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PRO-OPIOMELANOCORTIN NEURONS AND FEEDING

Andrija Meštrović
University of Zagreb, School of Medicine
0000-0003-2292-7926

Abstract

Food intake is a key component of metabolic homeostasis. The amount of nutrients and calories taken in is primarily regulated by POMC neurons, their activation prevents food intake. POMC neurons are situated in the arcuate nucleus in the hypothalamus and the dorsal motor nucleus of vagus in the medulla oblongata. Various neurotransmitters are secreted by POMC neurons, such as ACTH, α-MSH, β-endorphin, etc., and can be activated by leptin, cannabinoids, nicotine, serotonin and GLP-2. Their activation can result in various behaviours, depending on the agonist in question. Whereas leptin and nicotine cause a reduction in food intake, cannabinoids can increase food intake. Apart from central inputs, POMC neurons depend on inputs from visceral organs. GLP-2, secreted by the pancreas, induces satiety, and the vagal nerve carries signals from the stomach and the intestines. POMC neurons associated disorders can present with various phenotypes, varying from almost no food intake in anorexia to binge-eating present in MC4R mutations carriers.

KEYWORDS: cannabinoids, GLP-2, leptin, POMC, serotonin

INTRODUCTION

Eating disorders are a prominent topic in neuroscience today. Their pathophysiology and neural pathways are still unclear. The focus of current research lies on pro-opiomelanocortin (POMC) neurons. POMC neurons are situated in two nuclei, the arcuate nucleus (ARC) and the dorsal vagal motoric nucleus (DMV). POMC is a peptide synthesized in the soma of POMC neurons and can be cleaved by specific endopeptidases to yield various polypeptide fragments, such as ACTH, γ-MSH, β-lipotropin, α-MSH, CLIP, γ-lipotropin, β-endorphin and β-MSH. The arcuate nucleus is situated within the mediobasal hypothalamus adjacent to the third ventricle and the median eminence. It contains approximately 3000 anorexogenic pro-opiomelanocortin neurons. Orexigenic agouti-related protein (AgRP) neurons, neurons secreting growth hormone-releasing hormone (GHRH) and tubero-infundibular dopamine (TIDA) neurons are also present. Four hundred POMC neurons are present in the DMV, which lies ventral to the floor of the fourth ventricle and is a parasympathetic nucleus that sends its projection through the vagal nerve.[1] Both types of neurons send projections to the paraventricular nucleus (PVN) which regulates metabolism through its solitary tract projections that facilitate the sympathetic nervous system.[1]

POMC AGONISTS

POMC neurons can be activated by leptin, GLP-2, serotonin, cannabinoids and nicotine.[1] The activity of POMC neurons varies, as evidenced by studies showing that cerebrospinal fluid (CSF) levels of POMC exhibit a diurnal rhythm with a peak between 11PM and 2AM and the lowest activity at 11 AM. The activity pattern of POMC neurons is found to correlate with CSF levels of leptin, a known agonist of POMC neurons. Changes in CSF leptin concentration correlate with serum leptin levels, however occurring with 3-5 hours delay. Leptin passes the blood-brain barrier using a saturable transport system that appears to be inhibited by the soluble leptin receptor (sOB-R), which reaches its lowest levels during the leptin CSF peak.[2] Leptin binds to leptin receptors (LEP-R), causing receptor dimerization and phosphorylation of a tyrosine residue of the intracellular domain by a Janus kinase (JAK). Signal transducers and activators of transcription (STATS 3, 5, and 6) then dock onto the phosphorylated domains and are phosphorylated themselves. The STATS dimerize and move to the nucleus where they bind to specific DNA sequences to stimulate transcription of genes such as *POMC*.[1]

However, there is a population of POMC neurons not sensitive to leptin but to serotonin. Specifically, in the rostral arcuate nucleus 46% of neurons are activated by both 5-hydroxytryptamine receptor 1B ($5HT_{1B}R$) and 5-hydroxytryptamine receptor 2C ($5HT_{2c}R$) agonists and 25% by each agonist specifically. $5HT_{1B}$receptors are coupled to Gi/Go-protein and decrease cellular levels of cAMP, while $5HT_{2c}$receptors are Gq/G11-protein-coupled and increase cellular levels of IP3 and DAG. Serotonin has been shown to modulate K+ currents. The M-current is a non-inactivating, subthreshold outward K+ current that is suppressed during diet-induced obesity and during $5\text{-}HT_{1B}/5\text{-}HT_{2C}$ receptor activation. Moreover, $5\text{-}HT_{2C}$ receptor antagonists abrogated the actions of diet-induced obesity in suppressing the M-current.[3] Locaserin, a $5HT_{2c}R$ agonist has been shown to reduce food intake and is the only obesity treatment drug approved by the FDA in the last 13 years. Furthermore, its anorexigenic effect can be increased by combining it with a $5HT_{1B}R$ agonist and thus a lower dosage is needed to achieve the wanted effects.[4]

