CellPress

Review

Metabolism and Mental Illness

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Over the past century, overwhelming evidence has emerged pointing to the hypothalamus of the central nervous system (CNS) as a crucial regulator of systemic control of metabolism, including appetite and feeding behavior. Appetite (or hunger) is a fundamental driver of survival, involving complex behaviors governed by various parts of the brain, including the cerebral cortex. Here, we provide an overview of basic metabolic principles affecting the CNS and discuss their relevance to physiological and pathological conditions of higher brain functions. These novel perspectives may well provide new insights into future research strategies to facilitate the development of novel therapies for treating mental illness.

Trends

Hypothalamic neurons in the arcuate nucleus regulate feeding behavior and are modulated by a complex network of peripheral signals.

Changes in feeding behavior and energy metabolism are common symptoms of mental illness and side effects of psychopharmacological treatment, indicating a possible connection between feeding and mental illness.

Peripheral signals acting on hypothalamic neurons in the arcuate nucleus may help explain some of the molecular mechanisms by which feeding and mental health can be connected.

In particular, serotonin signaling and metabolic pathways appear to be critical for such connections, as they are linked to both mental illness and feeding behavior.

Introduction

A major focus of modern medicine is on chronic disease, and, there are few that are as challenging as depression and obesity. Both affect a large proportion of the global population: 7.6% of the USA population, 12 years of age and older, report moderate to severe depressive symptoms [1]. Obesity is estimated to affect 2.1 billion people worldwide [2]. Even though there does not seem to be any apparent link between the two problems, evidence accumulated over the past few decades suggests that not only is there a link but there also seems to be a general connection between feeding disorders and mental illness [3]. The association between depression and feeding disorders is most apparent in the case of depression and obesity, as shown by the data from the National Health and Nutrition Examination Surveys: 43.2% of adults with depression also suffer from obesity, which is significantly greater than the 33% in the control group [4]. These data, as well as others, only show correlation and not causation. Often, the criticism is that this effect could be due to antidepression therapy since weight gain is one of the most common side effects, with 5–10% of patients gaining significant weight during long-term treatment [5]. However, anorexia and bulimia nervosa are feeding disorders and mental illnesses, thus demonstrating the inherent connection between the mechanisms that control feeding and higher cognition (affected in eating disorders). The comorbidity between depression and anorexia, for instance, is even greater than obesity, with major depression occurring in 63.9% to 74.5% in patients suffering from anorexia (anorexia nervosa restrictive and anorexia nervosa with bulimic symptoms, respectively) [6]. In this review article, we first provide a summary of the hypothalamic neurons involved in regulation of feeding and energy homeostasis, and some of their regulatory hormones, to describe the basic circuitry potentially connecting feeding behavior (and energy homeostasis) and mental illness. We focus on depression and eating disorders (specifically anorexia nervosa) to give insight into possible future directions regarding therapy and research. The core of this review is centered on the serotoninergic system since it is deeply involved in energy homeostasis and the aforementioned mental illnesses. Lastly, we present some novel data concerning the endocannabinoid system, which may have an important impact on future research related to feeding and depression.

Hypothalamic Circuitry and Feeding Behavior

Feeding behavior is complex and many parts of our brain contribute to its control. However, one structure stands out in the central nervous system (CNS), the hypothalamus, which is considered to be the main regulatory organ for mammals, and regulates feeding behavior. Two subsets

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of neurons are key players in feeding: the orexigenic (promoting feeding) and anorexigenic (suppressing feeding) within the arcuate nucleus, which is a cluster of neurons located in the mediobasal hypothalamus, lying on either side of the third ventricle, just above the median eminence. These two distinct groups of neurons communicate with many areas of the brain both within and outside of the hypothalamus. One anorexigenic population is situated more laterally in the arcuate nucleus expressing proopiomelanocortin (POMC), and when stimulated, suppresses feeding [7]. POMC neurons project to numerous areas involved with feeding and appetite control, such as the parabrachial nucleus (PBN), the paraventricular nucleus of the hypothalamus (PVH), the dorsal vagal complex (DVC), and the intermediolateral column of the spinal cord (IML) [8]. They produce α-melanocyte-stimulating hormone (α-MSH), which serves as an agonist for the anorectic melanocortin receptors (MC3R and MC4R) [9]. Through these G_s-protein-coupled receptors, melanocortins activate neurons by increasing cAMP levels [10]. The other population of neurons, coexpressing neuropeptide Y (NPY) and agouti-related protein (AgRP), is located more medially in the arcuate nucleus and upon stimulation increases feeding. The NPY/AgRP neurons project to the PVH, PBN, and to the POMC neurons [8]. While NPY produces it orexigenic effects via NPY receptors (NPY1R, NPY2R, NPY3R, NPY4R, NPY5R), AgRP functions as an inverse agonist for the melanocortin receptors, thus producing an opposite effect. NPY receptors are $G_{i/o}$-protein-coupled receptors that decrease cAMP levels inside the cell. Through this mechanism, NPY can inhibit MC4R-expressing PVH neurons via NPY1R [11], as well as suppress neuronal activity in the arcuate nucleus (POMC and GABAergic neurons) and the ventromedial hypothalamic nucleus (VMN) [12,13].

Leptin and Insulin: Regulators of Feeding and Obesity

Leptin, from the adipose tissue, and insulin, from the pancreas, are considered long-term adiposity signals. They control energy balance and food intake, in part, by promoting or inhibiting hypothalamic neurons in the arcuate nucleus. The effects of leptin are thought to be mediated by hypothalamic KLF-4 (a zinc finger-type of transcription factor), as shown in rats overexpressing KLF-4, which induced food intake, increased body weight, and blunted leptin sensitivity via stimulation of AgRP [14]. By contrast, downregulation of KLF-4 inhibited food intake and diet-related obesity [14]. Stimulating anorexigenic POMC-expressing neurons appears to be another mechanism of the inhibitory effects of leptin on food intake [15]. However, their role cannot be simplified to on/off mechanisms, as research has suggested that leptin receptor resistance plays an important role in obesity [16]. Studies on rats have shown that leptin directly influences serotonin metabolism, by increasing serum serotonin levels, while serotonin in brain tissue (hypothalamus and hippocampus) seems to be decreased after leptin administration [17]. Like leptin, insulin resistance has been proposed to contribute greatly to obesity and feeding behavior in general. Similar to leptin, insulin is thought to have central effects on feeding, although less effective; this is believed to be accomplished through the inhibition of NPY/AgRP neurons in the arcuate nucleus [18]. Insulin resistance contributes to many metabolic abnormalities including obesity and, as such, suggests its importance in feeding regulation. Pharmacological intervention with insulin sensitivity-improving drugs, such as metformin, has shown inhibition of food intake and weight loss in rats and humans, which is thought to be mediated via inhibition of NPY and AgRP in the hypothalamus [19,20]. In line with this, insulin receptors have been found in areas of the brain crucial to food intake regulation and also seem to be important in energy homeostasis [21].

Role of Gut Hormones in Feeding

Feeding control is multifaceted and involves numerous other players, all of which act in concert to control appetite (Boxes 1 and 2 and Figure 1). One such player is the gut, which is the largest endocrine organ in the human body. The gastrointestinal (GI) tract produces various peptide hormones, which are thought to be important in short-term energy intake control by playing a critical role in meal initiation and termination. The key peptides in question are cholecystokinin