J Physiol Sci (2015) 65:385–395
DOI 10.1007/s12576-015-0386-3

REVIEW

Anorexia in human and experimental animal models: physiological aspects related to neuropeptides

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Received: 27 March 2015 / Accepted: 16 June 2015 / Published online: 30 June 2015

Abstract Anorexia, a loss of appetite for food, can be caused by various physiological and pathophysiological conditions. In this review, firstly, clinical aspects of anorexia nervosa are summarized in brief. Secondly, hypothalamic neuropeptides responsible for feeding regulation in each hypothalamic nucleus are discussed. Finally, three different types of anorexigenic animal models; dehydration-induced anorexia, cisplatin-induced anorexia and cancer anorexia-cachexia, are introduced. In conclusion, hypothalamic neuropeptides may give us novel insight to understand and find effective therapeutics strategy essential for various kinds of anorexia.

Keywords Hypothalamus · Feeding-regulating neuropeptides · Anorexia · Behavior · Rodents

Introduction

Anorexia is caused by various physiological and pathophysiological conditions. Focusing on psychological eating disorders, the numbers of patients are increasing all over the world, among both men and women [1]. Eating disorders result in about 7,000 deaths a year (as of 2010) in the world, and therefore are a mental illness that results in substantial mortality [2]. Although, complexities of biological, psychological and/or environmental abnormalities are considered to be the cause of eating disorders, many things remain unknown. Investigating not only psychological aspects but also physiological aspects, including hypothalamic feeding-regulating neuropeptides, may be useful to understand its mechanism or to find effective therapeutics.

It is well established that appetite and feeding behaviors are primarily controlled by a feeding center and a satiety center in the hypothalamus, which is called the two-center theory [3–6]. Bilateral destruction of the ventromedial hypothalamus (VMH) produces a condition of voracious appetite, resulting in marked hyperphagia, which ultimately causes the animals to become remarkably obese [4]. On the other hand, bilateral destruction of the lateral hypothalamic area (LHA) produced an anorexic condition that results in animals failing to feed and ultimately wasting [6]. Although this two-center theory has been useful to understand the mechanisms of feeding behavior, it cannot be interpreted simply, because such ablation experiments may involve the destruction of many nerve fibers in the vicinity of those nuclei. For example, destruction of the LHA also damages the medial forebrain bundle, which includes abundant dopamine fibers responsible for feeding behavior and reward behavior.

Recently, the central mechanisms related to feeding behavior have been clarified on the basis of specific neuropeptides or neuronal networks rather than the two-center theory as previously described. The development of genetically modified mice using the Cre-loxP system enables us to examine the effects of specific neuronal cell populations on feeding behavior or body weight control [7]. In addition, functional neuronal mapping using optogenetics enables the identification of the neuronal circuits related to feeding control [8].

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For a deeper understanding of the human eating disorders, it may be important to conduct experiments using anorexia animal models. Although anorexia, the eating disorder, in humans includes psychological problems as well as biological problems, it is difficult to imitate human eating disorders in animals. Various types of physiological and pathophysiological anorexia models have been proposed, although these models are not the same model as human anorexia because of its complexities of biological, psychological and/or environmental abnormalities. The typical models of physiological anorexia are dehydration-induced anorexia and stress-induced anorexia [9–12]. On the other hand, the typical models of pathophysiological anorexia are drug-induced anorexia, lipopolysaccharides (LPS)-induced anorexia, anti-cancer drug-induced anorexia as a side effect and cancer-induced cachexia-anorexia [13–15]. From the point of view of hypothalamic neuropeptides, distinct patterns of the orexigenic or anorexigenic neuropeptides are seen among these anorexia models. For example, dehydration-induced anorexia primarily causes up-regulation of the hypothalamic anorexigenic peptides, whereas LPS-induced anorexia causes down-regulation of orexigenic peptides in addition to the up-regulation of the anorexigenic peptides [16].

In the present review, we summarize the brief aspects of human anorexia nervosa and explain the points of hypothalamic neuropeptides responsible for feeding control. We also introduce three different types of anorexia animal model; dehydration-induced anorexia, cisplatin-induced anorexia and cancer anorexia-cachexia.

Complexity of human anorexia nervosa

In standard medical manuals such as ICD-10 or DSM-5, eating disorders are specified as mental disorders. The classification of the eating disorders and diagnostic criteria for anorexia nervosa are shown in Fig. 1.

