levels. Insulin, CCK, peptide YY and glucagone-like peptide 1(GLP-1), for example, rise rapidly after food ingestion and circulating ghrelin begins to fall simultaneously.[45,71] Ghrelin and CCK exert opposite effects on feeding behaviour through the vagal afferent, thereby regulating food intake on a short-term basis as a meal initiator and terminator, respectively. Abnormalities in the release of or sensitivity to ghrelin and/or CCK may be involved in alterations of food intake.[20]

An especially large amount of attention was paid to the relationship between ghrelin and insulin. Although acute administration of ghrelin reduced insulin secretion and caused hyperglycaemia,[72] plasma ghrelin concentrations were not affected by glucose or insulin in healthy subjects.[73–76] However, the presence of at least circulating basal insulin concentrations is essential for prandial ghrelin suppression, as demonstrated in type 1 diabetic subjects. In absence of any insulin treatment, these diabetics did not manifest a postprandial ghrelin response to a standard breakfast meal. However, low basal dose of insulin, which maintains euglycemia during the hours before the meal, was sufficient to reduce circulating ghrelin.[77] Moreover, a recent work showed a relevant association between insulin-mediated glucose metabolism and the regulation of ghrelin secretion after food intake in children with different levels of overweight. It is possible that the maintenance of an adequate level of insulin sensitivity and glucose oxidation may affect appetite regulation by favouring a more efficient postprandial ghrelin reduction.[78] However, some authors showed that in type 2 diabetic subjects, hyperinsulinemia and insulin resistance were significantly associated with decreased plasma levels of acyl ghrelin.[79,80]

2.1.7. Acyl ghrelin and the long-term regulation of food intake

Ghrelin is considered as an "adiposity signal". Fluctuations of plasma ghrelin concentrations may reflect physiological adaptation to long-term alterations in the energy balance.[38] Ghrelin levels correlate inversely with adiposity at baseline.[76,81,82] Moreover, circulating ghrelin levels increase in response to weight loss resulting from multiple causes.[71,83–86] The increase in ghrelin concentration during starvation may promote eating and its fall in obesity may be a secondary response to over-eating.[87] Patients with Prader-Willi syndrome, who have profound obesity and voracious and uncontrollable appetite, have remarkably high level of ghrelin when compared with other obese individuals.[46] Patients with anorexia nervosa exhibit high plasma ghrelin concentrations compared with age- and sex-matched controls and weight gain decreases their elevated ghrelin concentrations.[85,88] Morbidly obese patients, who underwent Roux-en-Y gastric bypass operation (RYGB), experienced durably decreases in body weight by ~36%. RYGB is currently the most successful treatment for obesity.[89] Recent data suggest that neural and hormonal mechanisms may contribute to the decrease of appetite and greater efficacy of the bypass procedure compared with diet-induced weight loss.[90] It would expect the massive decrease of BMI achieved with RYGB to trigger an elevation of ghrelin levels; however, these patients had greatly reduced ghrelin concentrations and ghrelin pre-meal peaks.[86,91] The absence of the compensatory increase in ghrelin concentrations that usually occurs with diet-induced weight loss may contribute to maintain durably weight loss.[92] Some authors explain the paradoxical suppression of ghrelin levels with an "override inhibition". The uninterrupted diversion of food from contact with the distal stomach and the duodenum initially produces stimulatory signals to release gastric ghrelin and later paradoxically suppresses its release. Other authors suggest a neural based explanation. Since the effect of RYGB to reduce plasma ghrelin has been observed within a very short time after surgery, it is tempting to speculate that this effect is related to treatment of the vagal nerve in the procedure.[45,93] The influence of vagal nerve on ghrelin regulation has been described above in this review. However, other studies have shown no change in ghrelin levels [94,95] and one group has reported a rise in ghrelin levels after RYGB.[96]

2.1.8. The relationship between acyl ghrelin and leptin in the long-term regulation of food intake

Circulating ghrelin levels appears to track body weight. It would be of great interest to discern the means through which the ghrelin regulatory system detects changes in weight. It has recently shown that hypocaloric diet-induced weight loss induces a coordinated increase in circulating ghrelin levels and decrease in plasma leptin levels.[86] Because ghrelin is a potent orexigenic peptide and leptin is a satiety signal at the level of the CNS,[38] this coordinated change in hormone levels should elicit a strong compensatory increase in appetite that contributes to the poor long-term maintenance of weight loss achieved by caloric restriction.[97]

Plasma ghrelin concentrations show a diurnal variation, in phase with leptin, with highest levels in the morning and lower at night.[98] Various studies showed that reciprocal rhytmicities in 2 peripheral hormones are the major afferent signals for the timely activation of the NPY system in the arcuate nucleus of the hypothalamus.[99–101] It has been found that leptin inhibits both the secretion of gastric ghrelin and the stimulation of feeding by ghrelin.[102] It has been suggested that this dual leptin restraint is the major regulatory arm of the feedback communication between the periphery and the hypothalamus for weight homeostasis,[99,100,103] and the disruption in the rhythmic communication at any locus in the leptin–ghrelin–NPY feedback loop impels loss of hypothalamic control, leading to abnormal weight gain and obesity.[104]

