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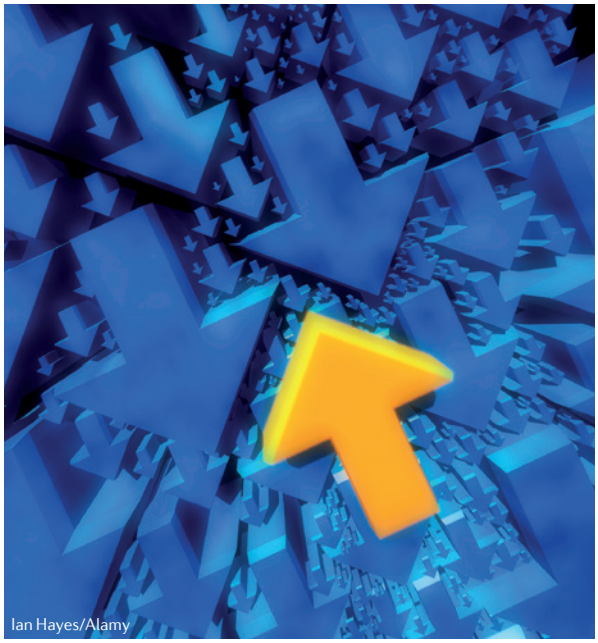
METABOLIC DISEASE

Mitochondrial uncoupler reverses diabetes

Reducing the accumulation of lipids in metabolically sensitive organs, which is believed to contribute to the development of insulin resistance and hyperglycaemia, is an attractive therapeutic strategy for type 2 diabetes (T2D). Now, Tao *et al.* demonstrate that a mitochondrial uncoupling agent safely averts this lipid accumulation, preventing and reversing T2D development in mice.

Mitochondrial uncoupling leads to energy inefficiency and increased energy expenditure, and uncoupling agents are anticipated to increase lipid oxidation and reduce intracellular lipid content. However, although a chemical mitochondrial uncoupler — 2,4-dinitrophenol (DNP) — was approved for treating obesity in the 1930s, it was withdrawn due to the risk of fatal hyperthermia. Tao and colleagues therefore set out to identify safe mitochondrial uncoupling agents that could potentially be used for T2D treatment.



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The authors focused on a salt form of niclosamide — an FDA-approved anthelmintic drug used for treating intestinal tapeworm infections, which acts by uncoupling their mitochondria — which exhibits higher water solubility and an excellent safety profile.

In mice, orally administered niclosamide ethanolamine salt (NEN) distributed primarily to the liver and had a short half-life. Mice fed NEN in conjunction with a high-fat diet (HFD) exhibited an increased rate of energy expenditure, in addition to an elevated oxygen consumption rate, a modestly increased carbon dioxide production rate and a lowered respiration quotient — effects which are indicative of increased lipid oxidation — compared with untreated HFD-fed control mice. Importantly, no differences in body temperature were noted.

Furthermore, NEN also prevented elevation of fasting blood glucose and basal plasma insulin concentrations, improved insulin sensitivity, and reduced body weight gain and fasting blood lactate concentrations (consistent with a mitochondrial uncoupling mechanism) in HFD-fed mice.

NEN was also effective in mouse models of established diabetes. Two weeks of NEN treatment reversed the metabolically deleterious effects of a HFD when fed to mice 4 months after diet initiation. Similarly, in 5-week-old *db/db* diabetic mice (which have a mutation in the leptin receptor gene), 60 days of NEN treatment lowered blood glucose concentrations and slowed the decline in plasma insulin concentrations as compared with control mice, indicating a slower disease progression. In addition, glycated haemoglobin (HbA1c) levels in the NEN-treated mice were more than 2% lower than levels in controls.

Histological analysis of mouse livers revealed massive hepatic steatosis in HFD-fed mice, whereas mice that were fed a HFD and NEN showed little intracellular lipid accumulation. Levels of the hepatic lipid metabolite, diacylglycerol, were also lower in NEN-treated mice. Electron microscopic analysis of mitochondria in the livers of NEN-treated mice showed that, overall, they had a healthier morphology than those of control mice.

Further studies of the effects of NEN in human liver carcinoma cells and in mouse livers suggested that NEN increases lipid oxidation through the activation of AMP-activated protein kinase, leading to the phosphorylation and inhibition of acetyl-CoA carboxylase 1, which is an inhibitor of mitochondrial β-oxidation.

In summary, this study reopens the possibility of developing mitochondrial uncouplers for treating metabolic disease, and supports further investigation of NEN as a potential T2D therapy.

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ORIGINAL RESEARCH PAPER Tao, H. *et al.* Niclosamide ethanolamine-induced mild mitochondrial uncoupling improves diabetic symptoms in mice. *Nature Med.* http://dx.doi.org/10.1038/nm.3699 (2014)