CARDIOVASCULAR DISEASE

Hormone mimic reduces cholesterol

Lowering levels of 'bad' cholesterol is a well-established approach to reduce the risk of cardiovascular disease (CVD), but a significant need remains for drugs that could help achieve this goal. Writing in *PNAS*, Baxter and colleagues present the first clinical data for a novel mimetic of thyroid hormone (TH) — KB2115 (eprotirome) — demonstrating its ability to lower cholesterol levels while lacking the adverse effects of TH itself.

TH is a key regulator of metabolic pathways and a modulator of several CVD risk factors; being capable of reducing low-density lipoprotein (LDL) cholesterol and triglyceride levels, as well as inducing weight loss. The TH receptor (THR) therefore holds promise as a novel therapeutic target for various conditions. However, owing to a number of deleterious effects of TH, particularly dose-limiting cardiotoxicity, the therapeutic potential of THR agonists in humans remains largely unexplored.

Direct effects of TH on heart rate are thought to be mediated largely by THRα, whereas the THRβ isoform predominates in the liver. So, it has been suggested that specific agonists of THRβ — especially those that are taken up selectively by the liver, as is the case with KB2115 — might mimic the therapeutically beneficial effects of TH on lipids, while bypassing unwanted effects on the heart. Indeed, recent studies in several animal models have indicated that selective THRβ activation and tissue uptake has therapeutic potential — cholesterol is lowered and metabolic rate is increased in the absence of cardiotoxicity. Therefore, the authors set out to explore whether these observations held true in humans.

Twenty four moderately overweight and hypercholesterolaemic patients were dosed with KB2115 once-daily for 2 weeks. This resulted in a decrease in LDL cholesterol levels of up to 40%, with no significant change in serum high-density lipoprotein (HDL) cholesterol levels. In addition, the apolipoprotein B to apolipoprotein A-1 ratio was decreased, indicating a reduced risk for myocardial infarction. There were no effects on triglyceride or lipoprotein(a) levels. Whole body total cholesterol synthesis was not changed but bile-acid synthesis appeared to be stimulated, suggesting that KB2115 may act to induce net liver cholesterol removal. Previous studies in mice showed that THRβ-selective agonists act differently to statins (the most popular class of LDL-lowering drugs). These agonists increase expression of the SR-B1 HDL receptor, which is involved in reverse cholesterol transport, and stimulate cytochrome P450 7A activity, which converts cholesterol to bile acids.

Importantly, KB2115 exerted no effects on the heart — there was no change in heart rate, blood pressure or electrocardiogram profile. No significant changes in metabolic rate or body weight were noted, but this was thought to be due to the low dose administered and the short duration of the study.

These data suggest that thyroid-hormone mimetics have promising potential as cholesterol-lowering agents. Moreover, if they prove to be safe and effective in the long term, they might be useful for patients who are intolerant to statin therapy, or could be used in combination with statins to attain treatment targets or limit adverse effects. A larger Phase IIb study is currently underway to further assess these possibilities.

Sarah Crunkhorn

ORIGINAL RESEARCH PAPER Berkenstam, A. *et al.* The thyroid hormone mimetic compound KB2115 lowers plasma LDL cholesterol and stimulates bile acid synthesis without cardiac effects in humans. *Proc. Natl Acad. Sci. USA* **105**, 663–667 (2008)

FURTHER READING Johansson, L. *et al.* Selective thyroid receptor modulation by GC-1 reduces serum lipids and stimulates steps of reverse cholesterol transport in euthyroid mice. *Proc. Natl. Acad. Sci. USA* **102**, 10297–10302 (2005)