Anorexia nervosa is characterized by food restriction, inappropriate eating habits or rituals, obsession with having a thin figure, and an irrational fear of weight gain. Often, "anorexia nervosa" and "anorexia" are used interchangeably, however, "anorexia" means simply lacking appetite and the majority of the patients with "anorexia nervosa" do not lose their appetite [17]. Anorexia nervosa is often coupled with a distorted self-image [17]. Patients often look at themselves as overweight even they are already underweight. Regardless of the feeling of continuous hunger, they restrict food due to their fear of gaining weight [18]. It is suggested the initial weight loss may in some cases be one of the triggering factors in developing anorexia nervosa, possibly because of an already inherent predisposition toward anorexia nervosa [19].

【Classification of eating disorder (DSM-5)】
- Anorexia nervosa
- Bulimia nervosa
- Binge eating disorder
- Other specified feeding or eating disorder

【DSM-5 Diagnostic Criteria for anorexia nervosa】
- **Restricting food intake**

eating less than needed to maintain a body weight that's at or above the minimum normal weight for your age and height
- **Fear of gaining weight**

intense fear of gaining weight or becoming fat, or persistent behavior that interferes with weight gain, such as vomiting or using laxatives, even though you're underweight
- **Problems with body image**

denying the seriousness of having a low body weight, connecting your weight to your self-worth, or having a distorted image of your appearance or shape

Fig. 1 Classifications of eating disorders and diagnostic criteria for anorexia nervosa

The history of anorexia nervosa begins with descriptions of religious fasting dating from the Hellenistic era and continuing into the medieval period [20]. The earliest medical descriptions of anorexic illnesses were shown by English physician Richard Morton in 1689 [20]. Many case descriptions considered to be anorexic illnesses were demonstrated until nineteenth century. The term "anorexia nervosa" [of Greek origin: *an-* (prefix denoting negation) and *orexis* ("appetite")], was coined in 1873 by Sir William Gull, one of Queen Victoria's personal physicians [21], and he provided some detailed case descriptions and treatments.

Anorexia nervosa has an average prevalence for the diagnosis of 0.9 % in women and 0.3 % in men in developed countries [19]. It is seen mainly in young adolescent women and is more prevalent in the upper social classes [19]. It is unclear whether or not the incidence of anorexia nervosa is on the rise because it is difficult to compare the incident rates over time. Studies demonstrate that since at least 1970 the incidence of anorexia nervosa in adult women has been fairly constant, whereas there are other studies which indicate that the incidence may have been increasing for girls aged between 14 and 20 [22].

Many biological and sociological causes, not single ones but complexities of these conditions, are considered to be responsible for the onset of anorexia nervosa. In terms of biological causes, obstetric complications [23], genetic predisposition [24], serotonergic dysregulation [25], feeding-regulating neuropeptides [26], infection [27], autoimmune system [28] and nutrition deficiencies [29] have been proposed to be the causes of anorexia nervosa. In addition to these biological causes, sociological causes can also be responsible for developing anorexia nervosa. Specific cultural factors, such as family interactions, individual

psychology, and media exposure, are also among the causes of one's likelihood of developing anorexia. People in particular professions such as models are much more likely to develop anorexia [30]. A study has suggested that patients with anorexia nervosa can be characterized by alexithymia, and that this was the case in both adult and adolescent anorexia nervosa patients [31, 32].

Early intervention and treatment for anorexia nervosa seems to be more effective, though there is no conclusive treatment [33]. Usually, treatments aim to restore patients to a healthy weight, to treat the psychological problems related to anorexia nervosa, and to reduce or eliminate the behaviors or thoughts that originally led to the disordered eating [17]. It has been reported that the drug olanzapine is effective in treating certain aspects of anorexia nervosa [34]. Psychotherapies such as cognitive behavioral therapy or acceptance and commitment therapy are also used for treatment [17]. Regardless of these treatments, relapse, binging or starving after initial weight gain occurs in 40–70 % of the patients [17, 35]. It can be said that treating anorexia nervosa is never easy.

Neuropeptides in the hypothalamic nuclei to understand anorexia

Each nucleus responsible for feeding behavior and examples of the gene expression pattern of the feeding-regulating neuropeptides in the hypothalamus are described in Fig. 2.

Arcuate nucleus (ARC)

The ARC is considered to be one of the most important hypothalamic nuclei related to feeding behavior. Two main neuronal populations involved in feeding behavior exist in the ARC: the neuronal cells that produce neuropeptide Y (NPY) and agouti-related peptide (AgRP), which are orexigenic peptides, and α-melanocyte stimulating hormone (α-MSH), which is an anorexigenic peptide [36–38].

