TOXICOLOGICAL HIGHLIGHT

Bile Pigments: Newcomers to the Cell Signaling Arena

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The article highlighted in this issue is “2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-Induced Accumulation of Biliverdin and Hepatic Peliosis in Rats,” by Marjo Nittynen, Jouni T. Tuomisto, Seppo Auriola, Raimo Pohjanvirta, Paula Syrjälä, Ulla Simanainen, Matti Viluksela, and Jouko Tuomisto (pp. 112–123).

The observation by Niittynen et al. that TCDD induces accumulation of biliverdin and causes hepatic peliosis is most intriguing and might possibly open a new window into the underlying molecular basis for toxicity of polychlorinated biphenyl complexes. The effects were most often observed in rats carrying the auxiliary TCDD resistance gene. The recent unexpected findings of the bioregulatory activities of bile pigments and enzymes that synthesize those pigments prompts this prediction. Relevant considerations that form this view are highlighted here.

The heme molecule is oxidatively cleaved by microsomal heme oxygenase resulting in release of iron and generation of biliverdin and CO (Maines, 1992, 1997). Biliverdin is subsequently reduced by the dual cofactor/pH dependent soluble enzyme, biliverdin reductase (Kutty and Maines, 1981). Bile pigments, biliverdin and its reduction product, bilirubin, have been traditionally viewed solely as toxic waste products of heme (Fe-protoporphyrin IX) catabolism. This view was dramatically changed when bile pigments, particularly bilirubin, were found to be potent antioxidants (Neuzil and Stocker, 1994). In more recent times, convincing data have been reported demonstrating that biliverdin and bilirubin are also effective modulators of cell signaling pathways, including their being activators of aryl hydrocarbon receptor (AhR) (Phelan et al., 1998; Sinal and Bend, 1997).

The relevance of biliverdin and bilirubin activation of AhR to real life conditions has been questioned (Adachi et al., 2001), the basis of the skepticism being whether in vivo concentration of the tetrapyrroles reaches sufficiently high levels to function as physiological ligands for AhR. The report by Niittynen et al. shows that indeed, in genetically susceptible rats, tremendous amounts of biliverdin can accumulate in the hepatocytes subsequent to TCDD treatment, hence permitting the suggestion that biliverdin can function in genetically predisposed animals as an endogenous activator of AhR. This line of reasoning can be extended to any toxic agent or drug that has such an effect on hepatic biliverdin concentration, allowing it to function as a “physiological” ligand for AhR. Because AhR-mediated signaling is essential for polychlorinated biphenyls, including TCDD, to elicit cellular response, the reported increase in hepatocytes’ biliverdin concentration underscores the significance of the observation. Biliverdin-mediated AhR activation may promote a host of biological and toxic effects that are mediated by TCDD, including control of cellular proliferation, cell-cycle arrest in G1 phase, protein kinase phosphorylation, and transcriptional activation of cell cycle regulators (Enan and Matsumura, 1995; Ge and Elferink, 1998; Puga et al., 2000).

Aside from affecting cellular functions through activation of AhR, increased levels of biliverdin are likely to exert dramatic regulatory effects on other signal transduction pathways and cellular antioxidant defense mechanisms. To elaborate, biliverdin is a feedback inhibitor of biliverdin reductase (Kutty and Maines, 1981), a newly identified serine/threonine kinase (Salim et al., 2001), and a transcription factor (Ahmad et al., 2002). Moreover, a recent study has identified a role for biliverdin IX in dorsal axis development in Xenopus laevis embryo (Falchuk et al., 2002). Considering the host of factors that participate in cell differentiation and the signaling cascades that control gene expression in the course of embryonic development, it is not unreasonable to suspect that in the mammalian hepatocyte as well, increased levels of biliverdin could also influence various signaling pathways. Consistent with this idea is the fact that biliverdin is a modulator of tumor cell growth (Lombard et al., 1994; Wen, 2002). Thus, in the case of TCDD-treated genetically susceptible rats, an additional component of TCDD toxicity may well be related to the biological activity of biliverdin in itself, independent of the tetrapyrrole’s activation of AhR.

One ponders why biliverdin is increased in the hepatocyte in the first place. A plausible explanation may be sought in cells attempting to defend against TCDD-mediated oxidative stress. Heme oxygenase-1 (HO-1), or HSP-32, is a stress/heat shock responsive gene that is induced by a vast number of agents that

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have in common the ability to mediate oxidative stress (Maines, 1992). Although in the study by Nittynen et al. heme oxygenase activity was not assessed in the treated rats, it is likely that the increased level of biliverdin was accompanied by an increased expression of HO-1. Because an increase in heme oxygenase activity accelerates the degradation rate of denatured hemoproteins (Maines, 1992), their potential prooxidant activity is attenuated. The conversion of the prooxidant heme to the antioxidant’s bile pigments would clearly reflect a defense response in the hepatocyte (Chiu et al., 2002) as well as other cell types. In the case of this particular strain of rats, however, the response appears highly exaggerated, thus effectively expunging the antioxidant benefits that increased bile pigment formation would offer. Most likely, in the presence of high levels of biliverdin, the activity of biliverdin reductase would be inhibited. The potent induction of the heme biosynthesis enzymes by TCDD would insure ample supply of heme for catalyses, and induction of cytochrome P450 1A1, which oxidizes bilirubin to vasoactive compounds (Clark et al., 2002; De Matteis et al., 1991), would promote hepatic peliosis. At the same time, an increase in CO production would further fuel the process, since CO is a modulator of sinusoidal tone and a vasodilator (Suematsu et al., 1995). The impact of this report would have been enhanced if heme oxygenase and biliverdin reductase activities were assessed and compared in the TCDD-treated rat strains.

In conclusion, the multifaceted and pluripotential actions of biliverdin and the heme oxygenase system underscore the significance of this article. The findings permit speculation as to the possibility that the concentration of biliverdin in the cell can reach levels required for activation of AhR. They also reveal an unsuspected aspect of TCDD toxicity that surely has bearing on the mechanism of action of numerous xenobiotics and compounds that cause oxidative stress and are AhR ligands.

REFERENCES


