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Invited review

Histamine receptor signaling in energy homeostasis

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ABSTRACT

Histamine modulates several aspects of energy homeostasis. By activating histamine receptors in the hypothalamus the bioamine influences thermoregulation, its circadian rhythm, energy expenditure and feeding. These actions are brought about by activation of different histamine receptors and/or the recruitment of distinct neural pathways. In this review we describe the signaling mechanisms activated by histamine in the hypothalamus, the evidence for its role in modulating energy homeostasis as well as recent advances in the understanding of the cellular and neural network mechanisms involved.

1. Introduction

Obesity is an important health problem because it is associated with an increased risk of metabolic and cardiovascular conditions such as diabetes mellitus, hypertension, and hyperlipidemia. Obesity results from an imbalance between energy intake and expenditure. The existent pharmacotherapy of obesity has very limited efficacy and therefore neurotransmitters and neuromodulators implicated in the regulation of energy metabolism represent opportunities for anti-obesity drug development. Several lines of evidence strongly suggest that histamine plays an important role in energy homeostasis by influencing both food intake and energy expenditure. Epidemiological evidence has revealed that use of antihistaminergic (H1 receptor antagonists/inverse agonists) medication, widely used against allergies, is associated with increased body weight and obesity. Moreover it has been proposed that other medications that have weight gain as a side effect (e.g. atypical antipsychotics) exert this action, at least in part, by acting also as antagonists at the H1 receptors (H1R). Transgenic animals in which histamine signaling is disrupted (H1R ko, H3R ko, HDC ko mouse) develop obesity and display increased food intake and decreased energy expenditure.

2. Histamine signaling in the brain

Histamine is synthesized in the tuberomamillary nucleus (TMN) neurons from histidine by the specific enzyme histidine decarboxylase (HDC). After release histamine is methylated by histamine N-methyl-transferase (which is located postsynaptically and in glia). The turnover of neuronal histamine is high, with its half-life being in the order of minutes (Dismukes and Snyder, 1974; Hough et al., 1984). Histaminergic fibers are especially dense in the cortex, hypothalamus, amygdala and striatum (reviewed in Haas and Panula (2003)). In the hypothalamus the histaminergic fibers are particularly dense in the anterior part (Wada, 1992). Another source of histamine, representing up to 50% of histamine contents in the brain, is represented by resident mast cells (Ulugol et al., 1996). Thus histamine released from mast cells induces wakefulness and plays a role in food seeking behavior during food deprivation (Chikahisa et al., 2013).

Four histamine receptors, which are GPCRs, have been cloned (H1–H4R). H1R, H2R and H3R are expressed in distinctive patterns in the brain (Arrang et al., 1995) and all three receptor types are highly expressed in the hypothalamus. The H1Rs mediate

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excitatory actions on central neurons usually by recruiting $G_{q/11}$ and PLC, which leads to the formation of the two second messengers, diacylglycerol (DAG) and inositol-1,4,5-triphosphate (Ins(1,4,5)P3) and Ca^{2+} release from internal stores. Several Ca^{2+}-dependent processes have been reported to be influenced by histamine: first, the opening of a cationic nonselective conductance, which causes depolarization (Smith and Armstrong, 1993); second, the activation of the electrogenic Na^{+}-Ca^{2+} exchanger in supraoptic neurons, which also causes depolarization (Smith and Armstrong, 1996); third, formation of nitric oxide and cyclic GMP (Richelson, 1978); fourth, hyperpolarization due to the opening of K^{+} channels (Weiger et al., 1997). In addition, blocking a leak potassium conductance through direct G-protein action, or through PLC, DAG and PKC, induces excitation in the thalamus (McCormick and Williamson, 1991), and in the striatum (Munakata and Akaike, 1994).

The H2Rs couple to G_s, adenylyl cyclase (AC) and PKA, which phosphorylates proteins and activates the transcription factor cyclic-AMP-response element (CRE)-binding protein (CREB). Usually H2R activation results in excitation or its enhancement. By activating H2Rs histamine reduces the small Ca^{2+}-dependent K^{+} conductance (Haas and Konnerth, 1983) and reduces a long-lasting after hyperpolarization thus affecting the accommodation of firing. Increased cyclic AMP concentration and PKA-mediated phosphorylation, shifts the activation of the inwardly rectifying I_h towards a more positive voltage and contributes to a depolarization that modifies the thalamic relay of sensory input (McCormick and Williamson, 1991).

H3Rs are present at histaminergic and other cell somata, dendrites and axons, where they provide negative feedback to restrict histamine synthesis and release. They also provide negative feedback on the release of other neurotransmitters, such as glutamate (Brown and Haas, 1999), acetylcholine and noradrenaline (Schlicker et al., 1992). H3Rs couple to $G_{i/o}$ and inhibit high-voltage activated Ca^{2+} channels, a common mechanism for the regulation of exocytosis. Three functional splice variants of the H3R have been identified in the rat. In mouse, both RNAse protection assay experiments and PCR results revealed the presence of only one H3R isoform (Chen et al., 2003). H3Rs can also couple to the phospholipase A2 (PLA2) via the Gi/o proteins which results in production of arachidonic acid (Leurs et al., 1994).

