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DEPRESSION

Bursting with depression

The aetiology of major depressive disorder (MDD) is not well understood, but the lateral habenula (LHb) has been implicated as playing a role. In some people with MDD, the NMDA receptor (NMDAR) antagonist ketamine has rapid antidepressant effects. The mechanisms underlying the action of ketamine, and whether they involve the LHb, are not known, but two *Nature* papers from the Hu lab now show that, in rodent models of depression, the LHb exhibits increased NMDAR-dependent bursting activity that can be blocked by ketamine. Moreover, they show that this bursting depends on the pacemaker T-type voltage-dependent calcium channel (T-VSCC), as well as the astrocytic inwardly rectifying potassium channel KIR4.1.

In one study, Yang et al. recorded the activity of LHb neurons and found that some neurons showed a burst-firing phenotype with a markedly hyperpolarized resting membrane potential compared with others, and that the burst frequency was positively correlated with the extent of hyperpolarization. LHb neurons from congenitally learned helpless (cLH) rats and mice with chronic restraint stress (CRS mice) showed a higher percentage of bursting neurons than did controls; moreover, LHb bursting was inhibited in both cLH rats and CRS mice by systemic injection of ketamine. Importantly, injection of ketamine bilaterally into the LHb of cLH rats was sufficient to reduce depressive-like behaviour in the forced swim test (FST), and anhedonia in the sucrose preference test (SPT). These results suggest that depressive-like behaviours may be accompanied by aberrant bursting in the LHb that can be suppressed by ketamine.

Next, Yang et al. showed that bath application of ketamine or another NMDAR antagonist to brain slices quickly abolished bursting activity in LHb neurons. In addition, in rat and mouse LHb neurons, the authors detected currents mediated by T-VSCCs — which, in response to transient hyperpolarization, elicit bursting. The probability of this bursting was reduced by specific T-VSCC blockade, and in cLH rats, systemic or local LHb injection of a T-VSCC inhibitor induced rapid antidepressant effects. Thus, the increased LHb bursting observed in a model of depression may depend on NMDARs and T-VSCCs.

Based on this T-VSCC- and hyperpolarization-dependent bursting mechanism, Yang et al. designed a strategy by expressing an inhibitory opsin in LHb neurons to induce transient hyperpolarization, followed by bursting activity. This caused depressive-like behaviour in the FST and anhedonia in the SPT, and these effects were reversed by ketamine.

In the accompanying study, Cui et al. carried out a proteomic screen of habenulae from naive and cLH rats and found KIR4.1, which buffers extracellular K^+, to be upregulated in the latter. Patch-clamp recordings from astrocytes confirmed that the KIR4.1-mediated current was also increased in LHb astrocytes in cLH rats. Using high-magnification imaging in mouse brains, Cui et al. observed that KIR4.1 in the LHb is expressed by astrocytes that wrap tightly around neurons and synapses. Blocking KIR4.1 in slices induced LHb neuronal depolarization and suppressed bursting activity. Thus, the upregulation of KIR4.1 in depression models may promote clearance of extracellular K^+, leading to neuronal hyperpolarization and bursting.

Virus-mediated overexpression of KIR4.1 in LHb astrocytes led to astrocytic and neuronal hyperpolarization and an increase in the proportion of bursting neurons in the LHb, and markedly increased depressive-like behaviours on the FST and SPT. By contrast, knockdown of KIR4.1 (using virus-encoded short hairpin RNA) or overexpression of a dominant negative KIR4.1 led to a general depolarization of LHb astrocytes and neurons and reduced depression-like behavioural symptoms in cLH rats. Thus, in rodents, upregulated KIR4.1 is both necessary and sufficient to drive LHb bursting and depression-like behaviours.

Together, these studies provide strong evidence that depressive-like behaviour in rodents is associated with a bursting LHb phenotype, and that this bursting depends on NMDARs, T-VSCCs and astrocytic KIR4.1.

Natasha Bray

> “Blocking KIR4.1 in slices induced LHb neuronal depolarization and suppressed bursting activity”

ORIGINAL ARTICLES Yang, Y. et al. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. *Nature* **554**, 317–322 (2018) | Cui, Y. et al. Astroglial Kir4.1 in the lateral habenula drives neuronal bursts in depression. *Nature* **554**, 323–327 (2018)

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