Alpha-melanocyte stimulating hormone in ghrelin-elicited feeding and gut motility

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Abstract: This review evaluates published studies regarding alpha-melanocyte stimulating hormone (α-MSH) in ghrelin-elicited feeding and gut motility. We have sought to integrate all available evidences to provide a complete review on the properties of melanocortin receptors (MCR). Five receptor subtypes with specific and distinct affinities for MSH/ACTH have been cloned: MC1, MC2 (or ACTH), MC3, MC4, and MC5 receptor. Five receptor subtypes with α-MSH displayed high affinity to the MC1 receptor, distinct from the other MCR.

1. INTRODUCTION

Propiomelanocortin (POMC) is an important precursor protein in the central melanocortin system. Immuno-histochemical studies have revealed that POMC precursor is most abundant in the arcuate nucleus of the hypothalamus (ARC) and the nucleus of the solitary tract (NTS) in the brainstem. POMC is a large molecule that is cleaved into several biologically regulatory peptides, termed melanocortins. These include α-, β-, and γ-melanocyte stimulating hormones (MSHs) and adrenocorticotropin (ACTH). These melanocortins exert their activity by binding to a family of melanocortin receptors (MCR). Five receptor subtypes with specific and distinct affinities for MSH/ACTH have been cloned: MC1, MC2 (or ACTH), MC3, MC4, and MC5 receptor. The MC3, MC4, and MC5 receptors are expressed in the brain. The MC4 receptor is widely expressed throughout the brain, including the thalamus, hypothalamus, cortex, and brain stem as well as in the spinal cord.

1.2. MC2 receptor

The MC2 receptor is abundant in the adrenal gland. It is not present in the hypothalamus and pituitary, based on the absence of detectable MC2 receptor mRNA. The MC2 receptor does not couple with MSH peptides but has high affinity with ACTH. Thus, MC2 receptor has been identified as the ACTH receptor and regulates steroid production in the adrenal gland.

1.3. MC3 receptor

The MC3 receptor is predominantly expressed in the brain (the arcuate nucleus), placenta, gut tissue, and human heart. MC3 receptor knockout mice display metabolic syndrome evident as decreased fat/carbohydrate oxidation, reduced energy expenditure, and increased adipose mass without increased food intake or weight gain. MTII is a potent MR agonist for both the MC3 receptor and MC4 receptor. MTII does not induce anorectic action and decreases food intake in MC4 receptor knockout mice. These findings support the speculation that MC3 receptor has limited importance in mediating MTII-induced anorectic action and decreased food intake.

1.4. MC4 receptor

The MC4 receptor is found mainly in the central nervous system, but is also expressed throughout the brain, including the thalamus, hypothalamus, cortex, and brain stem as well as in the spinal cord. Deletion of the gene encoding MC4 receptor...
results in hyperphagia, increased food consumption, and profound obesity. The MC4 receptor knockout mice do not respond to the anorectic action and reduced food intake of MTII. Mutation or deletion of the MC4 receptor is associated with obese, hyperphagic, and hyperinsulinaemic phenotypes. The MC4 receptor is expressed in the dorsal motor nucleus of the vagus within the hindbrain, which is the site of parasympathetic vagal efferent nerves that regulate the gastrointestinal system. Intracerebroventricular (ICV) injection of specific MC4 receptor antagonists (HS014, HS024, and HS028) significantly increases the food intake. These findings indicate that signaling of the MC4 receptor regulates food intake and body fat mass. MC4 receptors are up-regulated in food-limited rats but down-regulated in diet-induced obese rats. Subtle alterations in MC4 receptors function and density may be essential in the regulation of weight control.

1.5. MC5 receptor

The MC5 receptor is expressed abundantly in a variety of peripheral tissues, such as skeletal muscle, lung, stomach, spleen, kidney, liver, and testis. The expression of MC5 receptor in the brain is inconsistent, being very low in the rat but abundant in the mouse. The MC5 receptor has a role in the regulation of exocrine gland function.

