Animal Source

Brain Growth Receptors Control Lifespan

Richard Robinson

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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.

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PSU Animal Resource Program

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Inside this issue:

Criteria for Prediction of Imminent Death in Aged Mice

A recent study at Southern Illinois University identified physical indicators that can be used to predict death within one week in aged mice. The ability to predict imminent death would allow investigators to euthanize an animal for collection of tissues or blood prior to spontaneous death without significantly impacting longevity outcomes. Mice are frequently found dead without prior signs of clinical illness, and as such, become unusable for sample collection.

Mice in this study were retired ICR breeders of both sexes implanted with microchips for remote measurement of body temperature. Mice were monitored weekly for body temperature, body weight and visible signs of illness until either spontaneous death or euthanasia based on clinical signs. Animals that were unable to walk, did not respond to manipulation, had large or ulcerated tumors and/or clinically obvious hypothermia were euthanized. Twenty four of 105 mice were euthanized, the rest died spontaneously. Data from both groups were analyzed to identify clinical signs that preceded death.

Weight loss was the most common and earliest sign of impending death. Mice lost approximately 20% of their body weight during the three month period preceding death, with about half of that loss occurring during the last week of life. Body temperatures were stable until the last week of life, during which they fell by over 1°C. Forty three percent of mice exhibited slow and/or labored breathing within 24 hours of death.

The authors concluded that mice showing two or more of the following clinical signs could be accurately predicted to die within a maximum of one week: sudden loss of body weight (>10% loss), decreased body temperature (>1°C decrease) or slow or labored respiration. More frequent evaluation of high-risk mice could potentially allow even more accurate prediction. Euthanasia of mice based on these criteria would allow collection of tissues or blood for analysis without significantly reducing longevity (i.e., one week represented about 1% of the median life span of animals in this study).

[Editor's note: Body temperature measurement in mice requires the use of either a rectal probe, a specially designed infrared thermometer or surgical implantation of a microchip. All of these methods can be stressful for the animal and/or require anesthesia.]

References:

Ray, M.A., Johnston, N.A., Verhulst, S.J. and Toth, L.A. (2008). Prediction of imminent death in mice used for longevity research. *Experimental Gerontology* 44: 134.

The next Mouse Biomethodology Seminar will be held on January 23, 2009 from 1-4 pm in the Centralized Biological Laboratory. Please call 865-1495 to register to attend.

How old is this mouse pup?

It can be challenging to determine the age of mouse pups during the first two weeks of life. However, the correct age can be estimated to within a day or two if you know when certain physical characteristics appear in developing pups.

In this photo the pup is starting to develop a fuzzy covering of white fur over the back. How old is it?

Answer on page 4.

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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.

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.

Animal Resource Program

101 Centralized Biological Laboratory
Pennsylvania State University
University Park, PA 16802

(814) 865-1495
Fax: (814) 865-3685

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Mouse Social Behavior Test Scores Not Dependent on Light Phase

A recent study by Yang, M, et al. has shown that inbred mice subjected to a social approach task obtained similar scores irrespective of whether testing was conducted during the light or dark phase of the day. Mice are considered to be nocturnal animals whose social interactions usually occur during the dark phase of the day. However, behavioral testing during the dark phase presents practical difficulties for investigators. A review of the literature found that commonly used social tests have been conducted during both the light and dark phase without consideration for how time of day affects social behavior in mice.

Based on the results obtained in this study, the authors speculated that modern laboratory mice have evolved to be able to adjust physiologically and behaviorally to light phase disruptions (e.g., experimental testing, cage changing, etc…) without significant changes in social behavior.

Reference: Yang, M., Weber, M.D. and Crawley, J.N. (2008). Light phase testing of social behaviors: not a problem. *Frontiers in Neuroscience* 2: 186-191.

Answer to "How old is this mouse pup?"

Mice start to develop colored fuzz behind the ears and/or on the neck at around day 6 of age. The colored fuzz will start to cover the back of the pup around day 7. Fur begins to grow on the belly at around day 8 and fur growth will be complete by day 10.

This pup is approximately seven days old.