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Involvement of BCRP/ABCG2 in Protective Mechanisms of Resveratrol against Methotrexate-Induced Renal Damage in Rats

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Abstract : Resveratrol (RES) is a well-known polyphenol antioxidant. We have previously shown that testicular protective effect of RES against the anticancer drug methotrexate (MTX)-induced toxicity involves transporter-mediated mechanisms. Here, we investigated the effect of RES on MTX-induced nephrotoxicity. Rats were administered RES (10 mg/kg/day) for 8 days, with or without a single MTX dose (20 mg/kg i.p.) at day 4 of the experiment. MTX induced nephrotoxicity evident by significantly increase in serum blood urea nitrogen and creatinine compared to control, as well as distortion of kidney microscopic structure. MTX also significantly increased renal nitric oxide level, with induction of inducible nitric oxide synthase expression. MTX also significantly up-regulated fas ligand and caspase 3. Administering RES prior to MTX significantly improved kidney function and microscopic picture, as well as significantly decreased nitrosative and apoptotic markers compared to MTX alone. RES, but not MTX, caused significant increase in expression of breast cancer resistance protein (BCRP), an apical efflux renal transporter that participates in urinary elimination of both MTX and RES. Interestingly, concomitant MTX and RES caused further up-regulation of renal Bcrp compared to RES alone. Using Human BCRP ATPase assay, both RES and MTX exhibited dose-dependent increase in ATPase activity, with Km values of 0.52 ± 0.03 and 30.9 ± 4.2 μM, respectively. Furthermore, combined RES and MTX caused ATPase activity which was significantly less than maximum ATPase activity attained by the positive control; sulfasalazine (12.5 μM). In conclusion, RES exerted nephro-protection against MTX-induced toxicity through anti-nitrosative and anti-apoptotic effects, as well as via up-regulation of renal Bcrp.

Keywords : methotrexate, resveratrol, nephrotoxicity, breast cancer resistance protein
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