Ghrelin and sleep-wake regulation

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Peptides play a key role in the regulation of sleep-wake-behavior (11). There are many hints that also the endogenous ligand of the growth hormone (GH)-secretagogue (GHS) receptor ghrelin participates in the regulation of vigilance states. In a previous editorial focus (10) I wrote that study results by Bodosi et al. (1) on the relationship between sleep, feeding, ghrelin and its antagonist in the energy balance, leptin "are a challenge to search for the answers to new questions". In this issue of the *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* the group of researchers from the U.S. and Hungary led by James M. Krueger contributes again a highlight in the physiology of ghrelin. Szentirmai et al. (13) report the effects of ghrelin microinjections into forebrain sites on sleep-wake behavior and feeding in rats.

It is well established that beside GH-releasing hormone (GHRH) ghrelin stimulates the release of GH (4). Furthermore it is a powerful orexigenic factor stimulating food intake and conserving fat (15). Since GHRH promotes sleep after various routes of administration in several species including humans (6) the question arose whether ghrelin shares this effect. Furthermore synthetic GHSs affect sleep in humans. After GH-releasing peptide-6 non-rapid eye movement sleep (NREMS) stage 2 increased in humans (3). In contrast after hexarelin slow-wave sleep (SWS) decreased, probably due to suppression of endogenous GHRH by elevated GH levels (2). In rats the effects of repeated intravenous ghrelin injections on ghrelin levels, GH, feeding behavior and sleep-wake pattern were evaluated (14). Sleep was inhibited during 30 min after the injections when feeding was induced. Obál et al. (5) stated that in this report (14) "although not
analyzed statistically, enhancement in NREMS time could be observed during the subsequent 10 min time blocks in the published figure depicting NREMS. After systemic administration of ghrelin to mice NREMS increased. This effect was absent in mice with non-functional GHRH receptors (5). Similarly SWS was elevated after pulsatile iv administration of ghrelin to normal male subjects (17). After sleep deprivation ghrelin levels increased earlier by trend and the ghrelin maximum occurred advanced in humans when compared to baseline (9). All these findings suggest that ghrelin is a sleep-promoting factor.

This hypothesis is challenged however by a recent study by Szentirmai et al. (12). Intracerebroventricular ghrelin injection at light onset and at dark onset suppressed NREMS and REMS for 2 hours in ad libitum fed rats. This decrease was followed by an increase in NREMS during hours 3 to 12 after some doses of ghrelin. In feeding-restricted rats ghrelin suppressed NREMS in hours 1 and 2 and NREMS in hours 3 to 12. Similarly Bodosi et al. (1) concluded from their findings that there are no strong links between sleep and ghrelin in the rat. In the present study Szentirmai et al. (13) examined the sleep and feeding responses on microinjections of three dosages of ghrelin into hypothalamic sites which are implicated in the related regulation, such as the lateral hypothalamus, the medial preoptic area and the paraventricular nucleus at dark onset in rats. Similar to their previous findings (12) microinjections were followed by an increase of wakefulness. At the same time food consumption was stimulated. The decrease of the EEG slow-wave activity after injections into the medial preoptic area was followed by an increase. The authors discuss that, since
sleep and feeding are mutually exclusive behaviors, an increase in feeding might result in shortened sleep time. Alternatively hunger due to ghrelin injections may cause discomfort that could also interfere with sleep. However the lowest injected dose of ghrelin into the paraventricular nucleus stimulated feeding as strongly as the higher dose, but did not affect sleep. The authors hypothesize that decreased wakefulness and increased feeding are two parallel outputs of the hypothalamic ghrelin sensitive circuitry. Its activation appears to trigger the behavioral sequence during the first hours of the activity period in rats, the "dark onset syndrome".

Species differences and different routes of administration may explain the opposite effects of ghrelin in humans and mice (sleep-promoting) and in rats in the studies by Szentirmai et al. (12; 13). Interestingly findings in humans suggest that a threshold in ghrelin concentrations exists for stimulation of hunger. During the night slight increases, as reported after sleep deprivation (9) appear to promote sleep. In contrast higher levels may disrupt sleep due to hunger. Whereas a dose of 4 x 50 µg ghrelin injected around sleep onset increased SWS (17) in a single case the nocturnal injection of 100 µg ghrelin increased hunger and food intake at night and disrupted sleep (16). Accordingly very high ghrelin levels were found in a patient with a night-eating syndrome (7). On the other hand administration of 100 µg ghrelin in the morning increased appetite and induced imagination of food, but also in 6 of 9 subjects fatigue (8).
In all the question remains open whether depending on time, concentration and site of action ghrelin may act as sleep- and wake-promoting substance as well.