1.6. α-MSH

α-MSH is the principle identified agonist in the brain. Immunocytochemical staining data indicate that α-MSH strongly activates the hypothalamus, thalamus, brainstem, the arcuate region of the hypothalamus, and paraventricular nuclei of hypothalamus neurons, which send axonal projections to many areas of the limbic system and brainstem. α-MSH can also induce a cAMP response in the cellular production of MC1, MC3, MC4, and MC5 receptors. The MC3 and MC4 receptors have been cloned and primarily expressed in the brain, which has revealed the avid affinity of α-MSH for both receptors. By acting on MC3 and MC4 receptors following ICV injection, α-MSH is very effective in suppressing food intake. If α-MSH is persistently delivered into the hypothalamus in rats, the suppression of food intake and decreased body weight will persist. α-MSH is considered as an agonist of MC3 and MC4 receptors and a stable agonist concerning the modulation of food intake. This view is compatible with the finding that underweight and normal-weight children have higher circulating plasma α-MSH levels compared with obese children.

2. EFFECTS OF α-MSH IN GHRELIN-ELICITED FOOD INTAKE

2.1. Ghrelin elicits food intake

Ghrelin is an endogenous ligand for growth hormone (GH) secretagogue receptors (GHS-R). It potently stimulates GH secretion and ghrelin-immunoreactive neurons in the hypothalamic arcuate nucleus. Acyl ghrelin activates GHS-Rs on neuropeptide Y/agouti-related protein (NPY/AgRP) neurons in arcuate nuclei and releases NPY and AgRP to stimulate food intake, body weight gain, and diabetic hyperphagia (Figure). Chemical ablation and double knockout of NPY and AgRP attenuates ghrelin-induced increased food intake. However, a single knockout NPY mouse model features preserved the AgRP activity, which partially compensates for the decreased ghrelin-induced food intake. ICV administration of AgRP is a competitive antagonist of MCRs and acts to increase feeding. AgRP is also a potent antagonist of MC receptors in weight control.
2.2 α-MSH attenuates ghrelin-elicted food intake

In rats allowed to feed ad libitum, the plasma acyl ghrelin concentration is reportedly low and reaches a peak during fasting. The effect can persist for 8 h but has ceased by 12 or 24 h (Table 1). ICV administration of α-MSH to rats (1.0 and 2.0 nmol/rat) significantly suppresses the ghrelin-induced increased food intake 2 h after injection. The suppression can persist for 8 h after injection with an apparent dose-dependent effect. ICV injection of ghrelin can rapidly stimulate increased food intake. The effect of acyl ghrelin on food intake is mediated by MCRs in the brain. The intraperitoneal injection of ghrelin can reverse postoperative gastric ileus.

3. EFFECTS OF α-MSH IN GHRELIN-ELICITED GASTRIC EMPTINGY

3.1. Ghrelin elicits gastric emptying

Ghrelin reportedly increases gastric emptying in conscious food-deprived rats and humans. ICV administration of ghrelin can increase gastric motility in a dose-dependent manner. However, this was not apparent in totally vagotomized rats. Ghrelin induces orexigenic effects by means of vagal nerve and afferent activities, and is a very powerful gastrokinetic agent. ICV injection of ghrelin can induce c-fos expression in the nucleus tractus solitaries and the dorsomotor nucleus of the vagus, and can directly stimulate the enteric neural pathway.

The ICV injection of ghrelin also potently stimulates feeding behavior and increases gastric emptying by activating hypothalamic NPY/AgRP neurons in arcuate nuclei. However, in rats the ICV administration of NPY suppresses postprandial antral contraction and delays gastric emptying. No effect is evident at 24 h after injection. The acceleration of small intestinal transit can be affected upon the down-regulation of GHS-R1A in small intestinal muscle layers. The intraperitoneal injection of ghrelin can reverse postoperative gastric ileus in rats.

3.2. α-MSH fails to attenuate gastric emptying elicited by ghrelin

α-MSH acting in a competitive role with AgRP on MC3 and MC4 receptors does not attenuate the gastric emptying that is accelerated by central acyl ghrelin stimulation. These results indicate that the accelerated gastric emptying induced by the ICV injection of ghrelin is not mediated by MCRs in the brain.

