The role of leptin and orexins in the dysfunction of hypothalamo-pituitary-gonadal regulation and in the mechanism of hyperactivity in patients with anorexia nervosa

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Abstract

Anorexia nervosa (AN) belongs to a group of eating disorders and is characterized by extreme body weight loss. AN patients show combination of physical, psychological and behavioral disturbances. Neuropeptides partly control energy homeostasis and modulate hormone release. Leptin, a peptide secreted by adipocytes, may influence the interactions between central and peripheral signals. Hypoleptinaemia found in AN is connected with disturbed control of appetite and hormonal dysfunction as well as has implications for the hypothalamo-pituitary-gonadal axis, bone mineral density and physical hyperactivity. Low leptin levels are increased with refeeding. However, the prolonged hypoleptinaemia in weight recovered AN patients may result in persistent hypothalamic amenorrhoea. The hyperactivity has been observed in 31–80 % of AN cases. The mechanisms underlying the hyperactivity found in patients with anorexia nervosa seem to be more complicated as many factors including neuropeptides may be involved. Orexins may affect not only appetite but also behavior and psychophysical activity as they may regulate reproductive and stress hormone secretion, stimulate a variety of stereotypic behaviors including eating and stress reaction, and affect the hypothalamo-pituitary-adrenal (HPA) axis, alter glucocorticoid and catecholamine secretion and activate the sympathetic nervous system. Orexins influence the mechanism regulating arousal and sleep, cardiovascular function, temperature, metabolic rate and locomotive activity. It is worth considering how abnormal activity of hypothalamic neuropeptides or their receptors may play a role in the mechanisms of hyperactivity, disturbed control of appetite and hormonal dysfunction in patients with anorexia nervosa.

MINI REVIEW

Neuropeptides are reported to play a role in the control of energy homeostasis and in the mechanism of hormone release [1, 2, 3, 4, 5]. Many peptides such as β-endorphin (β-E), neuropeptide Y (NPY) and galanin are important orexigenic factors and they can regulate appetite by influence on hypothalamic appetite centers, thermogenesis and catecholamine activity [6, 7]. Moreover, orexins, CRH (corticotrophin releasing hormone), CART (cocaine- and amphetamine-regulated transcript), MCH (melanin concentrating hormone), serotonin and cytokines (interleukins – IL-1, IL-6, tumor necrosis factor – TNF) are also involved in the modulation of activity of orexigenic peptides [8, 9, 10, 11, 12].

Leptin, a peptide secreted by adipocytes, may influence the interactions between central and peripheral signals [13]. Furthermore, leptin is able to penetrate through the blood brain barrier and to decrease expression of NPY mRNA through hypothalamic receptors [14, 15].

We published previously that leptin and NPY plasma concentrations are significantly higher in the group of obese patients and they are significantly lower in patients with anorexia nervosa (AN) [7]. Thus, we indicated that neuroendocrine disturbances in obesity and anorexia nervosa are opposite. Moreover, the feedback mechanism between leptin and NPY is disturbed in both pathologies: obesity and anorexia nervosa [16, 17]. Additionally, we observed in animal model disruptive release of neuropeptides and hormones during starvation. We found low plasma levels of leptin, and NPY, a decrease in estradiol and progesterone release as well as impaired hormonal response to leptin and NPY in starved rats [18]. These findings confirm the thesis that neuropeptides respond to the altered metabolic signals [19].

Interestingly, it has been also reported that dysfunction in reproductive functions occurs under conditions of food restriction and/or increased energy expenditure [4, 5, 20]. On the other hand, leptin not only may modulate the activity of peptides controlling feeding behavior but also the normal leptin secretion is necessary for reproductive functions [21]. It has been published that leptin injected into ob/ob mice, which are genetically deficient to leptin, not only produced body weight reduction but also restored fertility [22]. Moreover, in vitro experiments showed that leptin stimulates release of GnRH (gonadotrophin-releasing hormone) in medial basal hypothalamus (MBH) and gonadotrophin secretion from the pituitary [23]. Additionally, administration of leptin enhances LH release and causes an increase in ovaries weight [24].

The secretion of leptin is related to changes in time of food intake. After 22 h of fasting leptin production in lean and obese patients is decreased; however, the decline observed in obese subjects is smaller as compared with lean patients [25].

It has been indicated that hypoleptinaemia in patients with anorexia nervosa may play a pivotal role in the disturbed control of appetite and hormonal dysfunction [5, 7, 16, 17]. Eckert et al. showed that low leptin levels in patients with anorexia nervosa are increased with refeeding [26]. However, the study conducted by Djurovic et al. contributed to the clinically important conclusion that the prolonged hypoleptinaemia in weight recovered AN patients may result in persistent hypothalamic amenorrhoea. [27]. The therapeutic implications of the above findings have been demonstrated by Welt et al. [28] as the therapy with recombinant human leptin in women with hypothalamic amenorrhoea resulted in improvement of reproductive and neuroendocrine functions. Moreover, Hebebrand et al. [29] indicated that hypoleptinaemia in anorexia nervosa may have implications for the hypothalamo-pituitary-gonadal axis, bone mineral density and physical hyperactivity.

