ANTI-OBESITY DRUGS

Improving sleep may promote weight loss

Various genetic, behavioural and social factors contribute to the development of obesity. Recently, a possible link between sleep and weight control has emerged. Now, writing in the *Journal of Clinical Investigation*, Uebele and colleagues identify a novel role for T-type Ca^{2+} channels in the central regulation of sleep and weight maintenance, revealing channel inhibition as a potential anti-obesity strategy.

Sleep and metabolic activity probably share central regulatory networks — some studies suggest that diet affects sleep, and others indicate that disrupted sleep can lead to changes in appetite and food preference, weight gain, central hormonal imbalance, as well as decreased insulin sensitivity and glucose tolerance. Interestingly, central T-type (or low-voltage-activated) Ca^{2+} channels are involved in controlling vigilance state, and mice with constitutive deletion of the $Ca_v3.1$ isoform ($Ca_v3.1$ knockout mice) display disrupted sleep–wake patterns. Given these findings, Uebele and colleagues postulated that T-type Ca^{2+} channels could also be involved in weight control.

To explore this theory, the authors first tested the effect of an 11-day high-fat diet (HFD) in $Ca_v3.1$ knockout mice. These mice displayed resistance to the diet, gaining significantly less weight and body fat than wild-type mice.

Next, using compound screening and optimization approaches, Uebele and colleagues identified a potent and selective T-type Ca^{2+} channel antagonist, TTA-A2. Oral administration of TTA-A2 to wild-type mice during the wake phase reduced active wake duration and promoted sedation. When administered directly before the inactive phase, TTA-A2 improved the sleep–wake cycle: animals exhibited decreased locomotor activity and body temperature during the inactive phase and increased activity during the wake phase.

Such improvements in the sleep–wake cycle following inhibition of T-type Ca^{2+} channel activity contrast with the $Ca_v3.1$ knockout mouse phenotype, which the authors think might be due in part to the lack of T-type Ca^{2+} channel subtype specificity of TTA-A2. To eliminate a potential reduction in food intake owing to daytime sedation, they administered TTA-A2 directly before the inactive phase for subsequent studies, resulting in undetectable circulating TTA-A2 levels during the wake phase. When simultaneously subjected to a 13-week HFD, TTA-A2-treated mice gained less weight, showed decreased fat mass and reduced diurnal activity disruptions compared with vehicle-treated mice.

Finally, to assess the potential of T-type Ca^{2+} channel antagonism as an obesity therapy, the authors treated diet-induced obese (DIO) mice with TTA-A2. After just 14 days of treatment, mice exhibited an almost 5% decrease in body weight and an improved sleep–wake cycle. Results were further confirmed with a comparable antagonist, TTA-A7, in DIO rats: body composition was improved beyond that observed with the appetite suppressant fenfluramine.

Overall, these findings provide support for further investigation of the regulation of sleep as a therapeutic strategy for obesity.

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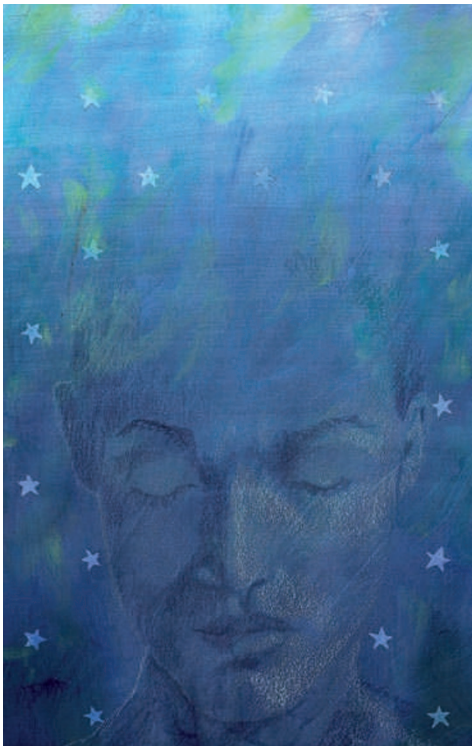

ORIGINAL RESEARCH PAPER Uebele, V. *et al.* Antagonism of T-type calcium channels inhibits high-fat diet-induced weight gain in mice. *J. Clin. Invest.* **119**, 1659–1667 (2009)