Obesity: Hypothalamic Regulation of Food Intake

Abstract

Current estimates suggest that over 1 billion people are overweight and over 300 million people are obese. Weight gain is due to an imbalance between energy expenditure and dietary intake. This review discusses the hypothalamic control of appetite. Nuclei within the hypothalamus integrate peripheral signals such as adiposity and caloric intake to regulate important pathways within the central nervous system controlling food intake to energy expenditure. These pathways involve the orexigenic NPY/AgRP and the anorexigenic POMC/CART neurons in the arcuate nucleus (ARC) of the hypothalamus.

Keywords: Arcuate nucleus; NPY/AgRP; Hypothalamus; Glucose intolerance; cardiovascular diseases; Type 2 diabetes; Certain types of cancer

Introduction

Obesity etiology encompasses several factors; many of which are related with nutrition and behavioral disorders, endocrine alterations, drug use, neurologic and genetic diseases. The intriguing “fat epidemic”, with its staggering ever-growing numbers, has been the focus of speculation regarding the true reasons for its expansion, since sedentary lifestyle and changes in diets with fat intake alone cannot fully explain it [1]. The clustering of dyslipidemia, hypertension and glucose intolerance, predominantly in overweight individuals, at risk of heart disease, has been of concern and this increasing prevalence is partly attributable to a lack of exercise and partly to the availability of high caloric palatable food. In addition, obesity is highly heritable, with the estimated genetic contribution ranging from 60-84%. Current estimates suggest that over 1 billion people are overweight and over 300 million people are obese.

Central circuits in the brain rely on peripheral signals indicating satiety levels and energy stores, as well as higher cortical factors such as emotional and reward pathways [2]. The hypothalamus is critical in the relaying of afferent signals from the gut and brainstem as well as processing efferent signals that modulate food intake and energy expenditure. The hypothalamus is subdivided into interconnecting nuclei, including the arcuate nucleus (ARC), paraventricular nucleus (VMN), dorsomedial nucleus (DMN) and lateral hypothalamic area (LHA). Neuronal pathways between these nuclei are organized into a complex network in which orexigenic and anorexigenic circuits influence food intake and energy expenditure.

Hypothalamic Nuclei involved in Appetite Control

Arcuate nucleus (ARC)

The ARC is the key hypothalamic nucleus in the regulation of appetite. Its proximity to the median eminence and the fact that the ARC is not fully insulated from the circulation by the blood brain barrier means it is strategically positioned to integrate a number of peripheral signals controlling food intake [3-5]. There are two major neuronal populations in the ARC implicated in the regulation of feeding. One population increases food intake and co-expresses neuropeptide Y (NPY) and agouti-related transcript (AgRP). The second population of neurons co-expresses cocaine and amphetamine-related transcript (CART) and pro-opiomelanocortin (POMC) and inhibits food intake.

NPY/AgRP neurons

Within the hypothalamus, NPY is an important regulator of body weight through its effects on food intake and energy expenditure. NPY acts at five different receptors (Y1-Y5 receptors), although NPY appears to exert its orexigenic effect predominantly via the Y1 and Y5 receptors [6]. The majority of neurons expressing NPY in the hypothalamus are found within the ARC. ICV injection of NPY potently stimulates food intake.

CART/ POMC neurons

Melanocortin peptides bind to downstream MC4-Rs to inhibit food intake. The MC4-R is highly expressed in the hypothalamus, most notably the PVN. AgRP is the endogenous antagonist at the MC3-R and MC4-R suggesting that melanocortinergic neurons may exert a “tonic” inhibition on feeding and permit increased energy expenditure; which is relaxed following AgRP antagonism of the MC3 and MC4-Rs, ultimately resulting of feeding and a lower metabolic rate. Many studies have demonstrated the importance of the melanocortin system in regulating energy homeostasis in humans.

Nutrient sensing

There is evidence that the hypothalamus can sense nutrients and adjust food intake accordingly. When cellular energy stores are depleted, the enzyme adenosine monophosphate-activated protein kinase (AMPK) is activated in order to increase substrate uptake [7]. In the ARC, activation of AMPK leads to increased food intake

Abbreviations: ARC: Arcuate Nucleus; VMN: Paraventricular Nucleus; DMV: Dorsomedial Nucleus; LHA: Lateral Hypothalamic Area; AgRP: Agouti-Related Transcript; CART: Cocaine and Amphetamine-Related Transcript; POMC: Pro-opiomelanocortin

Keywords: Arcuate nucleus; NPY/AgRP; Hypothalamus; Glucose intolerance; cardiovascular diseases; Type 2 diabetes; Certain types of cancer
and body weight; an effect which is inhibited by both insulin and leptin. AMPK in the VMN also appears to play a key role in the detection of acute hypoglycaemia and initiation of the glucose counter-regulatory response. Acute hypoglycaemia also increases hypothalamic NPY and AgRP and reduces POMC expression. Other nutrients such as plasma long chain fatty acids and the amino acid leucine can regulate food intake via the hypothalamus. ICV administration of the long chain fatty acid, oleic acid inhibits food intake by reduction of ARC AgRP and NPY expression and ICV administration of leucine reduces food intake in rats.

Adiposity signals acting on the hypothalamus

Adipokines are secreted by adipose tissue and include leptin, adiponectin and resistin. They have been shown to act via the hypothalamus to affect food intake and energy expenditure. Leptin is secreted by adipocytes and circulates at concentrations proportional to fat mass [8-10]. Circulating leptin crosses the blood brain barrier and binds to the long form of the leptin receptor, ObRb, in the hypothalamus. The Ob receptor is expressed widely within the hypothalamus but particularly in the ARC, VMN, DMN and LHA. Using viral mediated gene expression, chronic leptin over-expression in the ARC, PVN and VMN results in reduced food intake. Leptin directly activates anorectic POMC neurons and inhibits orexigenic AgRP/NPY neurons resulting in an overall reduction in food intake.

Gut hormones

The gastrointestinal tract releases an array of peptide hormones that are sensitive to gut nutrient content. Besides, short-term feelings of hunger and satiety are believed to be partly mediated by co-ordinated changes in circulating gut hormone concentrations.

Knowledge and Commitment

The management of obesity is a major public health and economic global concern. Although obesity can be simply defined as a disorder of excess body fat, the major pathobiology occurs in other tissues such as hepatic, vascular system, musculoskeletal, etc. Obesity is an important risk factor for serious diseases such as cardiovascular diseases, type 2 diabetes and certain types of cancer.

Environmental factors, such as social networks and global “westernization” concerning the dietary preferences and sedentary lifestyle have a strong influence on obesity pandemics. Finally, we need to expand our efforts towards primary prevention, by advocating healthier lifestyle and eating habits.

Acknowledgement

None.

Conflict of Interest

None.

References