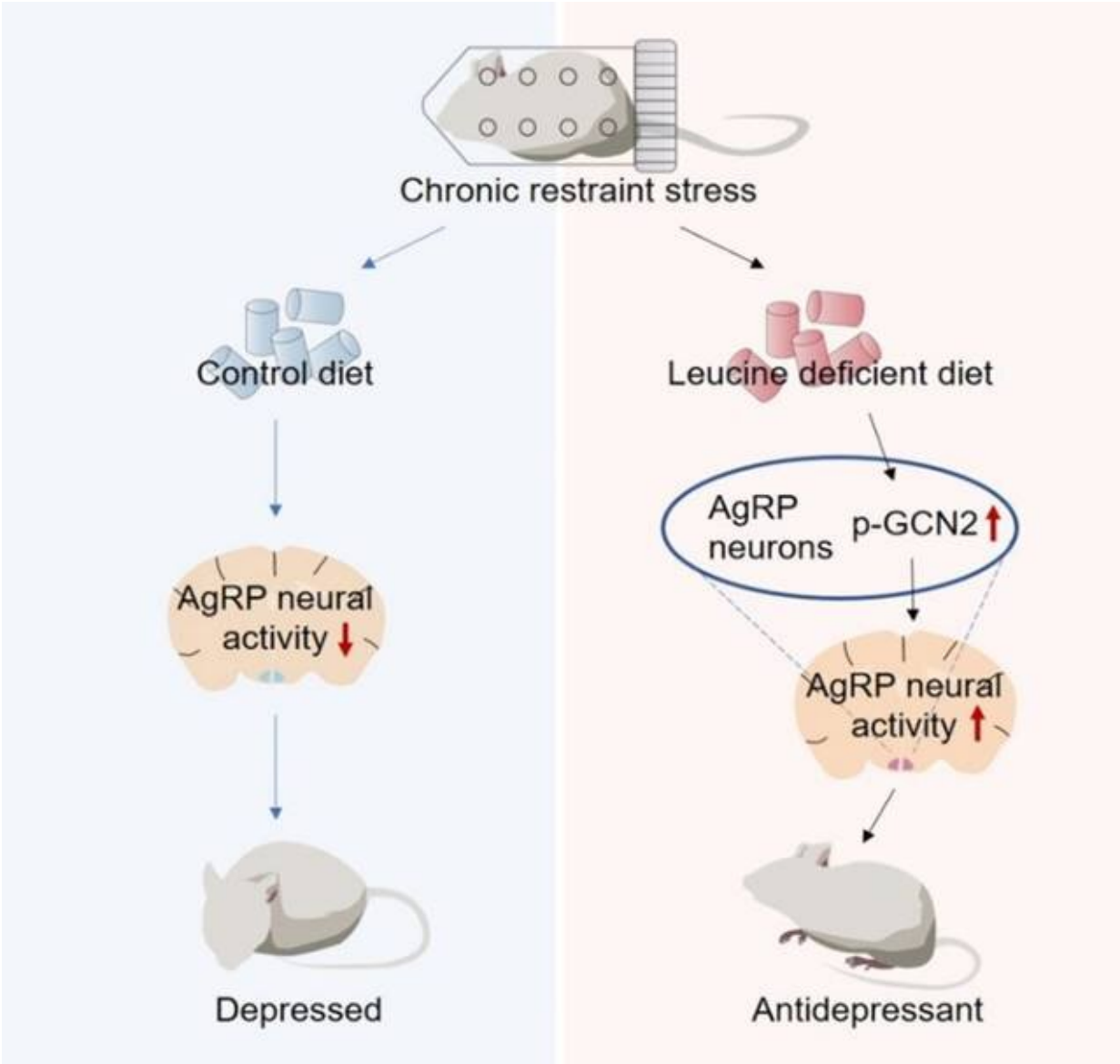
Scientists discover roles of hypothalamic amino acid sensing in antidepressant effects

March 3 2023



Deprivation of an essential amino acid leucine exhibits antidepressant effects

under chronic stress by stimulating GCN2 and neural activity in AgRP neurons. Credit: Feixiang Yuan, Shangming Wu, Ziheng Zhou, Fuxin Jiao, Hanrui Yin, Yuguo Niu, Haizhou Jiang, Shanghai Chen, Feifan Guo

Depression is a leading cause of disability around the world and contributes greatly to the global burden of disease. Nutrition is essential for the maintenance of normal emotional states. Nutritional therapy is rising up in many disease treatments, but little is known in the depression field. Unbalanced nutrition is implicated in the etiology of depression, potentially hindering treatment.

For example, many essential amino acids (EAAs) in serum are changed in patients with depression, such as tryptophan, threonine, leucine, isoleucine, and valine. However, whether EAA contributes to depression and the underlying mechanisms remain largely unknown.

Now, researchers in China, led by Feifan Guo, the professor in the Institute for Translational Brain Research at Fudan University, have found that leucine deficient diet has antidepressant effects on chronic restraint stress-induced depression-related behaviors and revealed the mechanism of amino acid sensing in hypothalamic agouti-related peptide (AgRP) neurons. They published their results in *Life Metabolism*.

In this study, leucine deficient diet was found to have antidepressant effects on chronic restraint stress-induced depression-related behaviors in both genders of mice. Interestingly, the amino acid deficient effects apply to all essential amino acids. By intracerebroventricular injection, the researchers found that the response to leucine deprivation is mediated by the hypothalamus, a specific region that mainly regulates appetite and energy metabolism.

Moreover, scientists found a group of neurons in the hypothalamus, AgRP neurons, were activated during leucine deprivation, and silencing AgRP neurons abolished the leucine deprivation-induced antidepressant effects. Furthermore, general control non-derepressible 2 (GCN2), an amino acid sensor, in AgRP neurons, was activated during leucine deficiency after stress, and GCN2 knockdown in AgRP neurons blocked leucine deficiency-induced behavioral alterations, which was reversed by activating AgRP neurons.

This study established that an unexpected dietary pattern, leucine deprivation, not nutrition supplement, results in antidepressant effects, and this regulation is mediated by a group of orexigenic neurons, AgRP neurons. Furthermore, these results suggest a new function of GCN2 signal in AgRP neurons under imbalanced amino acid and chronic stress.

As leucine deprivation could also help with losing weight and improve glucose metabolism, this diet pattern may help to relieve the antidepressant drug-induced obesity in future applications. This study provides a new perspective for exploring the relation of nutrition, hypothalamus, and depression.

More information: Feixiang Yuan et al, Leucine deprivation results in antidepressant effects via GCN2 in AgRP neurons, *Life Metabolism* (2023). DOI: 10.1093/lifemeta/load004

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