Researchers identify possible therapeutic target for depression, addiction

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Researchers studying mice are getting closer to understanding how stress affects mood and motivation for drugs.

According to the researchers, blocking the stress cascade in brain cells may help reduce the effects of stress, which can include anxiety, depression and the pursuit of addictive drugs.

A research team from St. Louis and Seattle reports in the Aug. 11 issue of the journal *Neuron* that in mice exposed to stress, a protein called p38? mitogen-activated protein kinase (MAPK) influences the animal's behavior, contributing to depression-like symptoms and risk for addiction.

The first author is Michael R. Bruchas, PhD, assistant professor of anesthesiology and of anatomy and neurobiology at Washington University School of Medicine in St. Louis, and the senior investigator is Charles Chavkin, PhD, professor of pharmacology at the University of Washington in Seattle.

The researchers demonstrate that p38? MAPK protein is activated by kappa-opioid receptors on neurons to regulate serotonin, a key neurotransmitter that helps regulate mood. When exposed to stress, the brain releases hormones that specifically interact with kappa-opioid receptors on neurons. Those receptors, in turn, activate p38? MAPK, which then interacts with the serotonin transporter in the cells to reduce the amount of available serotonin.

In this study, funded by the National Institute on Drug Abuse, the researchers looked at a brain region, called the dorsal raphe nucleus, where many stress-related factors and serotonin converge. They found that after stress exposure, mouse brains activate p38? MAPK, lowering serotonin levels and triggering depression-like behaviors as well as drug-seeking behavior in the mice.

Stressed animals withdrew and did not interact with other mice. In animals that had been given cocaine injections while in specific places in their cages, stress made them more likely to physically seek out those locations where they had received the drug.

"We call these responses 'depression-like' and 'addiction-like' behaviors because, we can't ask mice if they're addicted or sad," Bruchas says. "But just as depressed people often withdraw from social interactions, stressed mice do the same thing. We also observed that stressed mice return more often to the place where they received cocaine."

Next, investigators used a relatively novel genetic technology to disable the p38? MAPK protein only in cells of the brain's serotonin system. Without the p38? protein, the stress-exposed mice no longer withdrew from social interactions, displayed depression-like behavior or sought drugs.

While working in Chavkin's laboratory at the University of Washington, Bruchas and his colleagues studied mice exposed to what they call social defeat stress.

"We put a mouse into an enclosure with an 'aggressor' mouse," Bruchas says. "Some mice, like some humans, are more dominant and aggressive. When a non-aggressive mouse is put into a cage with an aggressive animal, that aggression causes stress similar to what we might see in an adult human working for a difficult boss or a teenager who has to deal with a bully at school."

Just as interacting with a "bully" mouse is similar to dealing with stressful environments, Bruchas and Chavkin say the cascade of events in the brain that contributes to serotonin reduction appears to be similar in both mice and humans.

"When people take antidepressant drugs called selective serotonin reuptake inhibitors, or SSRIs, to

relieve depression, the drugs act on a cellular pump called the serotonin transporter, and this results in more serotonin in the brain," Bruchas says. "We think that the involvement of the p38? protein and kappa-opioid receptors represents an important finding in figuring out how it is that cells regulate depressive and addictive behaviors."

In his new laboratory at Washington University, Bruchas says he plans to test whether the same p38? MAPK protein is involved when the drug is nicotine or amphetamine.

"It will be important to determine whether this pathway is conserved for drugs of abuse other than cocaine," he says. "If so it will further highlight the importance of working with chemists to target this pathway for potential therapies."

Bruchas also plans to look at other brain areas to learn whether similar responses are occurring in response to stress.

Meanwhile, in Seattle, Chavkin's group continues to examine stress effects on addiction, long-term addiction models and whether humans regulate stress through the same kappa-opioid/p38? pathway.

"Our data demonstrate that p38? is required for local regulatory control of serotonin transport, which ultimately controls behavioral responses, including social avoidance and relapse of drug-seeking," Chavkin says. "These results are important because they highlight novel therapeutic targets to promote stress resilience."

More information: Bruchas MR, Schindler AG, Shankar H, Messinger DI, Miyatake M, Land BB, Lemos JC, Hagan C, Neumaier JF, Quintana A, Palmiter RD, Chavkin C. Selective p38? MAPK deletion in seretonergic neurons produces produces stress-resilience in models of depression and addiction. Neuron, vol. 71 (3), Aug. 11, 2011. doi:10.1016/j.neuron.2011.06.011

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