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A talk between fat tissue, gut, pancreas and brain to control body weight

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ABSTRACT

The incidence of obesity and its related disorders are increasing at a rate of pandemic proportions. Understanding the mechanisms behind the maintenance of energy balance is fundamental in developing treatments for clinical syndromes including obesity and diabetes. A neural network located in the nucleus of the solitary tract–area postrema complex in the hindbrain and the hypothalamus in the forebrain has long been implicated in the control of energy balance. In the hypothalamus this central neuronal network consists of small populations of nuclei with distinct functions such as the arcuate nucleus (ARH), the paraventricular nuclei of the hypothalamus (PVH), the dorsomedial (DMH), the ventromedial (VMH) and the lateral hypothalamus (LH). These hypothalamic areas form interconnected neuronal circuits that respond to fluctuations in energy status by altering the expression of neuropeptides, leading to changes in energy intake and expenditure. Regulation of these hypothalamic nuclei involves the actions of orexigenic peptides (ie ghrelin), which act to stimulate energy intake and decrease energy expenditure, and anorexigenic peptides (ie. leptin and insulin), which act to reduce energy intake and stimulate energy expenditure. Here we review the role of the ARH, DMH and PVH in the control of energy homeostasis and how recent advances in research technologies (Cre-loxP technology, optogenetics and pharmacogenetics) have shed light on the role of these hypothalamic nuclei in the control of energy balance. Such novel findings include the implication of ARH POMC and AgRP neurons in the browning of white adipose tissue to regulate energy expenditure as well as the likely existence of divergent hypothalamic pathways in the DMH and PVH in the control of food intake and energy expenditure.

1. Introduction

In the past 40 years, the human lifestyle has been undergoing drastic changes, where increased availability and accessibility to food as well as food marketing contribute to create an obesogenic environment. In parallel the incidence of obesity worldwide has grown to pandemic proportions (Ng et al., 2014; Ogden et al., 2013). Obesity is associated with a range of metabolic diseases, cardiovascular diseases and the development and progression of several cancers (Renehan et al., 2008; Wajchenberg, 2000). To prevent the development of obesity it is crucial to understand the mechanisms that regulate energy balance. The past two decades have shown unprecedented growth in our understanding of the neural and neuroendocrine systems that regulate energy homeostasis (Dietrich and Horvath, 2013); recent advances in mouse genetics (Cre-loxP technology) and the use of optogenetic and pharmacogenetic techniques has shed light on the correlation between neural activities with specific behaviors (Betley et al., 2013).

This review describes some of the neuroendocrine factors that modulate energy intake, energy expenditure, and body energy stores and illustrates how an understanding of energy balance can help us to develop strategies to reduce obesity.

2. Energy balance. Some basic concepts

The basic components of energy balance include energy intake, energy expenditure, and energy storage (Hill et al., 2012). The sources of energy for humans are in proteins, carbohydrates and fats. When energy intake equals energy expenditure, the body is in energy balance and body weight is stable. Body weight can change only when energy intake is not equal to energy expenditure over a

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given period of time. Humans expend energy through resting metabolic rate, which is the amount of energy necessary to fuel the body at rest, the thermic effect of food, which is the energy cost of absorbing and metabolizing food consumed (~10% of total energy ingested); and the energy expended through physical activity, which consists of the amount of physical activity performed multiplied by the energy cost of that activity (Hill et al., 2012).

Body weight is remarkably stable despite large random daily fluctuations in food intake. Two main theories have been postulated to explain this stability, the set point model and the settling point model. The first hypothesizes that there is an active feedback mechanism linking adipose tissue (stored energy) to intake and energy expenditure, and it is regulated by a set point, located in the brain. The settling point model is based on a passive regulatory system that does not involve any set point and postulates that the fat stores (or body weight) settle to a balance determined by diet and lifestyle (Speakman et al., 2011). Both models are consistent with some aspect of energy balance but fail to explain many other significant aspects of energy homeostasis (Muller et al., 2010).

3. How is energy balance maintained?

The complex homeostatic mechanism regulating body weight involves interactions between peripheral tissues and organs, such as white adipose tissue (WAT), the gastrointestinal system (GIS), the pancreas and the central nervous system (CNS), through signals that inform brain centers of the nutritional and metabolic status of the animal (Yi and Tschop, 2012).

The brain receives signals via vagal afferents or through circulating hormones and peptides. The enteric nervous system that interconnects with the autonomic nervous system transmits information of mechanical (distension, contraction), chemical (presence of nutrients in the gut lumen) and neuro-humoral stimuli (gut hormones, neurotransmitters and neuromodulators) to the CNS through vagal and sympathetic nerves (Berthoud, 2012). The hindbrain (caudal brainstem) contains neurons and circuits that involve autonomic control of ingestion, digestion, and absorption of food (Berthoud, 2012) independently of the forebrain (Grill and Hayes, 2012). The nucleus of the solitary tract (NTS) is one of the major processors of vagal afferent signals that conveys messages to higher neural centers involved in appetite control, such as hypothalamic centers (Badman and Flier, 2005). The integration of all these afferent signals related to food presence in the gut in turn regulates the meal size of individuals (Badman and Flier, 2005; Berthoud, 2012; Grill and Hayes, 2012; Naslund and Hellstrom, 2007). Therefore, vagal afferent nerves are the major conduit by which nutrients signal to the brain and influence motility and secretion, as well as hunger and satiety (Berthoud, 2012; Naslund and Hellstrom, 2007; Thompson et al., 2004).

