Ghrelin and sleep-wake regulation

Axel Steiger
Max Planck Institute of Psychiatry, Munich, Germany

Submitted 30 August 2006; accepted in final form 31 August 2006

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) examined the sleep and feeding responses on microinjections of three doses of ghrelin into hypothalamic sites that 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 circuity. 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
3. Frieboes RM, Murck H, Maier P, Schier T, Holsboer F, Steiger A. Growth hormone-releasing peptide-6 stimulates sleep, growth hormone,