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METABOLIC DISORDERS

Hormone conjugate combats metabolic syndrome

Dyslipidaemia, the elevation of plasma cholesterol and/or triglycerides, is a central risk factor for metabolic syndrome and can lead to insulin resistance, fatty liver and atherosclerosis. Although therapies exist to treat these conditions, such agents are often associated with side effects, and drug combinations are typically necessary. Now, writing in *Cell*, Finan, Müller and colleagues report the development of a hormone conjugate, which is comprised of glucagon and thyroid hormone, that reversed metabolic disorders in mice.

The thyroid hormone T3 exerts profound effects on energy expenditure, fat oxidation and cholesterol metabolism, but the therapeutic use of T3 is limited by adverse effects on the heart and bone. Similarly, although glucagon acts to lower lipids in the blood circulation and liver and promotes lipolysis and energy expenditure in adipose tissue, it increases blood glucose concentration by stimulating the liver to convert stored glycogen into glucose. Therefore, Finan *et al*. set out to devise a strategy that harnesses the beneficial metabolic effects of T3 and glucagon, while it mitigates their adverse effects.

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To do this, the authors engineered a hormone conjugate comprised of a 40-mer glucagon (rendered resistant to dipeptidyl peptidase 4 degradation) with a T3 moiety covalently attached to the side-chain amine of the C-terminal lysine of the glucagon moiety through a γ-glutamic acid spacer. Studies in rats, following subcutaneous injection of a single bolus of the conjugate (glucagon–T3), showed that glucagon (rather than T3) was driving the pharmacokinetics of the conjugate, whereby it predominantly trafficked to the liver.

Next, they tested the effects of the conjugate in mouse models of metabolic disorders. In diet induced obese (DIO) mice, daily subcutaneous injections of glucagon–T3 for 2 weeks reduced circulating cholesterol and triglyceride levels and lowered hepatic cholesterol content. Similar improvements in lipid handling were seen in low-density lipoprotein receptor knockout mice (a model of exaggerated dyslipidaemia) in conjunction with reversal of atherosclerotic plaque formation.

Glucagon–T3 also normalized serum levels of cholesterol, lowered triglycerides, improved blood glucose and reduced body weight in a mouse model of non-alcoholic fatty liver disease (NAFLD)-induced steatohepatitis and metabolic syndrome, when administered daily for 3 weeks. Body weight was also dose-dependently reduced by the conjugate in DIO mice owing to an increase in energy expenditure; chronic daily treatment for 14 days delivered a detectable amount of T3 to inguinal white adipose tissue, which stimulated its conversion to thermogenic brown-like adipose tissue.

Importantly, the preferential delivery of the conjugate to the liver prevented adverse effects of T3 on cardiac function and bone health. In DIO mice, although T3 monotherapy increased heart rate and respiration rate, glucagon–T3 did not affect either parameter. In contrast to T3 monotherapy, chronic treatment of lean mice with a dose of glucagon–T3 that lowered both body weight and lipid levels did not affect bone volume or markers of bone turnover.

In addition, the T3 action of glucagon–T3 overcame the potential hyperglycaemic effects of glucagon. In DIO mice, the conjugate prevented hyperglycaemia and glucose intolerance that were evident with glucagon monotherapy.

Together, these data support the potential therapeutic utility of combining glucagon and T3 in a single molecule to reverse disorders of metabolic syndrome.

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ORIGINAL ARTICLE Finan, B. et al. Chemical hybridization of glucagon and thyroid hormone optimizes therapeutic impact for metabolic disease. *Cell* **167**, 843–857 (2016)