Brain Growth Receptors Control Lifespan

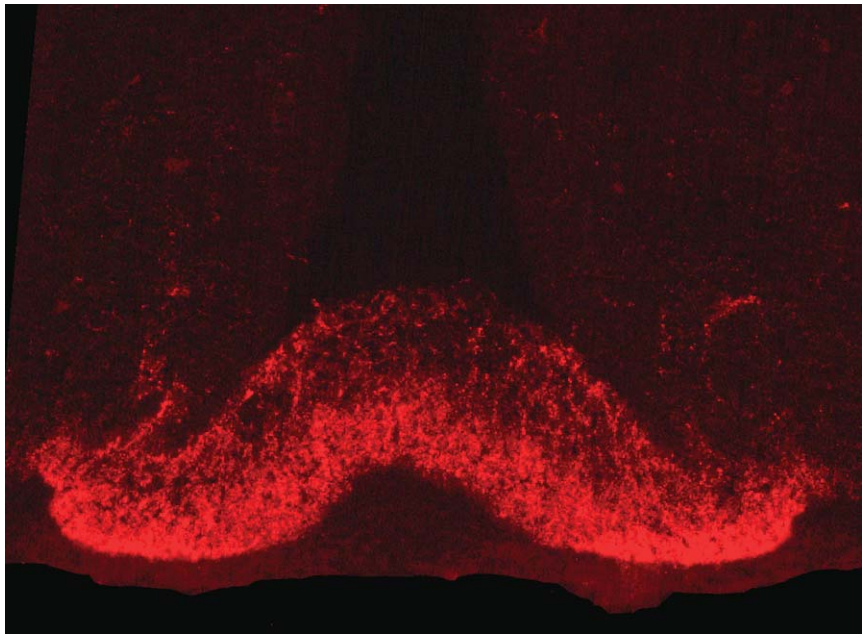
Richard Robinson | doi:10.1371/journal.pbio.0060274

When resources are short, growing organisms face an existential choice: should you ignore the shortage and hope for better times soon, or scale back and live within your limited means? And if you do scale back, will there be any payoff later in life? For animals, these choices are played out hormonally, with environmental fluctuations leading to internal rearrangements in endocrine signal and response throughout the growing body.

In mammals, two principal hormones—growth hormone (GH) and insulin-like growth factor 1 (IGF-1)—promote growth. Remarkably, inhibiting one or both of these two not only retards growth, but also extends lifespan, not just in lab animals, but possibly also in people: mutations that reduce the function of the IGF-1 receptor have recently been discovered in centenarians (who are also short). Growth occurs throughout the body, and receptors for IGF-1 are found in every organ on virtually every cell. But Laurent Kappeler et al. now show that it is the IGF-1 receptors in the brain that set the pattern for growth and lifespan.

The authors were led to the brain by the hierarchy of the endocrine system itself. While the pituitary gland, which sits just beneath the cranium, is often called the "master gland," it is really more of a first mate, taking its orders directly from the brain's hypothalamus. The hypothalamus controls differentiation and daily function of the pituitary, sending it instructions in the form of "releasing hormones," including growth hormone releasing hormone (GHRH). The pituitary, in turn, releases its own corresponding hormones into the blood stream, including growth hormone, which travels to the liver, triggering the production of IGF-1. Collectively, this cascade is known as the "somatotropic axis," and the authors reasoned that if the axis is ultimately controlled from the brain, then its ability to respond to resource fluctuations might be found there as well.

To test this, they selectively knocked out IGF-1 receptors in the brains of mice, leaving peripheral receptors (including those in the pituitary) alone. While homozygous knockouts—missing both gene copies, and producing no brain receptors—had significant developmental defects, the heterozygotes, which had one normal and one missing copy, were healthy and behaved normally. But by 20 days after birth, the knockout mice lagged in growth, and by 90 days, had fallen behind by 10% in body weight and 5% in length compared with their normal littermates.



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Somatoliberin produced by the developing hypothalamus (the red label represents hypothalamic somatoliberin, or GHRH) has an impact on late life mortality and lifespan in the mouse.

Despite normal levels of IGF-1 receptors on the pituitary, the size of the gland was reduced, and its ability to produce GH was correspondingly smaller. In the hypothalamus, production of GHRH was diminished, although somatostatin, a hormone with opposite effects, continued to be produced normally. While most organs were smaller than normal, fat tissue was increased, likely as a consequence of reduced GH. The effects of IGF-1 receptor knockout did not extend to other hormonal control axes—both gonadal and thyroidal functions remained normal, emphasizing the specificity of reduced IGF-1 stimulation.

Mean lifespan was also increased in the knockout mice, by about 10%. The effect on lifespan was curious, however. While the mean was extended, the maximum was not—more knockout mice lived longer, but the oldest knockout mouse lived no longer than the oldest normal mouse. The increased mean lifespan can be explained by low peripheral GH and IGF-I, which is itself a consequence of reduced central IGF sensitivity, in keeping with previous studies that have shown that reduced peripheral IGF-I and GH extend lifespan. The reason for the second effect (unchanged maximum lifespan) is unclear and will require more investigation.

These results suggest that IGF-1 feedback onto the hypothalamus during development plays a key role in determining the set-point of the somatotropic axis throughout life. While previous experiments have implicated IGF-1 suppression in lifespan extension, this study shows that central, rather than peripheral, suppression is sufficient to trigger the effect. Longer lifespan can also be the consequence of caloric restriction, and these results may indicate one mechanism that mediates that

phenomenon. They also open the door to a multitude of experiments to further explore the interplay of environment and endocrine control in setting the trajectory of metabolism, growth, and longevity.

Kappeler L, De Magalhaes Filho C, Dupont J, Leneuve P, Cervera P, et al. (2008) Brain IGF-1 receptors control mammalian growth and lifespan through a neuroendocrine mechanism. doi:10.1371/journal.pbio.0060254