Chemical may be new tool for depression therapy

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A chemical discovered in the Bruce Hammock laboratory at the University of California, Davis, may be a new, innovative tool to control depression, a severe and chronic psychiatric disease that affects 350 million persons worldwide.

The research, published March 14 in the journal *Proceedings of the*

National Academy of Sciences, involves studies of an inhibitor of soluble epoxide hydrolase in rodents. Soluble epoxide hydrolase, or sEH, is emerging as a therapeutic target that acts on a number of inflammatory or inflammation-linked diseases.

"The research in animal models of depression suggests that sEH plays a key role in modulating inflammation, which is involved in depression," said Hammock, a distinguished professor of entomology with a joint appointment at the UC Davis Comprehensive Cancer Center. "Inhibitors of sEH protect natural lipids in the brain that reduce inflammation and neuropathic pain. Thus, these inhibitors could be potential therapeutic drugs for depression."

Researchers from Hammock's laboratory, collaborating with depression expert Kenji Hashimoto and colleagues at the Chiba University Center for Forensic Mental Health, Japan, examined the role of the potent sEH inhibitor known as TPPU, in a rodent model of depression, "social defeat."

They found that TPPU displayed rapid effects in both inflammation and social-defeat-stress models of depression. Expression of sEH protein was higher in key brain regions of chronically stressed mice than in control mice, they found.

New therapeutic approach:

"Most drugs for psychiatric diseases target how neurons communicate; here we are targeting the wellness and environment of the neurons," said UC Davis researcher Christophe Morisseau.

In further explaining the significance of the findings, UC Davis researcher Karen Wagner said: "The rapid antidepressant action of the sEH inhibitor in these murine (mouse) models of depression is truly

noteworthy because current antidepressants used in humans and animal models take weeks to have full effects."

The researchers also discovered that postmortem brain samples of patients with psychiatric diseases, including depression, bipolar disorder and schizophrenia, showed a higher expression of sEH than controls.

The researchers found that pretreatment with TPPU prevented the onset of depressionlike behaviors in mice after induced inflammation or repeated social-defeat stress. Mice lacking the sEH gene did not show depressionlike behavior after repeated social-defeat stress.

"All these findings suggest that sEH plays a key role in the pathophysiology of depression and that epoxy fatty acids, and their mimics as well as sEH inhibitors, are potential therapeutic or prophylactic drugs for depression," Hashimoto said.

Addresses a pressing need:

Robert E. Hales, distinguished professor of clinical psychiatry and the Joe P. Tupin Endowed Chair of the Department of Psychiatry and Behavioral Sciences at UC Davis School of Medicine, said new medication treatment approaches are needed to treat depression.

Hales, who was not involved in the research, said the new paper represents "an important and novel approach to treating depression."

"With lifetime prevalence rates of major depressive disorder being in the range of 16 percent and with nearly two-thirds of patients failing to respond to pharmacologic treatments, there is a pressing need to discover new medication treatment approaches," Hales said. "Their findings lend support to the potential use of TPPU, a sEH inhibitor, as a new therapeutic medication to prevent and treat depression."

More information: Gene deficiency and pharmacological inhibition of soluble epoxide hydrolase confers resilience to repeated social defeat stress, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1601532113

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