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REVIEW ARTICLE

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Prader-Willi syndrome: A model for understanding the ghrelin system

Maithé Tauber[1,2,3] | Muriel Coupaye[4] | Gwenaelle Diene[1,5] | Catherine Molinas[1,2,3] | Marion Valette[1,2] | Veronique Beauloye[6]

[1]Centre de Référence du Syndrome de Prader-Willi, Hôpital des Enfants, CHU Toulouse, Toulouse, France

[2]Axe Pédiatrique du CIC 9302/INSERM. Hôpital des Enfants, Toulouse, France

[3]INSERM U1043, Centre de Physiopathologie de Toulouse Purpan, Université Paul Sabatier, Toulouse, France

[4]Service de Nutrition, Centre de Référence du Syndrome de Prader-Willi Assistance-Publique Hôpitaux de Paris (AP-HP), CHU Pitié-Salpêtrière, Sorbonne Université, Paris, France

[5]INSERM, UMR 1027- Université Toulouse III Hôpital Paule de Viguier, Toulouse, France

[6]Unité d'Endocrinologie Pédiatrique, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

Correspondence
Maithé Tauber, Unité d'Endocrinologie, Hôpital des Enfants, 330, Avenue de Grande Bretagne, TSA 70034, 31059 Toulouse, Cedex 9, France.
Email: tauber.mt@chu-toulouse.fr

Abstract

Subsequent to the discovery of ghrelin as the endogenous ligand of growth hormone secretagogue receptor 1a, this unique gut peptide has been found to exert numerous physiological effects, such as appetite stimulation and lipid accumulation via the central regulating mechanisms in the hypothalamus, stimulation of gastric motility, regulation of glucose metabolism and brown fat thermogenesis, and modulation of stress, anxiety, taste sensation, reward-seeking behaviour and the sleep/wake cycle. Prader-Willi syndrome (PWS) has been described as a unique pathological state characterised by severe obesity and high circulating levels of ghrelin. It was hypothesised that hyperghrelinaemia would explain at least a part of the feeding behaviour and body composition of PWS patients, who are characterised by hyperphagia, an obsession with food and food-seeking, and increased adiposity. Initially, the link between hyperghrelinaemia and growth hormone deficiency, which is observed in 90% of the children with PWS, was not fully understood. Over the years, however, the increasing knowledge on ghrelin, PWS features and the natural history of the disease has led to a more comprehensive description of the abnormal ghrelin system and its role in the pathophysiology of this rare and complex neurodevelopmental genetic disease. In the present study, we (a) present the current view of PWS; (b) explain its natural history, including recent data on the ghrelin system in PWS patients; and (c) discuss the therapeutic approach of modulating the ghrelin system in these patients and the first promising results.

KEYWORDS

feeding behaviour, ghrelin, hyperphagia, Prader-Willi syndrome

1 | BACKGROUND ON THE GHRELIN SYSTEM

1.1 | Ghrelin synthesis

Ghrelin is a 28-amino acid peptide that is primarily produced and secreted by X/A-like cells in the oxyntic glands of the gastric mucosa, especially in the gastric fundus.[1] The ghrelin gene encodes the 117-amino acid precursor peptide preproghrelin, which in turn is cleaved by the endopeptidase proconvertase 1 (PC1) to produce the mature 28-amino acid ghrelin peptide.

1.2 | Acylated ghrelin (AG)

Prior to secretion, des-acyl ghrelin (DG) is acylated by the transmembrane enzyme ghrelin-*O*-acyltransferase (GOAT).[5,6] This acylated form of ghrelin results from the attachment of a fatty acid

