AuPS/ASB Meeting - Adelaide 2010

Symposium: Regulation of metabolic balance through co-ordination of central and peripheral signalling

Monday 29th November 2010 - The Gallery - 11:00

Chair: Chen Chen

Integrating peripheral and central mechanisms that regulate growth hormone (GH) secretion during periods of altered food consumption

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Growth hormone (GH) has gained most of its recognition for its role in stimulating linear growth. However it is also a key anabolic hormone in the regulation of energy balance; in this role GH stimulates muscle growth and bone density, and also regulates body fat mass and lipid metabolism. Somewhat reciprocally, body composition and meal pattern are both major determinants of GH secretion in that the central and peripheral peptides normally involved in the regulation of food intake mediate GH secretion. As a result, nutritional status impacts the regulation of the GH axis culminating in reduced or increased levels of GH secretion during periods of excessive or restricted energy consumption, respectively.

To fully understand the impact of energy flux on GH secretion, one must consider interactions between multiple endocrine systems and their integration with the central mechanisms that drive GH secretion. At its core, central regulation of GH secretion from the anterior pituitary gland is modulated by stimulating GH releasing hormone (GHRH) and inhibitory somatostatin (SRIF) neurons. These neurons are dispersed between populations of orexigenic (primarily NPY and AgRP expressing neurons) and anorexigenic neurons (including neurons expressing POMC and CART). Despite the fact that direct interactions between hypothalamic appetite regulatory neurons and those regulating GH secretion are still under investigation, clear relationships between peripheral factors coupled to food intake and GH secretion have been established. For example, ghrelin - a potent orexigenic hormone secreted by the stomach - stimulates both NPY/AgRP neurons and GH secretion.

The endogenous cannabinoid system has gained favour as a central regulator of appetite. Treatment with cannabinoid receptor subtype-1 (CB1) agonist result in a biphasic response in food intake; low dosages stimulate food consumption whereas high dosages have an inhibitory effect. Of particular importance regarding GH secretion and food intake is the potential role of the endogenous cannabinoid system in integrating peripheral with central mechanisms that are involved in mediating GH secretion. Early observations suggest that activation of the CB1 receptor by exogenous cannabinoids result in suppression of GH secretion. These studies do not take into account the biphasic effects of CB1 receptor activation, and consequently do not address potential stimulatory or inhibitory effects of cannabinoids on GH secretion. Furthermore, as fasting stimulates the endogenous cannabinoid system, early attempts do not address the potential interaction of cannabinoids on GH secretion during periods of reduced food intake.

Our recent observations confirm that central activation of the CB1 receptor suppresses the initial fasting-induced increase in GH secretion. Gene analysis studies confirm that these effects are mediated *via* an interaction with GHRH neurons. It should be noted, however, that the impact of fasting and the mechanisms that drive GH secretion during early periods of food restriction differ from those regulating pulsatile GH secretion during times of adequate food consumption. In this scenario we observe a differential impact following CB1 activation, where low levels of cannabinoid treatment (0.5mg/kg IP) resulting in increased food intake is coupled with an increase in GHRH mRNA within the arcuate nucleus. In contrast, elevated dosages (1.0mg/kg IP) of cannabinoid treatment do not affect food intake nor do they induce any alterations in GHRH mRNA expression. This finding was surprising considering that the same dosage (1.0mg/kg IP) was sufficient to inhibit the initial fasting-induced increase observed in GHRH mRNA. We are currently extending these observations to determine whether the differential impact on GHRH neurons relates to changes in peripheral GH secretion. Overall, our observations suggest that the endogenous cannnabinoid system may prove to be yet another mechanism involved in the already complicated array of integrated systems that regulate GH secretion during periods of altered food consumption.

Control of energy balance by nutrient sensing neurons

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Obesity confers significant health risks, and rates of obesity continue to rise within the developed and developing world. The Cowley lab has discovered how Proopiomelanocortin (POMC) neurons in the brain detect levels of leptin, which signals adipose stores. This signal allows the brain to regulate food intake and energy expenditure to maintain homeostasis. We have also discovered that the melanocortin circuits transduce the appetite reducing actions of the gut hormone PYY3-36, and the appetite stimulating actions of ghrelin. This suggests that the melanocortin circuits are a major neural center for processing signals of energy status to regulate long term body weight. More recently the lab has discovered how the brain becomes resistant to leptin, and how leptin resistance in a hallmark of obesity. The lab has developed several therapies that bypass leptin resistance and regulate food intake and energy expenditure to reduce adipose stores and cause weight loss. One of these therapies has recently completed Phase 3 trials.

Regulation of hypothalamic GHRH neuronal activity by ghrelin and obestatin

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Ghrelin, a natural ligand of the Growth Hormone Secretagogue Receptor (GHS-R), is synthesized in the stomach but it may also be expressed in lesser quantity in the hypothalamus where the GHS-R is located on Growth Hormone Releasing Hormone (GHRH) neurons. Obestatin, a 23 amino acid peptide derived from the same precursor as ghrelin, antagonizes ghrelin-induced increase of Growth Hormone (GH) secretion *in vivo* but it is not active on pituitary explants *in vitro*. Thus, the blockade of ghrelin-induced GH release by obestatin is likely mediated at the hypothalamic level within the neuronal network which controls pituitary GH secretion. Ghrelin increased GHRH and decreased somatostatin (somatotropin releasing inhibitory factor, SRIF) release from hypothalamic explants while obestatin only reduced ghrelin-induced increase of GHRH release. Thus, the effect of ghrelin and obestatin is targeted to GHRH neurons. Patch-clamp recordings on mouse GHRH-eGFP neurons indicate that ghrelin and obestatin do not affect glutamatergic synaptic transmission. In sharp contast, ghrelin decreases GABAergic synaptic transmission, an effect which is blocked in the presence of the GHS-R antagonist BIM-28163. Ghrelin also stimulates the firing rate of GHRH neurons. Obestatin blocks the effects of ghrelin on GABAergic synaptic transmission. These data suggest that 1) ghrelin increases GHRH neurons excitability by increasing their action potential firing rate and decreasing the strength of GABA inhibitory inputs, thereby leading to an enhanced GHRH release and 2) obestatin can counteract ghrelin actions. Such interactions between metabolic regulatory neuropeptides on GHRH neurons are likely to participate in the control of GH secretion.