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PHYSIOLOGICAL REVIEW

Ghrelin and its interactions with growth hormone, leptin and orexins: Implications for the sleep–wake cycle and metabolism

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SUMMARY

Several studies have shown that ghrelin administration promotes wakefulness in rodents, while in human males it induces sleep but has no effect in women. Ghrelin also plays an important role in metabolism and appetite regulation, and as described in this review may participate in the energy balance during sleep. In this review, we summarize some of the effects induced by ghrelin administration on the sleep–wake cycle in relation to the effects of other hormones, such as growth hormone, leptin, and orexin. Finally we discuss the relationship between sleep deprivation, obesity and ghrelin secretion pattern.

Introduction

Ghrelin's role in appetite and energy balance regulation is well documented. In recent years new evidence has emerged demonstrating the role of ghrelin in the sleep–wake cycle, both in animals and humans. This topic has been addressed in two excellent reviews published by the group of A. Steiger.[1,2] However, to our knowledge there are no reviews addressing the role of ghrelin regulating both behaviors. In this review we summarize some of the effects induced by ghrelin administration on the sleep–wake cycle in experimental animals and humans. We also discuss the possible interactions of ghrelin with growth hormone, leptin, and orexins in the regulation of the sleep–feeding circuit, emphasizing ghrelin's potential role on the energy balance during sleep. Finally, we address how the lack of sleep could be a trigger for the development of obesity and whether ghrelin is part of it.

Ghrelin is a 28 amino acid peptide secreted mainly by the stomach and is an endogenous ligand for the growth hormone secretagogue receptor 1a (GHS-R1a).[3] GHS-R1a is a G protein-coupled receptor widely expressed in peripheral tissues, as well as in various brain regions, such as the hypothalamus, thalamus, cortex, hippocampus and the pituitary gland.[4,5] The hypothalamus is the main brain region of ghrelin synthesis,[6] although overall peptide brain levels are much lower than those found in the stomach.

Ghrelin is derived from a preprohormone called preproghrelin, which generates, by post-translational cleavage, a second peptide of 26 amino acid called obestatin,[7] and a third peptide of 60 amino acids, called C-ghrelin (reviewed by Seim et al.[8]). In addition, the primary mRNA encoded by the ghrelin gene can also generate multiple transcripts by alternative splicing, some of them may encode peptides of unknown function.[8] Ghrelin is involved in growth hormone release, metabolism and appetite regulation (reviewed by Chen et al.[9]), as well as in the sleep–wake cycle regulation as described[1,2] and in this review. Obestatin was initially reported as a ligand for the orphan G protein-coupled receptor GPR39, involved in satiety and decreased food intake[7]; however there is controversy on these findings, and the role of this peptide is not well established (reviewed by Seim et al.[10]). Obestatin also induces sleep when centrally administered to rats.[11] On the other hand, C-ghrelin circulates at high levels in plasma; however, its function and putative receptor are unknown.[8]

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Abbreviations

AgRP	agouti-related peptide
ARC	arcuate nucleus of the hypothalamus
BMI	body mass index
CART	cocaine and amphetamine-related transcripts
CORT	corticosterone
EEG	electroencephalogram
EMG	electromyogram
GH	growth hormone
GHRH	growth hormone releasing hormone
GHS-R1a	growth hormone secretagogue receptor 1a
icv	intracerebroventricular
ip	intraperitoneal
iv	intravenous
LC	locus coeruleus
LDTg	laterodorsal tegmental nucleus
LHA	lateral hypothalamic area
MPA	medial preoptic area
NPY	neuropeptide Y
NREM	non-rapid eye movement
OSAS	sleep apnea syndrome
PeN	periventricular nucleus of the hypothalamus
PGO	ponto-geniculo-occipital
POMP	proopiomelanocortin
PPT	pedunculopontine tegmental nucleus
PVN	paraventricular nucleus
REM	rapid eye movement
SRS	sleep-regulatory substances
SST	somatostatin
SWA	slow-wave activity

