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Review

Ghrelin in eating disorders

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ABSTRACT

Ghrelin is the only known circulating hormone that acts on peripheral and central targets to increase food intake and promote adiposity. The present review focuses on the possible clinical relevance of ghrelin in the regulation of human feeding behavior in individuals with obesity and other eating disorders such as Prader–Willi syndrome, anorexia nervosa, bulimia nervosa and binge-eating.

Contents

1. Introduction

Ghrelin is a 28-amino-acid peptide hormone produced mainly by the X/A-like cells in the oxyntic mucosa of the stomach (Kojima et al., 1999) and epsilon cells of the pancreatic islets (Assmann et al., 2009). Ghrelin is synthesized as a precursor, the preproghrelin, which consequently can produce acyl ghrelin and des-acyl ghrelin. Acylation of ghrelin requires a medium-chain fatty acid (MCFA) at its Ser3 residue in order to become a suitable ligand for the growth hormone secretagogue receptor-1a (GHS-R1a) (Kojima et al., 1999). The acylation is catalyzed by the enzyme ghrelin O-acyl transferase (GOAT) (Gutierrez et al., 2008; Yang et al., 2008).

Ghrelin is an endogenous regulator of energy homeostasis. Central or peripheral administration of ghrelin have been found to promote feeding and adiposity (Druce et al., 2005; Tschop et al., 2000). In the central nervous system, ghrelin activates hypothalamic neuropeptide Y and agouti related protein expressing neurons (Kamegai et al., 2001) among other targets and actions. Circulating

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concentrations of total ghrelin increase after fasting and decrease by re-feeding or oral glucose administration (Cummings et al., 2001; Tschop et al., 2000). Obese individuals have decreased levels of total ghrelin (Tschop et al., 2001), while acyl ghrelin levels specifically may actually be higher in the circulation of obese individuals compared to lean control (Rodriguez et al., 2009). Together, these and a large body of other pre-clinical and clinical data provide compelling evidence for ghrelin as a relevant regulator of appetite, food intake and energy homeostasis. Therefore, much research has been focused on translational studies, investigating the physiology and pathophysiology of ghrelin in human eating disorders.

2. Ghrelin and obesity

In animal models, several studies have reported that either ghrelin or GHSR deficiency leads to a resistance to diet-induced obesity when animals are placed on a high fat diet at a young age (Wortley et al., 2005; Zigman et al., 2005). Obese adults were shown to have lower total plasma ghrelin levels compared to non-obese controls (Tschop et al., 2001). Additionally, obese children were found to have significantly decreased plasma ghrelin. When these children reduced their BMI by 50% ghrelin levels remain decreased compared to controls (Soriano-Guillen et al., 2004). The authors suggest that the decreased ghrelin levels could represent an adaptation to the continued negative energy balance. The same phenomenon was seen in obese adults who normalized their BMI (Cummings et al., 2002a; Hansen et al., 2002). Intriguingly, more recent studies appear to indicate that acyl ghrelin levels specifically may actually be higher in the circulation of obese individuals compared to lean controls (Rodriguez et al., 2009).

