Abstract

Thyroid hormones (TH), particularly triiodothyronine (T3), are key regulators of thermogenesis and energy metabolism. Despite extensive research, the mechanisms underlying TH-mediated body temperature elevation and their link to glucose homeostasis remain incompletely understood.

This thesis examined the effects of chronic hyperthyroidism on thermoregulation and hepatic metabolism in mice. Continuous core body temperature recordings combined with PET/CT imaging and multi-omics profiling revealed T3-dependent activation of thermogenic tissues and hepatic metabolic reprogramming.

Systemic hyperthyroidism elevated core body temperature across all tested ambient temperatures (10 °C, 23 °C, 30 °C), most pronounced during the resting phase. This was accompanied by increased energy expenditure and food intake. Interestingly, brown adipose tissue (BAT) was not responsible for the temperature elevation. Instead, a newly developed, unbiased PET/CT-UMAP workflow identified white adipose tissue (WAT) as a relevant contributor to T3-mediated thermogenesis. These findings were further supported by characteristic browning signatures of WAT.

Multi-omics profiling revealed pronounced suppression of glycogen metabolism, glycolysis and gluconeogenesis under hyperthyroid conditions, shifting hepatic energy metabolism towards lipogenesis and cholesterol turnover.

This metabolic reprogramming in the liver led to pronounced metabolic inflexibility, with declining blood glucose levels during fasting and anaesthesia. Reduced hepatic glycogen stores were identified as the primary cause of these disturbances. We could further show that liver-specific inhibition of TRβ-signalling restored glycogen synthesis and prevented fasting-induced glucose decline, confirming direct hepatic mediation.

These results provide mechanistic insights into T3-mediated thermogenesis and hepatic glucose dysregulation. The latter is particularly essential for understanding and developing liver-selective thyroid hormone analogues for obesity and type 2 diabetes therapy.