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, a group of researchers from the United States and Hungary led by James M. Krueger (13) 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 in addition to 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 on this report (Ref. 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 nonfunctional GHRH receptors (5). Similarly, SWS was elevated after pulsatile intravenous administration of ghrelin to normal male subjects (17). With sleep deprivation, ghrelin levels increased earlier by trend and the concentration of ghrelin to normal male subjects (17). After sleep deprivation, ghrelin injections may cause discomfort that could also interfere with sleep. However, the lowest injected dose of ghrelin into the paraventricular nucleus increased 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 × 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 induced 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.

REFERENCES
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