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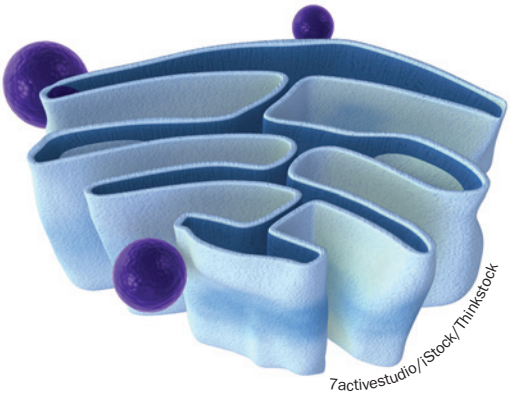
DIABETES

Antihelminthic drug for T2DM therapy?



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Niclosamide, a drug used to treat intestinal tapeworm infections, has potential as a new antidiabetic therapy, suggest findings published in *Nature Medicine*. Niclosamide ethanolamine, a salt form of niclosamide, improved features of type 2 diabetes mellitus (T2DM) in mice by inducing mitochondrial uncoupling.

"Developing drugs for reducing hepatic or muscular accumulation of lipids is the way to go for treating T2DM," says Shengkan Jin, senior author of the study. "The challenge is to find a safe and practical approach to do so."

Jin's group had previously generated a mouse model in which autophagy is defective in adipose tissue. These mice are lean and do not develop insulin resistance when consuming a high-fat diet (HFD). Mitochondria accumulate and are uncoupled in the adipose tissue of the mice. "This amazing phenotype prompted us to seek pharmacological approaches to achieve the same effect," Jin explains.

Drugs that induce mitochondrial uncoupling, such as 2,4-dinitrophenol (DNP), have previously been used in humans, but adverse effects at high doses have prevented their establishment as safe antidiabetic therapies. In 2013, a liver-targeted derivative of DNP with a higher therapeutic index than DNP was shown to reduce accumulation of fat in the liver and improve insulin resistance in rats.

Niclosamide acts by uncoupling the mitochondria of parasitic worms. Niclosamide ethanolamine has a good safety profile and is more bioavailable than niclosamide. The researchers observed that C57BL/J mice consuming a HFD that were treated with niclosamide ethanolamine had increased energy expenditure and improved metabolism. Mice with HFD-induced T2DM that were treated with niclosamide ethanolamine had lower fasting blood glucose and basal plasma insulin levels, were more insulin-sensitive and had less hepatic steatosis than diabetic mice that did not receive the drug. Glycaemic control was also improved in *db/db* mice receiving niclosamide ethanolamine.

Jin comments that the study findings are consistent with the previous reports on the effects of DNP. "The outcome is also consistent with data documenting that transgenic mice with ectopic expression of UCP1 (uncoupling protein 1) in liver, muscle or white adipose tissue exhibit exactly the same phenotypes as our mice treated with niclosamide ethanolamine."

The potential to use niclosamide ethanolamine and related compounds to treat T2DM in humans is now going to be investigated in preclinical studies required by the FDA, says Jin. The researchers are also synthesizing and testing new compounds with better efficacy and safety profiles than niclosamide ethanolamine.

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Original article Tao, H. *et al.* Niclosamide ethanolamine-induced mild mitochondrial uncoupling improves diabetic symptoms in mice. *Nat. Med.* doi:10.1038/nm.3699