NPY-producing neurons and AgRP-producing neurons are described as NPY/AgRP neurons because they are approximately the same cell populations. NPY receptor subtype 5 is considered to be the key site of action in feeding promotion [39, 40]. The neurons that express NPY in rodents also express receptors for leptin and insulin and so are linked to plasma-derived feeding signals [41, 42]. AgRP is an antagonist for the anorexigenic peptides as it blocks the melanocortin 3 (MC3R) and 4 receptors (MC4R) for γ- and α-MSH, respectively [43, 44].

Administration of diphtheria toxin in mice expressing the diphtheria toxin receptor in NPY/AgRP neurons induces anorexia and body weight loss [45]. Feeding behavior is suppressed when the function of NPY and vesicular GABA transporter (VGAT) are simultaneously blocked [46]. This indicates that there are redundant mechanisms for feeding control. Projections from the NPY/AgRP neurons to the paraventricular nucleus (PVN) are important for the execution of feeding behavior. NPY/AgRP neurons suppress single-minded homolog 1 (sim1) and MC4R-

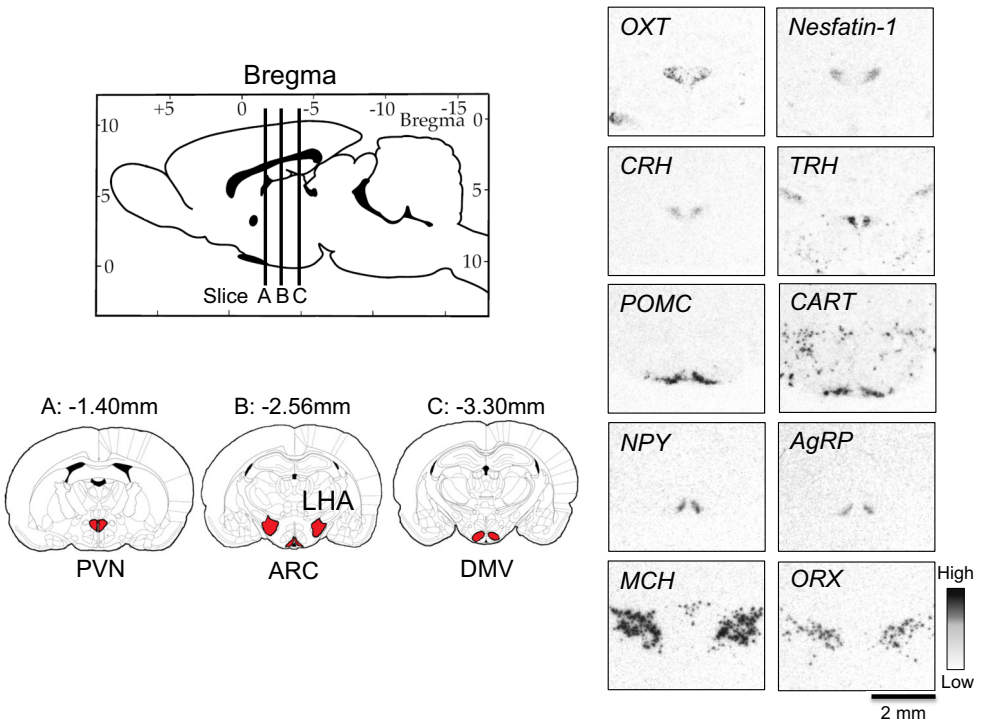

Fig. 2 Hypothalamic nuclei responsible for feeding behavior and feeding-regulating neuropeptides

positive cells through MC4R, GABA-A receptor and Y1 receptor, resulting in feeding behavior [47, 48].

α-MSH is processed from proopiomelanocortin (POMC), and POMC-producing neurons are known to exist in the ARC [49]. POMC neurons also produce cocaine-amphetamine-regulated transcript (CART) and are sometimes described as POMC/CART neurons [50]. In addition to these peptides, Galanin-like peptide (GALP), which is an anorexigenic peptide, is also expressed in the ARC [51]. Leptin receptors are strongly expressed in the ARC [52], and the number of phosphorylated Stat3-positive cells, a marker for activated leptin receptor signaling, is markedly increased after leptin administration [53]. Most of the POMC/CART neurons are not GABAergic, unlike NPY/AgRP neurons. Abundant expression of orexin type 2 receptors, leptin receptors, serotonin receptors and NPY receptors are observed in the POMC/CART neurons [54]. POMC/CART neurons receive excitatory projection from the VMH and feeding behavior is suppressed by this projection [55]. Estrogen receptors are abundantly expressed in the ARC and the gene expression of the POMC/CART is increased by estrogen [56].