Hormones and peptides act in several specific brain regions to modulate energy balance via the circulation. Among these regions, the NTS—area postrema (AP) complex in the hindbrain and the hypothalamus in the forebrain are two of the major targets of these hormones.

Energy balance is primarily controlled by the hypothalamus; a region that is intimately associated with the regulation of basic functions such as reproduction, temperature, hormonal balances and biological rhythms. Hypothalamic nuclei and areas that are associated with the regulation of energy balance include the ARH, VMH, DMH, PVH and LH (Sohn et al., 2013). These hypothalamic areas form interconnected neuronal circuits that respond to changes in energy status by altering the expression of specific molecules, especially neuropeptides, resulting in changes in energy intake and expenditure. These neurons also project to other regions of the brain, such as the brainstem and spinal cord.

4. Peripheral factors regulate food intake and energy expenditure

There is a long list of peripheral factors involved in the regulation of energy homeostasis that includes but is not limited to leptin, insulin, ghrelin, glucagon like peptide-1 and 2 (GLP-1 and GLP2), cholecystokinin, bombesin, amylin, peptide YY, oxyntomodulin, somatostatin and enterostatin (Naslund and Hellstrom, 2007; Williams et al., 2009; Yi and Tschop, 2012). In this review we will put special emphasis on the role of leptin, insulin and ghrelin in regulating body weight through the modulation of hypothalamic neurons.

Peripheral metabolic signals are often categorized as long-acting adiposity signals, and short-acting factors. Long-acting signals characteristically reflect the levels of fat stores and regulate body weight as well as the amount of energy stored as fat over time. The predominant adiposity signal that has been well characterized is leptin (Enriori et al., 2006; Sohn et al., 2013; Zhang et al., 1994). Leptin is an essential endocrine signal for energy homeostasis. It is secreted from adipocytes in proportion to fat stores (Considine et al., 1996; Maffei et al., 1995; Zhang et al., 1994). The discovery that rodents and humans with mutations in leptin (*Lepob/ob*) or its receptor (*Leprdb/db*) are hyperphagic and severely obese (Tartaglia et al., 1995; Vaisse et al., 1996; Zhang et al., 1994) accelerated the identification of neural networks regulating food intake and energy expenditure. Accumulating evidence suggests that hypothalamic and extra-hypothalamic sites contribute to the effects of leptin on food intake and energy balance. Indeed the high expression of leptin receptor b (LRb, the functional isoform) within the hypothalamus (Munzberg, 2008) is consistent with the crucial role of leptin in regulating diverse homeostatic processes. Activation of hypothalamic LRb decreases appetite and increases the activity of the sympathetic nervous system (SNS), which stimulates energy expenditure in brown adipose tissue (BAT) (Haynes et al., 1999; Scarpace and Matheny, 1998). BAT is abundantly innervated exclusively by the SNS. In rodents, and likely in humans, it plays a major role in the adaptive thermogenic response to environmental challenges (Nedergaard and Cannon, 2010). The postulated mechanism for adaptive thermogenesis involves the uncoupling of oxidative phosphorylation to generate heat via increased expression and activity of mitochondrial uncoupling protein 1 (UCP-1) in BAT (Scarpace and Matheny, 1998).

Considerable evidence suggests that insulin also acts as a negative feedback control for adiposity and body weight. However, the physiological importance of insulin as an adiposity negative-feedback signal remains uncertain, particularly its mode of action to regulate energy homeostasis, likely due to the difficulty in correlating the rapid changes in insulin levels in circulation and the metabolic changes at the neuronal level. Insulin is secreted by the pancreatic β-cell, dependent on blood glucose levels in the short term, and on the level of adiposity in the long term. However, available data suggests that of the two, leptin has the predominant role in the control of energy homeostasis (Velloso and Schwartz, 2011).

Insulin receptors (IR) are highly abundant (but selectively distributed) throughout the CNS (Adamo et al., 1989) and some hypothalamic centers show a high expression of these receptors (Bruning et al., 2000; Konner et al., 2007). Similar to leptin, insulin has a strong anorexigenic effect despite the apparent opposite effect in some arcuate neurons (Plum et al., 2006b; Williams et al., 2010). The action of both hormones in arcuate neurons is discussed in more detail later in this review.

Several hormones work as short-acting signals to regulate appetite, the majority of which decrease food intake. However, ghrelin, a hormone secreted predominantly by the stomach, is an