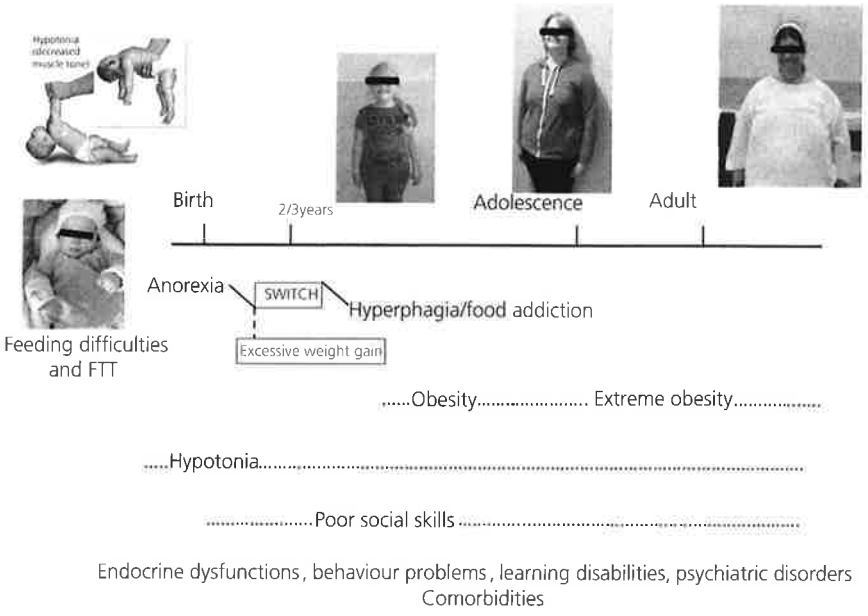

FIGURE 1 Natural history of Prader-Willi syndrome. FTT, failure to thrive

2 | PRADER-WILLI SYNDROME (PWS) AS A MODEL OF HYPERPHAGIA

PWS is today considered a complex disorder primarily characterised by impaired hypothalamus development. Indeed, a defect in the hypothalamus explains most of the phenotype first described in 1956 by Prader et al[28] and the natural history of the disease. PWS is the first known example of a human disorder involving genomic imprinting, which was first documented in 1989 and can explain the genotype subtypes observed in patients. The incidence at birth is about 1 in 20 000.[29,30] Today, approximately 50% of the newborns diagnosed with PWS in the first month of life present a deletion of the chromosome 15q11-q13 region inherited from the father and almost 50% have a maternal disomy of this region.[31,32] Very few infants have an imprinting deficit or chromosomal translocations. The rise in the prevalence of maternal uniparental disomy over the last two decades is associated with the increasing age of mothers.[33]

The phenotype illustrated in Figure 1 includes neonatal hypotonia, poor oral skills and social abilities, a decreased appetite that mimics anorexia, facial dysmorphia with acromicria, and, subsequently, in the absence of proper care and management, early excessive weight gain with hyperphagia and impaired satiety, which induce severe obesity, multiple endocrine dysfunction (see below), learning disabilities and behavioural problems with psychiatric phenotypes.[34,35] Even though most patients cannot be diagnosed as having autism spectrum disorder (ASD), many of them display features of ASD. Indeed, PWS is now considered a chromosomal disorder with ASD in the DSM-5 classification of mental diseases.[36]

Given the severity of the hypotonia displayed by neonates and the increased knowledge of this disease, diagnosis is now made during the first months of life. A recent French survey documented the age at diagnosis as 18 days of life.[30]

TABLE 1 Comorbidities in patients with Prader-Willi syndrome: a complex disease that requires comprehensive evaluation and care, and for which ghrelin dysfunction may be related to most of the comorbidities

Apneas, sleeping disorders 100% ± narcolepsia
Excessive daily sleepiness
Catatonia and epilepsy
Scoliosis 80%
Skin picking
Dysautonomia
Gastrointestinal problems
Ophthalmology and dental issues
Speech and language problems
Oral skills and communication issues
Cognitive deficit, learning deficits
Behaviour and psychiatric troubles

This complex disease has severe consequences and raises difficult management issues for patients, families and caregivers. High rates and varied causes of morbidity (Table 1) and mortality have been reported, mainly as a result of respiratory problems in infancy and childhood and obesity complications later on.[37-39]

2.1 | Endocrine dysfunction

The hypothalamic-pituitary dysfunctions include growth hormone deficiency (GHD), which explains the short stature and abnormal body composition, central hypothyroidism, and hypogonadism (Table 1), with rare situations of corticotrophin deficiency. Hypogonadism is now documented along a continuum, from pure central hypogonadism to pure peripheral hypogonadism in both

TABLE 2 Summary of studies published on circulating ghrelin levels in PWS and controls