Lateral hypothalamic area (LHA)

There are melanin-concentrating hormone (MCH)-producing neurons, orexin-producing neurons and polyglutamylated arginine-phenylalanineamide peptide (QRFP)-producing neurons in the LHA. Although, orexin has been reported as a peptide which promotes feeding, subsequent studies have reported that it is also a substantial neuropeptide in sleep–awake control [57]. Because increased food intake by orexin administration is confined during the light phase in rodents [58], it can be said that food consumption increased by orexin is an effect associated with arousal. In addition to orexin, MCH also promotes eating behavior [59]. Since the phenotype of orexin-deficient mice is obesity, and that of MCH-deficient mice is lean, the actions of orexin and MCH in terms of body weight regulation are opposite [60, 61]. The detailed mechanism of obesity in orexin-deficient mice remains unknown. One possible explanation is that, although orexin deficiency cause decreased food intake, energy expenditure may decrease much more than energy consumption. Another possible explanation is that orexin neuron deficiency causes deletion of other factors which are co-localized in orexin neurons and these factors might have important roles in the regulation of energy homeostasis. Fujiki et al. reported that the obesity in orexin-deficient mice is gender-specific and prominent in female mice [62]. They suggested that sexual dimorphism of leptin signaling likely exists, and alteration of this signaling may contribute to the gender difference in orexin-deficient obesity.

QRFP has been reported to be an orexigenic peptide in humans and rodents [63, 64]. In rats, the orexigenic effects of centrally administered QRFP are mediated by factors associated with an increased motivation to eat. The gene expression of *QRFP* is increased by the intake of a high fat diet but not by a low fat diet [65]. Effects of QRFP effects on food intake are considered to be mediated by the adiposity signal, leptin, and hypothalamic neuropeptides [66].

Paraventricular nucleus (PVN)

The PVN contains magnocellular neurosecretory cells (MNCs) whose axons extend into the posterior pituitary, parvocellular neurosecretory cells (PNCs) which project to the median eminence, and several populations of peptide-containing cells which project to many different brain regions, including parvocellular preautonomic neurons which project to the brainstem and spinal cord. Afferent outputs and inputs to the PVN from many important integrative centers of the hypothalamus and medulla have been identified. The PVN is important as a projection target from the NPY/AgRP neurons and POMC/CART neurons in the ARC [67, 68]. MC4R, the receptors for α-MSH, are expressed abundantly in the PVN [69, 70], and reducing MC4R in the PVN results in the development of obesity [71]. The POMC/CART neurons exhibit excitatory effects on MC4R-positive cells and the NPY/AgRP neurons exhibit inhibitory effects on MC4R via α-MSH, in addition, most of these MC4R-positive neurons are oxytocin (OXT)-producing neurons [47, 48].

Various neurohypophysial hormones related to feeding behavior are synthesized in the PVN. MNCs in the PVN produce and secrete two different types of neuropeptides: OXT and arginine vasopressin (AVP). A recent study has revealed that OXT neurons in the PVN may play a key role in suppressing appetite and that other hypothalamic neurons may trigger eating via inhibition of these OXT neurons [47]. This population of oxytocin neurons are absent in Prader–Willi syndrome, a genetic disorder which leads to uncontrollable feeding and obesity, and OXT is considered to play a key role in its pathophysiology [47].

In addition to one of the most important roles of AVP being regulating water retention, it also acts synergistically to stimulate adrenocorticotropic hormone (ACTH) secretion as well as corticotropin-releasing hormone (CRH) [72]. The main function of CRH is the stimulation of the pituitary synthesis of ACTH, resulting in the activation of the hypothalamo–pituitary–adrenal (HPA) axis and it is recognized as an anorexigenic neuropeptide [73].

Thyrotropin-releasing hormone (TRH) is a hormone produced in the PVN. It stimulates the release of thyroid-

stimulating hormone (TSH) and prolactin (PRL) from the anterior pituitary. Excess levels of TRH inhibit dopamine, resulting in a disinhibition of prolactin and a subsequent decrease in gonadotropin-releasing hormone (GnRH) release [74]. Food, but not water intake, is greatly reduced following an i.c.v. injection of TRH in rats [75]. Other studies have also revealed that TRH is an anorexigenic neuropeptide [76, 77].

