Bilirubin decreases NOS2 expression via inhibition of NAD(P)H oxidase: implications for protection against endotoxic shock in rats.

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We investigated a possible beneficial role for bilirubin, one of the products of heme degradation by the cytoprotective enzyme heme oxygenase-1 in counteracting Escherichia coli endotoxin-mediated toxicity. Homozygous jaundice Gunn rats, which display high plasma bilirubin levels due to deficiency of glucuronyl transferase activity, and Sprague-Dawley rats subjected to sustained exogenous bilirubin administration were more resistant to endotoxin (LPS)-induced hypotension and death compared with nonhyperbilirubinemic rats. LPS-stimulated production of nitric oxide (NO) was significantly decreased in hyperbilirubinemic rats compared with normal animals; this effect was associated with reduction of inducible NO synthase (NOS2) expression in renal, myocardial, and aortic tissues. Furthermore, NOS2 protein expression and activity were reduced in murine macrophages stimulated with LPS and preincubated with bilirubin at concentrations similar to that found in the serum of hyperbilirubinemic animals. This effect was secondary to inhibition of NAD(P)H oxidase since 1) inhibition of NAD(P)H oxidase attenuated NOS2 induction by LPS, 2) bilirubin decreased NAD(P)H oxidase activity in vivo and in vitro, and 3) down-regulation of NOS2 by bilirubin was reversed by addition of NAD(P)H. These findings indicate that bilirubin can act as an effective agent to reduce mortality and counteract hypotension elicited by endotoxin through mechanisms involving a decreased NOS2 induction secondary to inhibition of NAD(P)H oxidase.
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