The relationship between ghrelin and leptin has to be considered, in order to understand why the most popular diets are based on varying macronutrient distribution. In humans, low fat, high carbohydrate diet produced loss of body weight without a compensatory increase in plasma leptin and ghrelin concentrations.[97] Conversely, high-protein diet induces sustained reductions in appetite, *ad libitum* caloric intake and body weight despite compensatory changes in diurnal plasma leptin and ghrelin concentrations. In this work, increased protein intake enhances the satiating effect of circulating leptin in the CNS. The anorexic effect of dietary protein, which may be due in part to increased CNS leptin sensitivity, is apparently stronger than any orexigenic effect of increased ghrelin concentrations accompanying weight loss with high-protein diet.[105]

However, a recent study has suggested that the leptin and the ghrelin systems play energy homeostasis function independently of each other in healthy humans. In these subjects, the circulating ghrelin concentrations were regulated by changes in adiposity independently by leptin levels.[106]

2.2. Des-acyl ghrelin

To date, little is known about the physiological role of des-acyl ghrelin. Some authors suggested that des-acyl ghrelin might have an anorexigenic activity that is contrary to the orexigenic activity of acylated ghrelin.[107,108] Conversely, a recent study showed that both ghrelin and des-acyl ghrelin function as orexigenic peptides in the hypothalamus.[109]

Since the acylation of ghrelin is required for the activation of the type 1 growth hormone secretagogue-receptor, it was assumed that des-acyl ghrelin was void of endocrine properties.[4] The des-acyl ghrelin showed no effect on the elevation of intracellular Ca^{2+} concentrations in cells that express the GHS-R or on the increasing of plasma GH concentrations in rats.[110] Later, a paper reported that des-acyl ghrelin is able to antagonize the metabolic but not the

neuroendocrine response elicited by acylated ghrelin in humans.[111] Serum GH levels correlated closely with plasma acylated, rather than des-acylated ghrelin.[112] Transgenic mice overexpressing des-acyl ghrelin exhibited thin phenotype although their plasma GH levels showed no differences with non-transgenic littermates. This thin phenotype may be due, at least in part, to a decrease in food intake.[19] In another experiment, transgenic mice showed decrease body weight and nose-to-anus length associated with normal nutritional conditions. It has been suggested that des-acyl ghrelin may modulate the GH-insulin growth factor-I axis in the pituitary and in the hypothalamus of transgenic mice, resulting in the small phenotype.[113]

Moreover, recent studies indicate that ghrelin and des-acyl ghrelin exhibit similar GHS-R-independent biological activities, including a cytoprotective effect on cultured cardiomyocytes and endothelial cells,[114] the inhibition of cell proliferation in human breast and prostate cancer lines,[115,116] the reduction of glycerol released from rat epididymal adipocytes.[117] Des-acyl ghrelin promotes adipogenesis directly *in vivo* in bone marrow fat in rats.[13] Overall, these findings suggest des-acyl ghrelin plays its actions by a different receptor than GHS-R1a, as yet unknown.

2.2.1. Des-acyl ghrelin as an anorexigenic peptide

Several studies showed that des-acyl ghrelin induces a state of negative energy balance. It reduces body weight by decreasing the food intake and delaying the gastric emptying in mice. These effects are mediated in the hypothalamus. The peripheral administration of des-acyl ghrelin increases the neuron c-Fos expression in the arcuate nucleus and in the paraventricular nucleus of the hypothalamus. The anorexigenic cocaine and amphetamine regulated transcript (CART) and the urocortin [19] as well as the corticotropin-releasing factor type 2 receptor, but not type 1, are involved in this action.[118] Peripheral des-acyl ghrelin may directly activate the brain receptor by crossing the blood-brain barrier [24] but not by the activation of vagal afferent pathways.[19] According to these results, the intracisternal administration of des-acyl ghrelin decreased food intake and inhibited gastric emptying without altering small intestine transit in food-deprived rats.[108]

2.2.2. Des-acyl ghrelin as an orexigenic peptide

Interestingly, a recent work shows that des-acyl ghrelin stimulates feeding via a mechanism independent of GHS-R. In rats, the intracerebroventicular administration of des-acyl ghrelin increased feeding and locomotor activity by stimulating orexin neurons in the lateral area of the hypothalamus. Orexin-A and -B are involved in the hypothalamic regulation of feeding, energy homeostasis and arousal. It has been found that des-acyl ghrelin does not compete with ghrelin for binding to the GHS-R in orexin neurons. Thus, there are three possible subtypes of orexin neurons: those that express the GHS-R as a receptor for ghrelin, those expressing an as-yet unknown receptor or target protein of des-acyl ghrelin and neurons possessing both proteins.[109] Further studies examining the physiological and neuroanatomical interactions between des-acyl ghrelin and its targets will help to highlight the roles of ghrelin-related peptides in the regulation of feeding and energy homeostasis.

