Nature Reviews Endocrinology | Published online 21 Oct 2016; doi:10.1038/nrendo.2016.176

THERAPY

Targeted delivery of thyroid hormone improves metabolic outcomes

> …mice given glucagon/T_3 had reduced cholesterol and triglyceride levels

Glucagon and thyroid hormone have beneficial metabolic affects, but are also associated with adverse effects. New research has demonstrated that a conjugate of glucagon and thyroid hormone can improve metabolic outcomes in animal models of metabolic diseases, without the adverse effects common when either is administered as a monotherapy.

The researchers generated three conjugates of glucagon and thyroid hormone. In the first conjugate (glucagon/T_3), T_3 was added to a side chain amine on glucagon via a spacer added to the carboxylate of T_3. In the second conjugate (glucagon/iT_3), the orientation of T_3 was inverted relative to that in glucagon/T_3. The third conjugate (glucagon/rT_3) included reverse T_3, an inactive metabolite of thyroid hormone. Labelling glucagon/T_3 with a fluorescent probe showed that the conjugate preferentially targets the liver and is present to a lesser extent in the pancreas, inguinal fat and heart.

Next, the team administered the three conjugates to mice fed a high-fat, high-cholesterol diet. Liquid chromatography–mass spectrometry analyses showed that T_3 accumulated in the liver. Furthermore, mice given glucagon/T_3 had reduced cholesterol and triglyceride levels. These effects were not seen with the other two conjugates, which shows that the form of T_3 and its orientation in the conjugate are important. Liver analysis also revealed that glucagon/T_3 upregulated several genes involved in cholesterol metabolism and uptake, fatty acid oxidation and triglyceride cycling.

These findings were confirmed in *Ldlr*$^{-/-}$ mice, which exhibit dyslipidaemia and are used to model human atherosclerosis. In addition, after 2 weeks of treatment with glucagon/T_3, atherosclerotic plaque size and lesion coverage were reduced in these mice, which suggests that the treatment could reverse atherosclerosis.

To determine whether the conjugate could ameliorate fatty liver disease, the researchers treated a mouse model of nonalcoholic steatohepatitis with glucagon/T_3 for 3 weeks. Compared with control mice, markers of steatohepatitis improved in the mice treated with glucagon/T_3, including reduced serum levels of cholesterol and alanine aminotransferase and blood levels of glucose.

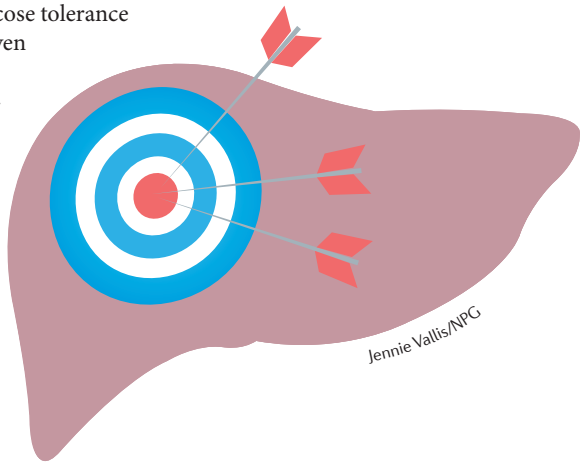
Although glucagon monotherapy was expected to have beneficial effects on lipid levels, its use as a therapeutic for obesity had not previously been considered due to its stimulating effect on hepatic glucose production. To test whether adding T_3 to glucagon affected the adverse effect profile, the researchers administered glucagon/T_3 to mice with diet-induced obesity (DIO). These mice had improved glucose tolerance compared with mice given glucagon alone and the development of hyperglycaemia and glucose intolerance were prevented with chronic treatment. Similarly, T_3 monotherapy was effective against obesity in preclinical models, but its negative effects on the cardiovascular system preclude its use in patients.

DIO mice given high-dose T_3 monotherapy had a reduced heart rate and increased respiration rate; these effects were not seen in mice given glucagon/T_3.

"Our work demonstrates that glucagon targeting of thyroid agonists improves glucose metabolism and levels of triglycerides and cholesterol in obese mice without the overt cardiac toxicity of unopposed T_3 or the diabetogenic characteristics of unopposed glucagon," concludes Richard DiMarchi, one of the authors. In the discussion section, DiMarchi and colleagues speculate that pairing glucagon and thyroid hormones in a single molecule could be used to treat a range of metabolic disorders, such as fatty liver disease, obesity, type 2 diabetes mellitus and atherosclerosis, in the future.

Claire Greenhill

ORIGINAL ARTICLE Finan, B. *et al.* Chemical hybridization of glucagon and thyroid hormone optimizes therapeutic impact for metabolic disease. *Cell* http://dx.doi.org/10.1016/j.cell.2016.09.014 (2016)



Jennie Vallis/NPG