The hyperactivity has been observed in 31–80 % of AN cases. Furthermore, not only higher levels of physical activity but also increased nervousness and anxiety are reported in AN patients as well as in semi-starved rats [30]. In addition, the excessive motor activity seen in humans with anorexia nervosa may be connected with hypoleptinaemia [30]. Semi-starvation-induced hyperactivity (SIH) was observed in the animal model of AN, and link with low circulating leptin levels was confirmed in the study with subcutaneous implantation of minipumps releasing leptin [31]. This finding suggests that leptin administration might reduce hyperactivity in acute AN [32]. However, the mechanisms underlying the hyperactivity found in patients with anorexia nervosa seem to be more complicated as many factors including neuropeptides may be involved.

It has been described before that failure of adaptive feeding response that is initiated by a reduction in leptin levels, which leads to changes in orexigenic and anorexigenic signals, is characteristic for anorexia nervosa [33]. Moreover, it has been established that leptin acts via specific receptors in the hypothalamus, the effects of which are mediated by many orexigenic peptides such as neuroepeptide Y, as well as anorexigenic peptides like corticotrophin-releasing factor [9, 34]. NPY is known to be widely expressed throughout the brain. The interconnection of NPY with neuroepeptides such as galanin, opioid peptides, MCH, orexin and Agouti-related protein (AGRP) is well known [9, 34, 35]. Furthermore, the disturbances of orexigenic and anorexigenic signals in the brain and periphery occur in patients with anorexia nervosa [34].

Some peptides, orexins among them, may affect not only appetite but also behavior and psychophysical activity. Orexins/hypocretins are recently discovered neuropeptides synthesized by neurons located in the posterolateral hypothalamus. Orexin A/hypocretin 1 is 33 an amino acids peptide and orexin B/hypocretin 2 is a linear peptide of 28 amino acids [36]. Orexin A but not orexin B is able to cross the blood-brain barrier [37]. The physiological role of orexins includes the

control of food intake and energy expenditure, regulation of hormones release, and, in addition, orexins might be responsible for the pathogenesis of narcolepsy [38]. Furthermore, orexin A has a more potent and prolonged effect on appetite as compared with orexin B [39].

Our previous studies demonstrated a decrease in plasma orexin A levels in obese patients [40]. We showed that orexin A levels correlate negatively with leptin plasma concentrations. These results are in agreement with the studies of Adam et al. [41]. Nevertheless, Komaki et al. observed that plasma orexin A concentration is increased during fasting and returnes to the basal values after refeeding [42]. It has also been reported that during starvation orexin neurons are disinhibited by low levels of leptin and glucose, and they are excited by ghrelin [43]. Peripheral metabolic signals including glucose, leptin, cholecystokinin and ghrelin may as well activate orexin neurons via vagal afferents and partly via the nucleus of the solitary tract (NTS) [44, 45]. Orexin neurons are reported to be an important factor in the maintenance of interaction between peripheral energy balance and the central mechanisms coordinating sleep/wakefulness and motivated behavior [46]. In addition to its behavioral and metabolic effects, orexin signaling may play a key role in learning, memory and reward-seeking [47, 48, 49, 50, 51]. Moreover, orexins may regulate reproductive and stress hormone secretion, stimulate a variety of stereotypic behaviors including eating and stress reaction, and might also affect the hypothalamo-pituitary-adrenal (HPA) axis, alter glucocorticoid and catecholamine secretion and activate the sympathetic nervous system [52].

Orexin fibers innervate hypothalamic regions important for regulation of pituitary hormones release. The studies of Kok et al [53] showed that orexins are involved in the regulation of hypothalamo- pituitary-gonadal axis in humans. The reduction of basal LH levels and normal response of LH to GnRH stimulation in narcoleptic men strongly suggest that orexins may modulate the GnRH secretion [53]. The animal model has shown that orexins may also contribute to LH and PRL surges in the proestrus in rats [54]. Moreover, orexins administered centrally activates hypothalamo-pituitary-adrenal axis [55]. In addition, orexins play an inhibitory role in GH secretion and may be involved in regulatory mechanism of nutritional status [56].

Apart from appetite control and pituitary secretion, orexins influence the regulation of arousal and sleep, cardiovascular function, temperature, metabolic rate and locomotive activity [57, 58, 59]. Kiwaki et al. [60] demonstrated that injection of orexin A into the hypothalamic paraventricular nucleus (PVN) of rats increases their SPA (spontaneous physical activity). These authors suggested that orexin A may be a mediator of NEAT (non-exercise activity thermogenesis).

Presenting the wide-range of effects of leptin and orexins that are outlined above, it is worth considering whether some abnormal activity of hypothalamic neuropeptides or their receptors may play a role in the mechanisms of hyperactivity, disturbed control of appetite and hormonal dysfunction in patients with anorexia nervosa.

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