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Valproate-induced liver injury: modulation by the omega-3 fatty acid DHA proposes a novel anticonvulsant regimen.

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Abstract

BACKGROUND: The polyunsaturated, ω-3 fatty acid, docosahexaenoic acid (DHA), claims diverse cytoprotective potentials, although via largely undefined triggers. Thus, we currently first tested the ability of DHA to ameliorate valproate (VPA)-evoked hepatotoxicity, to modulate its anticonvulsant effects, then sought the cellular and molecular basis of such actions. Lastly, we also verified whether DHA may kinetically alter plasma levels/clearance rate of VPA.

METHODS AND RESULTS: VPA (500 mg/kg orally for 14 days in rats) evoked prominent hepatotoxicity that appeared as a marked rise (2- to 4-fold) in serum hepatic enzymes (γ-glutamyl transferase [γ-GT], alanine aminotransferase [ALT], and alkaline phosphatase [ALP]), increased hepatic lipid peroxide (LPO) and tumor necrosis factor-alpha (TNFα) levels, as well as myeloperoxidase (MPO) activity (3- to 5-fold), lowering of serum albumin (40 %), and depletion of liver reduced-glutathione (GSH, 35 %). Likewise, histopathologic examination revealed hepatocellular degeneration, replacement by inflammatory cells, focal pericentral necrosis, and micro/macrovesicular steatosis. Concurrent treatment with DHA (250 mg/kg) markedly blunted the elevated levels of liver enzymes, lipid peroxides, TNFα, and MPO activity, while raising serum albumin and hepatic GSH levels. DHA also alleviated most of the cytologic insults linked to VPA. Besides, in a pentylenetetrazole (PTZ) mouse convulsion model, DHA (250 mg/kg) markedly increased the latency in convulsion evoked by VPA, beyond their individual responses. Lastly, pharmacokinetic studies revealed that joint DHA administration did not alter serum VPA concentrations.

CONCLUSIONS: DHA substantially ameliorated liver injury induced by VPA, while also markedly boosted its pharmacologic effects. DHA manipulated definite cellular machinery to curb liver oxidative stress and inflammation, without affecting VPA plasma levels. Collectively, these protective and synergy profiles for DHA propose a superior VPA-drug combination regimen.

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