Glycomics & Lipidomics

Extended Abstract

Regulation of hypothalamic neuronal function in obesity

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Abstract

Obesity develops with chronic consumption of palatable energy-dense diets, and also with increasing age. With persistent positive energy balance, the increase in body weight is accompanied by a steady rise in circulating leptin levels, indicating the progressive development of counter regulatory mechanisms to antagonize leptin's anorexigenic effects. Hypothalamic neurons co-expressing agouti-related peptide (AgRP) and neuropeptide Y are direct leptin targets. We have recently shown that AgRP neurons are the predominant cell type situated outside the blood-brain barrier in the mediobasal hypothalamus. AgRP neurons are able to sense slight changes in plasma metabolic signals, such as leptin, but they also more quickly develop cellular leptin resistance in contrast to proopiomelanocortin (POMC) and other hypothalamic neurons that remain leptinsensitive. AgRP neurons also display age-dependent increase in innervation onto their target neurons, and this process is accelerated by chronic high-fat feeding. Our studies suggest that AgRP neurons are critical sensors for peripheral metabolic hormones and that they play a dynamic role in metabolic fine tuning in response to acute changes in nutritional status. Our studies also suggest that these neurons, with their unique anatomical relationship with the blood-brain barrier, could serve as important targets for therapeutic intervention for the treatment of metabolic disorders. Obesity affects more than 300 million humans worldwide and projections for the next 20 years predict a global prevalence of up to 20%, amounting to more than one billion obese individuals by the year 2030.

As a major risk factor for diabetes mellitus, hypertension, dyslipidemia, arteriosclerosis, as well as joint and skeletal deterioration, respiratory failure, and certain types of cancer, the burden of disease posed by the looming obesity epidemic is staggering. Unfortunately, lifestyle or behavioral interventions designed to correct nutritional overload and increase physical activity have yet to halt or even slow the increase of obesity prevalence. Similarly, the few drugs currently approved for obesity treatment are limited by both side effects and lack of efficacy, and although bariatric surgery can achieve substantial reduction of body weight and improve metabolic control, it is an invasive and costly intervention that is not uniformly effective and realistically can be offered to only a tiny fraction of those affected. The highly integrated and redundant nature of neurocircuits involved in energy homeostasis offers important insight into the question of why common forms of obesity have proven so difficult to treat. Energy homeostasis is the biological process that promotes stability in the amount of body energy stored as fat, and weight loss triggers robust activation of this homeostatic system in obese as well as in lean individuals. This response in turn limits the capacity to sustain voluntary weight loss and explains why non-surgical interventions typically cannot sustain weight loss of 5-7%—an amount that activates compensatory responses that limit further weight loss and favor recovery of lost weight. Stated differently, obesity arises not simply via passive accumulation of excess calories as fat but involves an upward re-setting of the biologically defended level of body fat.

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