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Experimental models for investigating IAPP regulation of food intake in rats and mice

AKADEMISK AVHANDLING

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ABSTRACT

Background: Maintenance of energy balance is one of the fundamental processes of living organisms and involves complex regulatory pathways. Appetite regulation is an important component of this, because it modulates energy intake. Islet amyloid polypeptide (IAPP or amylin) is a 37-amino-acid peptide that is produced primarily by the β-cells in the pancreas and is co-secreted with insulin in response to a meal. A reduction in food intake and body weight is seen following several routes and modes of IAPP administration in rodents and the peptide has been suggested to be necessary for normal satiety to occur.

Objectives: The present studies investigated whether IAPP acts as a satiety hormone. In addition, the mechanisms through which IAPP exerts its effects were investigated.

Methods: The effects of chronic IAPP treatment on energy homeostasis were investigated in rats by subcutaneous (SC) infusion of IAPP (25 pmol/kg-min) for 2-7 days. Ad libitum fed and pair fed rats were used as controls for the IAPP groups. The effects of peripheral and central administration of IAPP were compared by analyzing food intake, meal pattern, and body weight in rats after 7 days of SC infusion of IAPP (0, 0.25, 2.5 or 25 pmol/kg-min) or intracerebroventricular (ICV) infusion (0, 0.025, 0.25 or 2.5 pmol/kg-min). The expression of neuropeptide Y (NPY) mRNA, agouti-related protein (AgRP) mRNA, and proopio-melanocortin (POMC) mRNA was measured in the arcuate nucleus of the hypothalamus of rats after ICV infusion (2.5 pmol IAPP/kg-min for 5 days). Pair-fed and ad libitum fed rats receiving vehicle only were used as controls. Food intake, meal pattern, and body weight were measured during a long-term, 27-week study in 8 adult male IAPP knockout mice (IAPP-/-, strain C57BL/6) and 8 adult male wild-type mice (IAPP +/+, strain C57BL/6). After the long-term experiment was completed, a short-term experiment was conducted in which food intake and body weight were analyzed in the mice after a 3-day infusion of IAPP (25 pmol/kg-min).

Results: Transient inhibition of food intake following IAPP infusion was seen in all the rat experiments. The minimal effective dose for SC infusion was 2.5 pmol/kg-min compared to 0.25 pml/kg-min for the ICV infusion. SC infusion of IAPP decreased the weight of epididymal fat pads and lowered circulating levels of triglycerides, free fatty acids, leptin, and insulin. Glucose metabolism and protein metabolism were largely unchanged. No changes in expression of AgRP or NPY mRNA were seen after ICV infusion of IAPP, but a decrease on POMC mRNA was seen in both IAPP and pair fed animals. In the mouse experiments, no differences in food intake or body weight were seen between knockout and wild-type mice during the long-term study. In the short-term study, food intake was significantly lower in the knockout mice than in the wild-type group.

Conclusion: The data from these studies provide support for the hypothesis that IAPP is a satiety hormone which acts primarily in the brain to inhibit food intake. Inhibition of food intake does not appear to be mediated by POMC at the time point studied. The lack of differences in food intake and body weight between IAPP KO and wild-type mice indicate that food intake can be controlled in the absence of IAPP. The more marked anorectic effect seen in the KO mice during IAPP infusion suggests that IAPP receptors and/or IAPP post-receptor signalling pathways are up-regulated in mice lacking endogenous IAPP.

Keywords: adiposity, agouti-related protein, amylin, body weight, food intake, hypothala-mus, IAPP, knockout mice, leptin, meal pattern, neuropeptide Y, proopiomelanocortin, satiety.

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