2.2.3. Ghrelin system and glucose and lipid metabolism

The ghrelin system, using both the acylated and des-acylated molecules, is actively involved in the acute- and the long-term control of glucose metabolism and insulin concentrations.[111] It has been demonstrated that glucose-output by primary hepatocytes is time- and dose-dependently stimulated by acyl ghrelin and inhibited by des-acyl ghrelin. Furthermore, it has been reported that des-acyl ghrelin is able to antagonize acyl ghrelin induced glucose-output. These actions might be mediated by a different receptor than GHS-R1a, which is not expressed in the hepatocytes. Apparently, the two forms of peptides must be considered as separate hormones able to modify each other's actions on glucose handling, at least in the liver.[119]

In humans, the acute administration of acyl ghrelin induced a rapid rise of glucose and insulin levels. In healthy humans, physiological increments in plasma ghrelin concentrations do not change glucose flux and circulating concentrations of glucose, insulin, C-peptide and glucagons.[120] The acute administration of des-acyl ghrelin has no effect on insulin secretion in humans. However, des-acyl ghrelin prevented the acyl ghrelin-induced rise of insulin and glucose when co-administered. The combination of acylated and des-acylated ghrelins significantly improved insulin sensitivity.[121] This finding might lead to new therapeutic approach for many disorders in which insulin sensitivity is disturbed.

Ghrelin as well as des-acyl ghrelin promotes bone marrow adipogenesis *in vivo* by a direct peripheral action, in rats. This action is mediated via a receptor other than GHS-R1a. The ratio of ghrelin and des-acyl ghrelin production could help to regulate the balance between adipogenesis and lipolysis in response to nutritional status.[13,117]

2.3. Obestatin

Obestatin, a 23 amino acid peptide recently isolated from the rat stomach, is encoded by the same gene of ghrelin. Similarly to ghrelin, which requires post-translational process by acylation, the biological activity of obestatin requires the amidation at its conserved glycine residue at the carboxyl terminus.[5] Obestatin is expressed in cells of gastric mucosa and myenetric ganglion cells and this peptide is biologically active on central neurons.[122]

First reports have showed that obestatin plays opposite actions to ghrelin on food intake,[5,123] body weight and gastric emptying.[5] Obestatin injection suppressed food intake and decreased body weight gain in rats. These activities are induced whether obestatin is administered intraperitoneally or intracerebroventricularly. Serum leptin concentrations were not affected after treatment with either obestatin or ghrelin, suggesting minimal modulation of body fat content. Furthermore, treatment with obestatin led to a sustained suppression of gastric emptying activity. The contractile activity of jejunal muscle were decreased and antagonized by the stimulatory effects of ghrelin. The observed inhibition of jejunal contraction may trigger an afferent vagal signal to induce a central satiety response.[5]

Zhang et al.[5] reported that obestatin activates the orphan G protein-coupled receptor GPR39, which is a member of a family including the receptors for ghrelin and motilin. Real-time reverse-transcription polymerase chain reaction analyses indicate that GPR39 is expressed in jejunum, duodenum, stomach and other peripheral tissues. It is also expressed in the amygdala,[124] the hippocampus and the auditory cortex.[125] Low levels of GPR39 mRNA were found in several other brain regions. Surprisingly, there is no expression of GPR39 mRNA in the hypothalamus, expected to be the site of the anorexigenic action of obestatin.[125] It has been hypothesized that obestatin may simply suppress appetite by triggering nausea or visceral illness.[126] Unlike ghrelin, neither intravenous nor intracerebroventricular administration of obestatin affects the secretion of GH, PRL, TSH and ACTH, despite the presence of GHRP39 in the pituitary of rats.[127]

Recent works do not support a role of the obestatin/GPR39 system in the regulation of energy balance. Several *in vivo* and *in vitro* studies failed to confirm that obestatin reduces food intake and inhibits gastrointestinal motility.[128–132] In mice, obestatin did not show any effect on food intake, body weight, body composition, energy expenditure, locomotor activity, respiratory quotient or

hypothalamic neuropeptides involved in energy balance regulation. In agreement with the first reports, it has been found no effect on GH secretion *in vivo*.[130] In rodents, the peripheral administration of obestatin did not affect gastric emptying nor inhibited the prokinetic effects of ghrelin. Moreover, the intestinal contractility was not affected.[131] Zizzani et al.[133] confirmed that exogenous obestatin *per se* did not modify food intake in fasted and fed mice. However, they found that obestatin inhibited the orexigenic effects as well as the stimulation of GH levels by ghrelin administration. It remains to be clarified whether obestatin modulates endogenous ghrelin actions.[133] Taken together these results suggest that peripheral obestatin is not a satiety signal that play a role in the regulation of gastric emptying and do not support the concept that it is a physiological opponent of ghrelin.