	Reference (Year), Country	Population	Total ghrelin or [AG], [UAG] levels (pg/mL)
1	Cummings et al.[4] (2002), France, USA	n = 48 adults 18 PWS 16 controls 14 obese	Total ghrelin (Mean) 1542 in PWS 608 in lean controls 344 in obese controls
2	Delparigi et al.[52] (2002), USA	n = 37 adults Seven PWS 30 controls	Total ghrelin (Mean) 307 in PWS 109 in lean controls
3	Haqq et al.[53] 2003, USA	N = 50 children 13 PWS 20 lean controls 17 obese controls	Total ghrelin (Mean) 429 in PWS 270 in lean controls 146 in obese controls
4	Goldstone et al.[60] 2004, UK	N = 51 adults 6 PWS male 12 PWS male 26 lean controls female 13 obese female	Total ghrelin (Mean) 564 in PWS male 661 in PWS female 363 in lean controls 191 in obese
5	Tauber et al.[54] 2004, France	N = 162 children 32 PWS 32 lean controls 72 obese controls 32 iGHD Six Pituitary stalk interruption (PSI)	Total ghrelin (Mean) 995 in PWS 605 in lean controls 396 in obese controls 517 in GHD children 1029 in PSI children
6	Butler et al.[61] 2004, USA	N = 12 children with PWS	Total ghrelin (Mean) 1152 in PWS
7	Choe et al.[62] 2005, Korea	N = 22 children 11 PWS 11 sex-age-BMI-matched controls	Total ghrelin (Median) 19 600 in PWS 6928 in sex-age-BMI-matched controls
8	Goldstone et al.[63] 2005, UK	N = 72 adults 26 PWS 15 lean controls 16 obese controls Six craniopharyngioma without obesity Nine craniopharyngioma with obesity	Total ghrelin (Mean) 3431 in PWS 2744 in lean controls 1571 in obese controls 2366 in craniopharyngioma without obesity 1601 in craniopharyngioma with obesity
9	Paik et al.[52] 2006, Korea	N = 21 children 11 PWS 10 obese controls	AG, UAG (Median) [120], [290] in PWS [44], [180] in obese controls
10	Butler et al.[64] 2007, USA	N = 32 children and adults 16 PWS 16 lean controls	Total ghrelin (Mean) 626 in PWS 521 in lean controls
11	Haqq et al.[65] 2007, USA	N = 28 children 14 PWS 14 BMI-matched controls	Total ghrelin (Median) 435 pmol/L in PWS 249 pmol/L in BMI-matched controls
12	Feigerlova et al.[56] 2008, France	N = 124 children 40 PWS 84 lean controls	Total ghrelin (Median) 568 in PWS 173 in lean controls
13	Haqq et al.[53] 2008, USA	N = 89 children 33 PWS ≤3 y 28 controls ≤3 y 11 PWS >3 y 11 BMI-matched controls >3 years	Total ghrelin (Median) 2217 in PWS ≤3 y 1964 in controls ≤3 y 1468 in PWS >3 y 840 in BMI-matched controls >3 years

(Continues)

total ghrelin is elevated at this age. Interestingly, the total hyperghrelinaemia at this age was a result of the increased UAG, as opposed to the findings in the older population. This indicates that infants and young children have a relative excess of UAG, in contrast to that found later in life when patients with PWS display obesity and hyperphagia. We concluded that the high UAG may explain why infants with PWS have a poor appetite that is comparable to anorexia. We therefore propose that the poor feeding skills of neonates with PWS are related to the low AG/UAG ratio, which may drive anorexia and poor sucking and swallowing skills.[32] Of interest, the elevated total ghrelin levels with normal AG levels were also found in *Magel2* knockout (KO) mice at P8,[77] which supports our findings. Interestingly, *Magel2* mutations reproduce in mice, as in men, the post-natal phase observed in PWS with the same findings in circulating ghrelin. *Magel2* mutations in humans cause Schaaf-Yang syndrome, a PWS-like syndrome characterised by an early feeding deficit and hypotonia, in association with severe autistic features and hormonal deficits without obesity.[78-80]

3.3 | Ontogenesis of the impaired ghrelin system in PWS

In a study by Beauloye et al,[59] we documented a developmental switch between AG and UAG from infancy to early childhood (Figure 4). The ghrelin system shows an impaired development in PWS patients, starting with excessive UAG, which then decreases, followed by an excessive increase in AG and a relative deficit in UAG. We hypothesised in line with the work cited[74] that this impaired switch in the ghrelin system would explain the early excessive weight gain and subsequent obesity with hyperphagia observed in PWS. This switch occurs concomitantly with hypothalamic ontogenesis and the implementation of the circadian rhythm, and may explain the impaired energy balanced documented in PWS.

3.4 | Pathophysiology of the impaired ghrelin system in PWS

The remarkable findings in neurones reprogrammed from the induced pluripotent stem cells of patients with PWS and our very rare patient carrying a small deletion of the *Snord116* gene cluster, although incompletely understood and not consistently reproduced, nevertheless suggest a pathophysiological mechanism that would at least partly explain the hypothalamic dysfunction.

