

Combined docosahexaenoic acid and thyroid hormone supplementation as a protocol supporting energy supply to precondition and afford protection against metabolic stress situations

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Liver preconditioning (PC) refers to the development of an enhanced tolerance to injuring stimuli. For example, the protection from ischemia-reperfusion (IR) in the liver that is obtained by previous maneuvers triggering beneficial molecular and functional changes. Recently, we have assessed the PC effects of thyroid hormone (T3; single dose of 0.1 mg/kg) and n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFAs; daily doses of 450 mg/kg for 7 days) that abrogate IR injury to the liver. This feature is also achieved by a combined T3 and the n-3 LCPUFA docosahexaenoic acid (DHA) using a reduced period of supplementation of the FA (daily doses of 300 mg/kg for 3 days) and half of the T3 dosage (0.05 mg/kg). T3-dependent protective mechanisms include (i) the reactive oxygen species (ROS)-dependent activation of transcription factors nuclear factor- κ B (NF- κ B), AP-1, signal transducer and activator of transcription 3, and nuclear factor erythroid-2-related factor 2 (Nrf2) upregulating the expression of protective proteins. (ii) ROS-induced endoplasmic reticulum stress affording proper protein folding. (iii) The autophagy response to produce FAs for oxidation and ATP supply and amino acids for protein synthesis. (iv) Downregulation of inflammasome nucleotide-binding oligomerization domain leucine-rich repeat containing family pyrin containing 3 and interleukin-1 β expression to prevent inflammation. N-3 LCPUFAs induce antioxidant responses due to Nrf2 upregulation, with inflammation resolution being related to production of oxidation products and NF- κ B downregulation. Energy supply to achieve liver PC is met by the combined DHA plus T3 protocol through upregulation of AMPK coupled to peroxisome proliferator-activated receptor- γ coactivator 1 β signaling. In conclusion, DHA plus T3 coadministration favors hepatic bioenergetics and lipid homeostasis that is of crucial importance in acute and clinical conditions such as IR, which may be extended to long-term or chronic situations including steatosis in obesity and diabetes. © 2019 IUBMB Life, 71(9):1211-1220, 2019.