Interestingly, the intracerebroventricular administration of obestatin inhibited water drinking in rats. This effect preceded and was more pronounced than any on food intake and it did not appear to be the result of altered locomotor/behavioural activity. It has been suggested that obestatin not acts in the pituitary to regulate GH secretion but may act in the brain to alter thirst mechanisms. From this point of view, the effects of obestatin on food intake may be secondary to an action of the peptide to inhibit water drink in rats.[134]

Convergent reports affirm that obestatin is not the cognate ligand for GPR39 receptor.[128,135,136] It has been found that obestatin does not bind GPR39. It has been observed no effects of obestatin on GPR39-transfected cells in various functional assays (cyclic adenosine monophosphate production, calcium mobilization and GPR39 internalization). Similarly observations have been reported by other researches.[128,136] No specific binding of obestatin could be detected in two different types of GPR39-expressing cells using three radioiodinated forms of obestatin.[128]

GPR39 appears to be involved in gut motor functions,[124] since in GPR39 knockout mice gastric emptying is accelerated. However, food intake, body weight and adiposity were similar between GPR39 (+/+) and GPR39 (−/−). Obestatin injection did not affect food intake in both phenotypes. It has suggested that the role of GPR39 should be conducted independently of the function of obestatin.[137] Taken together, existing reports curtail the initial promise that obestatin is a new regulator of appetite and digestive motility.

Despite the sequence homologies between rodent and human obestatin is 87% and 93% for GPR39, the effects of obestatin have yet to be determined in humans.[126] Some studies were performed in subjects suffering from Prader-Willi Syndrome with contradictory results. Park et al.[138] reported that plasma obestatin levels are not elevated and are not regulated by insulin in children both suffering from Prader-Willi Syndrome and from obesity. On the contrary, Butler and Bittel[139] found higher levels of obestatin in infants affected by Prader-Willi syndrome compared to controls.

Obestatin, like ghrelin, is secreted in a pulsatile manner, although their levels were not strictly correlated.[133] Obestatin appears to have an extremely fast influx rate to the brain. Absence of the blood-brain barrier permeation by obestatin was in contrast to the saturable transport of human ghrelin reported previously. Obestatin lacked specific bindings and endocytosis, and the small amount internalized showed rapid intracellular degradation. The differential interactions of obestatin and ghrelin with the blood-brain barrier illustrate their distinctive interactions with the CNS.[140] Further studies are necessary to highlight the physiological role of obestatin and GPR39 in both animals and humans.

3. Conclusion

The identification of obestatin, a novel peptide hormone derived from the same gene as ghrelin, has recently added further complexity to ghrelin physiology. Three peptide hormones (acyl ghrelin, des-acyl ghrelin and obestatin) derive from the same precursor act through distinct receptors and exert opposing physiological actions. This finding highlights the importance of post-translational regulatory mechanisms. Despite the rapid progress, many questions remain unanswered, including the regulation of acyl ghrelin, des-acyl ghrelin and obestatin secretion, the downstream pathways that mediate their effects, and their precise physiologic endocrine and paracrine roles. Further investigations are required to highlight the intricate balance of energy homeostasis and body weight control and to provide a successful treatment of eating disorders, obesity and cachexia.

Conflict of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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NPY受容体
——摂食調節ペプチドと摂食障害
Neuropeptide Y receptors

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◎ニューロペプチドY(NPY)は中枢神経系を中心に非常に多く分布しており，その生理作用は摂食調節やエネルギー調節のほか，行動，情動系，アルコール摂取，消化管運動，痙攣調節など多岐にわたっている．NPY受容体には6種類のサブタイプが存在し，各サブタイプのアゴニスト，アンタゴニスト化合物投与による薬理作用の検討やトランスジェニック動物を用いた各サブタイプ遺伝子のノックアウトあるいは過剰発現による表現型の観察により，その生理作用が検討されている．摂食調節におけるNPY受容体の役割についても広く研究されており，とくにY1およびY5受容体が摂食亢進作用として，Y2受容体が摂食抑制作用として報告されている．しかし単一受容体サブタイプだけでは摂食調節機構を説明することは困難であり，NPY受容体サブタイプ間における相互作用や他の神経ペプチドによる代償作用あるいは重複作用が想定されている．

Key word：ニューロペプチドY(NPY)，NPY受容体，摂食調節，エネルギー調節，摂食障害

生活習慣病が問題となる現在，肥満の原因である食行動の調節機構が注目されている．とりわけ摂食調節ペプチドの研究が盛んに行われており，ニューロペプチドY(neuropeptide Y：NPY)およびその受容体もそのひとつである．本稿ではNPY受容体と摂食との関連を中心に概説する．

ニューロペプチドY(NPY)

NPYは中枢投与により強い摂食亢進を示し，ほかにもエネルギー消費の減少，褐色脂肪組織の代謝抑制，白色脂肪組織における脂肪合成の亢進作用などがあり，エネルギーバランスを正に向ける作用がある．NPYは36個のアミノ酸からなる神経ペプチドで，NPY遺伝子はヒト7番染色体のlocus 7p15.1に存在する．NPY遺伝子は4つのエクソンからなり，pre-pro NPYが合成された後，NPYとC末端ペプチドが産生される．またNPY断片としてNPY2-36，NPY13-36，NPY20-36，NPY22-36などが存在するが，NPYの摂食亢進作用はNPY1-36(whole)がもっとも強い．

