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Editorial
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A New Potential of a Sleeping Pill

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Editorial

Orexin was identified as a peptide expressed in specific neurons of the lateral hypothalamic area which is stimulated by falls in circulating glucose but inhibited by feeding-related signals from the visceral organs [1]. Intra-cerebroventricular administration of orexin reduced fasting plasma glucose levels in both normal and streptozotocin-induced diabetic mice [2]. Orexin has been reported to function as a time keeper to regulate the daily on-off rhythm in hepatic glucose production along the sleep-wake cycle, by bi-directionally regulating hepatic gluconeogenesis via control of autonomic balance [3].

Since September 2014, suvorexant, an orexin receptor antagonist, has been approved as a drug for the treatment of insomnia and widely used to date in Japan. The daily resting-phase administration of suvorexant improved glucose metabolism in db/db mice, without affecting body weight, food intake, and insulin sensitivity [4], which was associated with reduced expression of factors-related with hepatic gluconeogenesis. In contrast, the daily awake-phase administration of suvorexant had no effect on glucose metabolism.

In human, suvorexant was reported to be generally effective and well-tolerated in both women and men with insomnia [5], and also in elderly patients with insomnia [6], by analyses of pooled phase-3 data. However, effects of suvorexant on metabolic parameters remained unknown.

Orexin neurons have been reported to be regulated by monoamines and acetylcholine as well as metabolic factors including leptin, glucose, and ghrelin [7]. Activity of orexin neurons is inhibited by glucose and leptin, and stimulated by ghrelin [7]. Leptin is secreted by adipocytes and is required for the maintenance of energy homeostasis and body weight [8]. Leptin deficiency causes obesity, and leptin resistance is the key risk factor for obesity [8]. Ghrelin has been recognized as an important regulator of growth hormone secretion and energy homeostasis, and ghrelin stimulates appetite and induces a positive energy balance leading to body weight gain [9,10]. A ghrelin antagonist has been considered to be a potential anti-obesity drug [11]. Leptin and ghrelin are complementary, yet antagonistic, signals reflecting changes in energy balance, and are mediated by hypothalamic neuropeptides such as neuropeptide Y and agouti-related peptide [10]. Therefore, orexin is considered to be closely associated with hormones associated with energy homeostasis and obesity.

Increased hepatic gluconeogenesis is commonly observed in patients with type 2 diabetes, and is also the target for the treatment of type 2 diabetes. I think that orexin-related metabolic factors including glucose metabolism are closely associated with obesity, metabolic syndrome and type 2 diabetes. However, an effect of suvorexant on glucose metabolism in patients with diabetes or an influence of suvorexant on the development of diabetes in normal glucose tolerant humans remain unknown, which is very exciting field of study. Disturbed sleep and circadian rhythms has been also reported to represent modifiable risk factors for prevention and treatment of metabolic diseases such as obesity [12], supporting my suggestion.

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