Recently, nesfatin-1, a newly identified anorexigenic neuropeptide, has been found to also exist in the PVN [78]. Nesfatin-1 participates in the regulation of hunger and fat storage. It is also distributed in the ARC or the LHA, important nuclei for feeding regulation [78]. Nesfatin-1 influences the excitability of a large proportion of different subpopulations of neurons located in the PVN, and it is reported that MNCs' OXT neurons are activated by nesfatin-1during feeding, while i.c.v. administration of an OXT antagonist increases food intake, indicating a possible interaction between nesfatin-1 and OXT in the regulation of feeding behavior [79, 80]. Because nesfatin-1 neurons in the ARC are activated by simultaneous injection of ghrelin and desacyl ghrelin, they may be involved in the desacyl ghrelin-induced inhibition of the orexigenic effect of peripherally administered ghrelin in freely fed rats [81]. Nesfatin-1 is co-expressed with MCH in tuberal hypothalamic neurons [82], indicating a complex role not only in the regulation of food intake but also in other essential integrative brain functions involving MCH signaling, including autonomic regulation, stress, mood, cognition and sleep [83].

Ventromedial hypothalamus (VMH)

The VMH is known to be most commonly associated with satiety. Rats with VMH lesions were found to eat substantially more food and gained twice as much weight as those with PVN lesions [84]. It has been reported that there is a higher concentration of cannabinoid receptor mRNA within the VMH in comparison to other nuclei within the hypothalamus [85]. Cannabinoid ingestion has been linked to reward processes, and also with the release of dopamine in the brain [86]. Because leptin receptors and orexin receptors are abundantly distributed in the inner part of the VMH, it is considered one of the most important hypothalamic nuclei in feeding behavior [87, 88]. There are many projections between the VMH and other hypothalamic nuclei. Especially, excitatory projections from the pituitary adenylate cyclase-activating polypeptide (PACAP)-positive neurons in the VMH to the POMC/CART neurons in the ARC is thought to be one of the most important projections in suppressing feeding behavior [48].

Experimental anorexia animal models

Dehydration-induced anorexia

Because pathophysiological models of anorexia may involve multiple factors as previously described, developing a simple method to induce anorexia in animal models is necessary in order to improve our understanding of the neuronal and molecular mechanisms responsible for anorexia [16]. To resolve this problem, several groups have proposed the use of dehydration-induced anorexia in animal models [10, 89–91]. Dehydration-induced anorexia involves an important physiological adaptation that limits the intake of osmolytes from food and helps maintain the integrity of fluid compartments [92]. This model supports the existence of complex and varied neural network interactions that provide animals with the ability to adapt their feeding behaviors to deal with the many pressures imposed by the environment [93]. With this physiological aspect in mind, we examined several reports on dehydration-induced anorexia in animal models [11, 90, 91].

Watts and colleagues showed that rats develop profound anorexia from dehydration when hypertonic saline (2.5 % NaCl) instead of drinking water was given for 5 days [11, 94]. This model seems likely to be advantageous for examining the neuronal networks and feeding-regulating neuropeptides because slowly developed anorexia induced by dehydration is rapidly reversed once they regain access to drinking water.

According to their report, in dehydrated rats, the gene expression of the *NPY* in the ARC significantly increased in comparison with euhydrated rats [94]. In addition to this change, the gene expression of *POMC* and *neurotensin/neuromedin N* (*NT/N*) in the ARC and gene expression of *CRH* in the PVN were significantly decreased in comparison to euhydrated rats [94]. These changes were consistent and a result of the negative energy balance due to the animals developing anorexia with being dehydrated. Of interest, they also demonstrated that the gene expressions of *CRH* and *NT/N* in the LHA were significantly increased after dehydration. In addition, they reported that the gene expression of *CRH* in the LHA strongly correlated with the intensity of anorexia. These results suggest that the gene expressions of *CRH* and *NT/N* in the LHA increased by dehydration-induced anorexia act upon the PVN and suppress feeding in dehydrated rats [11, 90, 94].

Several studies have demonstrated that the gene expression of *TRH* in the PVN was significantly up-regulated in the dehydration-induced anorexia animal model [95–97]. These results indicate an inhibitory role of TRH in the PVN in feeding control as well as CRH or NT/N in the LHA.

We have previously demonstrated that the gene expression of *nesfatin-1* in the PVN is also up-regulated in rats dehydrated for 2 days or drinking hypertonic saline (2 % NaCl) for 5 days instead of drinking tap water [10]. Dehydration causes hyperosmolality and hypovolemia. Chronic salt loading causes hyperosmolality without hypovolemia. The gene expression of *nesfatin-1* was correlated with the degree of hyperosmolality and hypovolemia in this study. Moreover, i.c.v. injection of nesfatin-1 neutralizing antibody after 48 h water deprivation resulted in an almost complete cancelling of the anorexia induced by dehydration [10]. These results suggest that nesfatin-1 is one of the potential candidates involved in the development of anorexia induced by dehydration.