Regardless of the different agonists, both neuronal populations in the ARC reduce food intake upon activation, probably because they converge on similar second-order neurons and predominantly those expressing melanocortin 4 receptors (MC4Rs).[5] Furthermore, both the 5-HT agonists and the

leptin reciprocally regulate the activity of POMC and AgRP neurons by directly activating POMC neurons, inhibiting GABAergic inputs onto POMC neurons, and directly inhibiting AgRP neurons. [4]

In addition, 5-HT_{2c}R activation has been shown to mediate the anorexigenic effect of UCN1 (Urocortin), a CRF1 agonist used to mimic the effects of stress. Stress induces neurohormonal responses that lead to reduced food intake. Neurons situated in the amygdala (AMG) send projections to the paraventricular nuclei (PVN) of the hypothalamus where they activate corticotropin releasing factor (CRF) neurons, stimulating CRF synthesis. CRF binds to CRF1 and CRF2 receptors to induce the endocrinal and neural response to stress. Urocortin has been shown to induce 5HT_{2c}R protein expression in the ARC, ventromedial hypothalamus (VMH), lateral hypothalamus (LH), area postrema (AP), nucleus tractus solitarii (NTS) and dorsal motor nucleus of vagus (DMV). However, significantly higher c-fos mRNA, a marker used to identify recently activated neurons and 5-HT_{2c}R protein co-expression has only been observed in the NTS and rostral ventrolateral medulla (RVLM). Although stress does not enhance the 5-HT biosynthesis, it suppresses 5-HT turnover which may enable 5-HT_{2c}R activation. POMC activation in RVLM has been shown to mediate the cardiovascular effects of stress through sympathetic nervous system activation. NTS however relays peripheral stress information from the vagal nerve to the PVN. Interestingly, 5-$HT_{2c}R^{KO}$ mice injected with cholecystokinin or GLP-1 failed to reduce food intake, which can be explained by the fact that expression of c-fos protein, a marker used to track cell activity, did not appear in the NTS in 5-HT_{2c}RKOmice. 5-HT_{2c}R activation in the NTS seems to be indispensable for transmitting peripheral satiation signals to the PVN.[6]

Other POMC agonists are GLP-1 and GLP-2 which are co-secreted from endocrine L cells in the gut and preproglucagonergic neurons in the brain. They have been shown to control energy intake by inducing satiety and slowing gastric emptying.[7] The GLP2 receptor is expressed on POMC neurons which suppress food intake and gastric emptying through the MC4R activation. The activation of MC4R positive cholinergic neurons in the dorsal motor nucleus of the vagus (DMV) that has efferent motor projections to the myenteric plexus could modulate gastric mobility. GLP-2 is directly involved in the short-term control of food intake but can indirectly affect obesity, intestinal dysfunction and diabetes.[7]

Nicotine is known to suppress appetite. Nicotine is an agonist of α3β4 nicotinic acetylcholine receptors present on POMC neurons and activates POMC neurons.[8]

DIFFERENCE BETWEEN THE EFFECTS OF LEPTIN AND SEROTONIN

Although the activation of 5HT- and leptin-sensitive neurons has similar effects, the absence of either one of those populations causes various phenotypes depending on which one is missing. Loss of leptin receptors alone effects body weight; the loss of leptin and insulin receptors in POMC neurons induces hepatic insulin resistance. In contrast, loss of 5HT receptors causes obesity less often but exhibits defects in glucose homeostasis more easily. The dysregulation of blood glucose can be contributed to the findings that central MC4R signalling, thought to receive projections from 5HT sensitive POMC neurons, directly regulates the endocrine function of pancreas. All these defects can be reversed by reactivating the 5HT sensitive POMC neurons.[5]

BIOCHEMICAL CASCADES AND POMC NEURON ACTIVITY

Intracellular mechanisms extensively modulate the effects of POMC activity and their sensitivity to certain agonists. Depending on the external stimuli, POMC neurons can secrete different neurotransmitters.

