Receptor-mediated therapeutic potential of lumirubin and 6-formylindolo[3,2-b]carbazole in phototherapy of neonatal hyperbilirubinaemia

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Abstract

Background and purpose: Bilirubin toxicity in newborn infants leading to kernicterus disturbs immune and neuronal functions through proinflammatory cytokines and a hyperglutamatergic state. Tryptophan metabolism along the kynurenine pathway may underpin both features. Phototherapy of neonatal hyperbilirubinemia (NNH) converts bilirubin to harmless products, mainly lumirubin. Lumirubin possesses protective properties, though its precise mechanism(s) of action is less understood. The tryptophan metabolite and photooxidation product 6-formylindolo[3,2-b]carbazole (FICZ) may also be formed during NNH phototherapy. Experimental approach: We have explored the basis of potential mechanisms of lumirubin and FICZ actions by their molecular docking to the following receptors: the aryl hydrocarbon (AhR), NMDA, kainate and GABA receptors. We compared their docking to the AhR with those of bilirubin and biliverdin and the potent AhR agonists FICZ, indirubin and 2,3,7,8-Tetrachlorodibenzo-p-dioxin and their docking to the other receptors with those of kynurenic (KA) and quinolinic (QA) acids. Key results: lumirubin and FICZ dock very strongly to the AhR, whereas biliverdin and bilirubin do not. Both lumirubin and FICZ also dock strongly to the NMDA and GABA receptors, as do KA and QA. Conclusions and implications: AhR activation by lumirubin may form the basis of NNH phototherapy. FICZ is also likely to play a role in NNH phototherapy. Interaction of lumirubin and FICZ with glutamate and GABA receptors may underpin antagonism of the excitotoxicity of kernicterus. Development of lumirubin- and FICZ-based pharmaceuticals may advance NNH therapy. Interaction of KA and QA with GABA receptors requires investigation at the pharmacological and behavioural levels.

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