Appetite 108 (2017) 141–150

Contents lists available at ScienceDirect

Appetite

journal homepage: www.elsevier.com/locate/appet

Plasma kisspeptin and ghrelin levels are independently correlated with physical activity in patients with anorexia nervosa

Tobias Hofmann [a, *], Ulf Elbelt [a, b], Verena Haas [c], Anne Ahnis [a], Burghard F. Klapp [a], Matthias Rose [a], Andreas Stengel [a]

[a] Center for Internal Medicine and Dermatology, Department of Psychosomatic Medicine, Charité – Universitätsmedizin Berlin, Berlin, Germany
[b] Center for Internal Medicine with Gastroenterology and Nephrology, Division for Endocrinology, Diabetes and Nutrition, Charité – Universitätsmedizin Berlin, Berlin, Germany
[c] Department of Child and Adolescent Psychiatry, Charité – Universitätsmedizin Berlin, Berlin, Germany

ARTICLE INFO

Article history:
Received 16 June 2016
Received in revised form
1 September 2016
Accepted 27 September 2016
Available online 28 September 2016

Keywords:
Accelerometry
Eating disorder
Endocrine
Exercise
Psychosomatic
SenseWear™ armband

ABSTRACT

While physical hyperactivity represents a frequent symptom of anorexia nervosa and may have a deleterious impact on the course of the disease, the underlying mechanisms are poorly understood. Since several food intake-regulatory hormones affect physical activity, the aim of the study was to investigate the association of physical activity with novel candidate hormones (kisspeptin, ghrelin, oxyntomodulin, orexin-A, FGF-21, R-spondin-1) possibly involved in patients with anorexia nervosa. Associations with psychometric parameters and body composition were also assessed. We included 38 female anorexia nervosa inpatients (body mass index, BMI, mean ± SD: 14.8 ± 1.7 kg/m^2). Physical activity was evaluated using portable armband devices, body composition by bioelectrical impedance analysis. Blood withdrawal (hormones measured by ELISA) and psychometric assessment of depressiveness (PHQ-9), anxiety (GAD-7), perceived stress (PSQ-20) and disordered eating (EDI-2) were performed at the same time. Patients displayed a broad spectrum of physical activity (2479–26,047 steps/day) which showed a negative correlation with kisspeptin ($r = -0.41$, $p = 0.01$) and a positive association with ghrelin ($r = 0.42$, $p = 0.01$). The negative correlation with oxyntomodulin ($r = -0.37$, $p = 0.03$) was lost after consideration of potential confounders by regression analysis. No correlations were observed between physical activity and orexin-A, FGF-21 and R-spondin-1 ($p > 0.05$). Kisspeptin was positively correlated with BMI and body fat mass and negatively associated with the interpersonal distrust subscale of the EDI-2 ($p < 0.01$). Depressiveness, anxiety, and perceived stress did not correlate with kisspeptin or any other of the investigated hormones ($p > 0.05$). In conclusion, kisspeptin is inversely and ghrelin positively associated with physical activity as measured by daily step counts in anorexia nervosa patients suggesting an implication of these peptide hormones in the regulation of physical activity in anorexia nervosa.

1. Introduction

Anorexia nervosa is a serious psychosomatic disease associated with increased chronification and mortality (Steinhausen, 2002). Besides dietary restriction and other weight loss behaviors like self-induced vomiting or intake of thyroid hormones and/or laxatives (Zipfel, Giel, Bulik, Hay, & Schmidt, 2015), affected patients display more pronounced physical activity than healthy controls (El Ghoch et al., 2013). In absence of a common definition of physical hyperactivity in terms of quantity and quality, its measurement has been performed by different methods like activity diaries, interviews, rating scales and direct measurement with

Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; EDI, eating disorder inventory; EDI-2, eating disorder inventory, 2nd version; FGF-21, fibroblast growth factor 21; GAD-7, generalized anxiety disorder questionnaire, 7-item anxiety subscale of the patient health questionnaire; ICD-10, International Statistical Classification of Diseases and Related Health Problems of the World Health Organization, 10th revision; KISS1, KISS1 metastasis suppressor gene; KISS1R, kisspeptin receptor; LGR4, leucine-rich repeat-containing G protein-coupled receptor 4; MET, metabolic equivalent of a task; PHQ, patient health questionnaire; PHQ-9, patient health questionnaire, 9-item depression subscale; PSQ-20, perceived stress questionnaire, 20-item version; SD, standard deviation.

