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Up-regulation of stearoyl-CoA and δ6-desaturase expression following MEK/ERK inhibition alters the fatty acid composition of HepG2 human hepatic cell line

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Background and Aims: The extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase pathway, also known as the MEK/ERK kinase cascade, has recently been implicated in the regulation of lipid metabolism and fatty liver disease. However, its role in the control of hepatic fatty acid metabolism is unknown. Herein, we examined the effect of a pharmacological inhibitor of MEK, the upstream kinase activator of ERK, on fatty acid metabolism of hepatocellular carcinoma cell line HepG2.
Methods: HepG2 cells cultured in RPMI-1640 were exposed to a range of concentrations [from 10 5M (2.7 mg/L) up to 10 4.3M (13.3 mg/L)] of the MEK/ERK inhibitor PD-98059, and investigated with respect to stearoyl-CoA (SCD1) and Δ6-desaturase (Δ6D) gene expression by RT-PCR and fatty acid composition by gas-liquid chromatography (GLC).
Results: Inhibition of MEK/ERK by addition of the MEK inhibitor PD-98059, induced both SCD1 and Δ6D gene expression in vitro at a concentration as low as 10-4.8M (4 mg/L; P = 0.03). Exposure of cells to the MEK/ERK inhibitor induced a time and dose-dependent increase in monounsaturated fatty acids (MUFA) and the Δ6D index (20:4/18:2). Specifically, 10 4.3M (13.3 mg/L) PD-98059 induced a significant increase of oleic acid (+29%; P=0.003) and 20:4/18:2 ratio (3.5-fold; P<0.001) in HepG2 cells.
Conclusions: We found that suppression of ERK/MEK signaling pathway leads to enhanced expression SCD1 and Δ6D. These findings identify a role for MEK/ERK kinase cascade in the regulation of hepatic fatty acid metabolism, and thus in maintaining lipid homeostasis.

Keywords: PD-98059; Δ6 desaturase; SCD1