Indeed, these reprogrammed neurones exhibited low levels of the hypothalamic transcription factor NHLH2 that regulates the gene for PSK1, which then in turn encodes for the proconvertase PC1 enzyme.[81] This endopeptidase drives the maturation of several hypothalamic and non-hypothalamic peptides, including ghrelin. Indeed, *Ghrl* transcript was increased in the stomachs of the *Snord116* KO mice with an elevated ratio of proghrelin to mature ghrelin protein in stomach lysates. This processing defect in *Snord116* KO mice appears to be less severe than that of *Pc1*-null mice, consistent with the approximate 50% decrease in PC1 protein in their stomachs. Therefore, this study demonstrated that numerous peptides (pro-opiomelanocortin hormone/melanocyte-stimulating hormone, oxytocin, ghrelin, brain-derived neurotrophic factor, insulin, gonadotrophin-releasing hormone and GH-releasing hormone) affecting eating, endocrine function and behaviour that are abnormal in PWS may be ineffectually processed as a result of the relative PC1 deficiency.

According to Zhu et al,[82] proghrelin is acylated because post-translation acylation occurs independently of proteolytic processing, meaning that the octanoylation of ghrelin does not require prior processing of the peptide. Pro-ghrelin is octanoylated before it is transported to the Golgi apparatus,[6] where it is cleaved by PC1/3 to form mature ghrelin. Of note, the antibodies used in conventional ghrelin assays detect both mature and unprocessed acyl and unacyl-ghrelin. Thus, the reported hyperghrelinaemia in patients with PWS, as well as in the *Snord116* KO mice, likely reflects elevated circulating proghrelin, consistent with the results in the *Snord116* KO mice stomach lysates.

Moreover, we do not know how and why excessive ghrelin acylation occurs thereafter. Interestingly, it has been shown in mice that the loss of *Magel2* impairs the development of hypothalamic anorexigenic circuits, with these mice also displaying high ghrelin levels as pups and adults. As noted above, *Magel2*-null mice displayed elevated levels of total ghrelin at P8, although the levels of the acylated form of ghrelin (the "active" form) were normal. In addition, the levels of both total and acylated ghrelin appeared to be similar in *Magel2*-null and wild-type mice at post-natal days 12 and 16. The total ghrelin levels were increased in the adult *Magel2*-null mice, whereas the AG levels appeared normal in the adult mutant mice. This mouse model recapitulates the first phase of PWS but not the subsequent nutritional phases.

Finally, the loss of the two imprinted genes, *Snord116* and *Magel2*, in the PWS chromosomal region drives the abnormal regulation of the ghrelin system, impairing both hypothalamus structure and function. In addition, impaired maturation/secretions of oxytocin has been shown in *Magel2*-null mice. Moreover, the cross-talk between

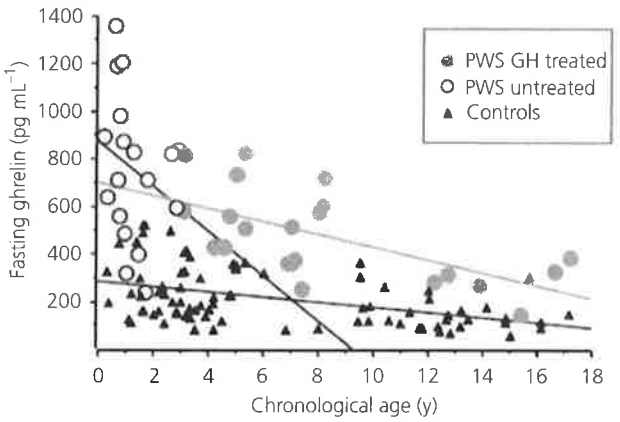

FIGURE 2 The values of total ghrelin levels are plotted against age in controls (filled triangles), untreated patients with Prader-Willi (PWS) (empty circles) and patients treated with growth hormone (GH) (filled circles) (from Feigerlova et al[42])

