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Weight struggles? Blame new neurons in your hypothalamus

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New nerve cells formed in a select part of the brain could hold considerable sway over how much you eat and consequently weigh, new animal research by Johns Hopkins scientists suggests in a study published in the May issue of *Nature Neuroscience*.

The idea that the brain is still forming new nerve cells, or neurons, into adulthood has become well-established over the past several decades, says study leader Seth Blackshaw, Ph.D., an associate professor in the Solomon H. Snyder Department of Neuroscience at the Johns Hopkins University School of Medicine. However, he adds, researchers had previously thought that this process, called neurogenesis, only occurs in two brain areas: the hippocampus, involved in memory, and the olfactory bulb, involved in smell.

More recent research suggests that a third area, the hypothalamus — associated with a variety of bodily functions, including sleep, body temperature, hunger and thirst — also produces new neurons. However, the precise source of this neurogenesis and the function of these newborn neurons remained a mystery.

To answer these questions, Blackshaw and his colleagues used mice as a model system. The researchers started by investigating whether any particular part of the hypothalamus had a high level of cell growth, suggesting that neurogenesis was occurring. They injected the animals with a compound called bromodeoxyuridine (BrdU), which selectively incorporates itself into newly replicating DNA of dividing cells, where

it's readily detectable. Within a few days, the researchers found high levels of BrdU in an area of the hypothalamus called the median eminence, which lies on the base of the brain's fluid-filled third ventricle.

Further tests showed that these rapidly proliferating cells were tanycytes, a good candidate for producing new neurons since they have many characteristics in common with cells involved in neurogenesis during early development. To confirm that tanycytes were indeed producing new neurons and not other types of cells, Blackshaw and his colleagues selectively bred mice that produced a fluorescent protein only in their tanycytes. Within a few weeks, they found neurons that also fluoresced, proof that these cells came from tanycyte progenitors.

With the source of hypothalamic neurogenesis settled, the researchers turned to the question of function. Knowing that many previous studies have suggested that animals raised on a high-fat diet are at significantly greater risk of obesity and metabolic syndrome as adults, Blackshaw's team wondered whether hypothalamic neurogenesis might play a role in this phenomenon.

The researchers fed mice a diet of high-fat chow starting at weaning and looked for evidence of neurogenesis at several different time points. While very young animals showed no difference compared with mice fed normal chow, neurogenesis quadrupled in adults that had consistently eaten the high-fat chow since weaning. These animals gained more weight and had higher fat mass than animals raised on normal chow.

When Blackshaw and his colleagues killed off new neurons in the high-fat eaters by irradiating just their median eminences with precise X-ray beams, the mice gained significantly less weight and fat than animals who had eaten the same diet and were considerably more active, suggesting that these new neurons play a critical role in regulating

weight, fat storage and energy expenditure.

"People typically think growing new neurons in the brain is a good thing — but it's really just another way for the brain to modify behavior," Blackshaw explains. He adds that hypothalamic neurogenesis is probably a mechanism that evolved to help wild animals survive and helped our ancestors do the same in the past. Wild animals that encounter a rich and abundant food source would be well-served to eat as much as possible, since such a resource is typically scarce in nature.

Being exposed to such a resource during youth, and consequently encouraging the growth of neurons that would promote more food intake and energy storage in the future, would be advantageous. However, Blackshaw explains, for lab animals as well as people in developed countries, who have nearly unlimited access to abundant food, such neurogenesis isn't necessarily beneficial — it could encourage excessive weight gain and fat storage when they're not necessary.

If the team's work is confirmed in future studies, he adds, researchers might eventually use these findings as a basis to treat obesity by inhibiting hypothalamic neurogenesis, either by irradiating the median eminence or developing drugs that inhibit this process.

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