NPYは中枢神経系と末梢神経系に存在し，とくに齧歯類やヒトでは中枢神経系にもっとも豊富に広く分布する．脳内では視床下部，扁桃体，海馬，孤束核，青斑核，側坐核および大脳皮質に分布しており，ノルエピネフリン，GABA，AgRP(agouti-related protein)などと共存している．とくに視床下部の弓状核(arcuate nucleus：ARC)に多く存在し，室傍核(paraventricular nucleus：PVN)，視床下部背内側核(dorsomedial hypothalamus：DMH)，視床下部外側野(lateral hypothalamic area：LHA)などに投射し，摂食調節の中心的役割を果たしていると考えられている．一方，末梢神経系では交感神経に存在し，末梢組織では血管，肺，腎，副腎，胃，大腸，心臓，膵など多くの組織に分布する．

NPY受容体の生理作用

NPY受容体はG蛋白質共役型の7回膜貫通型の受容体であり，すくなくとも5種類のサブタイプ(Y1，Y2，Y4，Y5，Y6)がクローニングされている．Y3受容体は実験的にはその存在が想定されて

表 1　各受容体の代表的な内因性リガンド

受容体サブタイプ	リガンド
Y1	NPY, PYY
Y2	PYY, NPY3-36, NPY13-36
Y4	PP
Y5	NPY

いるが，単独の遺伝子としては存在しない．Y6 受容体はほとんどの動物で正常な構造を保持しておらず，マウスのみ機能的な蛋白質である．Y7 受容体も発見されているが，哺乳類には存在しない．Y1 受容体は Y4 および Y6 受容体と高い相同性を有しており，アミノ酸配列の約 50%が一致する．Y2 受容体はほかのサブタイプともっとも相同性

表 2　各受容体サブタイプの薬理学的検討およびトランスジェニック動物を用いた検討[16]

(1) 薬理学的検討		
①動物実験		
Y1 受容体	アンタゴニスト	・自発的な摂食量の低下，絶食時の摂食の低下，自由摂食あるいは NPY により誘発される摂食の減弱
	アゴニスト	・用量依存的に摂食を亢進
Y4 受容体	アゴニスト	・絶食下における摂食を抑制
Y5 受容体	アンタゴニスト	・自発的な摂食量の低下，絶食時の摂食の低下，自由摂食あるいは NPY により誘発される摂食の減弱 ・体重増加率の減少，脂肪量の減少，満腹下での摂食行動の亢進 ・NPY により誘発される摂食行動への影響なし ・PP による摂食亢進作用は阻害するが，NPY による摂食亢進作用は阻害しない
	アゴニスト	・摂食亢進 ・過食，体重増加，高コレステロール・高インスリン・高レプチン血症の誘発
②臨床研究		
Y2 受容体	アゴニスト	・エネルギー摂取量の減少，高率に副作用あり
Y4 受容体	アゴニスト	・Prader-Willi 症候群の摂食阻害作用なし
Y2Y4 受容体	アゴニスト	・肥満者の摂食を抑制
Y5 受容体	アンタゴニスト	・肥満者の体重減少について統計学的有意差は認めたが，その差は小さく臨床的意義は乏しい ・食事ダイエット後の体重増加抑制作用について統計学的有意差は認めたが，その差は小さく臨床的意義は乏しい
(2) トランスジェニック動物を用いた検討		
NPY KO		・インスリン欠損による糖尿病マウスの過食を減弱 ・レプチン欠損 *ob/ob* マウスの内分泌学的変化を減弱 ・“おいしいもの”に対する摂食行動を減弱 ・インスリンによる低血糖に対する摂食行動を減弱
NPY 過剰発現		・摂食行動，摂食量とも変化なし(通常食) ・スクロース負荷で体重増加，一過性の摂食量の増加，高血糖，高インスリン血症あり
Y1 KO		・脂肪量増加，摂食量はほとんど変化なし，絶食による誘発された摂食行動の減弱 ・絶食マウスで軽度高インスリン血症あり ・レプチン欠損 *ob/ob* マウスの過食の減弱 ・NPY の中枢投与による摂食亢進作用の減弱
Y2 KO		・体重増加，摂食量増加，脂肪沈着 ・レプチンへの反応減弱，NPY による摂食亢進作用は変化なし，絶食後の摂食や体重増加は変化なし ・摂食量の増加はあるが，一過性の体重減少あり，血漿 PP 値の増加
Y4 KO		・体重の減少，白色脂肪の減少，血漿 PP の基礎値の増加，24 時間当りの摂食量の減少
Y2Y4 KO		・暗期の水分摂取の亢進 ・Y2 受容体あるいは Y4 受容体単独の欠損に比べて脂肪量，レプチン血症，インスリン血症の著明な減少と摂食量の増加
Y1Y2Y4 KO		・Y1 単独欠損よりも NPY 過剰発現マウスにおける体重増加を減弱
Y5 KO		・遅発性の体重，摂食，脂肪量の増加を伴う肥満が発現

が乏しい(アミノ酸配列の30%以下). 各受容体サブタイプの内因性リガンドについて表1に示し, 生理的に重要と考えられるY1, Y2, Y4, Y5受容体について以下に概説する. また各受容体サブタイプの生理作用を検討する目的で, 多くの薬理学的検討やトランスジェニック動物を用いた研究が報告されており, その一部を表2に示す.

