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Editorial

Ghrelin: what do we know about its role in health and disease?

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Ghrelin is a 28 amino acid peptide predominantly produced by the stomach that has been discovered to be a natural ligand of the orphan growth hormone (GH) secretagogue (GHS) receptor (GHS-R) type 1a. Like synthetic GHS, ghrelin possesses a strong GH-releasing effect provided that the molecule is acylated in serine3 and it is thought to be a natural GHS of major importance in the control of somatotropic function[1,2].

Evidence that GHS-R are expressed in the hypothalamus-pituitary unit as well as in many other areas of the central nervous system and in peripheral endocrine and non-endocrine tissues pointed to other endocrine and non-endocrine actions. Indeed ghrelin is now recognized as a major new orexigenic factor. However, again, there is evidence indicating that it is more than simply a natural GHS and an orexigenic factor. In particular, the hypothesis that acylated ghrelin is the only active form, specifically acting by activation of GHS-R1a, already seems to have been overridden; the existence of GHS-R subtypes and results showing that non-acylated ghrelin is an active molecule are reasonably clear[3]. Therefore, the roles and perspectives for ghrelin in health and disease will be briefly considered.

CONTROL OF GHRELIN SECRETION

The stomach is the major, but not the only, source of circulating ghrelin, which is mostly represented by its unacylated form. Ghrelin secretion undergoes marked variations with peaks that anticipate food intake. Circulating ghrelin levels are negatively associated with body mass index (BMI) and are increased in anorexia and cachexia, but reduced in obesity. This profile is the opposite of that of leptin and both hormones have been suggested to act as signals of metabolic balance and to manage the neuroendocrine and metabolic response to starvation. A unique and unexplained exception to the negative association between BMI and ghrelin secretion is Prader-Willi syndrome, in which obesity is surprisingly associated with ghrelin hypersecretion[4].

Ghrelin secretion is increased by energy restriction and is decreased by feeding and glucose load. Indeed, ghrelin secretion is also under the inhibitory influence of insulin, somatostatin and acetylcholine in agreement with the assumption that its regulation is mostly under metabolic and entero-pancreatic control. Many other factors, however, probably contribute to the control of ghrelin synthesis and secretion. The notable exception is probably GH, providing evidence against the existence of a feedback link between these two hormones[3,5].

Ghrelin hyposecretory states (e.g. after gastrectomy or gastric bypass, obesity, hyperthyroidism) and hypersecretory states (anorexia, cachexia, malnutrition, diabetes mellitus type 1, Prader Willi syndrome) including ghrelinomas (mostly gastrointestinal carcinoids) have also been described; however, the clinical consequences, if any, of altered ghrelin secretion remain to be demonstrated[3-5].

GHRELIN AND PITUITARY FUNCTION

Ghrelin, as well as synthetic GHS, possesses a strong and dose-related GH-releasing effect that is synergistic with that of growth hormone-releasing hormone (GHRH). Indeed, ghrelin and GHS need the integrity of GHRH activity to fully express their GH-releasing effect. This evidence *per se* explains why GHS potently stimulates GH secretion in physiological conditions but even the best synthetic molecules were unable to replace recombinant human growth hormone (rhGH) in the treatment of GH deficiency, in which GHRH activity and/or somatotroph cells are, by definition, frequently impaired[3,5].

Moreover, although the GH response to ghrelin and GHS is partially refractory to factors that usually inhibit somatotroph secretion, including even somatostatin, the GH-releasing action of GHS undergoes homologous desensitization under prolonged exposure. Again, GHS had been thought to be a possible drug

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intervention to counteract somatopause in aging and GH insufficiency in obesity but their GH-releasing action is known to progressively decrease as a function of age and body mass index[3,6].

In view of all the evidence, it is now clear that ghrelin does not play a major role in the physiological control of somatotroph function and that GH hyper- and hyposecretory states reflecting ghrelin excess or deficiency are highly unlikely; nevertheless, ghrelin might play a role in adapting GH secretion to energy restriction or excess i.e. in anorexia/cachexia or obesity. The potent GH-releasing effect of ghrelin alone or in combination with GHRH probably represents a reliable provocation test for the diagnosis of GH deficiency although not for its treatment[3,5].

That GHS and ghrelin are not specific for GH was soon clear from evidence that they also significantly stimulate lactotroph and corticotroph function. The stimulatory action on adrenocorticotropic hormone (ACTH) secretion looks more interesting given its peculiar increase in conditions of ACTH-dependent hypercortisolism such as Cushing's disease, as well as the anxiogenic effect of ghrelin, which is specifically abolished by corticotropin-releasing hormone (CRH) antagonists[3,5].

Again, more recently, it has been demonstrated that ghrelin probably has an inhibitory effect on gonadal function by exerting a negative action on gonadotropin secretion; this action could be implicated in the negative influence of energy restriction on gonadal function as in anorexia and cachexia[7].

CENTRAL ACTIONS OF GHRELIN

Like synthetic GHS, ghrelin induces adipogenesis by stimulating appetite and food intake, as well as by modulating energy balance with reduced fat utilization[3,8].

This orexigenic action is mediated by a specific central network of neurons that is also modulated by leptin; these hormones together could therefore represent complementary players of one regulatory system that has developed to inform the central nervous system about the status of energy balance. Indeed, ghrelin is expressed in a previously uncharacterized group of neurons adjacent to the third ventricle and is functionally linked to other hypothalamic neuronal circuits including those producing neuropeptide Y, agont-related peptide, pro-opiome-lanocortin and corticotimopin releasing hormone i.e. neuropeptides that are well known for their critical role in the control of appetite and energy balance[3,9]. Interestingly, acetylcholine probably mediates the impact of ghrelin on appetite and energy balance. The ghrelin null mouse is, however, fully normal in terms of body growth, body weight and metabolic profile. Moreover, genetic studies in humans do not support a major role of ghrelin in the pathogenesis of obesity, although low ghrelin levels have been shown to be associated with diabetes mellitus type 2, insulin resistance, and hypertension. Nevertheless, as stimulation of appetite and food intake after ghrelin administration has been demonstrated even in humans, ghrelin mimetics acting as agonists or antagonists are currently considered as potential drug interventions for the treatment of cachexia or obesity, respectively[3,9].