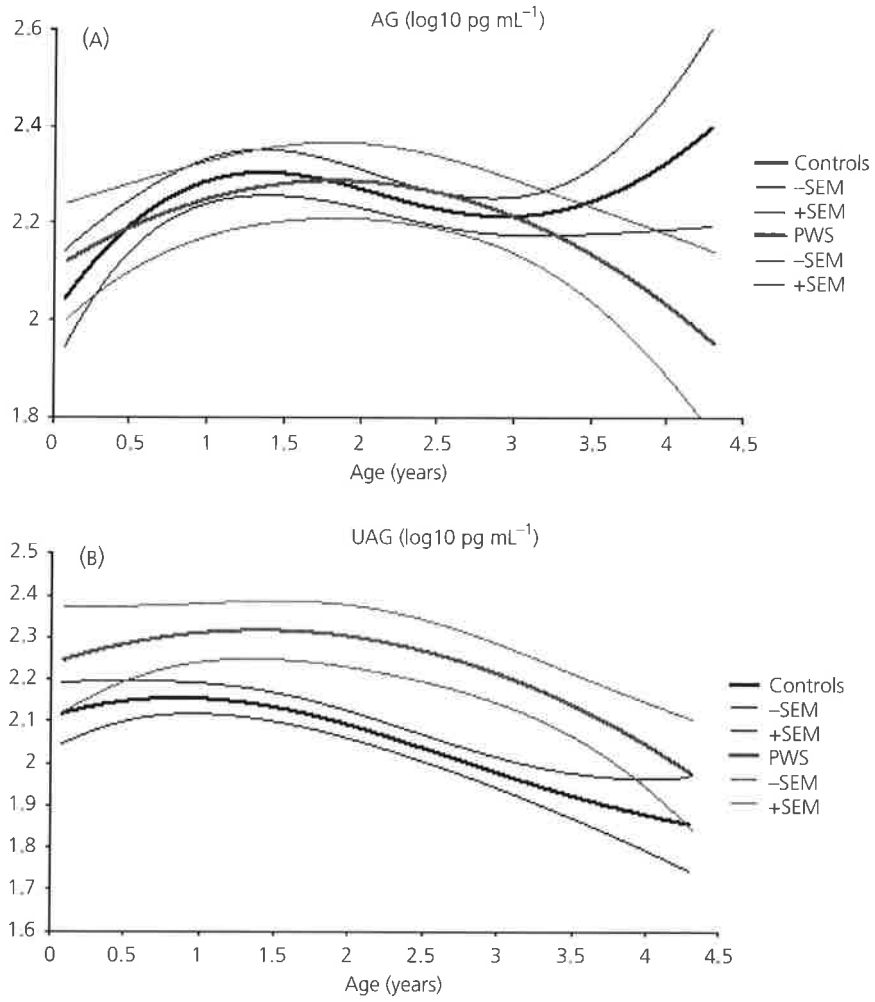

FIGURE 4 Nonlinear regression (mean ± SEM) of acylated ghrelin (AG) (A) and unacylated ghrelin (UAG) (B) levels according to age in both groups. Black line, controls; red line, Prader-Willi (PWS) infants. We used nonlinear regressions by B-splines to draw the curves. Because the curves are compatible with linear regressions, we did not use nonlinear regressions for the statistical analysis. From Beauloye et al[59]

deficit of UAG by using UAG or UAG analogs to counteract the AG effects and to induce specific UAG actions, especially in the brain; and (iv) restore the α-melanocyte-stimulating hormone signal and compensate the PC1 deficit.

Many pharmaceutical companies are working to develop treatments that target the ghrelin system. Because ghrelin is the only predicted substrate for GOAT, GOAT inhibitors mimicking ghrelin have the potential for high selectivity for GOAT, leading to reduced off-target effects. Various peptides with GOAT inhibiting activity were designed and the most recent study[85] proposed a comprehensive catalogue of the interactions responsible for ghrelin recognition and acylation by GOAT with respect to designing and optimising ghrelin-competitive GOAT inhibitors. Indeed, inhibiting GOAT activity will result in decreased AG and increased UAG.

Interestingly, *Goat* KO mice showed improvements in body fat mass, energy expenditure and blood glucose compared to the findings in control mice.[86] Therefore, GOAT inhibitors have potential as anti-obesity drugs, similar to GHS-R1a antagonists. Of note, a recent study reported reported the presence of GOAT and its ability to acylate UAG in the hippocampus, although GOAT was absent in the GHS-R1a KO mouse hippocampus, suggesting that the expression of GHS-R1a may be a pre-requisite for the production of GOAT.[87] Of note, it was reported a novel local mechanism for manipulating ghrelin activity by in situ extracellular acylation and subsequent binding to the GHS-R1a.

The increased knowledge on the regulation of ghrelin action via its receptor GHS-R1a offers new perspectives for the design of receptor antagonists. In addition, the very recent discovery of a peptide hormone, liver-expressed antimicrobial peptide 2 (LEAP2), as an endogenous antagonist of the ghrelin receptor revealed a previously unknown mechanism regulating ghrelin action that provide insights for the possibility of fine-tuning ghrelin regulation.[88] LEAP2 is a peptide with profound differentially regulated expression following bariatric surgery. The physiological role of LEAP2 has not been identified. Very recently, it was shown that both LEAP2 and its N-terminal region are able to inhibit ghrelin-induced food intake in mice. These data demonstrate an unexpected pharmacological activity of LEAP2 that is likely to have an important role in the control of ghrelin response under normal and pathological conditions. Moreover, the development of selective drugs to treat GHS-R1a-mediated disorders such as PWS might take into account the level of constitutive activity of the receptor and the multiple

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