1. Y1受容体

Y1受容体は多くの生理作用にかかわっており, NPYによる自発的な食行動の亢進に関与していると考えられている. また, 摂食行動やエネルギーバランスの変化により視床下部のY1受容体の機能や発現量に可塑性がみられることが報告されており, Y1受容体のシグナル伝達の程度により摂食行動や肥満が亢進することが示唆されている[1]. さらにY1受容体は迷走神経背側核(dorsal vagal complex：DVC)にも存在し, 胃の近位部を弛緩させると考えられている[2]. またストレス反応との関連も指摘されており, 抗うつ様の作用に関与している可能性がある[3].

2. Y2受容体

Y2受容体はN末端にグリコシル化部位を有する. また細胞外側に2つのシステインがS-S結合しており, 1つのシステインがN連結グリコシル化のために細胞質側末端に存在している. NPYおよびPYYに高い親和性を示し, NPY3-36およびNPY13-36についてもNPYと同様の親和性がある. Y2受容体はラットでは内側視索前野, 視床下部前核, PVN, ARC, LHAを含む視床下部においてY1受容体より発現量が多く, 乳頭体核では発現量が少ない. ほかにも大脳皮質, 海馬, 扁桃体, 線条体, 側坐核などに発現している. このように中枢神経系において広く分布するY2受容体であるが, とくにARCに高濃度に分布する. ARCではシナプス前受容体として存在し, NPYを介して摂食や体重調節とも関連していると考えられている.

Y2受容体アゴニストのひとつであるPYY3-36の末梢投与により, 摂食抑制作用と体重減少作用を示す. 一方で長期ではY2受容体アゴニストによる摂食抑制作用が減弱するという報告もある[4]. またラットではY2受容体は食後期の十二指腸の消化管運動を空腹期のパターンに変換させる作用がある. ストレス反応との関連性には十分な証拠はないが, Y2受容体ノックアウトマウスではストレス反応の消失やCRFレベルが低いなどストレスとの関連を示唆する報告がある[3].

3. Y4受容体

Y1, Y2およびY5受容体への親和性はNPYおよびPYYとも同程度であるが, PPに対する親和性は低い. 一方, Y4受容体はNPYやPYYよりもPPへの親和性が高く, PPの受容体と考えられている. ヒトではY4受容体は骨格筋, 冠動脈, 腸管, 膵, 前立腺, 子宮に多く存在し, 肺, 腎などは発現量が少ない. これらの末梢組織だけでなく, 視床下部を含む脳全体に分布している. Y4受容体の生理作用として消化管運動の調節や摂食抑制作用が報告されている[3].

4. Y5受容体

Y5受容体蛋白は他の受容体に比べて100アミノ酸ほど大きい. これは細胞内ループが長いためであるが, C末端はY1, Y2およびY4受容体に比べて短い. Y5受容体遺伝子の転写はY1受容体と同じDNA配列の逆ストランドから行われ, 共発現していると考えられている. Y5受容体は中枢神経系に広く分布しているが, Y1, Y2受容体よりは少ない. マウスではY5受容体発現細胞にはY1受容体を共発現していることが多い(逆にY1受容体発現細胞にはY5受容体は発現していないことが多い). Y1とY5受容体は大脳皮質, 海馬, 視床下部, 扁桃体, 脳幹などNPYのおもな作用部位と一致して分布している. 内側視索前野やARCはY1, Y2およびY5受容体発現細胞が存在し, PVNにはそのほかにY4受容体も存在する.

Y5受容体はY1受容体と同様に摂食亢進作用に関連していると考えられている. またY5受容体はY1, Y2, Y4受容体と異なり, NPY断片であるNPY2-36の脳室内投与後よりNPY投与と同等の摂食亢進作用をもつ. このことは, NPYによるY5受容体の摂食亢進作用はY1, Y2およびY4受容体とは別の経路で関与していることを示唆している. Y5受容体を活性化するアゴニストの力価は, NPY＞PYY＝NPY2-36＝PYY3-36＞NPY13-36 である[5].