In summary, H1Rs and H2Rs have mostly excitatory actions on neurons or potentiate excitatory inputs. By contrast, H3-receptor activation causes autoinhibition of TMN neurons and inhibition of neurotransmitter release. More recently morphological and physiological experiments demonstrate the presence of H3R also postsynaptically (Lazarov and Gratzl, 2006; Zhou et al., 2006; Lundius et al., 2010).

3. Role of hypothalamic histamine in feeding behavior

Several excellent reviews on this subject have been published (Jorgensen et al., 2007; Masaki and Yoshimatsu, 2009, 2010; Passani et al., 2011), therefore here we will only summarize the main observations. Hypothalamic histamine suppresses feeding behavior (Ookuma et al., 1989, 1993), mainly by activating H1R (Masaki et al., 2004). Histamine exerts its anorectic action by inhibiting appetite rather than by being a satiety signal (Valdes et al., 2010; Passani et al., 2011). The sites of action appear to be the ventromedial hypothalamus (VMH) and the paraventricular nucleus (PVN) and not the preoptic area/anterior hypothalamus (PO/AH) (Ookuma et al., 1989, 1993). Furthermore, HDC−/− (Hegyi et al., 2004), the H1R−/− (Masaki et al., 2004) and H3R−/− mice (Takahashi et al., 2002) display increased feeding and develop leptin-resistant obesity, demonstrating that histamine signaling regulates energy metabolism downstream of leptin. Furthermore, the reduction in body fat induced by central infusion of leptin is decreased in H1R−/− mice, indicating that this pathway is downstream of leptin (Masaki et al., 2001). Similarly, H1R signaling was shown to be downstream of amylin (Davidowa, 2007; Seth et al., 2012).

Besides the hypothalamus an important role in the control of feeding behavior is played by nucleus tractus solitarius (NTS) in the hindbrain which receives vagally mediated gastrointestinal satiation signals as well as blood-borne energy-related hormonal and nutrient signals (Grill and Hayes, 2012). Co-administration of amylin and leptin results in increased H1R expression in the VMH, arcuate as well as in the NTS (Seth et al., 2012).

The H1R pathway is independent or downstream of the melanocortin system (Masaki et al., 2003).

Epidemiological evidence as well as preclinical studies indicate that H1R antagonists/inverse agonists, widely used as antiallergic medication, are associated with increased food intake, body weight and obesity (Masaki et al., 2004; Ratliff et al., 2010). Furthermore, also other medications (e.g. atypical antipsychotics) that increase food intake and weight as a side effect have been shown to cause these actions, at least in part, by acting as H1R antagonists (Kim et al., 2007). The relative potencies of these drugs as H1 antagonists correlate with their orexigenic potencies (Kroeze et al., 2003). Conversely, H1R agonists and H3R antagonists have beneficial effects in obesity and several such drugs are in clinical trials (Celanire et al., 2005; Bonaventure et al., 2007; Barak et al., 2008; Poyurovsky et al., 2013). Furthermore, H1R agonists reduce the weight gain associated with antipsychotic treatment in humans and animal models (Deng et al., 2012; Poyurovsky et al., 2013). A recent study has found a significant association between H1R variants and body mass index in patients on antipsychotic medication (Vehof et al., 2011).

Histamine signaling in the hypothalamus, therefore, is relevant for the treatment of obesity since it has a dual action as an appetite suppressant acting in the (VMH and PVN) and as an enhancer of energy expenditure, acting in the PO/AH (see below).

4. Central control of thermoregulation

Homeothermia, the ability to regulate the core body temperature (Tcore) within a narrow range is observed in mammals and birds. The key role played by the PO/AH in the regulation of Tcore was established more than a 100 years ago, based on experimental brain lesions, and selective cooling and heating of brain regions with chronically implanted thermodes (reviewed in Simon (2000)). Sustained or alternating PO/AH cooling and heating induce physiological or behavioral thermoregulatory responses, causing Tcore to change in the direction opposite to that of the hypothalamic temperature (T_{hy}). Hammel and collaborators proposed that a particular net thermoregulatory response was proportional to ($T_{hy} - T_{set}$), where T_{set} was represents a hypothetical set reference, a complex parameter related to the level of activity of PO/AH thermoreceptors (Hammel et al., 1963). The nature of such thermoreceptors and the physiological relevance of central thermosensitivity are controversial (Barker and Carpenter, 1970; Kobayashi and Takahashi, 1993; Boulant, 2006). Furthermore, the thermosensitivity of PO/AH neurons is a plastic property both *in vivo* and *in vitro*. Thus, it has been found that the thermosensitivity can change rapidly in the presence of the pyrogens PGE2 (Tabarean et al., 2004) or IL-1 (Vasilenko et al., 2000; Sanchez-Alavez et al., 2006). Slower shifts in thermosensitivity are observed in PO/AH neurons during NREM sleep (Alam et al., 1995).

The neuronal network controlling brown adipose tissue (BAT) thermogenesis and the fever response has been studied

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