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INVITED REVIEW

Ghrelin in psychiatric disorders — A review

Dirk Alexander Wittekind*, **Michael Kluge**

Department of Psychiatry and Psychotherapy, University of Leipzig, Leipzig, Germany

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Summary Ghrelin is a 28-amino-acid peptide hormone, first described in 1999 and broadly expressed in the organism. As the only known orexigenic hormone secreted in the periphery, it increases hunger and appetite, promoting food intake. Ghrelin has also been shown to be involved in various physiological processes being regulated in the central nervous system such as sleep, mood, memory and reward. Accordingly, it has been implicated in a series of psychiatric disorders, making it subject of increasing investigation, with knowledge rapidly accumulating. This review aims at providing a concise yet comprehensive overview of the role of ghrelin in psychiatric disorders. Ghrelin was consistently shown to exert neuroprotective and memory-enhancing effects and alleviated psychopathology in animal models of dementia. Few human studies show a disruption of the ghrelin system in dementia. It was also shown to play a crucial role in the pathophysiology of addictive disorders, promoting drug reward, enhancing drug seeking behavior and increasing craving in both animals and humans. Ghrelin's exact role in depression and anxiety is still being debated, as it was shown to both promote and alleviate depressive and anxiety-behavior in animal studies, with an overweight of evidence suggesting antidepressant effects. Not surprisingly, the ghrelin system is also implicated in eating disorders, however its exact role remains to be elucidated. Its widespread involvement has made the ghrelin system a promising target for future therapies, with encouraging findings in recent literature.

Contents

* Corresponding author at: Semmelweisstrasse 10, 04103 Leipzig, Germany. Tel.: +49 341 25031.
E-mail address: dirkalexander.wittekind@medizin.uni-leipzig.de (D.A. Wittekind).

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1. Introduction

Ghrelin is a 28-amino-acid peptide hormone, which was first described in 1999 (Kojima et al., 1999). It is primarily synthesized by gastric neuroendocrine cells but has also been identified in a variety of other organs including bowels, kidney, thyroid, lung, lymphatic tissue, placenta, hypothalamus, and pituitary (Gnanapavan et al., 2002). The ghrelin molecule is processed from preproghrelin, a 117 amino acid peptide, which is transcribed from a complex gene on chromosome 3 in the human genome (Kanamoto et al., 2004). In the processing of preproghrelin to ghrelin, other peptides are produced, most importantly obestatin (Zhang et al., 2005). While obestatin has been reported to decrease pancreatic secretion, to enhance memory and to suppress thirst, its real physiological relevance remains elusive (Trovato et al., 2014). The genes encoding both ghrelin and its receptor are almost identical among vertebrates, being conserved in the evolution, suggesting the high relevance of the ghrelin system to the organism (Gahete et al., 2014).

Ghrelin was identified as an endogenous ligand for the Growth-Hormone (GH)-Secretagogue-Receptor 1a (GHSR-1a), which had been previously discovered (Howard et al., 1996). Consequently, ghrelin triggers the release of GH and was therefore named accordingly (Acronym for *Growth Hormone Release Inducing*) (Kojima et al., 1999; Takaya et al., 2000). In addition, ghrelin stimulates the hypothalamic–pituitary–adrenal axis (HPA)-axis: In the hypothalamus, it was shown to increase both gene expression of corticotropin releasing hormone (CRH) (Cabral et al., 2012) and release of CRH (Mozid et al., 2003). In addition, ghrelin increases serum levels of ACTH and cortisol in rodents (Wren et al., 2000) and man (Kluge et al., 2007b). Furthermore, ghrelin suppresses secretion of hormones of the hypothalamic–pituitary–gonadal (HPG) axis, namely follicle-stimulating hormone (FSH) (Kluge et al., 2009b, 2012) and luteinizing hormone (LH)(Kluge et al., 2007a). Ghrelin was also repeatedly shown to affect the hypothalamus–pituitary–thyroid (HPT) axis in humans causing an increase of thyroxine but a decrease of thyroid stimulating hormone (TSH) (Kluge et al., 2010b, 2013). Moreover, ghrelin is active in the gastroenteric tract, where it is involved in the regulation of glucose homeostasis, insulin and glucagon (Dezaki, 2013).

Ghrelin, which is released in a pulsatile manner (Natalucci et al., 2005) exists in an acylated (AG) and des-acylated form (DAG) (Kojima et al., 1999). The posttranslational acylation is performed by the Ghrelin-O-acyl-transferase (GOAT), which is expressed in most tissues and was only identified in 2008 (Gutierrez et al., 2008; Yang et al., 2008). In contrast to DAG, AG binds to the GHSR-1a and the majority of functions is mediated by this variant (Kojima and Kangawa, 2010). DAG represents the majority of circulating ghrelin and was initially considered to be inactive. However, more recent evidence indicates that DAG also exerts actions and might be a functional inhibitor of AG (Delhanty et al., 2014).

AG also exerts a multitude of other biological actions: As the only peripheral orexigenic (appetite-stimulating) hormone it is crucially involved in the regulation of energy homeostasis, appetite (Tschöp et al., 2000; Wren et al., 2000; Nakazato et al., 2001) and blood gluose (McFarlane et al., 2014). Ghrelin causes an increase of food intake (Tschöp et al., 2000; Wren et al., 2001) at least in part by stimulating hypothalamic neurons containing the orexigenic peptides neuropeptide Y (NPY) and agouti-related protein (Kamegai et al., 2001). Ghrelin levels rise in states of hunger and when anticipating food intake and drop afterwards (Cummings et al., 2001).

Ghrelin has been shown to be an important player in the regulation of many central nervous system (CNS) functions like sleep (Kluge et al., 2008), cognition (Andrews, 2011), mood (Chuang and Zigman, 2010) and reward (Jerlhag et al., 2009). Data considering to what extent ghrelin is expressed in the CNS is inconsistent (Furness et al., 2011). Ghrelin is actively transported across the blood–brain-barrier in a satiable mechanism (Banks et al., 2002; Banks, 2008) and can passively diffuse through fenestrated capillaries in the hypothalamus (Schaeffer et al., 2013). Ghrelin has been repeatedly shown to exert discrete central and peripheral actions and some evidence suggests that central and peripheral ghrelin signaling are at least partially distinct from each other. For example, when ghrelin transport into the CNS was blocked in mice, this did not alter