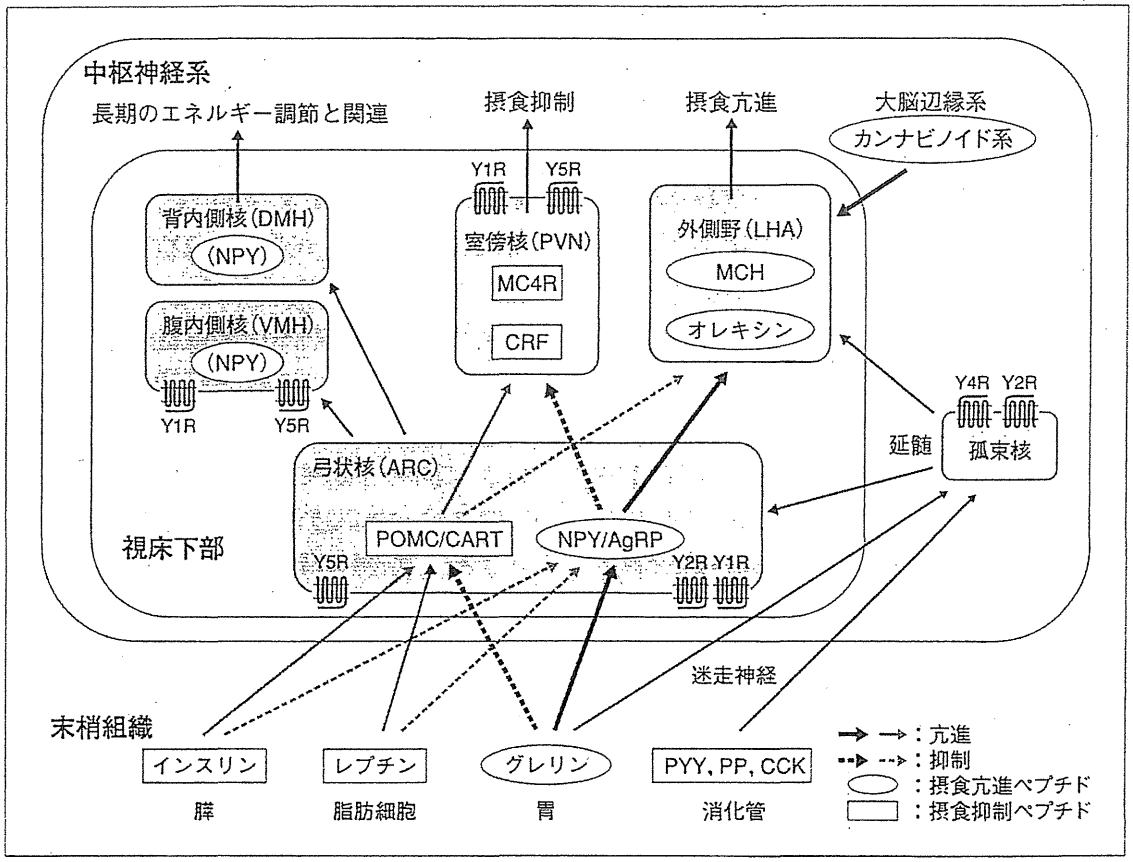

図 1　視床下部を中心とした摂食調節機構

視床下部はエネルギー調節の中枢である．弓状核(ARC)，室傍核(PVN)，視床下部腹内側核(ventromedial nucleus：VMN)，背内側核(dorsomedial nucleus：DMH)，外側野(LHA)などが摂食・エネルギー調節とかかわっている．最近になってさらに孤束核，扁桃体核，腹側被蓋野(ventral tegmental area：VTA)などの報酬系も重要であることが指摘されている[15]．このなかでとくに ARC に存在する 2 つの神経核が摂食調節に重要であり，ひとつは摂食亢進作用のある NPY と AgRP を含む NPY/AgRP ニューロン，他方はプロオピオメラノコルチン(proopiomelanocortin：POMC)とコカイン・アンフェタミン調節転写産物(cocaine and amphetamine-regulated transcript：CART)を含む POMC/CART ニューロンである．NPY，AgRP とも脳室内投与により摂食亢進作用を示すことが確認されている．POMC は食欲抑制作用のある α-MSH の前駆物質であり，POMC/CART ニューロンの活性化により摂食が抑制され，エネルギー消費が亢進する．NPY/AgRP ニューロンと POMC/CART ニューロンはたがいに拮抗しており，末梢の栄養状態を反映したシグナル(インスリン，レプチン，グレリンなど)の入力を受けてエネルギー・摂食の恒常性に中心的な役割を果たす．

NPY受容体と摂食調節

視床下部の Y1，Y2，Y5 受容体がおもに摂食調節と関連し，各受容体が異なったメカニズムでエネルギー調節にかかわっていると考えられている(図 1)．これらの受容体が脳内で持続的に活性化していることが示されており，Y1 受容体の持続的な活性化により栄養素分配の変化のみで体重増加をきたす．Y2 受容体の持続的な活性化は摂食低下による一過性の体重減少をきたすが，エネルギー消費にはほとんど影響はない．Y5 受容体の活性化は過食や栄養素分配効果により体重増加や脂肪増加に働き，エネルギー代謝の抑制をもたらす．また Y1 あるいは Y5 受容体を活性化すると NPY による摂食亢進がみられるが，Y1 受容体や Y5 受容体をノックアウトしても，摂食抑制による体重減少ではなく遅発性の摂食亢進を伴う肥満がみられる．一方で，リガンドである NPY をノックアウトしたマウスでは摂食行動や体重に変化はみられない．これらの結果は，摂食・体重が代償性に調節されていることを示している．

