The last decades have witnessed an upsurge of neuropeptide research. These substances regulate or influence various functions like appetite, water intake, learning and memory, adaptive responses to environmental stress, thermoregulation and fever, social behavior, and sleep. One function may be affected by several peptides, and a single peptide can be involved in different functions—a general approach is to find a coordinated pattern, which appears “meaningful” in explaining how a given peptide may participate in complex events.

Orexins (hypocretins) have originally been described as peptides regulating feeding behavior (30) and as neuroexcitatory substances setting the threshold for arousal (6). These two functions may be related, possibly offering a pattern (alertness is a natural precondition of feeding), but they may as well be unrelated. Although food intake regulation is an integral component of the overall energy balance (together with metabolic rate and body temperature regulations) (34), not necessarily all factors of energy balance are coupled with the regulation of sleep-wake behavior, even if feeding behavior and arousal state prove to be related. This is what makes very interesting the recent article by Mochizuki et al. (21) in the present issue of American Journal of Physiology: Regulatory Integrative and Comparative Physiology. This paper suggests a relationship between orexin’s effects on the regulations of body temperature and sleep/wake cycle. The article also indicates an increasing need to analyze the spectrum of orexin’s effects in a complex way.

The orexin-induced hyperphagia might be interpreted as part of a coordinated anabolic reaction. This approach resembles that applied in the analysis of neuropeptide Y’s (NPY’s) effects (33). Physiologically, NPY is activated during food deprivation and hunger. The anabolic regulatory pattern seen in fasting involves a tendency to gain calories (hunger) and another one to retain the already available calories by a regulated suppression of metabolic rate (decreased utilization of caloric substances in the body), with a consequent tendency for hypothermia. Central NPY administration induces food intake, tends to suppress metabolic rate (33), and enhances wakefulness (35). Because basal metabolic rate (BMR) cannot be decreased by physiological means, injections of NPY can only suppress the excess metabolism above BMR, for example, that seen during cold exposure or possibly during the active phase of the circadian cycle (33). Understandably, the hypometabolic-hypothermic action can be demonstrated mainly in cool environments. Later on, the hyperphagia, hypometabolism, and hypothermia are followed by a probably indirect catabolic effect causing a rise in metabolic rate and body temperature, as well as a suppression of normal food intake for 12–24 h. At or near thermoneutrality, only the catabolic effects are obvious (except for a persisting early hyperphagia), and here these appear somewhat earlier than in the cold.

Some, although not all (15), data suggest that orexins possibly follow a similar anabolic pattern. Certain orexin actions are known to involve NPY mechanisms (39). Central injections of orexin-A in rats enhanced food intake for about 30–60 min, and they induced hypometabolism and hypothermia for a similar period in rats kept slightly energy-deficient in a cool (but not at thermoneutral) environment (32). However, similarly to NPY, they did not influence heat loss as represented by tail skin temperature. Central orexin injections also attenuated the experimental fever (13). These primary orexin effects were followed by a secondary hypermetabolism and hyperthermia (32), particularly at relatively warm ambient temperatures, possibly due to activation of catabolic neuropeptides like corticotrophin-releasing hormone (28) or to enhanced activity of prostaglandins (22). In contrast, SB-334867, a food intake suppressing antagonist of orexin receptor (12), elevated thermogenesis (9). Although other data reported on hypermetabolism, hyperthermia (15, 22, 23), or increased nonexercise activity thermogenesis (25) upon central administration of orexin-A, most of these measurements were performed long (2–6 h) after the injection and/or at room (not cold) temperature, and likely reflected the secondary, indirect effects of the peptide.

The other line of orexin effects appears to be more clear-cut: orexins have an outstanding role in sleep-wake regulation. The hypothalamic orexin levels of rats exhibited a circadian pattern: the levels gradually increased in the active phase and gradually decreased in the rest phase (7, 41). Orexin-deficient mice showed severe abnormalities of their sleep-wake cycle (5, 8), with an enhanced number of behavioral phase shifts (20). In patients with narcolepsy-cataplexy, both the number of orexin neurons (36) and the orexin levels in the plasma (10) or cerebrospinal fluid (19) were decreased. In orexin neuron-ablated mice with narcolepsy and cataplexy exogenous orexin inhibited the cataplexy and improved wakefulness for hours (18). Conversely, SB-334867 prevented the orexin-induced reduction in paradoxical sleep and also the increase in latency of onset of such sleep (31). Sleep deprivation causes a rise in hypothalamic orexin levels (37), although the mediation of this process has not been clarified.
Because orexin-containing neurons have widespread connections between the hypothalamus and various sites of the central nervous system (2, 26), it is likely that they have simultaneous effects in different systems. It still remains an open question whether or not the orexin effects related to energy balance and to sleep-wake cycle can be explained as concurrent but independent activities, or rather as interrelated ones. Because, however, the activity of orexin neurons is influenced fundamentally just by the main factors of energy balance, namely, by monoamines, acetylcholine, nutrients, glucose, leptin, and ghrelin (3, 29), a rather strong coordination might be assumed to exist between the regulations of energy balance and sleep/wakefulness (38).

