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Effect of Auraptene on the Enzymatic Glutathione Redox-System in Nrf2 Knockout Mice

Authors : Ludmila A. Gavriliuc, Jerry McLarty, Heather E. Kleiner, J. Michael Mathis

Abstract : Abstract -- Background: The citrus coumarine Auraptene (Aur) is an effective chemopreventive agent, as manifested in many models of diseases and cancer. Nuclear factor erythroid 2-related factor (Nrf2) is an important regulator of genes induced by oxidative stress, such as glutathione S-transferases, heme oxygenase-1, and peroxiredoxin 1, by activating the antioxidant response element (ARE). Genetic and biochemical evidence has demonstrated that glutathione (GSH) and glutathione-dependent enzymes, glutathione reductase (GR), glutathione peroxidases (GPs), glutathione S-transferases (GSTs) are responsible for the control of intracellular reduction-oxidation status and participate in cellular adaptation to oxidative stress. The effect of Aur on the activity of GR, GPs (Se-GP and Se-iGP), and content of GSH in the liver, kidney, and spleen is insufficiently explored. Aim: Our goal was the examination of the Aur influence on the redox-system of GSH in Nrf2 wild type and Nrf2 knockout mice via activation of Nrf2 and ARE. Methods: Twenty female mice, 10 Nrf2 wild-type (WT) and 10 Nrf2 (-/-) knockout (KO), were bred and genotyped for our study. The activity of GR, Se-GP, Se-iGP, GST, G6PD, CytP450 reductase, catalase (Cat), and content of GSH were analyzed in the liver, kidney, and spleen using Spectrophotometry methods. The results of the specific activity of enzymes and the amount of GSH were analyzed with ANOVA and Spearman statistical methods. Results: Aur (200 mg/kg) treatment induced hepatic GST, GR, Se-GP activity and inhibited their activity in the spleen of mice, most likely via activation of the ARE through Nrf2. Activation in kidney Se-GP and G6PD by Aur is also controlled, apparently through Nrf2. Results of the non-parametric Spearman correlation analysis indicated the strong positive correlation between GR and G6PD only in the liver in WT control mice ($r=+0.972$; $p < 0.005$) and in the kidney KO control mice ($r=+0.958$; $p < 0.005$). The observed low content of GSH in the liver of KO mice indicated an increase in its participation in the neutralization of toxic substances with the absence of induction of GSH-dependent enzymes, such as GST, GR, Se-GP, and Se-iGP. Activation of CytP450 in kidney and spleen and Cat in the liver in KO mice probably revealed another regulatory mechanism for these enzymes. Conclusion: Thereby, obtained results testify that Aur can modulate the activity of genes and antioxidant enzymatic redox-system of GSH, responsible for the control of intracellular reduction-oxidation status.

Keywords : auraptene, glutathione, GST, Nrf2
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