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Spotlight

Overcoming Depression by Inhibition of Neural Burst Firing

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The N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine has been found to have rapid and long-lasting antidepressive effects. Two elegant studies from Hailan Hu's laboratory (Cui et al., 2018; Yang et al., 2018) showed that ketamine blocks burst firing of neurons in the lateral habenula (LHb), rapidly relieving symptoms of depression.

Depression is a serious mood disorder associated with complex and irreversible changes in the brain. Long-term administration of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), has been a standard treatment for patients with depression, but the effects of these agents do not persist after termination of treatment. In contrast, administration of a single dose of ketamine was found to relieve symptoms of depression much faster than other antidepressants (Berman et al., 2000). This rapid and long-lasting antidepressant effect of ketamine is one of the most important discoveries in the field of psychiatry in the past half-century, but the precise mechanism of action and the brain area targeted by ketamine remain unclear.

Hypofunction of the midbrain reward center has been reported in depression (Proulx et al., 2014). This center was found to be inhibited by the LHb, suggesting that this area of the brain is involved in negative emotions and in the etiology of depression and that ketamine may therefore act on the LHb. To test this hypothesis, Yang et al. (2018) assessed the effects of ketamine on rats with congenital learned helplessness (cLH), which show depression-like behaviors including early despair in stressful situations (learned helplessness) and insensitivity to positive stimuli (anhedonia). Surprisingly, local infusion of ketamine or of the specific NMDAR antagonist, 2-amino-5-phosphonopentanoic acid (AP5), into the LHb of cLH rats effectively reduced depression-like behaviors without affecting general motor activity in open field tests, supporting the habenula theory of ketamine action (Yang et al., 2018).

Investigating the activity patterns of LHb neurons, Yang et al., (2018) further revealed that while a small proportion of LHb neurons, around 7∼11%, showed burst firing in normal rats, a larger proportion of LHb neurons—approximately 23∼30%—showed burst firing in cLH rats as well as in a second animal model of depression, chronic restraint stress (CRS) mice. Administration of ketamine efficiently reduced the number of bursting LHb neurons and relieved depression-like symptoms in these animal models, suggesting that LHb bursts may be a target of ketamine action. To test this hypothesis, Yang et al. (2018) used inhibitory opsins, eNpHR3.0, to drive bursts in the LHb, and they provided photostimulation at a frequency mimicking the bursts in cLH rats. The optically induced bursts induced depression-like behaviors in normal rats, suggesting that this bursting activity of LHb neurons may contribute to the inhibition of reward centers and may lead to learned helplessness and anhedonia.

Interestingly, the bursting LHb neurons showed lower resting membrane potentials (RMPs) than other neurons with silent or tonic firing, providing hints regarding the mechanism linking neuronal bursting to depression. T-type Ca^{2+} channels (Ca_V3) remain inactive near the normal RMP of a neuron, and they require a transient hyperpolarization of membrane potential to prime the generation of rebound Ca^{2+} spikes crowned with multiple Na^+ potentials, called low-threshold burst firing, above the threshold of voltage-dependent Na^+ channels (McCormick and Bal, 1997). Therefore, local but prolonged hyperpolarization near a neuron would potentiate its tendency to generate recurrent burst firing. Indeed, Yang et al. (2018) found that the LHb burst was dependent on T-type Ca^{2+} channels and that pharmacological blockade of these channels abolished burst firing and relieved depression-like symptoms in animal models. A series of experiments, including biophysical simulations, showed that the depolarizing currents induced by T-type Ca^{2+} channels can activate NMDAR activity to induce burst firing in LHb neurons, explaining the mechanism by which the NMDAR antagonist ketamine blocks bursts and depression-like behaviors in animal models of depression (Figure 1).

Another important question addressed in the second study concerns the mechanism of RMP hyperpolarization in LHb neurons leading to the potentiation of T-type Ca^{2+} channels in depression. Cui et al. (2018) found that astroglial Kir4.1 potassium channels, which play an important role in buffering extracellular K^+ concentration, were upregulated in animal models of depression. Increasing the number of Kir4.1 channels facilitated the uptake of K^+ ions by glial cells, reducing the concentration of K^+ in the perisomatic space and facilitating outward currents to reduce the RMP of the neurons (Figure 1). To test the association of Kir4.1 channels with depression, Cui et al. (2018) then performed a loss of function experiment, finding that shRNA for the Kir4.1 gene rescued cLH rats from their depression-like phenotype.