Despite its widespread and important physiological actions, ghrelin gene precise transcriptional and translational regulatory mechanisms remain ambiguous. Further studies on the biogenesis, expression and functions of C-ghrelin and obestatin, and the identification of their receptors are required.[8]

Before entering to this reviews' topic, we consider important to describe the phenomenology of the sleep–wake cycle. According to a simple behavioral definition, sleep is a reversible behavioral state of perceptual disengagement and unresponsiveness to the environment.[12] Today it is universally accepted that mammals present at least two basic stages of sleep: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. The electrographic signals of cortical activity (electroencephalogram (EEG)), eye movements and muscle tone (electromyogram (EMG)) are the major signals, which determine a given sleep stage.[12] In humans, NREM sleep has been further divided into N1, N2 and N3 stages based on specific EEG patterns. The N2 and N3 stages have been characterized by the presence of slow (delta) waves in the EEG and thus, referred also as slow-wave sleep (SWS).[13] However, in the animal literature, the terms SWS and NREM sleep have been used interchangeably and often refer to the same sleep stage (non-REM sleep).[14]

NREM sleep in humans is associated with fragmented mental activity. REM sleep, by contrast, is defined by EEG activation, muscle atonia, and episodic burst of rapid eye movements. The mental activity during REM sleep is associated with dreaming, based on vivid dream recall reported after approximately 80% of arousals from this sleep state.

There is a large body of evidence demonstrating that sleep is influenced by a number of hormones and peptides, referred to as sleep-regulatory substances (SRS). Some of these peptides tend to accumulate within the brain and cerebrospinal fluid. Cerebrospinal or brain extracts taken from a sleep-deprived animal or from animals in the sleep-intense part of the cycle, promote sleep when injected into the ventricles of a normal animal, as demonstrated by several groups.[15–17] Thus, chemicals of different molecular sizes have been suggested to function as neurotransmitters, neuromodulators or neurohormones, providing the possibility for short-to-long acting molecules that could participate collectively in the generation and maintenance of the sleep–wake cycle.[17–19] Among these SRS, interleukin-1β, tumor necrosis factor α, growth hormone releasing hormone (GHRH), prolactin, and nitric oxide, are currently the best characterized; and many of their downstream biochemical mechanisms are also implicated in sleep regulation, e.g., adenosine, nitric oxide, prostaglandins, and others.[17] However, as discussed below, ghrelin, although it does not meet all the criteria established for SRS,[17,18] is significantly involved in regulating the sleep–wake cycle, in addition to its role in metabolism regulation.

Ghrelin's role on the sleep–wake cycle

Studies conducted in rodents indicate that central administration of ghrelin to rats and mice increases wakefulness, but the effects of systemic ghrelin administration are less clear, and depend on the species, the dose and route of administration (Table 1). On the other hand, the effects of ghrelin administration to humans depend on the gender and time of administration. Repeated intravenous administration of ghrelin increases NREM sleep in young and elderly men, but has no effect on women (Table 2). These studies are discussed in detail in the following pages.

Table 1
Effects of ghrelin administration on the sleep-wake cycle in rodents.

References	Species	Route of administration	Wake	NREM	REM
Tolle et al., 2002[23]	Rat	Repeated iv	Increase	Decrease	Decrease*
Szentirmai et al., 2006[20]	Rat	icv	Increase	Decrease	Decrease
Szentirmai et al., 2007[21]	Rat	Injection into Lateral Hypothalamus	Increase	Decrease	Decrease
Obál et al., 2003[26]	Mice	ip	No effect	Increase	No effect
Szentirmai et al., 2007[30]	G-KO mice		Increase	Decrease	Slight increase
Esposito et al., 2012[32]	GR-KO mice		No effect	No effect	No effect
Szentirmai, 2012[22]	Mice	icv	Increase	Decrease	Decrease
		ip	No effect	No effect	No effect

G-KO= preproghrelin knockout; GR-KO= ghrelin receptor knockout; icv= intracerebroventricular; ip= intraperitoneal; iv= intravenous; NREM= non-rapid eye movement; REM= rapid eye movement.
* Only in the dark period.