Some evidence, indeed, support the existence of this assumed coordination. Low plasma glucose or absence of food stimulated orexin expression in rats (4); and food deprivation improved vigilance and daytime performance in humans (17). Besides such factors of energy balance, forced physical exercise also elevated the orexin level of the cerebrospinal fluid in rats and dogs (16, 37) and sleep deprivation induced similar effects in dogs (37). The wakefulness induced by hunger (3), exercise (37), or sleep withdrawal (37) is often followed by overwhelming somnolence, for example, in postprandial states (1,3) and after exertion or sleep deprivation. Leptin deficiency, which primarily influences energy balance, also disrupts the normal sleep pattern in ob/ob mice (14), and orexin has also been implicated in the insomnia-associated obesity (11, 14).

Although the data are sometimes controversial, both early (24) and more recent (32) findings allow an interpretation that orexins have a primary hypothermic action. Well before discovering the existence of orexins, earlier reports (24) demonstrated an elevated mesor of 24-h body temperature in narcoleptic patients. The cited study of Mochizuki et al. (21), who used more sophisticated and precise experimental conditions, demonstrated somewhat similar findings: in orexin knockout mice, alterations were found in the circadian body temperature rhythm, and the characteristic temperature fall in the inactive phase (with or without sleep deprivation) was shown to lag behind that seen in control animals.

Healthy animals eat, move, exhibit various forms of activity in the active phase, and have a slightly elevated metabolic rate and body temperature, which may or may not be orexin-related. The reported observations (21) do not suggest orexin dependence because in this phase, orexin knockout mice had similar body temperatures, as their control counterparts did. In the inactive phase, the animals sleep and may develop a temperature fall by a decrease in metabolic rate (approaching BMR) and/or by a rise in heat loss (21). Orexins did not seem to influence heat loss mechanisms (32). Because in the active phase, the orexin levels increase gradually (7), participation of orexins in various phases might easily be understood, provided that orexins, indeed, enhance metabolic rate and body temperature. In this case, in the inactive phase, the low orexin levels could contribute to a temperature fall—in orexin knockout mice, a lack of fall in orexin level possibly explains the attenuated temperature fall during the resting period. Alternatively, orexins may be suppressors of metabolism. However, in the active phase, the metabolic rate may depend on general activity (an enhancer of metabolic rate) and may be unrelated to the presence of orexin, whereas the hypometabolic effects of the peptide may be more expressive in the inactive phase. In this phase, sleep starts, but the gradually falling orexin levels, now unopposed by general activity, may still be high enough to contribute to a metabolic suppression. In orexin knockout mice the lack of such a mechanism could also result in attenuation of temperature fall in the inactive period.

Apparently, the orexins (or their lack) seem to interfere normally mainly with processes of the inactive phase. Chronic orexin administration affected the daytime (inactive phase) food intake only, but it did not alter the whole-day consumption or the weight gain rate (40). In accordance with the short time of effectiveness, chronic orexin administration failed to induce any time-consuming tonic alterations in thyroid activity or brown fat metabolism (27). It follows that in the circadian temperature changes, the orexins possibly play a more important role during rest than in the active period: their action may be limited to a temporary modification (suppression) of metabolic rate and body temperature, without altering heat loss. Accordingly, a chronic lack of orexin’s effects should be presumed not to influence either the thyroid and brown fat functions or the metabolic rate during the active period. In contrast, they may be thought to impair the metabolic suppression during the rest period and to result in attenuation of temperature fall in this period (perhaps because of narcolepsy-cataplexy, the knockout animals do not have a proper quiet rest). Such interpretation of complex orexin effects still ought to be confirmed, or possible other explanations should be established through detailed analysis of orexins and energy balance vs. orexins and sleep/wake cycle. For understanding the mechanism of action of orexins in various physiological or pathological processes, it would be important to clarify whether they cause parallel enhancement of food intake and metabolic rate, together with increased alertness, or they act in a different way. Further studies may open new horizons regarding the problem of the role of orexins in these regulations and may reveal connections between abnormalities of food intake, body weight, body temperature, and sleep/wake state.

REFERENCES


