

Involvement of Kupffer cell-dependent signaling in T3-induced hepatocyte proliferation in vivo

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Thyroid hormone-induced calorigenesis triggers liver oxidative stress with concomitant TNF- α production by Kupffer cells and up-regulation of gene expression. Considering that cyclin-dependent kinase-2 (CDK-2) performs essential functions for cellular proliferation, our aim was to test the hypothesis that l-3,3',5-triiodothyronine (T3) stimulates liver cell proliferation by upstream mechanisms involving CDK-2 expression dependent on Kupffer cell signaling. T3 administration induced a calorigenic response at 60-70 h after treatment, with increased TNF- α generation and hepatic oxidative stress status, as shown by enhanced protein carbonyls and decreased glutathione content compared to controls. In this time interval, liver c-jun N-terminal kinase (JNK) phosphorylation, activator protein-1 (AP-1) DNA binding, and CDK-2 expression were enhanced, with concomitantly higher levels of the proliferation markers Ki-67 and proliferating cell nuclear antigen. These changes are abolished by adminis