Title: Beyond Jaundice: The Neuroprotective Roles of the Biliverdin Reductase/Bilirubin Axis

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Bilirubin is one of the most frequently measured metabolites in the blood, yet its exact functions in vivo are still obscure. Biliverdin reductase A (BVRA) is the main biosynthetic enzyme for bilirubin and a component of heme catabolism responsible for converting biliverdin to bilirubin. While the antioxidant and anti-inflammatory roles of bilirubin in vitro and in peripheral tissues have been well studied, the functions of bilirubin in the brain have been less explored. We show that bilirubin, being lipophilic, protects the lipid rich compartments of cells and prevents lipid peroxidation and plays a complementary role to the protective effects of the major water soluble antioxidant, glutathione (GSH), which predominantly protects the hydrophilic compartments. The brain is lipid-rich and metabolically highly active and is especially susceptible to lipid peroxidation. We have shown that mice lacking BVRA display elevated lipid peroxidation, mitochondrial dysfunction and compromised ability to neutralize free radicals and are highly susceptible to neuronal damage. Furthermore, we have shown that bilirubin directly scavenges superoxide radicals ($O_2^{\bullet-}$) generated during mitochondrial respiration and mediates neuroprotection. Additionally, we show that BVRA, mediates synaptic signaling through the focal adhesion kinase (FAK) and also neuroprotective signaling through the nuclear factor erythroid-derived factor-like 2 (Nrf2), the master regulator of redox homeostasis. Thus, studying the actions of BVRA and bilirubin will yield deeper insights into a novel and hitherto underappreciated neuroprotective pathway in the brain, which can be harnessed to develop therapeutics for neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and stroke.

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