Cannabinoids are known for their ability to induce cannabis-triggered feeding in a state of satiety and that is one of the primary targets in their clinical application. The neural mechanism seems to rely on the activation of POMC neurons through cannabinoid receptor 1 (CB1R) present on GABAergic and glutamatergic presynaptic terminals on POMC neurons. This paradox can be explained by the release of a different neurotransmitter called β-endorphin that is stored separately from α-MSH. The ability of POMC neurons to switch the neurotransmitter they release has been attributed to mitochondrial uncoupling protein 2 (UCP2). CB1R are present on mitochondria and their activation increases the number of mitochondria-ER contacts and ROS production which induces the expression and function of UCP2.[9]

Peroxisome proliferator-activated receptor gamma (PPAR-γ) is present in POMC neurons and can significantly affect their sensitivity to leptin. It is known that leptin activates POMC neurons and that increased POMC activity is associated with increased ROS levels.[10] However, during diet-induced obesity, leptin resistance prevents leptin from inducing Stat 3 phosphorylation. Stat 3 binds to LEP-R, a JAK-STAT kinase and is phosphorylated by receptor-associated kinases and translocated to the cell nucleus, where it acts as a transcription activator. Thus STAT3 inhibition inhibits POMC transcription. Furthermore, there is a simultaneous increased expression of cytokine signalling suppressor 3 (SOC3). SOC3 is presumed to be the cause of the positive correlation between leptin and intracellular ROS levels and its suppression lowers intracellular ROS levels. Furthermore, diet-induced obesity (DIO) mice have increased peroxisome density in POMC neurons.[10] Peroxisomes are cellular organelles involved in the catabolism of long-chain fatty acids through β-oxidation and also contain catalase. Catalase can use hydrogen peroxidase to oxidize several substrates and detoxify cells from ROS. Research has shown that constitutive loss of PPAR-γ lowers peroxisome density and induces an increase in ROS levels, thus increasing mitochondria-ER interaction and POMC activity.[10]

CLINICAL MANIFESTATIONS OF POMC RELATED PATHOLOGY

Clinical disorders that can be related to the POMC pathway vary from leptin resistance present in metabolic syndrome to anorexia nervosa. Leptin resistance has been shown to depend more on hyperleptinemia rather than obesity itself. Orexigenic agouti-related peptide (AgRP) expressing neurons innervate POMC neurons and the number of synapses increases with age, the rate of formation of new synapses positively correlates to leptin levels. AgRP neurons release NPY and γ-aminobutyric acid (GABA) which hyperpolarize POMC neurons. This is a plausible explanation for the difference between acute and chronic effects of leptin. Acute leptin administration has an anorexigenic effect, whereas chronic administration causes obesity and glucose intolerance.[11]

The genetics of anorexia nervosa and bulimia nervosa Low weight and loss of appetite are the key features of anorexia nervosa (AN). However there is still no conclusive explanation of its pathophysiology. A study used a gene array to analyse samples derived from 745 individuals diagnosed with anorexia nervosa.[12] No significant difference was found in the allele frequency of the analysed genes between patients with AN and the control group. However, a gene in the AGRP system *(AGRPrs13338499)* was significantly associated with lowest illness-related BMI. AgRP plasma levels have been found to be elevated in acute AN. The gene *rs13338499* is a transcription factor-binding site, that is located upstream of the AGRP gene it may play a regulatory role. This is intriguing because AgRP has an orexygenic role, and in the case of acute AN, plasma AgRP levels are reported to be elevated.[12] The key symptoms in bulimia nervosa (BM) are binge eating and regurgitating. The pathophysiology of this disorder is also not well understood. The same study used an gene array to sample 245 individuals diagnosed with bulimia nervosa, no genes were found to have a significant difference in allele frequency between patients with BN and the control group.[12]

THE GENETICS OF BINGE EATING

Obesity is a multifactorial disease, a result of interaction between genetic factors and the environment. Mutations of the MC4R and leptin receptor (LEPR) gene have been identified as causes of monogenic obesity. A study found that the prevalence of MC4R mutations in severely obese subjects was 5.1% compared to 4% in normal BMI control subjects, which are similar values. However, all control group subjects with MC4R mutations had the Val103Ile polymorphism which has the similar prevalence in the obese group, and is thought not to predispose subjects to obesity. Furthermore, 100% of obese subjects with MC4R mutations were given a diagnosis of binge-eating disorders compared with only 14.2 percent of non-carriers. On the other hand α-MSH and LEPR mutation carriers had binge eating prevalence similar to those without any mutations.[13]