Rinaman and colleagues demonstrated that dehydration-induced anorexia was attenuated in OXT-deficient mice [98]. In addition, significantly fewer neurons within the hindbrain dorsal vagal complex were activated in OXT knockout dehydrated mice compared to wild-type dehydrated mice [98]. These results suggest that OXT neuronal projections from the hypothalamus to the hindbrain are necessary for the full expression of compensatory behavioral and physiological responses to dehydration. Taken together with the fact that OXT neurons are activated by nesfatin-1, these results are highly consistent with our study of nesfatin-1 in dehydration-induced anorexia.

Just and colleagues report that neuronal activity in the PVN and the LHA was increased in dehydrated anorexic female rats, using manganese-enhanced MRI, a noninvasive method for the investigation of the neuronal pathway [99]. It can be said that this study supports the previous reports, which indicate that activation of the PVN and LHA is induced in dehydrated animal models.

These studies raise the hypothesis that dehydration primarily causes up-regulation of the gene expression of the anorexigenic neuropeptides in the hypothalamus, and then anorexia-induced starvation, namely the negative energy balance, up-regulates the gene expression of the orexigenic neuropeptides (Fig. 3). The reason why dehydration primarily causes up-regulation of the anorexigenic neuropeptides, but not down-regulation of the orexigenic neuropeptides, remains unclear. Possible involvement of peripheral humoral factors such as circulating leptin, ghrelin, OXT and nesfatin-1 on dehydration-induced anorexia should be clarified by further study.

Cisplatin-induced anorexia

A pathophysiological anorexic animal model as well as a physiological anorexic model may also be important in examining the mechanisms of anorexia. Because it may involve multiple factors, investigating respective hypothalamic feeding-regulating neuropeptides could help us to understand molecular mechanisms or the central circuit responsible for anorexia.

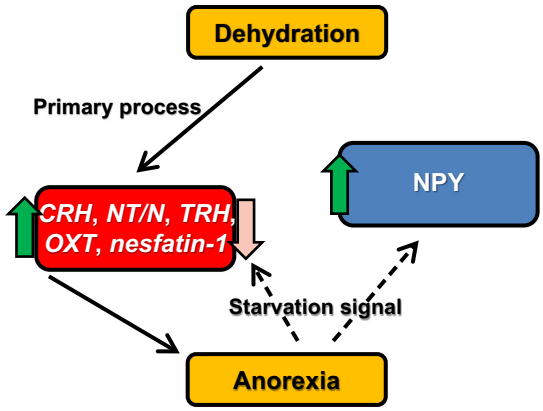

Fig. 3 The hypothalamic feeding-regulating peptides in dehydration-induced anorexia

Cisplatin-induced anorexia, one of the pathophysiological anorexic animal models, has been proposed by previous researchers. Cisplatin is widely used for various types of malignant tumors. It demonstrates anti-tumor effects by inhibiting the replication of DNA [100]. Although it is useful for treating diverse tumors, many disadvantageous side effects, such as loss of appetite, nausea and vomiting, afflict patients. It has been suggested that serotonin receptors are involved in the occurrence of nausea and vomiting from the use of cisplatin [101].

Yakabi and colleagues demonstrated that hypothalamic ghrelin secretion was markedly reduced 24 and 48 h after cisplatin treatment in cisplatin-treated rats compared to saline-treated rats, though their plasma ghrelin levels did not differ [102, 103]. In this study, it was found that the plasma acylated ghrelin level returned to the normal level within 24 h after a single administration of cisplatin, though the decreased food intake lasted for more than 48 h. They also demonstrated that i.c.v administration of ghrelin reversed the decreased in food intake in cisplatin-treated anorexic rats [102].

We previously described changes in the gene expression of the hypothalamic feeding-regulating neuropeptides in cisplatin-treated rats [13]. In this study, the gene expression of *CRH* in the PVN and the gene expression of *NPY* in the ARC were significantly decreased, while the gene expressions of *POMC* and *CART* in the ARC were markedly increased in cisplatin-treated rats compared to saline-treated rats. These results suggest that cisplatin primarily causes the up-regulation of the *POMC* and *CART*, anorexigenic neuropeptides, and down-regulation of *NPY*, an orexigenic neuropeptide, in the ARC, and that the ensuing decreased appetite, namely the negative energy balance, induced by cisplatin causes down-regulation of *CRH*, an anorexigenic neuropeptide, in the PVN.