* Corresponding author. Center for Internal Medicine and Dermatology, Department of Psychosomatic Medicine, Charité – Universitätsmedizin Berlin, Hindenburgdamm 30, 12203 Berlin, Germany.
E-mail address: tobias.hofmann@charite.de (T. Hofmann).

http://dx.doi.org/10.1016/j.appet.2016.09.032
0195-6663/

accelerometers (Hebebrand et al., 2003). High-level physical activity has been reported to occur in 30% up to 80% of anorexia nervosa patients (Dalle Grave, Calugi, & Marchesini, 2008). In addition, higher levels of physical activity are associated with increased treatment dropout (El Ghoch et al., 2013) and may be a predictor of relapse after recovery (Carter, Blackmore, Sutandar-Pinnock, & Woodside, 2004). There is evidence from animal studies that neurobiological mechanisms underlying increased physical activity are leading to an uncontrollable activity pattern as a consequence of the starved organism (Scheurink, Boersma, Nergardh, & Södersten, 2010) and several food intake-regulating hormones were reported to be implicated in the regulation of physical activity in humans (Hazell, Islam, Townsend, Schmale, & Copeland, 2016). In line with this neurobiological hypothesis, high levels of urinary cortisol (Klein, Mayer, Schebendach, & Walsh, 2007) and low levels of circulating leptin (Holtkamp et al., 2006) have been associated with increased physical activity in patients with anorexia nervosa. However, one has to note that the mechanisms underlying high-level physical activity in anorexia nervosa are far from being well-understood and several other endocrine factors might play a role in this complex network of the psychobiological regulation of starvation-associated physical activity in anorexia nervosa. Therefore, in the present study we investigated several novel neuropeptide candidates potentially involved in the regulation of physical activity in anorexia nervosa, which we briefly introduce below.

Kisspeptin is a neuropeptide initially described to play a role in human melanoma metastasis suppression (Lee & Welch, 1997). Subsequently, it has been shown in humans and other mammals to have an important function in reproduction and the onset of puberty through stimulation of gonadotropin-releasing hormone in the hypothalamus. This cerebral stimulation was shown to occur following both peripheral and central application of kisspeptin (Thompson et al., 2004). In line with its widespread distribution reported in rodents (placenta, pituitary, adipose tissue, liver, pancreas, small intestine), further roles of kisspeptin in the regulation of food intake, glucose homeostasis as well as body weight and body composition have been established in different species (for review: Sanchez-Garrido & Tena-Sempere, 2013). Reduced kisspeptin signaling results in reduced locomotor activity in mice. These effects appear to occur sex-specifically in female mice (Tolson et al., 2014) (for review: Hussain, Song, & Wolfe, 2015). While kisspeptin has been discussed in the etiology of functional hypothalamic amenorrhea in exercising women and in anorexia nervosa patients (for review: Allaway, Southmayd, & De Souza, 2016), human data in anorexia nervosa and regarding physical activity are lacking so far.

Ghrelin is produced in gastric X/A-like cells and has been established as the – so far – only known peripherally produced and centrally acting stimulator of food intake in rodents and humans (for review on X/A-like cell see: Stengel & Taché, 2012). It is involved in the regulation of body weight as obese subjects display reduced and patients with anorexia nervosa consistently show increased circulating total ghrelin levels (for review on ghrelin see: Müller et al., 2015). In contrast to healthy subjects, ghrelin plasma levels of anorexia nervosa patients do not decrease postprandially. However, a decline was observed after successful treatment although levels do not completely normalize (for review on ghrelin in anorexia nervosa see: Atalayer, Gibson, Konopacka, & Geliebter, 2013). Whereas a positive association of ghrelin with locomotor activity has been shown in rats (Verhagen et al., 2011), its function in the regulation of physical activity in humans is not yet entirely clarified. While acute exercise was reported to decrease circulating acylated ghrelin levels (Tiryaki-Sonmez et al., 2013), the effects of different forms of repeated exercise on total ghrelin levels were inconsistent (Kadoglou et al., 2012; Mason et al., 2015; Rigamonti et al., 2010).

