How does chronic stress induce bone loss?

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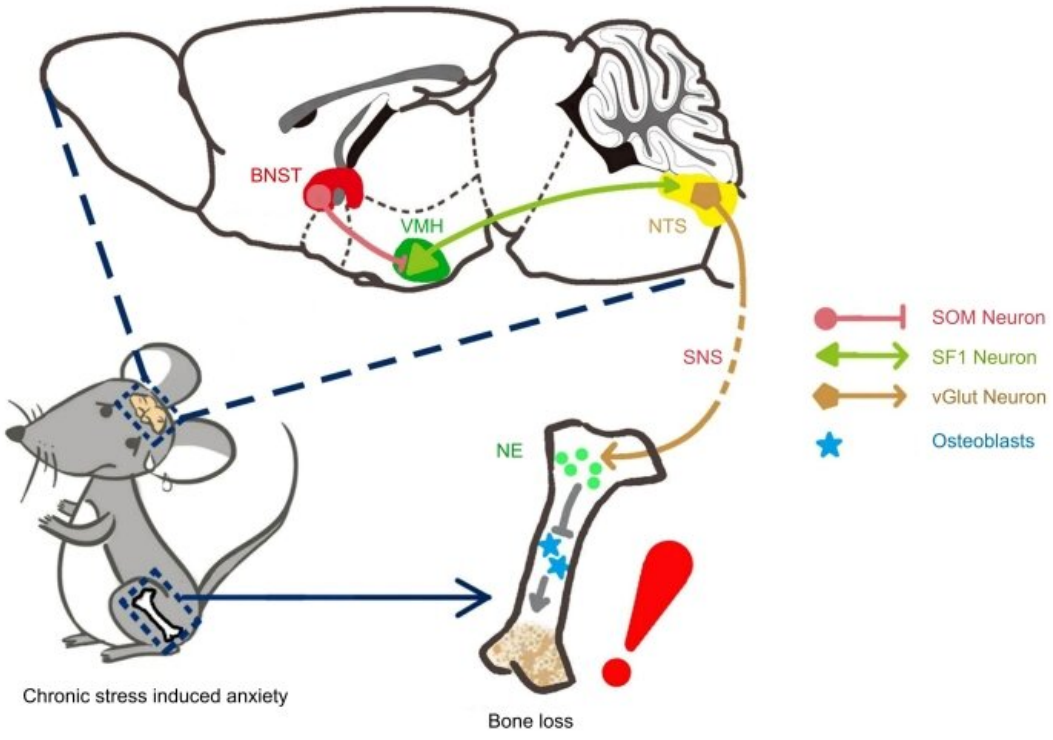

The BNSTSOM-VMHSF-1-NTSVglut2 neural circuit regulates chronic stress-induced bone loss. Credit: SIAT

Clinical studies have found that bone mineral density in patients with anxiety or depression is lower than in ordinary people.

The brain, commander of the body, receives and processes external signals, and then sends instructions to peripheral bones. But how does anxiety induce a decline in bone mineral density?

Researchers from the Shenzhen Institutes of Advanced Technology (SIAT) of the Chinese Academy of Sciences and their collaborators now have an answer. They found that a central neural circuit from the forebrain to the hypothalamus mediates chronic stress-induced bone loss via the peripheral sympathetic nervous system.

Their study was published in the *Journal of Clinical Investigation* on September 10.

The researchers found that isolation can significantly increase anxiety levels, thus inducing bone loss in human subjects.

Biochemical analysis showed that prolonged isolation increases the concentration of norepinephrine and decreases osteogenic markers in serum. These changes were consistent with the observation of elevated anxiety and reduced bone formation in subjects.

In order to identify the neural mechanism underlying chronic stress-induced bone loss, the research team used a mouse model where mice were subjected to unpredictable chronic mild stress.

They found that after four to eight weeks of chronic stress, the mice displayed significant anxiety behaviors. The bone mineral density of the mice in the stress group was significantly lower than in the control group.

These results confirmed the correlation between stress-induced anxiety and bone loss in experimental animals, and provided a good animal model for follow-up neural mechanism analysis.

Through extensive experiments, researchers identified a population of inhibitory neurons expressing somatostatin in the brain nucleus that are known as the bed nucleus of the stria terminalis (BNST) in the forebrain. These neurons were activated when animals showed anxiety behaviors and transmitted 'anxiety' information to the neurons in the ventromedial hypothalamus (VMH).

"Activating the BNST-VMH neural circuit can simultaneously induce anxiety-like behaviors and generate bone loss in the mice, whereas inhibition of this circuit can prevent stress-induced anxiety and bone loss at the same time," said Prof. Yang Fan from SIAT, the co-first and co-corresponding author of the study.

Furthermore, the researchers discovered that glutamatergic neurons in nucleus tractus solitaries (NTS) and the sympathetic system were employed to regulate stress-induced bone loss.

"This study provides a new perspective for the systematic study of the regulatory mechanism of brain homeostasis on metabolism and endocrine function of the body in special environments," said Prof. Wang Liping, Director of the Brain Cognition and Brain Disease Institute of SIAT.

More information: Fan Yang et al, A GABAergic neural circuit in the ventromedial hypothalamus mediates chronic stress-induced bone loss, *Journal of Clinical Investigation* (2020). DOI: 10.1172/JCI136105

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