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Eat, sleep, lose weight

By Kai-Jye Lou, Staff Writer

Researchers at **Merck & Co. Inc.** may have found a way to tackle obesity by antagonizing T-type calcium channels, which are involved in sleep regulation. In rodents, the approach reduced diet-induced weight gain and increased lean muscle.[1] However, potential side effects need to be assessed, given the channels' central role in brain function.

T-type calcium channels in the brain play a role in modulating the sleep and wake cycle.[2] Past studies have linked disruption of normal sleep and wake patterns to increased risks of pathological weight gain and metabolic diseases.[3,4] High-fat diets have also been shown to disrupt normal sleeping patterns.[5,6]

Bringing together these observations, the Merck team hypothesized that selective T-type calcium channel antagonists could reduce diet-induced weight gain.

"A number of studies have suggested that the sleep cycle can influence body weight," said Victor Uebele, a senior research fellow at Merck Research Laboratories. "What we did here is take that work a bit further by providing evidence that a drug which inhibits T-type calcium channels can modify sleep in a way that benefits weight maintenance."

When given prior to sleep phase, the T-type calcium channel antagonist TTA-A2 reduced diet-induced weight gain in normal-weight rodents. In rodents with diet-induced obesity, treatment with TTA-A2 prior to sleep phase reduced body weight and fat mass and increased lean muscle mass.

Uebele told *SciBX* that selective T-type calcium channel antagonists seem to realign feeding patterns with daily circadian-controlled changes in caloric expenditure. The result is a reduction in feed efficiency, which is a metabolic activity measure of the gain in body mass per kilocalorie of food intake.

Indeed, for TTA-A2-treated rodents placed on a high-fat diet, the increase in body mass per kilocalorie of food intake was significantly lower than that for vehicle-treated controls ($p<0.0001$). The compound also minimized high-fat diet–induced changes in feeding patterns and physical activity.

According to Uebele, the resistance to diet-induced weight gain in treated animals does not seem to stem from overall decreased food intake or increased locomotor activity.

The findings were published in *The Journal of Clinical Investigation*.

"The paper provides highly interesting new data on a potential therapeutic use of T-type calcium channel blockers for the treatment of obesity—especially as it relates to diets with high fat intake," said Terrance Snutch, founder and CSO of **Neuromed Pharmaceuticals Ltd.** "There is currently a large unmet need to effectively treat obesity from the pharmacological perspective, and the Uebele paper nicely points to the notion that T-type calcium channels may represent a potentially valuable physiological target for therapeutic intervention."

In addition, Snutch told *SciBX*, "the paper provides further supporting data that there is a strong physiological relationship between T-type calcium channel function, sleep patterns and metabolic activity."

Neuromed has subtype-selective T-type calcium channel blockers in preclinical development. The company is evaluating the compounds in multiple indications including pain, epilepsy, cardiovascular diseases and metabolic disorders.

Vetting safety

Although the *JCI* data potentially set the stage for a new way to target obesity and metabolic disorders, researchers contacted by *SciBX* wanted to see the mechanism and effects of T-type calcium channel antagonists studied in additional animal models before going into the clinic.

"They should perform additional studies *in vitro* and *in vivo* to evaluate the effects of these T-type calcium channel antagonists on the circadian rhythm," said Fred Turek, a professor in the Department of Neurobiology and Physiology and director of the Center for Sleep and Circadian Biology at **Northwestern University**.

Snutch noted that TTA-A2 does not distinguish between the three main T-type calcium channel subtypes. "Thus, we are left with no real insightful mechanistic information as to whether blockade of any particular T-type channel isoform underlies the very interesting phenotypic data concerning animal high-fat–mediated obesity and the relationship to circadian rhythm and metabolism," he said. "Moving forward it would be insightful to see the results of similar long-term pharmacological studies that test new blockers specific for the Cav3.1, Cav3.2 and Cav3.3 T-type isoforms."

The isoforms are differentially expressed in cells throughout the body and are typically found in neurons and cells with pacemaker activity.

Snutch also noted that the *JCI* experiments were performed in mice and rats, which have a very high basal metabolic rate. "Compounds such as TTA-A2 would need to be examined in nonrodent models of obesity," he said.

Regarding safety, Uebele noted that in a pair of 2008 papers, Merck reported that compounds from a different class of T-type calcium channel antagonists—the fluorinated piperidines—did not cause any cardiovascular side effects in canine models.[7,8]

Rimonabant, a cannabinoid CB_1 receptor antagonist to treat obesity, also has been shown to block T-type channels. Acomplia rimonabant from **sanofi-aventis Group** was withdrawn from the European market last year following a recommendation by the EMEA's Committee for Medicinal Products for Human Use because of serious CNS side effects.

In 2001, Philippe Lory, a research director at the **Centre National de la Recherche Scientifique** (CNRS), published data showing that rimonabant could block T-type calcium channel activity.[9]

"It is interesting to note that rimonabant was also described as a T-channel blocker in one of our studies," he told *SciBX*. "It would be important to provide data showing no associated side effects such as depression" with a T-type calcium channel antagonist.

Lory added that T-type calcium channels "may also be important for β-cell regulation, so alterations in insulin secretion also should be carefully checked."

Merck said it will continue to evaluate the potential of T-type calcium channel antagonists in multiple neurological indications.

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COMPANIES AND INSTITUTIONS MENTIONED

Centre National de la Recherche Scientifique, Paris, France
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Neuromed Pharmaceuticals Ltd., Vancouver, British Columbia, Canada
Northwestern University, Evanston, Ill.
sanofi-aventis Group (Euronext:SAN; NYSE:SNY), Paris, France