PROTECTIVE EFFECTS OF RESVERATROL ON HEPATOTOXICITY INDUCED BY ANTITUBERCULOSIS DRUGS

Inteviews: Tuberculosis (TB) is a major infectious disease that causes nearly two million deaths every year. Isoniazid (INH) and rifampin (RIF) are first line drugs used to prevent and treat TB. RIF has been extensively reported to exacerbate the hepatotoxicity caused by INH in patients with TB. Anti-TB drug-induced hepatotoxicity causes substantial morbidity and diminishes treatment effectiveness because they contribute to non-adherence, treatment failure and the emergence of drug-resistance (Tostmann et al., 2008). Resveratrol (RSV) is a naturally occurring polyphenol with significant anti-inflammatory and antioxidant properties. Moreover, hepatoprotective effects for RSV have been previously demonstrated (Baur et al., 2006). In this work we have investigated the effects of RSV in the hepatotoxicity caused by INH and RIF in mice. Methods: All the experimental protocols were approved by the local Animal Ethics Committee (09/00107). Mice were distributed into four groups: (i) control, (ii) RSV-treated control, (iii) INH-RIF, and (iv) RSV-treated + INH-RIF. Liver damage was acutely induced by dosing INH (50 mg/kg) and RIF (100 mg/kg) in male BALB/c mice (25–30 g), both p.o., for three consecutive days. RSV (100 mg/Kg) was administered orally 30 min prior to INH-RIF administration, and 2 times daily, each 6 h, until the third day after hepatotoxicity induction. Serum biochemical tests for liver function, histopathological examination, oxidative stress tests and myeloperoxidase (MPO) activity of liver tissues were determined. Results: Treatment of mice with INH+RIF induced hepatotoxicity as it was evidenced by elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Histopathological examination of liver tissue showed steatosis and increased apoptosis in the animals that received anti-TB drugs, which was accompanied by a marked increase of...
tissue MPO activity. As expected, catalase and glutathione activities were found to be reduced by INH-RIF treatment. The administration of RSV significantly decreased ALT and AST levels (58 ± 4 % and 36 ± 8 %, respectively), as well as the MPO activity (19 ± 3 %). Furthermore, the treatment with RSV completely reverted the decrease of both catalase and glutathione activities, and generally ameliorated the histopathological alterations associated to hepatotoxicity evoked by anti-TB drugs. **Discussion:** Recent data pointed out RSV as an antioxidant and anti-inflammatory agent able to prevent acetaminophen-induced hepatic failure in mice. Other studies show that RSV reduced mortality and liver damage induced by alcohol and partial hepatectomy in rats. In conclusion, the present study demonstrates, for the first time, that RSV protects against hepatotoxicity induced by INH-RIF. It is tempting to suggest that this natural compound might be useful for the treatment of liver injury due to anti-TB drugs.

**Financial support:** CNPq-INCT, BNDES.

**Referências**
