Leptin and PACAP: Possible Co-op?

Have you ever wondered what makes you hungry? Not in the superficial sense of “I see a cheeseburger,” but in the inherent, instinctual sense of “I need food.”

How do we know when to eat, and when to stop? This is where two signaling molecules, leptin and PACAP, come into play. Leptin is a hypophagic hormone secreted by fat cells (adipose), thought to regulate satiety. In other words, it’s one of our bodies’ ways of monitoring fat storage and energy intake. Leptin targets the hypothalamus, the region of the brain most associated with homeostasis and energy regulation, to regulate feeding behaviors and prevent excessive weight loss or weight gain.

Pituitary adenylate cyclase activating polypeptide (PACAP) is a neuropeptide which produces nearly the same effect, targeting the ventromedial nuclei (VMN) of the hypothalamus.

Together, leptin and PACAP play a role in our bodies’ hunger and feeding drives, preventing the extremes of obesity or starvation. Thanks to leptin and PACAP, we know when that cheeseburger is necessary, and when it isn’t.

Leptin and the Ile14 Residue:

Investigation whether changes to the Ile14 residue, a critical site for leptin binding, alters PACAP signaling may provide an opportunity to understand the degree to which leptin and PACAP signaling are related.

A Closer Look at Leptin and PACAP Signaling.

Figure 2: PACAP activity is required for leptin signaling.

After microinjection of leptin, administration of PACAP6-38 (a PACAP receptor antagonist) into the VMN of male rat lact rats counteracts the hypophagic effects of the pre-administered leptin, resulting again in excessive feeding and weight gain. This implies that in order for leptin to function, PACAP must bind with its receptor, suggesting the two signaling molecules may function together by the same signaling pathway.

Figure 5 shows leptin and PACAP signaling, which begins with their production in adipose tissue and the brain, respectively, targeting the hypothalamic VMN. Leptin has been strongly linked to activation of the JAK-STAT signaling cascade (Figure 6), which increases STAT3 phosphorylation and BDNF expression (both of which are necessary for leptin-induced hypoglycemia to take place). The proximity of leptin and PACAP receptors in the VMN combined with their similar functions suggest they may work together to induce hypoglycemia through a shared intracellular signaling cascade.

Implications of a Shared Cascade:

More than one-third of American adults are obese, and obesity-related conditions including diabetes, hypertension, and stroke are among the leading causes of preventable deaths. Interestingly, most overweight or obese individuals express high levels of leptin, indicating that the leptin signaling cascade is not functioning correctly, perhaps due to mutations in the Ile14 residue.

Resources:

Choi, S., PhD. (2016, February 10). Bilateral injections of leptin (0.025 ng/side) in the VMN produces hypoglycemia that is completely reversed by the PACAP antagonist, PACAP6-38 (0.32 pmol). MedMobil. [Quantitative PCR from VMN RNA collected 3 hours post PACAP6-38 (left) and saline (right) from control, unpublished raw data.]

Choi, S., PhD. (2016, February 10). [Bilateral injections of leptin (0.025 ng/side) in the VMN produces hypoglycemia that is completely reversed by the PACAP antagonist, PACAP6-38 (0.32 pmol). MedMobil. [Quantitative PCR from VMN RNA collected 3 hours post PACAP6-38 (left) and saline (right) from control, unpublished raw data.]

Shu-Chen Xu et al. (2016) The 14th Ile residue is essential for Leptin function in regulating energy homeostasis in rat. SREP 6:28508. DOI: 10.2210/pdb1ax8/pdb

Zhang et al. (2016) The 14th Ile residue is essential for Leptin function in regulating energy homeostasis in rat. SREP 6:28508. DOI: 10.2210/pdb1ax8/pdb

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