Adipose Tissue, Appetite, and Obesity

NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Serotonin as a Regulator of Leptin-Mediated Food Intake Control Within a Novel Neuronal Circuit Between the Hypothalamus and Raphe Nuclei

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The onset and exacerbation of obesity involves the overproduction of the adipocyte-derived hormone leptin, a key mediator of homeostatic appetite regulation and a signal for satiety. Although leptin's hypothalamic regulation of food intake has been extensively investigated, its role in tandem with the anorectic neurotransmitter serotonin (5-HT) has been less characterized. 5-HT is synthesized in the dorsal raphe nucleus (DRN) where anatomical projections to many hypothalamic nuclei have previously been identified. Preliminary studies in our lab have: (1) identified serotonergic neurons responsive to leptin in the DRN that project to the arcuate nucleus (ARC) of the hypothalamus and (2) demonstrated leptin injected into the DRN significantly decreases food intake. The objective of the current study was to identify the role of 5-HT in leptin's regulation of food intake first within the DRN, then between the DRN and the ARC. Adult male Sprague Dawley rats underwent stereotaxic surgery for guide cannula implantation in the DRN. After recovery, animals were administered 100 μg of p-chlorophenylalanine (PCPA), an inhibitor of 5-HT synthesis, in the DRN each day for four days. On the fourth day, leptin was also administered in the DRN (5 μg/rat) and food intake was measured over a 24-hour time course. ANOVA analysis revealed a significant difference in 24-hour food intake [$F(3, 18) = 3.972$; $P = 0.0246$] and post-hoc analysis showed that animals treated with leptin significantly decreased food intake (17.2 ± 2.0 g) compared to control rats (25.4 ± 0.9 g), whereas PCPA-treated rats did not differ from the control rats, suggesting that depletion of 5-HT attenuated leptin's ability to regulate food intake within the DRN. To examine the role of 5-HT on leptin's hypothalamic action, a subsequent experiment was conducted by implanting an additional cannula into the ARC for the administration of leptin or vehicle on the fourth day of treatment. ANOVA analysis revealed a significant difference in 24-hour food intake [$F(3, 16) = 5.998$; $P = 0.0061$] and post-hoc analysis showed that only rats treated with leptin in the ARC significantly decreased food intake (14.0 ± 1.5 g) compared to controls (21.8 ± 0.5 g). 5-HT depletion was assessed post-mortem using immunohistochemistry and was later quantified. Collectively, these results demonstrate that leptin's ability to regulate food intake is dependent on 5-HT, regardless of the area of regulation (i.e. DRN or the hypothalamus).