

The production and release of growth hormone during periods of metabolic stress – How and why?

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Growth hormone (GH) is a key regulator of pubertal linear growth, and a regulator of cell growth and cell regeneration. In addition to these anabolic actions, GH is also a regulator of energy homeostasis. For example, GH mediates insulin action during periods of excess energy intake. To facilitate these actions, the production and release of GH is tightly linked to physiological demand, and central and peripheral mechanisms couple GH secretion with energy intake.

We recently established the mouse as a suitable model for the assessment of mechanisms that mediate pulsatile GH release relative to short-term and long-term changes in energy intake. In doing so, we confirmed that the onset and timing of GH release in mice is tightly coupled to food availability, and that a progressive rise in body mass and adiposity in response to dietary excess is coupled with a progressive decrease in total and pulsatile GH release. To this extent dietary induced weight gain will advance the natural age-associated change in GH release. Using various transgenic mouse models we are now defining hypothalamic orexigenic and anorexigenic mechanisms that couple GH release with food intake and weight gain.

Our work has highlighted the role of hypothalamic neuropeptide-Y (NPY) expressing neurons in mediating GH release. Our observations confirm that the onset of GH pulsatility relative to meal availability is selectively controlled through interactions between NPY and somatostatin expressing neurons. This is mediated *via* interactions with the Y1 receptor (Y1R), whereas the Y2 receptor (Y2R) modifies GH release in *ad libitum* fed mice. We have also demonstrated that the long-term change in GH release that is seen with weight gain occurs in response to factors commonly associated with food intake. Using melanocortin-4 receptor deficient (MC4R^{-/-}) mice as a model, we demonstrated that the loss of GH secretion that is normally observed alongside weight gain occurs predominantly in response to hyperphagia, and presumably the corresponding development of hyperinsulinemia.

Collectively our observations demonstrate that the production and release of GH relative to food intake is tightly regulated via central and peripheral factors, presumably to sustain fatty acid and glucose homeostasis. Ultimately, derangements in GH release may impair our capacity to tolerate sustained alterations in energy intake, resulting in pathologies commonly associated with obesity.