ILLNESS - AND LEPTIN-INDUCED ANOREXIA

Anorexia and wasting are common symptoms associated with infectious diseases. Illness-induced anorexia seems to be an adaptive mechanism used to limit the proliferation of infectious organisms. However, a prolonged nutritional deprivation of the organism results in malnutrition, a compromised immune system and increased mortality. LPS (lipopolysaccharide) and Tat (HIV transactivation protein), both bacterial and viral products, cause activation of NF-κB, a transcription factor that binds to the POMC gene and stimulates transcription. Moreover, NF-κB is also activated by leptin and inhibition of hypothalamic NF-κB blocks the anorexigenic and weight-reducing effects of leptin. NF-κB dimers exist in an inactive form in the cytoplasmbound to the IκBα inhibitory protein. Inflammatory processes stimulate IKK (IκB kinase) which phosphorylates IκBα and releases NF-κB allowing it to stimulate POMC transcription. Cancer, neurodegenerative diseases, and obesity-related metabolic disease also activate NF-κB and can influence appetite and cause cachexia. NF-κB pathway controls feeding in two opposite metabolic situations, undernutrition and overnutrition. In overnutrition leptin activates NF-κB and POMC is transcribed to induce anorexogenic effects, adversely NF-κB activation may induce suppression of cytokine signalling-3 expression, which would constitute a negative feedback pathway of leptin signalling. The activity of central melanocortin signalling pathways are not determined by POMC activity only but by the relative amounts of melanocortins and AgRP as endogenous antagonist at the receptors. Moreover, hypothalamic AgRP MRNA expression tended to decrease following LPS and Tat administration and thus melanocortin receptor activation can also result from AgRP decreased level. Illness- and leptin-induced anorexia can be blocked by NF-κB and IKK inhibitors proving that NF-κB is a pathway crucial in POMC activation. Cancer induced cachexia also depends on NF-κB but is also associated with IL-1β activation and can be prevented with a IL-1β antagonist[14]

ACUTE AND CHRONIC FEEDING SUPPRESSION

The different effects of acute and chronic POMC neuron activation are caused by different populations of POMC neurons that are active. ARC neurons require chronic activation to decrease food intake and their ablation causes hyperphagia, obesity, and metabolic disorders. In contrast, NTS neurons respond to acute stimulation and their ablation does not lead to any obvious changes in feeding behaviour or body weight. This difference can be attributed to the distinction between efferent projections of different neuronal populations. ARC neurons send efferent projections to the forebrain, including the paraventricular nucleus, dorsomedial hypothalamus, lateral hypothalamus, and central amygdala and interact with AgRP neurons. Through those connections they can adjust the set point of body weight and metabolism. On the other hand, NTS POMC neurons mainly project to the caudal medulla and spinal cord where neural pathways are more directly involved in satiety-trigged feeding suppression.[15]

CONCLUSION

POMC neurons are crucial for the regulation of feeding behaviour and body weight. NTS neurons regulate acute satiety and food intake depending of signals coming from visceral organs whereas ARC neurons regulate long-term food intake and metabolism, all the key points that influence body weight. Although recent studies have given us insight into some pathophysiological manifestations of POMC system dysregulation, diseases such as anorexia nervosa and bulimia still lack a pathophysiological explanation and as such are difficult to treat.

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PROOPIOMELANOKORTINSKI NEURONI I UNOS HRANE

Sažetak

Unos hrane je ključan za održavanje metaboličke homeostaze. Proopiomelanokortinski (POMC) neuroni su ključni u regulaciji unosa hranjivih tvari i kalorija, a njihova aktivacija uzrokuje smanjenje unosa hrane. Oni su smješteni u arkuatnoj jezgri u hipotalamusu i u dorzalnoj motornoj jezgri vagusa u produljenoj moždini. Neuroni POMC kao neurotransmitere izlučuju razne peptide poput ACTH, α-MSH, β-endorfin, itd. Njih mogu aktivirati leptin, kanabinoidi, nikotin, serotonin i GLP-2. Rezultat njihove aktivacije ovisi o agonistu, odnosno različiti agonisti aktiviraju različite druge glasnike. Primjerice, kanabinoidi uzrokuju aktivaciju neurona POMC, ali i glad. Osim o centralnim signalima aktivnost neurona POMC ovisi i o signalima iz abdomena. GLP-2 prenosi signal sitosti iz gušterače do mozga, a vagus svojim vlaknima prenosi poruke iz probavnog sustava. Poremećaji povezani s POMC neuronima se fenotipski ispoljavaju kao razne varijacije u unosu hrane. Ti poremećaji mogu varirati od minimalnog unosa hrane u anoreksiji nervozi do takozvanog binge-eatinga u nositeljima MC4R mutacija.

KLJUČNE RIJEČI: GLP-2, kanabinoidi, leptin, serotonin, POMC

Received February 1, 2016.
Accepted June 20, 2016.