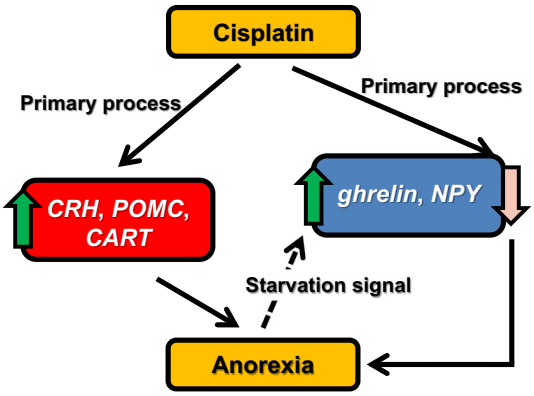

Fig. 4 The hypothalamic feeding-regulating peptides in cisplatin-induced anorexia

There are abundant serotonergic neuronal projections from the raphe nuclei, where 5-HT is synthesized, to the hypothalamus and many 5-HT receptors have been identified in the ARC [104]. Taken together, it is speculated that peripherally administered cisplatin decreases ghrelin secretion in the hypothalamus and increases 5-HT receptors in the hypothalamus, which cause up-regulation of *POMC* and *CART* and down-regulation of *NPY*. It is thought that these alterations are one of the causes of anorexia induced by cisplatin.

These studies raise the hypothesis that peripheral administration of cisplatin primarily causes up-regulation in gene expression of the anorexigenic neuropeptides and down-regulation of the orexigenic neuropeptides in the hypothalamus (Fig. 4). These are convincing results because these neuropeptide changes induced by cisplatin administration cause anorexia. In other types of pathophysiological anorexia models such as lipopolysaccharide (LPS)-induced anorexia or cancer anorexia-cachexia models, primarily down-regulation of the *MCH* and *orexin* were also observed [50, 105], which is not observed in dehydration-induced anorexia. As well as dehydration-induced anorexia, the distinct underlying mechanisms between physiological and pathophysiological models in developing anorexia, including possible involvement of the peripheral humoral factors, should be revealed by further study.

Cancer anorexia-cachexia

Anorexia-cachexia syndrome is reported in the advanced stages of cancer [106]. This syndrome is a cause of patients' increased rate of morbidity and mortality [107]. Metabolic and behavioral abnormalities and psychological distress are observed in this syndrome, whereas it is difficult to describe a common factor which is responsible for cancer cachexia-anorexia syndrome because multiple factors may be involved in the etiology of this syndrome [108]. Although the understanding of cachexia has progressed over the last decade, the lack of consensus on a definition, diagnostic criteria and classification have impeded a meaningful advancement in both clinical trials and clinical practice. New definitions have proposed to integrate the concept of cachexia as a complex metabolic disorder, which is distinctly different to malnutrition [109].

Investigating hypothalamic feeding-regulating neuropeptides may be a good strategy in order to understand the underlying mechanism or central pathways which mediate feeding behavior, though multiple factors are involved in the cancer anorexia-cachexia. Previous studies have demonstrated that cytokines and hypothalamic neuropeptides are involved in cancer cachexia-anorexia syndrome [110–112], and that cachectic factors such as cytokines mimic the effects of leptin on the hypothalamus and induce anorexia in cachexia-anorexia syndrome [16].

Several studies focused on the orexigenic neuropeptides in the hypothalamus in the cancer anorexia-cachexia animal model. We demonstrated that the gene expressions of *NPY*, *AgRP*, *MCH* and *ORX* in the hypothalamus were significantly increased in rats implanted with 85As2 cells (human stomach cancer cell line) [15]. Nara-ashizawa et al. reported that the gene expression of *NPY* was significantly increased in mice bearing human tumor cells (SEKI melanoma cells); however, the gene expressions of *MCH* and *ORX* were comparable compared to control mice [105]. The up-regulation of the gene expression of *NPY* has also been reported in rats bearing glucagonoma (MSL-G-AN) [113], tumor-bearing (methylcholanthrene-induced sarcoma) rats [114] and MAC16 (chronic adenocarcinoma)-bearing mice [115], whereas Plata-Salaman et al. demonstrated that *NPY* mRNA expression was not different between pair-fed normal rats and prostate adenocarcinoma tumor cell-bearing rats [116]. Treatment with i.c.v. administration of NPY worsened anorexia in tumor-bearing rats, suggesting that cachexia did not result from a selective reduction in NPY release [117].

It is difficult to explain the cause of the up-regulation of the gene expression of *NPY* or other orexigenic neuropeptides in cachectic tumor-bearing animal models. One possible explanation is that, downstream of *NPY* mRNA, functions such as protein synthesis, transport, secretion and its receptors are distributed by humoral factors such as cytokines and tumor-derived factors [118].

