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Regulation of Cytochrome P450 2E1 expression by ethanol: Role of oxidative stress-mediated PKC/JNK/SP1 pathway

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Our previous study has shown that CYP2E1 is induced by alcohol in HIV-1 system, monocytes. However, the signaling pathways involved in CYP2E1 regulation in this as well as other extrahepatic cells are not clear. This study has been designed to examine the signaling pathways by which ethanol regulates CYP2E1 in extra-hepatic cells. Our results showed that 100mM ethanol induced apoptotic cell death (MTT, TUNEL, Caspase-3, and Annexin V), which was rescued by inhibiting CYP2E1 using either a CYP2E1 selective inhibitor diallyl sulfide (DAS) or CYP2E1 siRNA, as well as, by antioxidants (vitamin C/E), in the SVGA astrocytes and U937 monocytes. Further, we showed that DAS and vitamin C/E abrogated ethanol-mediated (50 mM) induction of CYP2E1 as well as production of reactive oxygen species, suggesting the role of oxidative stress in ethanol-mediated induction of CYP2E1. We then investigated the role of the protein kinase C/c-Jun N-terminal kinase/specificity protein1 (PKC/JNK/SP1) pathway in oxidative stress-mediated CYP2E1 induction. Our results showed that staurosporine, an inhibitor of PKC, completely abolished ethanol-induced CYP2E1 expression. In addition, inhibitors of JNK and SP1 showed completely abrogated induction of CYP2E1 by ethanol in SVGA astrocytes. Finally, we showed that PKC/JNK/SP1 pathway is also involved in regulation of CYP2E1 in U937 monocytic cell line. This study has clinical implications with respect to brain toxicity, especially in HIV-infected individuals, because alcohol consumption is prevalent in the HIV+ population and is known to exacerbate HIV-1 pathogenesis.

Biography

Mengyao Jin has completed her Ph.D. at the age of 26 years from University of Missouri-Kansas City, where she has published 8 papers in reputed journals, along with awards from national conference as a young investigator.

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