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## How Stress Supercharges Learning

Whether it's a hot stove or a snarling dog, an emotional encounter supercharges learning in a way that indelibly imprints those experiences in memory. Now researchers have pinpointed a molecular pathway in the brain that underlies stress-induced learning enhancement. Their studies establish how the stress hormone norepinephrine boosts learning by strengthening connections between neurons.

The researchers said their studies also may aid understanding of the learning-enhancing effects of drugs such as methamphetamine, caffeine and nicotine. And the same biochemical mechanism might contribute to the addictive properties of cocaine and caffeine.

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— **Richard L. Huganir**

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The researchers, led by Roberto Malinow and Richard Huganir, published their findings in the October 5, 2007, issue of the journal *Cell*. Malinow is at Cold Spring Harbor Laboratory, and Huganir is a Howard Hughes Medical Institute investigator at Johns Hopkins University School of Medicine.

In their experiments, the researchers were seeking a better understanding of how norepinephrine influences the strength of connections among neurons in the brain and affects emotional learning. It was known that the strengthening of synaptic connections, called long-term potentiation (LTP), depends on an increase in the number of AMPA receptors at synapses between neurons. AMPA receptors are one of the major neurotransmitter receptors in the brain. In addition, it was known that phosphorylation of AMPA receptors was important in the LTP process. Phosphorylation is a mechanism that regulates the activity of proteins by the addition or subtraction of a phosphate group.

Malinow, Huganir and their colleagues first sought to establish a link between norepinephrine and AMPA receptor subunit phosphorylation. When they treated rat hippocampal tissue with norepinephrine, their analyses established that the compound does, indeed, induce phosphorylation in the AMPA receptor subunit. Furthermore, their studies showed that norepinephrine enhances LTP and the delivery of AMPA receptors to the

synapse. They also found that mice with mutations that prevented subunit phosphorylation eliminated norepinephrine's enhancement of LTP.

The researchers also went on to show that the fear responses in mice are associated with phosphorylation of the AMPA receptor subunit. They found that injecting mice with epinephrine or exposing the animals to fox urine, which provokes the fear response, triggered AMPA subunit phosphorylation.

In behavioral studies, the researchers found that the mutations that prevented receptor subunit phosphorylation also prevented epinephrine from triggering enhanced learning in the mice. In the behavioral experiments, epinephrine injection did not enhance the ability of the mutant mice to learn to associate a specific cage with an electric shock, as it did in the normal mice.

It has long been known that when a person is afraid or scared, norepinephrine is released along with epinephrine, producing the fight-or-flight response throughout the body, said Haganir. And it was known that norepinephrine affects the brain, activating learning to enable those stressful memories to be recalled more readily. Now we have shown how norepinephrine activates that learning—by producing a critical biochemical priming effect on AMPA receptors during states of stress, he said. That priming induces migration of more receptors to the synapse, enhancing the strength of those synaptic connections.

Haganir said that the findings suggest that other substances that may affect phosphorylation of the AMPA subunit may have similar priming effects. These phosphorylation sites are also affected by many compounds and neurotransmitters—including dopamine, serotonin and even drugs like Prozac, cocaine, nicotine, methamphetamine and caffeine, he said. So, we plan to test these mutant animals to see if they are deficient in the neuromodulatory effects on behavior of such chemicals.

Many people who study drug addiction believe that exposure to drugs such as cocaine rewires brain circuitry using similar LTP mechanisms. So, we can also use these mutant mice to test whether loss of AMPA receptor phosphorylation affects cocaine-induced behaviors and cocaine addiction, said Haganir.