Changes of anorexigenic neuropeptides in cancer anorexia-cachexia have also been reported. We demonstrated that the gene expressions of *CRH*, *POMC* and *CART* are significantly decreased in rats implanted with 85As2 cells (human stomach cancer cell line) [15]. In contrast, Nara-ashizawa et al. reported that *CRH* mRNA in the PVN was significantly up-regulated in cachectic tumor-bearing mice [105], and Jensen et al. reported that *CART*

mRNA in the hypothalamus was highly expressed in rats bearing glucagonoma [113]. However, Nakhate et al. indicated that a cancerous condition might down-regulate *CART* in the hypothalamus in rats with N-methyl-N-nitrosourea-induced mammary tumors [119].

Focusing on hypothalamic neuropeptide receptors, as opposed to the neuropeptides themselves, it has been demonstrated that MC4R expression in the PVN, which is one of the most important receptors that mediate feeding regulation, was significantly increased, resulting in decreased food intake and increased energy expenditure [120], while possible involvement of decreased ghrelin receptor signaling may be one of the causes of cancer anorexia-cachexia [121].

Because previous studies are discordant as mentioned above, it is difficult to decide the role of hypothalamic neuropeptides in appetite loss in cancer anorexia-cachexia animal models. Different models of tumor-bearing animals and different assays such as northern blot analysis, RNA protection assay and in situ hybridization histochemistry may be the reasons for the discrepancies. In addition, the studies have not examined all of the hypothalamic feeding-regulating neuropeptides at each stage of cachexia, and these cancer anorexia-cachexia animal models were not recovered by the therapeutic treatment, thus the hypothalamic neuropeptides changes cannot be readily compared.

The parathyroid hormone-related protein (PTHrP)-secreting tumor-bearing animal model, which is an ideal anorexia-cachexia animal model, has been proposed to resolve these issues. PTHrP is frequently produced and secreted in various types of cancer and is known to be a principal factor related to humoral hypercalcemia of malignancy [122, 123].

Peripheral administration of the antibody which neutralizes PTHrP exerted anti-hypercalcemic effects and improved anorexia-cachexia syndrome in PTHrP-secreting tumor-bearing animal models [124–126]. We demonstrated that, using a rat model, the gene expressions of the orexigenic neuropeptides in the hypothalamus were significantly increased, whereas those of anorexigenic neuropeptides were markedly decreased compared to non-tumor-bearing rats [127]. Bolus intravenous administration of anti-PTHrP neutralizing antibody reversed these changes in this study [127].

It is possible that hypercalcemia in plasma may inhibit appetite and feeding through the central nervous system (CNS), because severe hypercalcemia was observed in this model. However, a recent study has revealed that tumor-derived PTHrP triggers adipose tissue browning and cancer cachexia [128]. In addition, PTHrP and its receptor were widely expressed in the brain of the rat [129]. Taken together, PTHrP may act as a potent neurotransmitter or neuromodulator in the CNS.

Conclusion and perspectives

The etiology of diverse types of anorexia or appetite loss cannot be simply explained by the two-center theory in the hypothalamus as previously described. Thus, it may be useful to study from the perspective of respective feeding-regulating neuropeptides in the hypothalamus. It is hypothesized that dehydration-induced anorexia seems likely to be the result of up-regulation of the anorexigenic neuropeptides. In contrast, cisplatin-induced anorexia seems likely to be the result of the down-regulation of the orexigenic neuropeptides in addition to the up-regulation of the anorexigenic neuropeptides.

However, regardless of the up-regulation of the orexigenic neuropeptides induced by dehydration or cisplatin or cancer, these changes do not stimulate feeding. In the present review, because we have mentioned only restrictive models for anorexia, the complexity of the topic cannot be illustrated simply. Further studies should investigate not only homeostatic aspects of feeding but also hedonic aspects, to further understand the underlying mechanisms. Although human anorexia nervosa cannot be explained solely by the changes of the feeding-regulating neuropeptides in the hypothalamus, it may bring a unique strategy to the comprehension of the behavior and new therapeutics for its treatment.

Acknowledgments We thank A. Dickie (University of Glasgow) for language editing of the manuscript. This article was supported by a Grant-in-Aid for Scientific Research (B) (no. 25293055) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan; a Research Project for Improving Quality in Healthcare and Collecting Scientific Evidence on Integrative Medicine from the Ministry of Health Labour and Welfare, Japan; and by The Naito Foundation, Japan.

Conflict of interest All authors declare that there are no conflicts of interest, financial or otherwise.

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