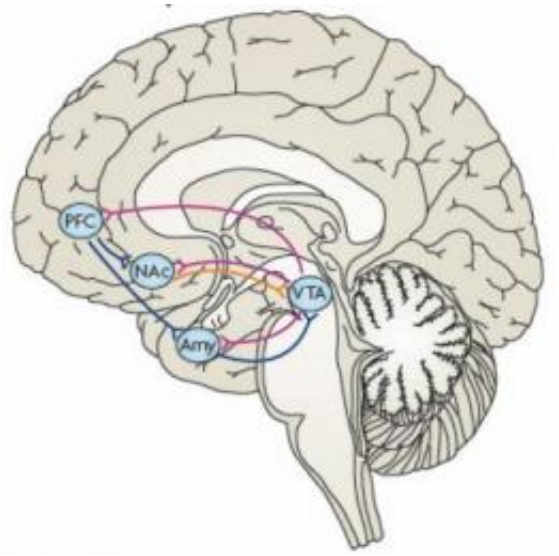
Resilience factor low in depression, protects mice from stress

May 16 2010



The transcription factor deltaFosB mediates resilience in the nucleus accumbens, hub of the brain's reward circuit. It is the target of an intensive high tech screening for small molecules that tweak it, which could lead to a new class of resilience-boosting antidepressants. Credit: Eric Nestler, M.D., Mount Sinai School of Medicine

Scientists have discovered a mechanism that helps to explain resilience to stress, vulnerability to depression and how antidepressants work. The new findings, in the reward circuit of mouse and human brains, have spurred a high tech dragnet for compounds that boost the action of a key gene regulator there, called deltaFosB.

A molecular main power switch - called a transcription factor - inside neurons, deltaFosB turns multiple genes on and off, triggering the production of proteins that perform a cell's activities.

"We found that triggering deltaFosB in the reward circuit's hub is both necessary and sufficient for resilience; it protects mice from developing a depression-like syndrome following chronic social stress," explained Eric Nestler, M.D., of the Mount Sinai School of Medicine, who led the research team, which was funded by the National Institute of Health's National Institute of Mental Health (NIMH).

"Antidepressants can reverse this social withdrawal syndrome by boosting deltaFosB. Moreover, deltaFosB is conspicuously depleted in brains of people who suffered from depression. Thus, induction of this protein is a positive adaptation that helps us cope with stress, so we're hoping to find ways to tweak it pharmacologically," added Nestler, who also directs the ongoing compound screening project.

Nestler and colleagues report the findings that inspired the hunt online May 16 2010 in the journal Nature Neuroscience.

"This search for small molecules that augment the actions of deltaFosB holds promise for development of a new class of resilience-boosting treatments for depression," said NIMH director Thomas R. Insel. "The project, funded under the American Recovery and Reinvestment Act of 2009, is a stunning example of how leads from rodent experiments can be quickly followed up and translated into potential clinical applications."

DeltaFosB is more active in the reward hub, called the nucleus accumbens (see diagram below), than in any other part of the brain. Chronic use of drugs of abuse - or even natural rewards like excess food, sex or exercise - can gradually induce increasing levels of this

transcription factor in the reward hub. Nestler and colleagues have shown that this increase in deltaFosB can eventually lead to lasting changes in cells that increase rewarding responses to such stimuli, hijacking an individual's reward circuitry - addiction.

The new study in mice and human post-mortem brains confirms that the same reward circuitry is similarly corrupted (though to a lesser degree than with drugs of abuse) in depression via effects of stress on deltaFosB.

Depressed patients often lack motivation and the ability to experience reward or pleasure - and depression and addiction often go together. Indeed, mice susceptible to the depression-like syndrome show enhanced responses to drugs of abuse, the researchers have found.

But the similarity ends there. For, while an uptick in deltaFosB promotes addiction, the researchers have determined that it also protects against depression-inducing stress. It turns out that stress triggers the transcription factor in a different mix of nucleus accumbens cell types - working through different receptor types - than do drugs and natural rewards, likely accounting for the opposite effects.

The researchers explored the workings of deltaFosB in a mouse model of depression. Much as depressed patients characteristically withdraw from social contact, mice exposed to aggression by a different dominant mouse daily for 10 days often become socially defeated; they vigorously avoid other mice, even weeks later.

Among key findings in the brain's reward hub:

- The amount of deltaFosB induced by the stress determined susceptibility or resilience to developing the depression-like

behaviors. It counteracted the strong tendency to learn an association, or generalize, the aversive experience to all mice.

- Induction of deltaFosB was required for the antidepressant fluoxetine (Prozac) to reverse the stress-induced depression-like syndrome.

- Prolonged isolation from environmental stimuli reduced levels of deltaFosB, increasing vulnerability to depression-like behaviors.

- Among numerous target genes regulated by deltaFosB, a gene that makes a protein called the AMPA receptor is critical for resilience - or protecting mice from the depression-like syndrome. The AMPA receptor is a protein on neurons that boosts the cell's activity when it binds to the chemical messenger glutamate.

- Increased activity of neurons triggered by heightened sensitivity of AMPA receptors to glutamate increased susceptibility to stress-induced depression-like behavior.

- Induction of deltaFosB calmed the neurons and protected against depression by suppressing AMPA receptors' sensitivity to glutamate.

- Post-mortem brain tissue of depressed patients contained only about half as much deltaFosB as that of controls, suggesting that poor response to antidepressant treatment may be traceable, in part, to weak induction of the transcription factor.

Reduced deltaFosB in the reward hub likely helps to account for the impaired motivation and reward behavior seen in depression, said Nestler. Boosting it appears to enable an individual to pursue goal-

directed behavior despite stress.

The high-tech screening for molecules that boost DeltaFosB, supported by the Recovery Act grant, could lead to development of medications that would help people cope with chronic stress. The molecules could also potentially be used as telltale tracers in brain imaging to chart depressed patients' treatment progress by reflecting changes in deltaFosB, said Nestler.

Provided by National Institutes of Health

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