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Introduction to Special Issue on Feeding Peptides

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Since the original landmark discovery by Starling and Bayliss (1902) it has been recognized that chemicals convey information between cells of multicellular organisms. At the time, Pavlov's work (for which he was awarded the Nobel prize in 1904) had demonstrated the importance of autonomic reflexes in gut physiology. The experiments of Bayliss and Starling demonstrated the existence of chemical messengers that can travel through the circulation to impart their effects on distant targets. Starling latter coined the term hormone, derived from the Greek root meaning "to set in motion or excite", to define this class of signaling molecules.

Feeding peptides, comprising both peripheral peptide hormones and central neuropeptides, are a critical component of the complex signaling process that regulates energy homeostasis orchestrated by the CNS. **Why this special issue now?** Obesity, and its associated comorbidities, is a major worldwide public health problem. According the World Health Organization, obesity rates have nearly tripled since 1975. Despite decades of research, effective therapies for obesity are elusive and the physical, emotional and economic costs of obesity continue to rise. The belief, often asserted dogmatically, that calories-in equals calories-out, has led to ineffective strategies that are over-reliant on exercise and reducing food intake. This view has arguably caused more harm than good not least because it has stigmatized individuals with obesity as being lazy and lacking in will power, while ignoring the complex pathophysiology of obesity resulting from compensatory mechanisms that defend against weight loss by altering brain circuits associated with reward, memory, and the feeling of fullness (Nordmo *et al,* 2020). Thus, there is a critical need for more therapeutic interventions with safer and more effective profiles. Invasive bariatric surgeries, that involve remodeling of the gastrointestinal tract, are currently the most effective treatment option, highlighting the therapeutic importance of the gut-brain axis. The effectiveness of these surgical procedures has been attributed, in part, to improvements in the signaling profiles

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of multiple gut peptides (Castagneto *et al,* 2018). Thus, the impetus for this special issue was to provide a snapshot of the field and assess feeding peptides as putative therapeutics for the treatment of obesity. This special issue is organized into reviews followed by empirical studies of gut, pancreatic and sex hormones that inhibit food intake, continues with neuropeptides that inhibit food intake, and finish with neuropeptides that stimulate feeding.

Reviews of hormonal peptides that inhibit food intake.

Cawthon and de la Serre provide an overview of the best-studied gut-derived satiety peptide, cholecystokinin (CCK). Their review comprehensively summarizes the metabolic stimuli responsible for CCK release, the mechanisms by which CCK controls meal size via CCK receptors of the vagus nerve and how high fat diets prevent CCK induced meal termination.

Krieger summarizes the role of intestinal glucagon-like peptide-1 (GLP1) in food intake control, identifying gaps in our knowledge and calls for reappraising the importance of intestinal GLP1 in the pathophysiology of obesity. A particular highlight is the reanalysis of existing transcriptomic data which identifies a previously overlooked subpopulation of peripheral sensory neurons that is predicted to respond to the paracrine actions of intestinal GLP1.

Huang et al provide insight into the sexual dimorphism of eating behavior, reviewing the impact of the sex hormone estrogen on feeding peptides. Their review discusses estrogen signaling, and highlights the impact of estrogen on key gut hormones that provide negative feedback information to inhibit food intake along the vagal-hindbrain axis. The development of novel therapeutics that target the interaction between estrogen and gut hormones is discussed.

Patil et al review the rapidly evolving field involving the role of glucagon in glucose homeostasis. Glucagon acts as the yin to insulin’s yang (Scott and Bloom, 2018). Their review provides a detailed and thorough assessment of progress of three new classes of glucagon-based therapies.

Amylin is a peptide produced primarily by the pancreas. Boccia et al provide a timely account on the central site of action of amylin, the brain circuits that are recruited, and the role of these central systems in various aspects of feeding behavior.

Experimental studies of gut hormones that decrease food intake

Enteroendocrine (ECC) cells are specialized cells of the gut capable of sensing nutrients and secreting peptides that control food intake via a neuroendocrine mechanism (Reiman *et al*, 2020). Kamakura et al hypothesize that various EEC cell lines express different levels of fatty acid receptors and/or the enzyme dipeptidyl peptidase-4 (DPP4) that degrades GLP1. STC1 cells express more GPR120 but less GPR40 than GLUTag cells, but soluble DPP-4 had negligible effects on GLP1 degradation.

Dalboge et al study the role of VGF-derived peptides in energy balance. These authors synthesized a large number of VGF derivatives that were screened for effects on hypothalamic electrical activity in ex vivo experiments, and for their effects on food intake and energy expenditure in vivo after ICV injections.

Reviews of neuropeptides that control food intake

The neuropeptide cocaine and amphetamine regulated transcript (CART) was discovered 25 years ago. Singh et al review the considerable advances since its discovery that support a role in energy balance. A summary of anatomical and transcriptional screens, including re-analysis of existing RNA sequencing data, highlight the heterogeneity of CART neurons along the gut-brain axis. Pharmacological and genetic studies are also discussed supporting a largely anorexigenic role for CART, along with some nuclei-specific discrepancies.

Lord et al discuss the orexigenic neuropeptide melanin concentrating hormone (MCH). Their review highlights the role of MCH as a within-meal appetitive signal that prolongs meals. Mechanistic insight is provided at the functional level via interactions with other metabolic signals and at the circuit level via synaptic release at mesolimbic nuclei involved in reward and hypothalamic nuclei involved in hunger.

Experimental studies of neuropeptides that promote food intake

Here Yu et al assess the effectiveness of adding the known orexigenic neuropeptide NPY to the feed as a mechanism for rapidly increasing the growth of the commercially important fish, *Tilapia*. Consumption for 8-weeks of NPY added to a high fish meal diet, but not a low fish meal diet, promoted fish growth. This suggests that NPY may be an effective additive to shorten the time needed to feed fish meal, but NPY is not sufficient to transition to lower cost fish meal diets.

Williams et al assess the mechanisms by which orexin in the hindbrain increases motivation to eat. Using pharmacological approaches combined with feeding measurements they demonstrate that release of endogenous orexin in the hindbrain increases food intake by preventing satiety of gut peptides signaled by the vagus nerve. These data suggest that the coordinated release of orexin in the forebrain and hindbrain increase motivation to eat by activating reward circuits while simultaneously inhibiting interoceptive satiety signals.

The publications in this special issue highlight the remarkable redundancy of peptides that control feeding behavior, underscoring the challenge of designing effective therapeutics against obesity. Modifying peptides will be most effective if the peptides target separate circuits (Calo' *et al*, 2018). Based on the data discussed in this special issue some important conclusions include that 1) the peptide hormone, amylin appears to have a unique signaling profile that would make it compatible with other satiety peptides; 2) the discovery of a putative receptor for the neuropeptide CART is intriguing because it allows for the development of new pharmaceuticals that could influence both homeostatic and hedonic targets; 3) VGF may not be a viable therapeutic strategy; 4) sex is an important biological variable that should be considered as a step toward personalized health care; and 5) the use of orexin receptor antagonists may be particularly effective when combined with analogs of

peripheral satiety peptides by simultaneously inhibiting orexigenic signaling and promoting vagally-mediated satiety signals.

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