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Review article

Bilirubin and brain: A pharmacological approach

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ABSTRACT

For many decades, the world scientific literature has accounted for a number of works on the biological effects of bilirubin-IXalpha (BR). The first studies focused on the neurotoxic effects of the excessive production of BR, in particular regarding both physiological neonatal jaundice and the more severe ones, typically as consequences of severe hemolysis or other underlying diseases. Only since 1987, has significant evidence, however, underlined the neuroprotective role of BR linked to the scavenging effect of free radicals as reactive oxygen species and nitric oxide and its congeners. Despite the presence in the literature of many excellent papers dealing with the multiple roles played by BR in health and disease, there were very few and somewhat dated reviews that summarize the key findings related to the neuroprotective and neurotoxic effects of the bile pigment and underlying mechanisms. In light of the previous statements, the aim of this review is to provide a summary of the main discoveries in the last years on the effects of BR on the central nervous system. An analytical description about the synthesis of BR, its distribution in the systemic circulation, liver metabolism and elimination through feces and urine will be provided, together with the main mechanisms claimed to describe the neurotoxicity and neuroprotection by the bile pigment. Finally, the possible translational aspects of pharmacological modulation in the production of BR in order to prevent or counteract toxic effects or enhance the protective actions, will be discussed.

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1. Introduction

The bile pigment bilirubin-IXalpha (BR) is the final product of heme metabolism in mammals. After a lifespan of about 120 days in the bloodstream, aged red blood cells undergo physiologic hemocatheresis mainly in the spleen, but also in the liver, releasing hemoglobin (Crosby, 1959; Franco, 2012). The prosthetic heme moieties of hemoglobin are sequentially oxidized into biliverdin-IXalpha (BV) by the heme oxygenase (HO) isoforms and, further, reduced into BR by the biliverdin reductase (BVR) (Maines, 1997). Definitely, both HO and BVR are ubiquitous enzymes, therefore almost all cell types can generate BR by degrading their own hemoproteins, [e.g. myoglobin, cytochromes, catalase, cyclooxygenase, etc (Maines, 1997)]. For several years, BR has been studied because of its pathologic relevance; indeed, an excessive production of BR or reduced clearance originate jaundice, namely a marked increase in BR plasma concentration, characterized by a yellow coloration of skin and sclerae (Stillman, 1990). Physiologic jaundice, common in newborns, is usually transient and resolves over a few days (Dennery et al., 2001; Watchko and Tiribelli, 2013). If BR plasma levels increase as an effect of specific underlying diseases, three types of jaundice are identified and classified as: hepatic, pre-hepatic and post-hepatic, depending on which step in BR production or elimination results dysfunctional (Beckingham and Ryder, 2001) (Table 1). A particular type of jaundice is kernicterus, namely the abnormal deposition of BR in selected brain areas of newborns, such as basal ganglia, *cornua ammonis* and *substantia nigra*, usually due to massive hemolysis (Field, 1938; Wiener and Brody, 1946).

Almost 30 years ago, Roland Stocker, a bright researcher in Bruce Ames' lab, was the first author of a revolutionary paper in which, together with Tony McDonagh and other smart scientists, proposed BR as a strong antioxidant molecule (Stocker et al., 1987a). Over the next years, the same Authors published many other papers on this topic, studying in more detail the scavenging ability of BR alone or complexed with albumin against reactive oxygen species (ROS) (Neuzil and Stocker, 1994; Stocker et al., 1987b). In 2003, my Collaborators and I published a paper on the ability of BR to scavenge nitric oxide (NO) providing the first lines of evidence, followed by the complete characterization in 2009, on the formation of N-nitro-BR as the result of such an interaction (Barone et al., 2009; Mancuso et al., 2003). It is also worth mentioning that other research groups, worldwide, provided novel insights in the biology of BR, starting from Mahin Maines and co-workers who characterized both the reductase and the kinase activities of BVR; Solomon Snyder and Dora Brites, who studied the neuroprotective/neurotoxic potential of BR in neurons and glial cells; Claudio Tiribelli who explored the bound/unbound BR balance in terms of biological effects and neurotoxicity, and many others (see below). Despite the huge amount of evidence provided and available in literature, only few review papers summarized the role of BR in the body by reporting the preclinical and clinical studies on both its kinetics and the multiple modifications induced on cell function through which the bile pigment exerts its biological and toxicological effects. The aim of this review is to provide an overview on the main findings on the synthesis, distribution, metabolism and elimination of BR together with the mechanisms of action involved in its pleiotropic effects in the brain. In addition, the review will discuss on the possibility to modulate BR production with the purpose to increase neuroprotection or reduce neurotoxicity.

Table 1
Some of the most common diseases leading to jaundice.

JAUNDICE		
Pre-hepatic	*Hepatic*	*Post-hepatic*
Hemolysis	Gilbert syndrome	Stones in the bile duct
ABO incompatibility	Crigler-Najjar syndrome	Pancreatic head cancer
Rh incompatibility	Viral hepatitis	Pancreatitis
Hereditary spherocytosis	Alcoholic liver disease	Budd-Chiari syndrome
G6PD deficiency	Drug toxicity	

G6PD, glucose-6-phosphate dehydrogenase.

2. The bilirubin generating system

Bilirubin-IXalpha is generated by the concerted action of the HO and BVR enzymes.

2.1. Heme oxygenase

Microsomal HO catalyzes the oxidative cleavage of heme moieties of hemoproteins in a 4-step, energy-dependent manner. From a chemical viewpoint, HO itself is not a hemoprotein, although it acquires this characteristic after binding to heme-Fe(III) (Takahashi et al., 1994). The activation of the heme catabolic pathway requires not only HO, but also oxygen and NADPH-cytochrome-P-450 reductase, the latter providing the electrons necessary to catalyze the transformation of the cyclic tetrapyrrole heme into equimolar amounts of Fe(II), carbon monoxide (CO) and biliverdin (BV) (Wilks and Torpey, 1994).

Heme oxygenase exists in two main isoforms, HO-1 and HO-2. They are the products of two different genes and their homology is limited (43%), but the active core of both enzymes is a conserved 24-amino-acid segment, which forms the hydrophobic heme-binding pocket in the folded protein (Maines, 1997). Although HO-1 and HO-2 catalyze the same reaction, they play different roles in protecting tissues against injuries. Heme oxygenase-1 (HO-1), also known as heat shock protein (Hsp)32, is induced by hemin, oxidative and nitrosative stressors, ischemia, heat shock, bacterial endotoxin and several drugs (Maines, 1997, 2000; Mancuso and Barone, 2009). Salinas et al. (2004) reported the specific post-translational modifications occurring on HO-1 structure and demonstrated that the phosphorylation of the aminoacidic residue Ser^{188} increases the enzymatic activity by about 20%. Together with Hsp70, Hsp60 and thioredoxin reductase, HO-1 forms the vitagene family whose main role is to enhance the adaptive stress response thus helping cells to counteract or survive different types of damage (Calabrese et al., 2004, 2007a; 2009). The constitutive HO-2, primarily involved in maintaining cell heme homeostasis, is regulated by developmental factors and adrenal glucocorticoids