Apart from its central orexigenic action, ghrelin is able to influence sleep, memory and anxiety-like behavioral responses; these effects could herald other central actions whose physiological relevance and implications in disease would not necessarily be less important[3,5].

PERIPHERAL ENDOCRINE AND METABOLIC ACTIONS OF GHRELIN

The pancreas expresses either ghrelin or GHS-R1a and GHS-R subtypes that are still uncloned. Ghrelin-secreting cells in the endocrine pancreas represent a new islet population that would mostly contribute to circulating ghrelin levels in fetal life[3,10].

As anticipated, insulin negatively affects the secretion of ghrelin which, in turn, modulates beta cell secretion as indicated by *in vitro* and *in vivo* studies in animals and humans[3,5,10].

Indeed, acylated ghrelin has been shown to be able to exert an inhibitory action on insulin secretion as well as a direct glycogenolytic action in the liver. Non-acylated ghrelin is, on the other hand, able to exert opposite actions and to counteract those of its acylated form. Surprisingly, in adipose tissue, acylated and unacylated ghrelin directly exert the same adipogenic action[3].

The assumption that ghrelin in its acylated form exerts a "diabetogenic" action is consistent with several past studies in animals and humans administered synthetic GHS. The insulin-sensitizing action of unacylated ghrelin is clearly indicated by the phenotype of a transgenic mouse selectively overexpressing non-acylated ghrelin. The importance and the potential implications of these findings in health and disease remain to be clarified but the functional balance between the two ghrelin forms may represent a new system with a major metabolic role in physiological conditions as well as in diabetes mellitus[3].

Among the peripheral endocrine targets for ghrelin actions, the gonads, the adrenal gland and the thyroid gland should also be taken into account.

PERIPHERAL, NON-ENDOCRINE ACTIONS OF GHRELIN

Importantly, ghrelin is a new gastro-entero-pancreatic hormone discovered as a motilin-related peptide. Thus, ghrelin not surprisingly exerts gastroenteropan-

creatic actions modulating gastric motility and acid secretion, stimulating ileal peristalsis and also inhibiting cholecystokinin-induced pancreatic protein secretion[3]. Again, it would not be surprising if the real clinical perspective emerged from this context; for instance, the prokinetic activity of ghrelin could predict potential clinical applications for its synthetic analogues.

Again, ghrelin could also represent a clinical marker of some gastric and intestinal carcinoids that synthesize and secrete ghrelin[3].

The cardiovascular system could represent another major target for peripheral, non-endocrine ghrelin actions. Indeed, GHS-R subtype expression has been demonstrated to be abundant in animal and human cardiovascular tissues. In cardiovascular tissues, as in the pancreas, GHS-R are able to recognize either acylated or non-acylated ghrelin and both ghrelin forms exert biological activities. However, peptidyl GHS, but not ghrelin, also bind the CD36 receptor through which they probably modulate atherogenesis[11,12].

The heterogeneous pattern of receptors for ghrelin and synthetic GHS within the cardiovascular system probably explain several cardiovascular actions exerted by these molecules. Indeed, the following cardiovascular actions of ghrelin and GHS have been demonstrated so far: *a)* inotropic action and enhancement of cardiac performance; *b)* protection from post-ischemic ventricular dysfunction, and *c)* anti-apoptotic action with protection from serum withdrawal-, doxorubicin- and FAS ligand-induced apoptosis of cardiomyocytes and endothelial cells[11,12].

However, the question of identifying the cardiovascular role of ghrelin, if any, in health and disease remains to be clarified.

Finally, attention should also be paid to evidence that ghrelin, whether acylated or not, significantly modulates both normal and neoplastic cell proliferation. Several endocrine and non-endocrine neoplastic tissues as well as their related cell lines express ghrelin as well as GHS-R1a and/or binding sites able to recognize ghrelin independently from its acylation. The ghrelin system might therefore play a significant autocrine/paracrine modulatory role in cell proliferation. Both stimulatory and inhibitory influences on cell viability have been observed and probably depend on experimental conditions but could also be tissue specific. Further understanding of this issue is required and could have important implications[3,13].

CONCLUSIONS

The ghrelin story was born with orally active, synthetic GHS, which represented the clinical dream of orally active molecules able to replace rhGH for the treatment of GH deficiency and/or as anabolic treatment for anti-aging interventions. At the sunset of that dream, soon after the discovery of ghrelin, demonstration of its orexigenic action generated the new dream that ghrelin analogues acting as agonists or antagonists might be useful for the treatment of cachexia, eating disorders and obesity. Although the ghrelin knock-out mouse is not an anorectic dwarf (indicating an important difference from leptin whose knock-out mouse has a well known obese phenotype), this does not definitively close the ghrelin story and the potential perspectives of ghrelin analogues. Indeed, ghrelin is much more than simply a natural GH secretagogue and/or an orexigenic factor.

The wide spectrum of ghrelin actions indicates the need for systematic understanding of their physiological relevance before their therapeutic perspectives in disease are explored. There are several unanswered questions and unresolved problems in the understanding of the ghrelin system. Among these actions, the peripheral direct metabolic actions of either acylated or unacylated ghrelin seem to be the most interesting and promising.

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