Dynamic Duo: Leptin and PACAP Receptors Fight Obesity


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Leptin and Obesity

Obesity is a risk factor for cancer, diabetes, and stroke, causing 300,000 deaths annually in the U.S. Facets of obesity, such as adipose-tissue mass, hunger, and energy use are, in part, regulated by leptin, which binds to the leptin receptor (LR) within the hypothalamus, regulating mammalian feeding behaviors and promoting metabolic homeostasis. Leptin signaling leads to decreased appetite and increased metabolism resulting in weight loss. Understanding LR activation is crucial for obesity as studies have shown that defects in LR binding may disrupt normal metabolic function and overeating leading to metabolic disorders such as obesity. Overeating also occurs when PACAP (pituitary adenylate cyclase activating polypeptide) is blocked, similar to the actions of leptin. Understanding how leptin receptors function with PACAP receptors would advance the understanding of leptin signaling in obesity because current appetite suppressors are ineffective at treating obesity due to the tendency for the users to become tolerant to the drug. To date, effective treatments for obesity are lacking, therefore research focused on the relationship between PACAP and LR activation could lead to the development of new therapeutics.

The Relationship Between PACAP and Leptin

Leptin, synthesized by adipose tissue, was thought to have a unique signaling pathway that regulated metabolism. However, it appears that PACAP receptors can also activate the same neurological pathway in the hypothalamus, possibly changing the way researchers approach treating and preventing metabolic disorders. In fact, there are numerous similarities within the intracellular signaling between PACAP and LR. For example, both molecules suppress appetite and have been linked to the activation of JAK-STAT and STAT3 phosphorylation. Phosphorylated STAT3 (a PACAP receptor antagonist), or leptin alone. The solutions were bilaterally injected in the ventromedial nuclei of the hypothalamus (brain region important for regulating feeding behavior.) Figure 5 shows that food intake was similar to saline injections when injected with PACAP-38/leptin. When solely injected with leptin (black bar), food intake was significantly less. This illustrates that PACAP-38 reversed the effects of leptin (grey bar), which suggests a similar signaling pathway for leptin and PACAP. Rather than focusing on manipulating leptin, a possible therapy can be explored by taking into account the leptin receptor as well as PACAP signaling.

Structure of Leptin

Leptin, a signaling protein secreted by adipose tissue, regulates metabolic systems in mammals. Released from adipose tissue, it travels to the hypothalamus and binds to LR receptors extracellularly, specifically the Y1138 residue, which activates the JAK protein on the intracellular portion of the receptor. Six different forms of LR exist but only the Obrb form is part of the JAK-STAT signaling pathway (figure 4). The portion of the LR or Obrb modeled is the B chain. Once leptin binds with LR STAT3 is phosphorylated, which activates protein transcription for BDNF, which regulates metabolism. The same intracellular pathway is used by PACAP, which binds to the PAC1R (PACAP receptor) and activates a pathway similar to leptin (figure 3).

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Molecular Story

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Process of Science

Rats were divided into three groups and given saline, leptin and PACAP6-38 (a PACAP receptor antagonist), or leptin alone. The solutions were bilaterally injected in the ventromedial nuclei of the hypothalamus (brain region important for regulating feeding behavior.) Figure 5 shows that food intake was similar to saline injections when injected with PACAP-38/leptin. When solely injected with leptin (black bar), food intake was significantly less. This illustrates that PACAP-38 reversed the effects of leptin (grey bar), which suggests a similar signaling pathway for leptin and PACAP. Rather than focusing on manipulating leptin, a possible therapy can be explored by taking into account the leptin receptor as well as PACAP signaling.

Steps for the Future

This recent data demonstrates that PACAP and leptin regulate metabolic systems using the JAK/STAT3 intracellular phosphorylation pathway. Further studies may include examining whether leptin is a primer or activator in the release of PACAP. If this is true, then targeting PACAP could lead to normalizing leptin function as an appetite suppressant. By studying pathways with multiple hunger suppressant actions, insight can be gained to better understand the biological foundation of obesity. As the PACAP/leptin relationship is further understood, a possible treatment may be developed to aid individuals with obesity and other metabolic disorders.

References


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