Study suggests new target for treatment of depression

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A brain protein involved in fear behavior and anxiety may represent a new target for depression therapies, according to a study by researchers at the University of Iowa and the Iowa City Veterans Affairs Medical Center. The results appear in the April 29 issue of the *Journal of Neuroscience*.

Depression affects at least 14 million American adults and can be severely disabling. However, the causes of depression are not well understood. In addition, up to half of people diagnosed with depression are not helped by current therapies because either the drug is not effective for them, or the side effects are intolerable.

The UI research team found that disrupting ASIC1a -- an ion channel protein found in the brain -- produced an antidepressant-like effect in mice. The effect was similar to that produced by currently available antidepressant drugs, but the team also showed that ASIC1a's effect arose through a new and different biological mechanism.

"The mechanism issue is important because if a patient doesn't respond to one drug, the chances of them responding to another drug that works through the same mechanism are low," said study investigator John Wemmie, M.D., Ph.D., associate professor of psychiatry and neurosurgery at the UI Carver College of Medicine and a staff physician and researcher at the Iowa City Veterans Affairs Medical Center. "We need antidepressants with new mechanisms of action to help those people who don't respond to what is currently available."

Wemmie added that although there is no immediate therapy available based on the new findings, the results suggest that ASIC1a inhibition represents a new approach to antidepressant therapy. The channel can be blocked pharmacologically. In addition, manipulating brain pH (a measure of acidity) might be used to inhibit this ion channel, which is activated by acid (low pH).

The study also indicated that using antidepressant drugs and inhibiting ASIC1a at the same time produced an additive effect in mice, suggesting that ASIC1a inhibition used in conjunction with current medications might boost antidepressant effects in patients.

The researchers focused on ASIC1a because recent studies have pointed to a role for this ion channel in depression. In particular, previous animal studies from Wemmie's lab showed that ASIC1a plays an important role in fear responses (panic) and anxiety, conditions that often accompany depression. Other research has suggested a strong relationship between anxiety, depression and the brain's fear circuitry, including the amygdala, where ASIC1a is abundant.

In their latest study, Wemmie's team used experiments targeting the amygdala to show that this brain region is a key site of action for ASIC1a's antidepressant effect. The results support the idea that depression may be caused, at least in part, by abnormal amygdala activity.

"Because the ASIC1a protein is especially abundant in areas of the brain that regulate emotion, it is possible that interventions targeting ASIC1a could treat depression while having fewer effects on other brain areas and thus fewer side effects than available treatments. But much more work is needed to determine if this approach can be used therapeutically," said Matthew Coryell, Ph.D., lead study author and a recent graduate of the UI Neuroscience Program.

The researchers also found that ASIC1a function might underlie the connection between stress and depression. Stress can precipitate depression, and research from other labs has suggested this might be because stress lowers levels of protective brain hormones called neurotrophic factors. The UI team found that removing ASIC1a prevented stress from reducing levels of one neurotrophic factor called BDNF in mice. The findings might mean that inhibiting ASIC1a could increase the brain's ability to resist the negative effects of stress and perhaps reduce a person's likelihood of developing depression.

Source: University of Iowa (news : web)