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Regulation of Appetite by the Skeleton

ABSTRACT

The purpose of this project is to address the medical need for obesity treatment by translating the properties of a new anorexigenic hormone that we have discovered in the lab, Lipocalin 2 (LCN2). Loss- and gain-of-function experiments in mice demonstrate that osteoblast-derived LCN2 maintains glucose homeostasis and inhibits food intake. The suppression of appetite in mice occurs by LCN2 crossing the blood brain barrier and activating the MC4 receptor in hypothalamic neurons. Importantly, the suppression of appetite that occurs with LCN2 administration is chronic. In this proposal, we will examine whether the pattern of LCN2 regulation and suppression of appetite is reproduced in humans and non-human primates, respectively. Since LCN2 serum levels increase in fasted mice after feeding, we will perform fasting and re-feeding studies to assess LCN2 levels in patients' serum and the clinical effects of LCN2 on appetite. In addition, we will examine in non-human primates the mechanism of LCN2 action through is activating effects on the hypothalamus. We will determine in monkeys, using PET scans with injection of ^{18}F labeled recombinant LCN2, whether LCN2 crosses the blood-brain barrier, localizes to the hypothalamus and suppresses appetite after a meal. After completing this project, it is our expectation that we will have identified the pattern of LCN2 regulation with feeding in humans. Further, we expect to have shown that LCN2 has activating hypothalamic effects in monkeys in association with appetite suppression. Such findings would be important, because they would likely inform the development of a novel and much-needed approach to the therapy of obesity.