

Central and Peripheral Neuroendocrine Factors in Cancer-Associated Anorexia and Cachexia

AKADEMISK AVHANDLING

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av

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Avhandlingen baseras på följande arbeten:

- I. **Burgos JR, Iresjö B-M, Smedh U.** Pituitary adenylate cyclase-activating polypeptide 6-38 blocks cocaine- and amphetamine-regulated transcript peptide-induced hypophagia in rats. *PLoS ONE* 2013; 8(8): e72347.
- II. **Burgos JR, Iresjö B-M, Wärnåker S, Smedh U.** Presence of TSH receptors in discrete areas of the hypothalamus and brainstem with relevance for feeding controls—support for functional significance. Manuscript, *submitted*.
- III. **Burgos JR, Iresjö B-M, Olsson L, Smedh U.** Lipopolysaccharide immune challenge reduces TSHR and CART mRNA in the Arcuate nucleus and elevates circulating CART peptides in mice. Manuscript, *submitted*.
- IV. **Burgos JR, Iresjö B-M, Smedh U.** MCG101-induced cancer anorexia-cachexia features altered expression of hypothalamic *Nucb2* and *Cartpt* and increased plasma levels of cocaine- and amphetamine-regulated transcript peptides. *Oncology Reports*, *Accepted for publication* 9 November 2015.
- V. **Burgos JR, Iresjö B-M, Smedh U.** PACAP6-38, a functional CARTp antagonist, counteracts loss of adipose tissue in MCG101 tumor-bearing mice with elevated host plasma CART and anorexia-cachexia syndrome. Manuscript.



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ABSTRACT

Cancer anorexia-cachexia syndrome (CACS) develops in response to tumor-host biochemical interactions. A loss of appetite (anorexia) and increased metabolism results in a progressive wasting of adipose and skeletal muscle tissues (cachexia). This syndrome is linked to a reduced tolerance to anti-cancer treatments, lower quality of life, and poor prognosis. The specific mechanisms that cause CACS are still unknown, and there exists no curative treatment for this syndrome. In this thesis, rodent models for induced anorexia, MCG101 tumor-induced CACS, and acute inflammation paradigms were used.

The first stages of this thesis project were aimed at identifying central mechanisms by which cancer-associated anorexia could be overriding homeostatic feeding controls. Our initial investigations involved cocaine- and amphetamine-regulated transcript peptides (CARTp) and the thyrotropin receptor (TSHr). Centrally acting CARTp are known to potently inhibit feeding. Similarly, infusions of TSH into the lateral ventricles have been shown to reduce food intake in rats. The precise mechanisms through which CARTp elicits its effects, and the distribution of functional TSHr have been unknown.

A previous *in vitro* study showed CARTp activity was antagonized by PACAP6-38. We built upon previous findings by showing that PACAP6-38 could block CARTp-induced anorexia *in vivo* in rats; thus, we provided further support that PACAP6-38 is a useful tool for elucidating endogenous CARTp effects. In addition, we report that TSHr proteins are present in nuclei of the hypothalamus and brainstem with relevance for feeding. Indeed, putative stimulation of TSHr in the nucleus of the solitary tract reduced solid food intake in healthy rats.

Using mouse models for acute inflammation and CACS, we investigated gene expression changes in areas of the brain with relevance for feeding, namely the hypothalamic paraventricular nucleus (PVN), arcuate nucleus (ARC), and the dorsal vagal complex of the brainstem. We investigated mRNA for compounds expressed in brain regions involved in feeding behavior under healthy conditions: CART, TSHr, TSH, thyrostimulin, nesfatin-1, and corticotropin-releasing hormone (CRH). Acute inflammation was associated with reduced gene expression for TSHr and CART in the ARC and increased expression of CART mRNA in the pituitary. CACS also resulted in a decrease in CART gene expression in the PVN, which was a response secondary to reduced food intake as shown by pair-fed controls. Interestingly, we saw a tumor-specific effect on nesfatin-1 gene expression in the PVN. Therefore, it appears that CARTp is not inducing anorexia in CACS, but seems to participate in an adaptive response. In addition, hypothalamic nesfatin-1 may be a likely candidate for mediating a CACS response.

Acute inflammation induced a prostanoid-independent increase of plasma CARTp, which correlated positively with degree of inflammation. Tumor-bearing mice similarly had elevated plasma CARTp concentrations. Putative antagonism of circulating CARTp by PACAP6-38 in tumor-bearing animals protected against loss of fat mass, but did not improve food intake or any other metrics. These findings highlight plasma CARTp as a potential mediator of lipolysis in CACS.

Keywords: cancer anorexia-cachexia syndrome; MCG101; inflammation; CART; TSH receptor; CRH; nesfatin-1; hypothalamus; brainstem

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