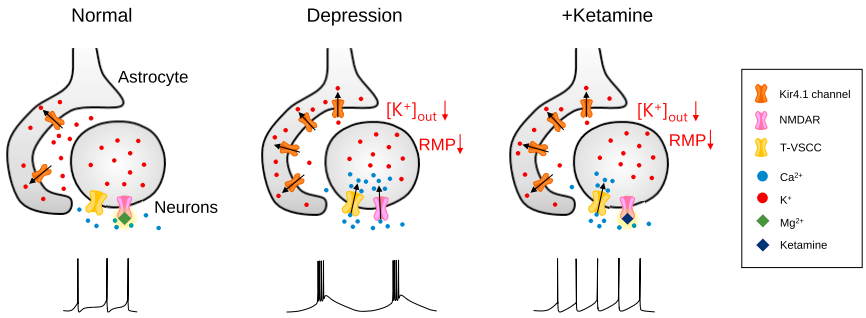

Figure 1. A Model for the Mechanism of Neuronal Bursting and Ketamine Action in the LHb
Normal state: LHb neurons show tonic firing under inactivation of T-type Ca^{2+} channels; Depression state: upregulation of Kir4.1 on astrocytic process decreases $[K+]_{out}$ to hyperpolarize neuronal RMP, which in turn de-inactivates T-type Ca^{2+} channels and initiates NMDA-dependent bursting, resulting in depression. Ketamine blocks NMDAR to stop bursting and relieve depression.

In sum, these two elegant studies provide compelling evidence on the mechanism of depression. Three molecules have been identified that together induce depression: Kir4.1, T-type Ca^{2+} channels, and NMDAR. The astrocytic mechanism may explain the prolonged burst firing of LHb neurons. At low K^+ concentrations, resulting from increased Kir4.1 expression in astrocytes, T-type Ca^{2+} channels can be repetitively activated to generate burst firing by LHb neurons. This recurrent loop, in which T-currents are activated by hyperpolarization and inactivated by depolarization, may explain, at least in part, the persistence of depression symptoms in patients. Their results also highlight the critical role of NMDAR currents in the generation of burst firing initiated by T-type Ca^{2+} currents. T-type Ca^{2+} currents may facilitate NMDAR activity, which enhances burst firing synergistically, with ketamine inhibiting this Ca^{2+}-dependent facilitation of NMDAR. However, the mechanism by which ketamine inhibition of NMDAR results in long-lasting antidepressive effects remains to be determined. Possibilities include the inability of the oscillating burst activity to continue once terminated or the induction by ketamine of irreversible changes in neuro-glia interactions. This mechanism may also explain the limitations of SSRIs, which strengthen serotonergic signaling. The antidepressant effects of SSRIs are not long lasting; patients frequently relapse after drug treatment is stopped. The finding that LHb bursts strongly inhibit the serotoninergic system suggests that serotonin release *per se* is not sufficient to overcome symptoms of depression, despite the presence of an SSRI.

Since their first description (Jahnsen and Llinás, 1984), T-type channel-mediated neuronal burst firings have been implicated in both normal and abnormal brain functions (Cheong and Shin, 2013). Stressors or specific causes of diseases may alter the local environment, hyperpolarizing membrane potentials and subsequent bursting activity. Although inhibition of diseased brain areas may prevent further abnormal functioning, paradoxical burst firing may lead to disease-specific symptoms as side effects, depending on the targeted brain areas. Specific inhibition of burst firing may reduce symptoms associated with various disorders. For example, pharmacological or genetic inactivation of T-type Ca^{2+} channels abolishes abnormally augmented burst firing and relieves symptoms in animal models of various neurological disorders including absence seizures, neuropathic pain, and post-traumatic stress disorders (Cheong and Shin, 2013) as well as tremor (Park et al., 2010), attention-deficit hyperactivity disorder (Kim et al., 2011), Parkinson's disease (Kim et al., 2017), and depression (Yang et al., 2018 and Cui et al., 2018). Precise investigation of the conditions and factors that facilitate hyperpolarization and activation of T-type Ca^{2+} channels may provide insights into the development of novel treatments of depression and other neurological disorders associated with burst firing. For example, in addition to T-type channel blockade, agents targeting neuron-glia interactions may be effective in treating depression.

Interesting questions arise from these studies. It was the pattern of firing rather than a mere increase in spikes that was important for the induction of depression. It will be interesting to define how the downstream targets respond to the two different patterns—tonic versus burst—of input signals from LHb neurons. Another interesting issue will be to find out what roles the astroglial Kir4.1 plays in normal and abnormal brain functions involving T-channel bursts.

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