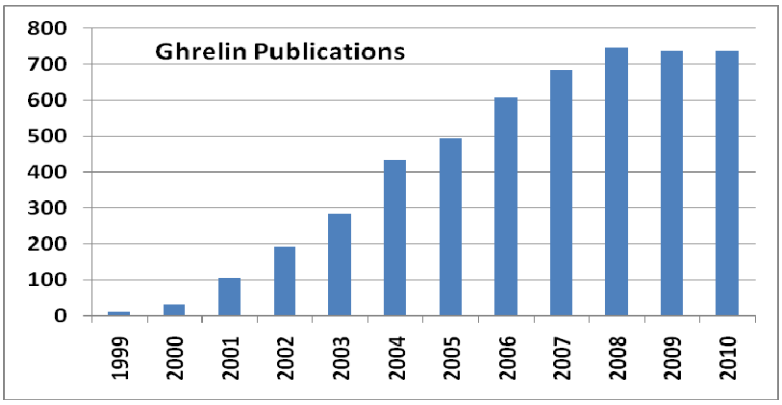
Foreword

Ghrelin was first identified in 1999 by Kojima and colleagues (Kojima et al. 1999) as the natural ligand of an orphan G-protein coupled receptor, the Growth Hormone (GH) secretagogue receptor (GHS-R), which had been identified several years earlier through the actions of a growing number of synthetic growth hormone releasing peptides (GHRPs) and non-peptidyl GH secretagogues (Howard et al. 1996). Early studies, therefore, focussed on the actions of ghrelin as an important regulator of GH secretion. As a result Kojima et al (1999) designated this GH-releasing peptide, ghrelin (ghre is the Proto-Indo-European root of the word 'grow'). We now recognise that the functions of ghrelin extend well beyond its GH releasing actions and that it is a multi-functional peptide with both endocrine and autocrine/paracrine modes of action.



The global interest in this field can be gauged by the rapid increase and sustained output of publications (see Fig) reporting on the cellular, molecular and clinical aspects of the ghrelin axis (4607 publications recorded in PubMed since 1999).

Over the past decade, like many newly discovered protein and peptide hormones, ghrelin has been shown to have a plethora of physiological and pathophysiological effects other than its original actions on GH secretion. Perhaps the most important of these, and certainly the most intensively studied, is ghrelin's core effect on appetite and metabolic regulation and its potential as a therapeutic target for obesity. However, many research teams around the globe have identified equally interesting roles for ghrelin in diabetes mellitus, inflammation, reproduction, cancer, memory, sleep, and mental health and addiction and in the regulation of gastrointestinal and cardiovascular function. Each of these primary and emerging roles has been expertly reviewed in this Special Issue, together with commentary regarding the wider potential therapeutic applications of components of the ghrelin axis.

In covering the diversity and range of effects of the components of the ghrelin axis there are inevitably some common recurring themes. This reflects the core roles of ghrelin in the regulation of energy balance and metabolism, and their strong mechanistic links or risk-factor correlations with the physiology and pathophysiology described in this collection of reviews. This Special Issue provides a range of views and interpretations of the published literature, reflecting the fact that ghrelin does not always present consistent effects in apparently similar experimental or clinical situations.

The actions of ghrelin itself are not the only issues that continue to stir considerable interest in this hormonal axis, however. Recent studies have highlighted a number of complexities and knowledge gaps regarding the molecular, biochemical and cellular components of the ghrelin axis and many of these have also been addressed in the articles in this Special Issue. The ghrelin gene gives rise to numerous transcripts which have the potential to generate multiple peptide products in addition to ghrelin. Of these, obestatin is the best characterised to date and, like ghrelin itself, is proving to be

rather enigmatic with initial reports suggesting that it had opposite effects to ghrelin on food intake and gastric motility and, intriguingly, that it acted via the receptor GPR39, a member of the ghrelin receptor family (Zhang et al. 2005). Later studies have refuted both of these observations but, nonetheless, have shown independent actions of obestatin in several cell systems. The post-translational modification (acylation) of ghrelin, via the recently identified enzyme ghrelin O-acetyl transferase (GOAT) (Gutierrez et al. 2008; Yang et al. 2008), is rather unique amongst proteins/peptides and this has a marked effect on its biological activity. The non-acylated form, desacyl ghrelin, constitutes about 70% of circulating immunoreactive ghrelin, and although it does not bind to or activate the ghrelin receptor, GHS-R1a, it does have independent actions on cells. In some cases desacyl ghrelin has the same effect as ghrelin, including cell proliferation and the inhibition of apoptosis, but in other cases has the opposite effect to ghrelin or distinct effects, including effects on glucose output, insulin sensitivity, and gastrointestinal motility (reviewed in Soares and Leite-Moreira, 2008). These observations, the fact that acylated ghrelin also has some actions in tissues that do not express the GHS-R, and the minimal phenotype of GHS-R knockout mice, have driven the hypothesis that an unidentified, alternative ghrelin receptor also exists (Smith et al 2005). Additional functional complexity concerns the role of the truncated form of the GHS-R (GHS-R 1b), which is believed not to be active in its own right. It has been reported to act as a dominant negative receptor by forming receptor heterodimers with GHS-R 1a (Leung et al. 2007), however this remains somewhat speculative and has not been formally addressed in this Special Issue.

More than a decade has passed since the identification of ghrelin and it is timely to bring together the views of some of the leading contributors to the field and provide an up-to-date synthesis of current knowledge and thinking in this rapidly emerging and diverse field. This Special Issue on the Ghrelin Axis in Disease highlights some of the uncertainties and important questions still remaining in the ghrelin field. We would like to thank our contributing authors for their expert and timely submissions and also the editorial staff at MCE for their support and coordination roles. We sincerely trust that you find this Special Issue of interest.

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