4. EFFECTS OF α-MSH SMALL INTESTINAL TRANSIT ELICITED BY GHRELIN

4.1. Ghrelin elicits small intestinal transit

Ghrelin introduced by ICV injection increases the geometric center of intestinal transit and running percentage of small intestinal transit. The intraperitoneal injection of ghrelin and oral administration of ghrelin receptor agonist also accelerate small intestinal transit. Ghrelin acts on the receptors in the intestinal neuromuscular tissue to accelerate the intestinal transit via cholinergic mechanisms. The acceleration of small intestinal transit can be affected upon the down-regulation of GHS-R1A in small intestinal muscle layers. The intraperitoneal injection of ghrelin is able to normalize the burn-induced and diabetic-related delay in intestinal transit. The intravenous injection of ghrelin can reverse postoperative gastric ileus in rats.

4.2. α-MSH fails to attenuate ghrelin-elicted small intestinal transit

α-MSH acts on the MC4 receptor, which is highly enriched in peptide YY expressing enteroneuroendocrine L cells, to induce the release of peptide YY. The intravenous administration of peptide YY inhibits intestinal transit. A study in rats reported that the ICV injection of α-MSH at a dose of 2 nmol/rat attenuated the increase in the geometric center, induced by ghrelin ICV injection, but not the running percentage in small intestinal transit. These results offer support for the view that central acyl ghrelin accelerates the small intestinal transit at least in part via MC receptors in the brain.

5. EFFECTS OF α-MSH IN GHRELIN-ELICITED COLONIC TRANSIT

5.1. Ghrelin elicits colonic transit

ICV injection of ghrelin can accelerate colonic transit time and increase fecal output. Intravenous injection of ghrelin does not have these effects. Intrapерitoneal injection of ghrelin does not accelerate colonic transit, but does increase fecal output. Central administration of ghrelin can moderate gastrointestinal motor functions at paraventricular nuclei mediated by NPY- and CRF, receptor-dependent mechanisms. Central or peripheral administration of NPY receptor antagonist can attenuate the ghrelin-induced increase of colonic transit. The effect of central acyl ghrelin on colonic motor functions through the action of AgRP on MC receptors is still uninvestigated.

5.2. α-MSH partly attenuates ghrelin-elicted colonic transit

α-MSH displays high affinity to the MC3 and MC4 receptors. It does not attenuate the accelerated colonic transit induced by ICV injection of ghrelin. However, α-MSH decreases the increases in fecal pellet and total fecal weight that are induced by ICV injection of ghrelin. These findings imply that distal colonic motility and secretion, similar to fecal pellet and total fecal weight, are partly mediated by MC receptors in the brain.

Table 1

<table>
<thead>
<tr>
<th>Authors</th>
<th>Species</th>
<th>Status</th>
<th>Route of drug administration</th>
<th>Food intake</th>
<th>α-MSH on food intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al., 2017</td>
<td>Rats</td>
<td>Free-feeding</td>
<td>ICV 0.1 nmol/rat: 1, 2, 4, 8H (↑), 12, 24H (↓)</td>
<td>1 nmol/rat: 1, 2, 4, 8H (↓), 12, 24H (↑)</td>
<td></td>
</tr>
<tr>
<td>Nakazato et al., 2001</td>
<td>Rats</td>
<td>Free-feeding</td>
<td>ICV 0.1 nmol/rat: 2H (↑), 4H (↑), 8H (↑), 12H (↑), 24H (↑)</td>
<td>2 nmol/rat: 1, 2, 4, 8H (↓), 12, 24H (↑)</td>
<td></td>
</tr>
<tr>
<td>Lucas et al., 2014</td>
<td>Rats</td>
<td>Free-feeding</td>
<td>ICV 50 pmol/rat: 2H (↑)</td>
<td>2 nmol/rat: 2H (↓)</td>
<td></td>
</tr>
</tbody>
</table>

H = hours; ICV = Intracerebroventricular; α-MSH = α-melanocyte stimulating hormones.
In conclusion, central-ghrelin-induced acceleration of gastric emptying is not mediated by MCRe, but the acceleration of the small intestinal transit at least is partly mediated by MCRs in the brain. Distal colonic motility and secretion, similar to fecal pellet and total fecal weight, is partly mediated by MCRs in the brain. The various interplays between acyl ghrelin and MCRs may provide a new therapeutic avenue for ameliorating anorexia and constipation.

Previous Presentations: Parts of the content were presented at the Asian Pacific Digestive Week in Kobe, Japan on November 5, 2016.

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