

## Eating and Sleeping

Eating and sleeping—their relationship to ghrelin and leptin

EATING AND SLEEPING is two kinds of behavior that are essential for the survival of humans and higher animals. Whereas it is obviously excluded that they occur exactly at the same time, there appear to be common regulators of both phenomena. With the identification of ghrelin as the endogenous ligand of the growth hormone (GH)-secretagogue (GHS) receptor by Kojima et al. a new endogenous regulator of food intake and possibly also of sleep was found. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Bodosi et al. report a sophisticated study on the relationship between sleep, feeding, ghrelin, and its antagonist in the energy balance, leptin.

The detection of ghrelin was preceded in the 1970s by the synthesis of GHSs and by the cloning of the GHS receptor. Although they act on a different receptor, the GHSs and ghrelin share the capacity of GH-releasing hormone (GHRH) to stimulate GH. In addition to this endocrine effect, GHRH stimulates non-rapid eye movement (REM) sleep in various species including humans. Similarly sleep-promoting effects of synthetic GHS were found in humans. Furthermore, some hints exist for a stimulating influence of GHS on food intake and body weight.

Soon after the identification of ghrelin, which is displayed mainly in the stomach and also in other tissues including the hypothalamus, it became clear that it is the most powerful endogenous orexigenic factor known so far. Ghrelin stimulates food intake and conserves fat, resulting in increasing body weight in rodents. Similarly, appetite and calorie intake increased after ghrelin administration in humans. Ghrelin levels were found to be changed in eating disorders, with high concentrations in anorexia and Prader-Willi Syndrome and blunting in obesity. In contrast to ghrelin, leptin is an anorexigenic

factor and it is thought that ghrelin and leptin regulate the energy balance in a reciprocal fashion.

Similarly to GHRH, non-REM sleep was enhanced after ghrelin in mice and humans. Intact GHRH receptors were shown to be the prerequisite for this effect in mice. Also, an effect of leptin on sleep was reported. Bodosi et al. compared plasma ghrelin and leptin levels and hypothalamic ghrelin contents, sleep, brain temperature, and feeding throughout the dark-light cycle in rats in three experimental conditions: free-feeding animals with normal diurnal rhythms, restricted feeding, and sleep deprivation. From their findings they conclude that intimate relations between feeding and plasma ghrelin and leptin are corroborated, whereas there are no strong links between sleep and these hormones in the rat. These study results are a challenge to search for the answers to new questions.

To what extent is ghrelin secretion under circadian regulation? In humans there exist controversial data whether ghrelin levels show major fluctuations throughout the day.

Whereas the fluctuations of hypothalamic ghrelin were not significantly under baseline conditions, according to the localization of ghrelin-containing neurons in the brain, Cowley et al. suggested a role of ghrelin in the regulation of rhythms, particularly in the timing of meals. Does ghrelin also play a role in the timing of sleep? This is not supported convincingly by the findings in the rat.

Sleep deprivation in the rat is accompanied by increases in ghrelin levels. In contrast, in humans a nocturnal ghrelin peak was found to be blunted during sleep deprivation. Findings in humans suggest dose-dependent differences in the behavioral effects of ghrelin. At night, a higher dose of ghrelin significantly induced hunger, whereas the lower dose promoted sleep. Interestingly, leptin peaks in humans and in rats during the night, whereas they have opposite sleep-wake patterns. Are there differences in the action of ghrelin and leptin between rats and humans?

So far little is known about gender differences in the effects of ghrelin. Given the fact that GHRH exerted sexually dimorphic effects on sleep-endocrine activity in humans similar studies appear to be necessary with ghrelin.

The GHS receptor appears to be an interesting target for pharmacological regulation of food intake, particularly for the treatment of obesity. During the development of such therapies side effects on sleep must be kept in mind.