Stress-induced changes in brain circuitry linked to cocaine relapse

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(PhysOrg.com) -- Stress-evoked changes in circuits that regulate serotonin in certain brain regions can precipitate a low mood and a relapse in cocaine-seeking.

Stress-evoked changes in circuits that regulate serotonin in certain parts of the brain can precipitate a low mood and a relapse in cocaine-seeking, based on mouse studies published online this week in the Proceedings of the National Academy of Sciences *Early Edition.*

"The impetus for this research was our interest in how stress alters the brain's cell receptors and protein signals in ways that lead to mood changes, depression, anxiety, and drug seeking," said Dr. Michael Bruchas, acting instructor of pharmacology at the University of Washington (UW), who with Dr. Benjamin Land, a former UW doctoral student now in the Department of Psychiatry at Yale University, co-led the recent study of the adverse effects of stress-activated brain pathways. The senior author was Dr. Charles Chavkin, the Allan and Phyllis Treuer Professor of Pharmacology and director of the UW Center for Drug Addiction Research

A common belief is that drug seeking is regulated by dopamine, a chemical nerve signal associated with motivating and rewarding behavior. Dopamine may still have a key role, the researchers noted, which is why they were surprised to find harmful effects of stress converging in a brain region-- the dorsal raphe nucleus --where nerve cells that use serotonin are abundant. These nerve cells also project to

other structures found on either side of the brain -- the nucleus accumbens -- which are thought to play roles in feeding and drug addiction. Serotonin is a chemical nerve signal that has been associated with wake and sleep cycles, mood, anger, status and aggression

In explaining their study, the researchers said that the dynorphin/kappa opioid system, found in certain brain cells, can be activated either through repeated stress or by giving a chemical that triggers a receptor on the cells. Activation of this system produces what is called conditioned place aversion in mice. They avoid smells, locations or tactile sensations similar to those present during a troubling experience. Research suggests that this response is mediated by the stress-evoked release of dynorphins, the "feel bad" brain signals.

For mice, meeting a dominant male mouse is disheartening. Dr. Land likened the stressfulness of this situation to sitting in a classroom with the schoolyard bully. Facing an aggressor, mice will admit social defeat by raising their paws in an "I give up" pose. If the lab mice have received cocaine before and are abstaining now, they will want the drug again.

"Stress appears to be a motivator for the relapse in drug seeking," Land said, "They feel crummy so they go where there might be something that will make them feel okay again." They head to a spot that had the drug available in the past, an action researchers call cocaine place preference.

Scientists had previously proposed that an activated dynorphin/kappa opioid receptor system stopped the release of dopamine and thereby made the mice feel miserable enough to cause aversions. However, even mice bred to be dopamine-deficient still responded with aversions. When scientists inactivated the kappa opioid receptors involved in the serotonin system in the dorsal raphe nucleus -- the serotonin-abundant region of the brain -- they were able to block both the aversive responses and the stress-induced reinstatement of cocaine-place preference.

Mice that had their kappa opioid receptors genetically "knocked out" did not develop aversive responses to chemical triggers. After the scientists genetically restored these missing receptors in the dorsal raphe nucleus of the brain, the mice responded to the trigger with place aversion. However, the researchers found that genetically installed, mutated receptors that can't activate a brain protein called p38 MAPK couldn't provoke aversive responses.

The researchers concluded that activation of the kappa opioid receptor, either pharmacologically or by stress-evoked release of dynorphins, may regulate a serotonin system through projections from the dorsal raphe nucleus of the brain to other parts of the brain, the nucleus accumbens. Theirs is one of the first investigations into sources of the serotonin system projections and how this connection is regulated by stress-evoked mediators. This pathway -- induced by dynophins released during stress -- might re-ignite extinguished drug-seeking behaviors by weakening the serotonin tone of the nucleus accumbens.

These findings, Bruchas said, are only a first, foundational step. Still to be discovered are: What are the activities of the kappa opioid receptor? Is it decreasing serotonin levels? Is it lowering the firing rates of nerve cells?

The researchers expressed hope that future work on how this pathway functions may provide more insight into the brain mechanisms linking stress, depression, and addiction.

When asked if it would be possible to intervene in this pathway, the researchers answered that work is under way by other groups on the kappa opioid receptor system as a possible target for treating depression.

Provided by University of Washington (news : web)