Brain networks strengthened by closing ion channels

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Yale School of Medicine and University of Crete School of Medicine researchers report in Cell April 20 the first evidence of a molecular mechanism that dynamically alters the strength of higher brain network connections.

This discovery may help the development of drug therapies for the cognitive deficits of normal aging, and for cognitive changes in schizophrenia, bipolar disorder, or attention deficit hyperactivity disorder (ADHD).

"Our data reveal how the brain's arousal systems influence the cognitive networks that subserve working memory-which plays a key role in abstract thinking, planning, and organizing, as well as suppressing attention to distracting stimuli," said Amy Arnsten, lead author and neurobiology professor at Yale.

The brain's prefrontal cortex (PFC) normally is responsible for so-called executive functions. The ability of the PFC to maintain such memory-based functions declines with normal aging, is weakened in people with ADHD, and is severely disrupted in disorders such as schizophrenia and bipolar disorder.

The current study found that brain cells in PFC contain ion channels called hyperpolarization-activated cyclic nucleotide-gated channels (HCN) that reside on dendritic spines, the tiny protrusions on neurons that are specialized for receiving information. These channels can open

when they are exposed to cAMP (cyclic adenosine monophosphate). When open, the information can no longer flow into the cell, and thus the network is effectively disconnected. Arnsten said inhibiting cAMP closes the channels and allows the network to reconnect.

The study also found alpha-2A adrenergic receptors near the channels that inhibit the production of cAMP and allow the information to pass through into the cell, connecting the network. These receptors are stimulated by a natural brain chemical norepinephrine or by medications like guanfacine.

"Guanfacine can strengthen the connectivity of these networks by keeping these channels closed, thus improving working memory and reducing distractibility," she said. "This is the first time we have observed the mechanism of action of a psychotropic medication in such depth, at the level of ion channels."

Arnsten said the excessive opening of HCN channels might underlie many lapses in higher cognitive function. Stress, for example, appears to flood PFC neurons with cAMP, which opens HCN channels, temporarily disconnects networks, and impairs higher cognitive abilities.

There is also evidence that this pathway may not be properly regulated with advancing age, resulting in destruction of cAMP. The dysregulation of the pathway may contribute to increased forgetfulness and susceptibility to distraction as we grow older.

The research is also relevant to common disorders such as ADHD, which is associated with weaker regulation of attention and behavior. ADHD is highly heritable, and some patients with ADHD may have genetic changes in molecules that weaken the production of norepinephrine. Treatments for ADHD all enhance stimulation of the norepinephrine receptors.

These new data also have important implications for the researchers' studies of more severe mental illnesses like schizophrenia and bipolar disorder, which can involve mutations of a molecule called DISC1 (Disrupted in Schizophrenia) that normally regulates cAMP. Loss of function of DISC1 in patients with schizophrenia or bipolar disorder would increase vulnerability to cortical network disconnection and profound PFC deficits. This may be especially problematic during exposure to even mild stress, which may explain the frequent worsening of symptoms following exposure to stress. "We find it remarkable to relate a genetic mutation in patients to the regulation by an ion channel of PFC neuronal networks," said Arnsten.

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Source: Yale University