Y5 受容体ノックアウトマウスを用いた検討では，ARC における POMC/CART 遺伝子の発現変化と代償機構との関連が指摘されており，摂食行動の中枢性代償調節として POMC/CART 遺伝子

の発現が重要であると考えられる[6]．また，Y1受容体を遮断した状態(Y1受容体アンタゴニスト投与あるいはY1受容体をノックアウトした状態)でY5受容体アンタゴニストを投与すると，Y1受容体のみを遮断した状態に比べてより強い抗肥満作用がみられることが報告されている[7]．このことは，Y1およびY5受容体が摂食調節において相乗的な相互作用を有することを示唆しており，Y5受容体がY1受容体の細胞内シグナル伝達に影響を及ぼす可能性があることも推察されている．また，肥満マウスに対しY2受容体アゴニスト(PYY3-36)とY5受容体アンタゴニストを同時投与したところ，各単体投与に比べ，より大きな体重減少が得られた(相加効果)．このことはY2受容体刺激とY5受容体遮断が異なった経路で抗肥満作用を呈することを示している[8]．

Y4受容体についても摂食や栄養状態との関連が示唆されている．脳幹のY4受容体のmRNAレベルは，末梢からレプチンを投与した場合や絶食48時間後に餌を与えた場合に増加する．レプチン濃度は絶食時に低下し摂食により増加することから，脳幹のY4受容体はレプチンによる食欲不振に関与しているのかもしれない[9]．

サイドメモ1　摂食障害の治療抵抗性

摂食障害はいまでも治療抵抗例をよく経験するが，その理由として，①多くの摂食障害患者にみられる認知の歪みがきわめて強固であること，②摂食障害に至る背景が症例によって多様であること，があげられる．①については辺縁系，視床下部などを中心とした情動・報酬系と新皮質系を中心とした高次機能の統合の結果，強固な認知が形成されていることが想定される．NPYやグレリンなどがこれらの認知性摂食調節機構についてかかわっている可能性があるが十分な解明には至っておらず，手探りで治療を行っている現状がある．②については患者背景の多様性が標準的な治療の確立を困難にしていると考えられる．したがって，今後は認知性摂食調節機構の解明とランダム化比較試験(randomized controlled trial：RCT)のようなエビデンスレベルの高い結果を集積し，標準化された治療法が確立されることが望まれる．

摂食障害との関連

若い女性を中心に増加傾向にある摂食障害は，神経性食欲不振症(anorexia nervosa：AN)と神経性過食症(bulimia nervosa：BN)に分類される．ANは制限型(AN-R)とむちゃ喰い/排出型(AN-BP)に分類され，BNは排出型(BN-P)と非排出型(BN-NP)に分類される．さらにどちらの診断基準も満たさない分類不能型(eating disorder not otherwise specified：EDNOS)も多く，全摂食障害患者の半数近くはEDNOSに該当すると考えられている(「サイドメモ1」参照)．

その病態は前述の摂食調節ネットワークの乱れにより，結果的に摂食行動の異常が惹起されることが想定されている．たとえば，飢餓状態では末梢からの飢餓シグナル，すなわち脂肪量低下によるレプチン分泌低下や胃からのグレリン分泌増加などにより，NPY/AgRPニューロンの亢進およびPOMC/CARTニューロンの抑制の結果，摂食行動が促される．しかしANの場合，生理的には飢餓状態であるにもかかわらず摂食行動はむしろ抑制されている．この理由として，AN患者では摂食亢進シグナルが飢餓状態に比較して強くないことが考えられる．すなわちAN患者ではNPYやグレリンなどの摂食亢進ペプチドの代償的な増加は認められるものの，その増加幅は空腹や飢餓に比べて少ないことが報告されている．これは摂食亢進シグナルが摂食抑制ペプチド(CRF，CCKなど)の脱抑制によって抑えられている可能性がある[10]．ほかにもAN患者ではグレリン増加の主体がデスアシルグレリンであることなどが加わり，相対的に摂食抑制系が優位となり，飢餓状態にもかかわらず摂食行動が抑制されるという病態が推定される．

NPYと摂食障害の関連性を直接示した報告は乏しいが，AN患者の血中NPYおよび脳脊髄液(CSF)中NPYレベルが高値であることが報告されている．しかし，摂食障害患者にみられるNPY増加が病態の原因であるのか，あるいは結果であるのかについては，結論は出ていない．たとえばAN患者のCSF中NPYレベルは栄養状態の改善とともに回復することが報告されており[11]，この結果からは飢餓状態そのものがNPY高値の原因