolateral complex (BLA). The BLA, and more precisely the lateral part of the BLA, is a major signal entrance into the AMG. The BLA interprets sensory information from the thalamus and cortical structures and, in turn, makes synaptic connections within the AMG itself, further projecting to the prefrontal cortex (PFC),

HPC, and the nucleus accumbens (NAc). The BLA is composed of gamma-aminobutyric acid–inhibitory interneurons and projecting glutamatergic principal neurons (PNs). The current view sees the BLA as a heterogeneous but central hub of circuits that controls actions and reactions prompted by a challenging environment.

With recent advances in circuit-tracing and circuit-probing techniques, a more exact parsing of a selective neuronal pathway's function in and contribution to naturalistic and pathological behaviors is now feasible. Combining transgenic tools, viral strategies, and optogenetics, several efforts have been successful in dissecting AMG circuit function, revealing a broad, functional heterogeneity of BLA-specific projections (2,4). Optogenetic manipulations in naïve animals have established that BLA neurons projecting to the NAc (BLA→NAc) support positive reinforcement, while terminal stimulation of BLA projections to the central AMG and ventral HPC (BLA→vHPC) are suggested to drive negative reinforcement and defensive behaviors (2,4). Specifically, BLA→vHPC PN terminal inhibition, mediated by halorhodopsin optomodulation, reduces anxiety-like behaviors. Conversely, BLA→vHPC PN activation via channelrhodopsin optomodulation promotes anxiety-like behaviors (2).

In a previous study, Zhang *et al.* (5) defined different morphological changes due to stress exposure, which depend upon the BLA PN projection target. In a follow-up study in this issue of *Biological Psychiatry*, Zhang *et al.* (6) investigate, in a projection-specific manner, BLA PN activity after acute or chronic stress exposure. While acute stress may engage and prime homeostatic processes and adaptive behaviors, chronic stress exposure often results in robust and pathological adaptations in neuronal activity and morphology, which ultimately drives anxiety-like behaviors and resulting mental health disorders. In line with previous observations (2,5), Zhang *et al.* (6) establish that while all projection neurons from the BLA recover from acute restraint stress, BLA→vHPC PNs but not BLA→medial PFC PNs become persistently active after chronic exposure to restraint stress.

Numerous human imaging studies have supported the notion that healthy cognitive and emotional responses require coordinated activity of a distributed brain macrocircuit. In line with this, Zhang *et al.* (6) show that chronic stress exposure induces disequilibrium between brain areas that are pivotal for the maintenance of adaptive behaviors: BLA→vHPC subcircuit strengthening over BLA→NAc and BLA→medial

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PFC subcircuits. Noteworthy BLA PN collaterals are limited, but BLA PNs do locally modulate neighboring neurons (4). Moreover, neuronal activity within the vHPC, NAc, and medial PFC are also directly disturbed in response to stress exposure. It is therefore unlikely that the imbalanced BLA PN subcircuit has a restrained impact solely onto the BLA→vHPC circuit; this imbalance is more likely to be associated with broader macrocircuit dysfunction. Future studies dissecting the specific contribution of pathological neuroadaptations of one circuit over others may provide further crucial, detailed information in the development of therapies aimed at macrocircuit homeostasis.

Altered neuronal activity may emerge from extrinsic and/or intrinsic modifications and, in part, is dependent on the presence or absence of specific ion channels. How a sole subpopulation, i.e. BLA→vHPC PNs, displays persistent, altered activity is a key component in depicting circuit-specific dysfunctions induced by stress and ultimately the identification of new therapeutic targets. Potassium channels, including small-conductance, calcium-activated potassium channels (SKs), are a key determinant of neuronal excitability. Upon intracellular calcium increase (e.g., action potential calcium influx), SK channels undergo a conformational change leading to an increased potassium current, hyperpolarization of the neuron, and subsequent reduction of excitability. Consequently, a reduction in SK channel function increases neuronal excitability. Three main SK channel families are expressed in the central nervous system (SK1, SK2, and SK3). By combining pharmaceutical tools and electrophysiological approaches, Zhang et al. (6) isolate SK2 channel hypofunction as the key contributor to BLA→vHPC PN hyperexcitability after chronic restraint stress exposure.

Using an elegant combination of circuit-specific, virally mediated overexpression of SK2 channels, Zhang et al. (6) causally link SK2 channel expression in BLA→vHPC PNs to anxiety-like behavior after chronic stress exposure. Indeed, circuit-specific overexpression of the SK2 channel prevents chronic restraint stress–induced anxiety-like behavior. Importantly, this result not only provides the cellular mechanism of BLA→vHPC PN hyperactivity, but also provides information regarding potential discrepancies with previous experiments (7). An earlier set of experiments (7) shows that while SK2 overexpression in the entire BLA reduces anxiety-like behavior in stress-naïve animals, accompanied by a reduction in BLA PN stress-induced dendritic hypertrophy, it does not fully prevent the expression of anxiety-like behavior after stress exposure. In light of the results of the Zhang et al. (6) study, the partial prophylactic effect of SK2 overexpression could be explained by the lack of circuit specificity in the earlier study.

As a key component of action potential after-hyperpolarization in several types of neurons, SK2 channels are also expressed at the dendritic level of BLA PNs, where they gate excitatory, sensory input (8). Consequently, decreased SK2 channel function after stress exposure will alter baseline activity of a neuron and its capacity to properly integrate sensory signal inputs. Interestingly, a blockade of SK channels increases HPC neuron excitability, facilitates HPC synaptic plasticity, and improves memory encoding (9). Taken together with the observations of Zhang et al. (6), an overall SK-specific channelopathy may magnify abnormal BLA→vHPC excitability and connectivity.

Tremendous efforts have been performed to depict the biological signature encoding anxiety behaviors, but our knowledge of the pathological mechanisms remains incomplete. Within this context, the Zhang et al. (6) study is intriguing on two main levels. First, it defines AMG circuit-specific dysfunction associated with pathological behaviors and thus has implications for clinical studies. Second, it reveals a selective cellular mechanism that could lead to future treatment development.

Over the past decade, clinical and preclinical studies have attempted to determine new therapeutic approaches. Although the development of more selective drugs for precise receptor or molecule targeting is highly promising and ongoing, drugs targeting the prototypical anxiety-associated gamma-aminobutyric acid–benzodiazepine system and selective serotonin reuptake inhibitors are foremost in terms of use and success rate. Benzodiazepine and selective serotonin reuptake inhibitors have a broad impact on the central nervous system. Thus, targeting SK channels, a broadly expressed, key physiological modulator of neuronal activity, may offer therapeutic promises. Future studies investigating the precise impact of existing SK2 channel positive allosteric modulators (10) on macrocircuit function and anxiety behavior may provide interesting results, based on the aforementioned discussion.

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Article Information

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