Study finds new neural brain-to-bone pathway controlling skeletal development

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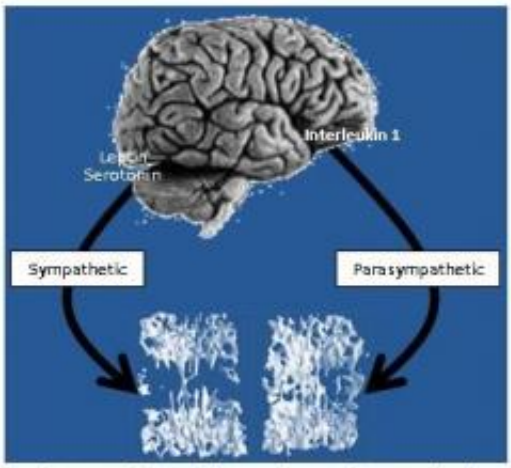

Regulation of spinal bone density by interleukin 1-based pathway that controls the parasympathetic nervous system

Researchers at the Hebrew University of Jerusalem have discovered that a neuronal pathway—part of the autonomic nervous system—reaches the bones and participates in the control of bone development.

The newly discovered pathway has a key role in controlling bone density during adolescence, which in turn determines the skeletal resistance to fracture throughout one's entire life, say the researchers. They emphasize that understanding the mechanisms connecting the brain and the bones could have implications for possible future therapies to better deal with

osteoporosis and various neural disorders. The findings of the Hebrew University team are published this week in the journal *PNAS* (Proceedings of the National Academy of Sciences).

Participants in the project were researchers from the Hebrew University's Bone Laboratory, headed by Prof. Itai Bab, in collaboration with Prof. Raz Yirmia, the head of the Laboratory for Brain and Behavioral Research, plus research students Alon Bajayo and Vardit Kram and master's students Arik Bar and Marilyn Bachar. Additional collaborators were Dr. Adam Denes from the University of Manchester, UK, and Prof. Alberta Zallone from the University of Bari, Italy.

The autonomic nervous system, by which the brain monitors and regulates the physiological functioning of the internal organs, includes two subsystems, called "sympathetic" and "parasympathetic." Each of these subsystems has its own, distinct neural pathways. In general, the sympathetic nervous system is perhaps best known for mediating the neuronal and hormonal responses to stress. The sympathetic pathway, on the other hand, generally works to promote maintenance of the body at rest.

Previous studies by the Hebrew University researchers and others showed that the sympathetic nervous system reaches the skeleton and slows down bone development. On the other hand, until now, there was no information on skeletal parasympathetic activity there.

To demonstrate that there are indeed parasympathetic responses in the skeleton, the researchers injected a weakened rabies virus into the thigh bones of mice. The rabies virus has a unique feature—it migrates from its injection site in the periphery along nerve fibers towards the brain. Following injection to the thigh bone, the virus was found in the brain in regions known to be specific for the parasympathetic subsystem.

In the past, these same researchers reported that the activity of a protein called interleukin-1 influences bone development. Now they noticed that this influence is very similar to that of the parasympathetic subsystem. Indeed, the researchers showed that deactivating interleukin-1 activity in the brain of laboratory mice paralyzes parasympathetic activity in the bone and slows down skeletal development. They further found that the newly discovered neuronal pathway, which includes interleukin-1 in the brain and the parasympathetic subsystem, also controls the heart rate.

As in the bone and the heart, the new pathway might have an important function as well in other organs controlled by the autonomic nervous system. Prof. Yirmiya said that "low bone density and osteoporosis often appear together with neuropsychiatric disorders such as depression, Alzheimer's disease and epilepsy, since interleukin-1 in the brain and the parasympathetic system are often damaged in these disorders. Finding the disease mechanisms in these cases has a huge potential for the development of new therapies," he added.

"The connection between the brain and the bone in general and the involvement of the newly discovered pathway in particular is a new area of research about which we still know very little," said Prof. Bab. "The new findings, discovered in our Hebrew University laboratories, highlight for the first time an important physiological role for the connection between interleukin-1 in the brain and the autonomic nervous system.

The research has been conducted as part of a project to study the connection between the activity of interleukin-1 in the brain, the parasympathetic system and the skeleton. It was supported by the German-Israeli Foundation for Scientific Research and Development and by the Israel Science Foundation.

More information: Skeletal parasympathetic innervation

communicates central IL-1 signals regulating bone mass accrual, *PNAS*, Sept. 3, 2012.

Provided by Hebrew University of Jerusalem