Oxyntomodulin is a derivative of glucagon with an additional eight amino acid carboxyterminal peptide. It is released from the gut and exerts its peripheral and central effects through the glucagon and glucagon-like peptide-1 receptors. Oxyntomodulin has been shown to reduce food intake and to increase energy expenditure and physical activity in humans (for review on oxyntomodulin see: Pocai, 2014). So far, data in anorexia nervosa patients are lacking.

The orexin system encompasses two neuropeptides, orexin-A and orexin-B. It is involved in a variety of physiological processes including sleep-wake cycle and emotional regulation, stress response and reward system. Orexin-A is also implicated in energy homeostasis and exerts orexigenic effects in rodents and induces thermogenesis. Moreover, orexin-A was reported to induce spontaneous physical activity in rodents (for review on orexin-A see: Sakurai, 2014). There is no clear picture regarding orexin-A plasma levels in anorexia nervosa patients compared to healthy controls with higher (Bronsky et al., 2011) or lower (Janas-Kozik et al., 2011) levels or no differences (Sauchelli et al., 2016) reported. Based on these data, it remains to be established whether orexin-A plays a role in the regulation of physical activity in humans, especially under conditions of anorexia nervosa.

Fibroblast growth factor 21 (FGF-21) is a member of the FGF family and primarily expressed in the liver. The peptide has been shown to exert beneficial effects in the regulation of glucose homeostasis, energy expenditure and thermogenesis in mice (for review: Giralt, Gavalda-Navarro, & Villarroya, 2015). While FGF-21 serum levels increase following physical activity in humans (Cuevas-Ramos et al., 2012), the regulation of FGF21 in anorexic patients has shown inconsistent results with a decrease (Dostalova et al., 2008), increase (Fazeli, Misra, Goldstein, Miller, & Klibanski, 2010) or no alterations of circulating levels (Fazeli et al., 2015).

R-spondin-1 is a member of the R-spondin protein family and exerts its effects through the leucine-rich repeat-containing G protein-coupled receptor 4 (LGR4). One main function of R-spondin-1 seems to be its implication in sexual development and differentiation as shown in mice (for review on R-spondin-1 see: de Lau, Snel & Clevers, 2012). R-spondin-1 has been implicated in the regulation of energy homeostasis as an anorexigenic factor and improved glucose tolerance and elevated energy expenditure have been observed in LGR4 knockout mice (for review on LGR4 see: Li, Zhang, & Mulholland, 2015). However, so far no data in anorexia nervosa patients are available.

The ability of the peripherally circulating hormones to act in the brain has been shown for ghrelin (Banks, Tschöp, Robinson, & Heiman, 2002), FGF-21 (Hsuchou, Pan, & Kastin, 2007), kisspeptin (Thompson et al., 2004), oxyntomodulin (Dakin et al., 2004) and orexin-A (Kastin & Akerstrom, 1999), and is likely for R-spondin-1 because of its peripheral and central actions, although for this peptide data are lacking so far.

In light of these data, we exploratorily examined the relationship of the hormones described above and potentially involved in the regulation of physical activity. Parameters of physical activity were assessed in patients with anorexia nervosa displaying a broad spectrum of physical activity. Thereby, we mainly focused on the quantitative measurement of physical activity as reflected by the mean number of steps per day. In addition, we investigated possible associations of the investigated hormones with parameters of body composition along with psychological parameters frequently affected in anorexia nervosa patients including disordered eating, depressiveness, anxiety and perceived stress.