Triglyceride metabolism in liver is regulated by non-canonical action of TRβ

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Abstract

Thyroid hormone (TH) signaling is essential for maintaining normal hepatic triglyceride (TG) metabolism and TH deficiency is associated with hyperlipidemia and nonalcoholic fatty liver disease. How TH influences TG metabolism is still unknown. TH and TH receptors (TRs) α and β act by binding to TH response elements (TREs) on promoters of target genes. This nuclear signaling is established as the canonical pathway for TH action. Therefore, the current paradigm of TH action attributes physiological TH effects to gene induction via canonical TR signaling on DNA. But TRs can also modulate intra-cellular second messenger signaling. Such TR signaling is considered non-canonical, because it is independent from DNA- and TRE-binding and does not require gene transcription or protein synthesis.

To determine whether TH regulate TG metabolism by canonical or non-canonical TRβ signaling, we studied wildtype, TRβ knock-out mice ($TR\beta^{KO}$) and TRβ knock-in mice with complete abrogation of either canonical TRβ signaling ($TR\beta^{GS}$ mice) or non-canonical TRβ signaling ($TR\beta^{147F}$), hypothesizing that a comparison of these mice would allow to attribute TG regulation to canonical or non-canonical TH/TRβ signaling. Absence of non-canonical TRβ signaling in $TR\beta^{KO}$ and $TR\beta^{147F}$ mice resulted in high TG serum and liver concentration compared to wildtype and $TR\beta^{GS}$ mice. High TG concentrations in $TR\beta^{KO}$ and $TR\beta^{147F}$ mice were associated with increased hepatic mRNA and protein expression of lipogenic key enzymes (fatty acid synthase (Fasn), stearoyl-CoA desaturase1 (Scd1) and malic enzyme 1 (Me1)). By contrast, expression of *Fasn*, *Scd1* and *Me1* was not increased in $TR\beta^{GS}$ and wildtype mice. These data show that TH regulate TG metabolism and serum concentration by non-canonical TRβ signaling.