

# **Improving the Pharmacokinetics of Naturally Occurring Peptides Involved in Satiety and Metabolism Disorders**

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## **Statement of Research Question and Hypothesis**

The long-term goal of the proposed research project will involve the development of novel unnatural peptides for the treatment and prevention of metabolic disorders such as obesity and diabetes. By incorporating unnatural amino acid residues into the structure of naturally occurring peptides, the degradation of these peptides by digestive enzymes can be slowed down or even prevented. Therefore, the novel peptide would have a longer half-life when taken orally, a characteristic that is necessary in order to produce a marketable drug.

The short-term goals of the project will be to synthesize several modified peptides, to develop a method to determine the rate of degradation by selected digestive enzymes, and to determine the effect of the unnatural modifications on the rate of degradation relative to the parent compound. Once a candidate is identified with improved pharmacokinetics, the compound would be tested for activity at the target receptor. A candidate with improved pharmacokinetics (i.e. adsorption, digestion, metabolism, and excretion) and comparable potency to the parent peptide would be the optimum product of the research project.

## **Significance of Research**

For the past 25 years, the prevalence of obesity and obesity-related illnesses has been increasing at an alarming rate. Statistics released by the Centers for Disease Control and Prevention (CDC) in late 2007 show that 34 percent of U.S. adults are considered obese (obesity is defined as a body mass index of 30 or greater).<sup>1,2</sup> That implies that 72 million Americans are at higher risk for many diseases and health conditions including coronary heart disease, type 2 diabetes, breast and colon cancer, hypertension, and stroke. Furthermore, obesity is no longer an adult issue only since 16.3 percent of children and adolescents ages 12-19 are considered obese based on the body mass index (BMI)-for age growth charts.<sup>3</sup> It is clear that obesity and obesity-related diseases are currently regarded as a health crisis and great effort is being put forth by scientists and doctors to better understand the biological processes responsible for weight gain and weight loss.

Weight gain is caused by consuming more calories than the body needs, which leads the body to store the excess calories as fat. That may sound simple, but the causes of the imbalance between calories consumed and calories burned can be attributed to many different sources including genetic, hormonal, behavioral, environmental, and cultural.<sup>4,5</sup> Genetic traits, metabolism (how the body expends energy), hormones that modulate how calories are processed, and other organ systems can affect appetite and energy homeostasis.<sup>6</sup> Therefore, the treatment and prevention of obesity must involve a multifaceted approach that would address the complexity of the biological systems governing appetite and metabolism. From a medicinal point of view, there are five general strategies for significant weight loss: 1) reducing food intake by amplifying anorectic signals (suppress appetite) or by inhibiting orexigenic signals (stimulate appetite); 2) blocking lipid absorption in the gut; 3) increasing

thermogenesis; 4) modulating fat metabolism and storage; 5) modulating the central controller regulating body weight.<sup>7,11-13</sup>

The central controller (satiety center) is found in the hypothalamus, a region of the brain connecting the central nervous system to the endocrine system via the pituitary gland.<sup>8</sup> The hypothalamus mediates regulation of short-term and long-term dietary intake by synthesizing a variety of orexigenic and anorectic neuropeptides including neuropeptide Y (NPY), melanocortins, agouti-related peptide (AGRP), cocaine and amphetamine regulated transcript (CART), melanin concentrating hormone (MCH) and orexins.<sup>7,9</sup> Of these chemicals, NPY and CART are the most important since they are counterbalancing chemicals that dictate whether the brain registers satisfaction or hunger. CART stimulates the surrounding hypothalamus to increase metabolism, reduce appetite, and increase insulin to deliver energy to muscle cells rather than store it as fat.<sup>10</sup> NPY has the opposite effect by lowering body temperature, decreasing the metabolism, and increasing appetite. The response to peripheral signals (i.e. leptin and ghrelin) ultimately depends on which neuropeptide arrives at the central controller first.

CART exerts a very potent anorectic effect and is able to completely block the feeding response induced by NPY in rats and mice.<sup>14</sup> CART peptides are formed from a proCART polypeptide that is 89 amino acids long in humans of which fragments 42-89 and 49-89 are biologically active.<sup>15-17</sup> Initial findings demonstrates that intravenous administration of CART peptide inhibited feeding in rats and administration of a CART antibody stimulated feeding.<sup>10,18</sup> These results suggest that endogenous CART peptides inhibit feeding, and potentially modified CART peptides could be synthesized to improve pharmacokinetics and activity.

## Literature Review

The literature is saturated with reviews and articles on the topic of obesity and obesity-related diseases. In the last 25 years there has been a concerted effort to educate individuals and the community on weight management and the imminent risk present for those individuals that are deemed overweight or obese. Since one in three American adults and one in seven children and adolescents are considered obese, there is an urgent need to understand the causes of obesity and to formulate a strategy to treat and prevent the disease, and that is reflected in the literature.

When searching the National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine and the National Institute of Health (NIH) simultaneously through PubMed, the keyword "obesity" rendered 114,289 articles of which 18,936 are reviews. That speaks volumes for the interest, funding, and effort being invested in the research of obesity related topics. Of the over one hundred thousand articles on obesity, about 4,000 focus on the role of neuropeptides in the biological pathways involved in feeding behavior and energy homeostasis.

CART is a relatively new target for the development of a weight loss drug. However, there are approximately 500 articles and 90 reviews on the subject, and a number of research groups (Kristensen and Kuhar) have made great strides towards understanding the role of this neuropeptide and its potential as a novel anti-obesity agent.

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