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ACCEPTED MANUSCRIPT

Mechanisms involved in the death of steatotic WIF-B9 hepatocytes coexposed to benzo[a]pyrene and ethanol: a possible key role for xenobiotic metabolism and nitric oxide

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ABSTRACT

We previously demonstrated that co-exposing pre-steatotic hepatocytes to benzo[a]pyrene (B[a]P), a carcinogenic environmental pollutant, and ethanol, favored cell death. Here, the intracellular mechanisms underlying this toxicity were studied. Steatotic WIF-B9 hepatocytes, obtained by a 48h-supplementation with fatty acids, were then exposed to B[a]P/ethanol (10 nM/5 mM, respectively) for 5 days. Nitric oxide (NO) was demonstrated to be a pivotal player in the cell death caused by the co-exposure in steatotic hepatocytes. Indeed, by scavenging NO, CPTIO treatment of co-exposed steatotic cells prevented not only the increase in DNA damage and cell death, but also the decrease in the activity of CYP1, major cytochrome P450s of B[a]P metabolism. This would then lead to an elevation of B[a]P levels, thus possibly suggesting a long-lasting stimulation of the transcription factor AhR. Besides, as NO can react with superoxide anion to produce peroxynitrite, a highly oxidative compound, the use of FeTPPS to inhibit its formation indicated its participation in DNA damage and

¹ equal supervision

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