Neuro-endocrinology
4 BRIEFINGS

GROWTH HORMONE RHYTHMS FROM THE BRAIN

SUMMARY

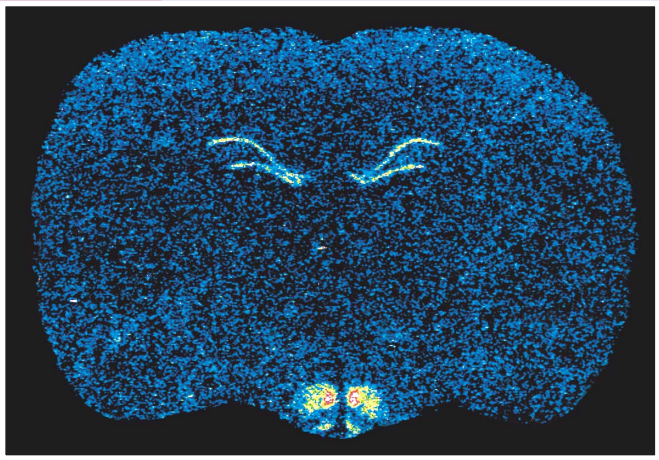
Growth hormone, like many hormones, is secreted into the blood in pulses, in a rhythm controlled by the brain. As we age, this rhythm becomes feebler, and past the age of thirty, this starts to limit our muscle function. However, insights into how the brain controls hormonal rhythms suggest ways to restore a young and healthy rhythm of growth hormone.

Growing importance

When I drive to work in the morning and indicate left, lights come on at the front and back of my car. Well, they don't just go on: they go on then off, then on then off again. If they worked better and stayed on, the driver behind would be less impressed and my insurance premium would go up.

My body feels much the same way about my hormones as the driver behind feels about my indicator lights – they've got to *pulse* to do their job properly.

When it matters, most of our hormones are released in spurts. This is true even for **growth hormone**. Growth hormone helped me to grow to my present fine height of 5 foot 8 inches, and even after I stopped growing, growth hormone continued to be important for building muscle.



Expression of the GHRP receptor gene in a rat brain section is abundant (bright colours) in the hippocampus and also in the arcuate nucleus at the base of the brain where the cells producing growth hormone releasing hormone are localised.

Now, between my ears is this supercomputer that can answer questions like "How can I switch off the alarm on my digital watch?*" and I use important chunks of it for *growing*. Tomatoes are happy with manure, but I need my brain. Every three hours, a few thousand cells in a part of my brain called the hypothalamus release a spurt of *growth-hormone releasing hormone*. This spurt is carried to the pituitary gland, which responds in turn by releasing a spurt of growth hormone. My brain makes sure that, every three hours, those brain cells are all activated together, or instead of a spurt of growth hormone I'll get just a dribble.

A dribble is not good enough. In the 1980's some British neuroendocrinologists described a strain of rats which didn't grow too well. These *dwarf* rats don't grow because they don't make enough growth hormone, but they grow normally if given regular injections of growth hormone. But to get normal growth the growth hormone must be given in the right *pattern*, of one injection every three hours or so.

Getting the rhythm

How the normal brain gets the rhythm right is not known. Part of the answer is that growth hormone, after it's released from the pituitary, acts back on the hypothalamus to

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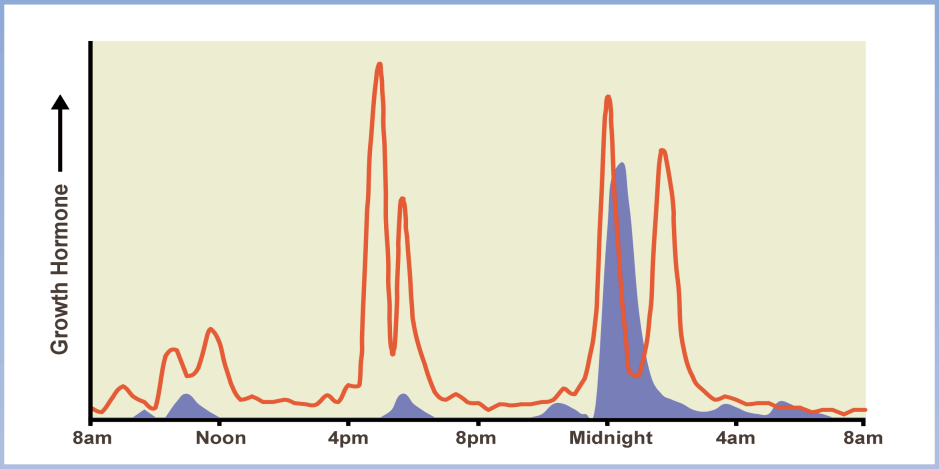
switch off the cells that release growth-hormone releasing hormone. But what activates the cells again three hours later, and what synchronises their activity, are not known.

This matters because, for just about everyone past the age of thirty, our brains aren't what they were. As we age, less growth hormone is released, and the *pattern* of release gets blurred; our bodies get pear-shaped, our skin wrinkles, and our muscles weaken. Neuroendocrinologists are studying how the hormonal rhythm is generated, and how it is are affected by exercise, by illness, and in aging.

"My brain makes sure that, every three hours, those brain cells are all activated together."

Some important insights have come from studies with a synthetic peptide discovered more or less by chance. GHRP (for growth hormone releasing peptide) stimulates growth hormone release by "tuning-up" the hypothalamus. What you get after GHRP is not just a *lot* of growth hormone, but the sort of pattern of repeated spurts that you'd expect to find in someone young and healthy. GHRP acts on the cells in the brain that make growth-hormone releasing hormone, but also acts at other sites in the brain, and at the pituitary.

GHRP acts at specific *receptors*, these have recently been cloned and sequenced, and appear to be of a wholly new type. The figure shows expression of the GHRP receptor gene in the brain of a rat, revealed by a technique called *in situ* hybridisation. The receptors are abundant in the hypothalamus, at the base of the brain, and in the hippocampus (the eye-like patterns in the upper half of the brain section). In the hypothalamus the *arcuate nucleus* (at the very bottom) contains the cells which secrete *growth hormone releasing hormone*.



Pattern of growth hormone levels in the blood of an elderly man before (blue line), and following (red line) daily treatment with a drug which acts like GHRP.

Illustrations courtesy of Roy Smith and Mark Bach.

"Our bodies get pear-shaped, our skin wrinkles, and our muscles weaken."

Some neuroendocrinologists are developing drugs to act on these receptors, which can be taken orally. In the graph, the blue line shows growth hormone secretion in an elderly man, and the red line shows growth hormone secretion in the same man during daily treatment with a drug which acts like GHRP – the result has been a restoration of the 'juvenile' pattern of growth hormone secretion. The hope is that these drugs will benefit some groups of growth-retarded children, and might also help to preserve muscle mass and function in some wasting disorders.

* Take the battery out.

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