2.1. SNPs in the human ghrelin (GHRL) gene and obesity

Ukkola et al. (2001) sampled 96 obese subjects and found 6 to have an Arg51Gln polymorphism in the *GHRL* gene. This polymorphism was not found among 96 control subjects. However, another study found the Arg51Gln variant occurred at a similar frequency among obese and control subjects (Hinney et al., 2002). Hinney and colleagues screened the coding sequence of *GHRL* in 215 extremely obese German children and adolescents and 93 normal weight students. They identified a novel variant (Gln90Leu: rs4684677) in *GHRL*. The frequency of the Leu90 allele was significantly higher in children and adolescents with extreme obesity compared to normal-weight controls. Additionally, the same team of scientists genotyped 134 underweight students and 44 normal-weight adults for the Gln90Leu SNP. Genotype frequencies were similar in extremely obese children and adolescents, underweight students, and normal-weight adults. In a healthy normal-weight individual a 2 bp deletion at codon 34 of preproghrelin was observed resulting in a shift in the reading frame of the gene. At the protein level this will result in 36 aberrant amino acids and a stop codon at position 71. This variant affects the coding region of mature ghrelin; presumably, this individual is haplo insufficient for ghrelin. Korbonits et al. (2002) studied the ghrelin gene in a group of 70 tall and obese children. The GHRL polymorphism Leu72Met, was associated with children with a higher BMI. Miraglia del Giudice et al. (2004) screened the *GHRL* gene in 300 Italian obese children and adolescents and 200 controls. Allele frequencies of Arg51Gln and Leu72Met were similar in both groups. Leu72Met was associated with differences in age at the onset of obesity. Patients with the Met72 allele became obese earlier than patients homozygous for the wild type allele. Three SNPs in *GHRL* (Arg51Gln, Leu72Met and Gln90Leu) were studied in a group of 856 Amish subjects. There was no association of any of these SNPs with hunger scores, but Leu72Met appeared to be associated with the metabolic syndrome (Steinle et al., 2005). Association studies in 234 juvenile-onset obese and 323 lean men from Denmark did not show any association between variants in GHRL and juvenile-onset obesity (Larsen et al., 2005). At this point it therefore seems unlikely that any of the examined ghrelin gene variations would cause obesity due to single-gene mutations alone. One the other hand, the Leu72Met polymorphism of the ghrelin gene seems to play a role in predicting the onset of obesity among children, which does suggest that ghrelin may be involved in the pathophysiology of human adiposity to some extent.

2.2. SNPs in the human GHSR gene and obesity

The GHSR gene was screened for 2 variants in extremely obese children and adults. The 171T allele (rs495225) was found to be more frequent in obese cases, although this observation could not be confirmed in a more extensive association study and in a transmission disequilibrium test (Wang et al., 2004). A further screen for new variants in *GHSR* in 93 obese, 96 normal weight, and 94 underweight individuals led to several variants; all of which, however, showed similar frequencies in all the weight groups (Wang et al., 2004).

In a family-based linkage disequilibrium study in 178 pedigrees as well as in an independent case-control study from the general population, Baessler et al. (2005) systematically explored the linkage disequilibrium and haplotype structure of the genomic region encompassing the *GHSR* gene. The authors reported evidence for linkage and association of five SNPs and the two most common five-marker haplotypes with obesity in their family cohort. In addition, they described the association of the same SNPs and haplotypes with obesity and BMI in the general population. This was the first report indicating that the *GHSR* gene region is associated with obesity (Baessler et al., 2005). Several SNPs in *GHRL* and *GHSR* were studied in a group of 1275 obese subjects and 1059 controls (Gueorguiev et al., 2009). Although some associations were identified, none of these associations remained significant when corrected for multiple comparisons. In addition, replication of the nominal associations with obesity could not be confirmed in a German genome-wide association (Gueorguiev et al., 2009). These data suggest that common polymorphisms in *GHRL* and *GHRS* are unlikely to represent major contributors to the typical pathogenesis of obesity.

3. Ghrelin and Prader–Willi syndrome

Prader–Willi syndrome (PWS) is an autosomal dominant disorder with a birth prevalence of 1 per 10,000–25,000. PWS was described for the first time in 1956 and is characterized by diminished fetal activity, muscular hypotonia, mental retardation, short stature, small hands and feet, hypogonadotropic hypogonadism, and obesity (Prader et al., 1956).

3.1. Genetic defect in Prader–Willi syndrome

PWS is an imprinting disorder: in about 70% of all cases it is caused by a 15q11–q13 paternal deletion. Alternatively, PWS may be caused by maternal uniparental disomy (UPD) of 15q or an imprinting defect. Previous studies suggested that expression of SNRP (small nucleoriboprotein N) was critical for prevention of PWS (Kuslich et al., 1999; Wevrick and Francke, 1996). However, a more recent study identified patients with small atypical deletions in the PWS critical region. The smallest deletions currently known are about 175 kb and encompass only a particular family of non-coding RNAs, the small nucleolar RNAs (snoRNAs). The region on chromosome 15 contains different clusters of snoRNAs. The deletion in the PWS patient affects snoRNAs HBII-438A, -85