DEHYDROEPIANDROSTERONE PROTECTS AGAINST ACETAMINOPHEN-INDUCED LIVER DAMAGE IN RATS BY UPREGULATION OF BCL-2 AND ACTIVATION OF SIRT SIGNALING

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The study examined the protective effect of exogenous administration of dehydroepiandrosterone (DHEA) against acetaminophen (APAP) -induced liver damage in rats and tested the underlying mechanism(s). Male rats were divided into 5 groups as control, control + DHEA, APAP, APAP + DHEA, and APAP + DHEA + EX-527 (SIRT1 inhibitor). Treatments were conducted for 10 days and then followed by intragastric administration of a single dose of APAP. DHEA not only reduced serum alanine transaminase (ALT) and aspartate aminotransferase (AST) but also preserved the liver structures. Besides, DHEA reduced hepatic levels of tumor necrosis factor-alpha (TNF-a), interleukin 6 (IL-6), Bax, cleaved caspase-3. In the livers of both the control and APAP-treated rats, DHEA suppressed the generation of reactive oxygen species (ROS) and malondialdehyde (MDA), increased levels of glutathione (GSH), MnSOD (SOD2), and Bcl-2 levels, lowered Bax/Bcl-2 ratio, enhanced the activity of nuclear factor erythroid-derived 2-like 2 (Nrf2), and inhibited nuclear factor kappaB (NF-kB) p65. All these effects coincided with a significant increase in the levels and activity of SIRT1 and a reduction in the acetylation of Nrf2, p53, forkhead box class O transcription factor 1 (FOXO1), and NF-kB p65. Except for Bcl-2, treating the rats with EX-527 abolished the beneficial effects of DHEA on all these markers. In conclusion, DHEA prevents APAP-induced liver damage by concomitant upregulation of Bcl-2 and SIRT1-dependent effect.