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Review

The anti-mutagenic properties of bile pigments

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Abstract

Bile pigments, including bilirubin and biliverdin, are endogenous compounds belonging to the *porphyrin* family of molecules. In the past, bile pigments and bilirubin in particular were thought of as useless by-products of heme catabolism that can be toxic if they accumulate. However, in the past 20 years, research probing the physiological relevance of bile pigments has been mounting, with evidence to suggest bile pigments possess significant antioxidant and anti-mutagenic properties. More specifically, bile pigments are potent peroxyl radical scavengers and inhibit the mutagenic effects of a number of classes of mutagens (polycyclic aromatic hydrocarbons, heterocyclic amines, oxidants). Coincidentally, persons with elevated circulating bilirubin concentrations have a reduced prevalence of cancer and cardio-vascular disease. Despite the encouraging *in vitro* anti-mutagenic effects of bile pigments, relatively little research has been conducted on their inhibitory capacity in bacterial and cultured cell assays of mutation, which might link the existing *in vitro* and *in vivo* observations. This is the first review to summarise the published data and it is our hope it will stimulate further research on these potentially preventative compounds.

Keywords: Bilirubin; Bilirubin ditaurate; Biliverdin; Mutagenicity; *Salmonella*

Contents

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1. Introduction

1.1. Metabolism

Bile pigments, unconjugated bilirubin (BR, **1**), biliverdin (BV, **2**) and bilirubin ditaurate (BRT, **3**; see Fig. 1) are compounds that share *porphyrin* structure [1], however, they possess unique, divergent, three dimensional structures (Fig. 1). Unconjugated bilirubin and biliverdin are formed in humans via the catabolism of heme. Hemoglobin, released from senescent red blood cells and heme containing enzymes, are the major source of heme for bile pigment synthesis [2]. The catabolism of heme occurs in the cells of the reticulo-endothelial system (e.g. liver, spleen), resulting in the excretion of approximately 300 mg of bile pigments from the body each day [3]. The metabolism of bile pigments in the human body is illustrated in Fig. 2. Heme is converted by heme oxygenase (HO-1) forming biliverdin, carbon monoxide and iron. Biliverdin is reduced to unconjugated bilirubin, by biliverdin reductase [2]. Interestingly, the metabolism of heme is colourfully displayed in the time course of bruising where the blue-green colour of biliverdin is followed by the yellow colouration of bilirubin. After bilirubin is formed, this hydrophobic compound is bound to serum albumin, for which it has a strong affinity [4,5]. The circulation delivers bilirubin to the liver where it is actively and passively absorbed into the hepatocyte (see Kamisako et al. for review [6]). Intercellular glutathione-*S*-transferase then transports bilirubin to the endoplasmic reticulum where glucuronic acid conjugates are formed by UDP glucuronosyl transferase (UGT1A1) [6]. Conjugation renders bilirubin water soluble. It is then actively transported into the bile caniculi by multidrug resistance protein 2 (MRP2) [7] and the bilirubin conjugates are then directed into the duodenum via the bile duct. As bilirubin glucuronides enter the gastrointestinal tract, bacterial enzymes including β-glucuronidase, hydrolyse the bilirubin esters forming unconjugated pigment [8]. Some of the unconjugated bilirubin is reabsorbed [9,10] and re-excreted. The remaining pigments are reduced by the intestinal bacterial flora to urobilins and stercobilins, which provide the distinctive colouration of faeces [11].

2. Potential adverse effects

2.1. Toxicity

Severe and chronically elevated bilirubin production/re-absorption, which exceeds the liver's capacity to excrete bilirubin, i.e. in neonatal hyperbilirubinemia, can result in bilirubin toxicity and acute or chronic neurological dysfunction [12]. Disordered hepatic function, including mild (Gilbert's syndrome) and severe (Crigler–Najjar syndrome) deficiencies in UGT1A1 also result in elevated circulating bilirubin concentrations. However, bilirubin toxicity is rarely noted in these persons and the bilirubin load can be controlled with phototherapy or cured with liver transplantation [13].

2.2. Cell proliferation

A small but significant body of knowledge concerning a specific cell stimulating effect of biliverdin is documented in the literature [14,15]. Biliverdin promotes neoplastic cell formation in liver epithelial cells after they are pre-incubated with aflatoxin B_1 [15]. It is possible this effect is related to the up-regulation of ornithine decarboxylase activity by biliverdin [16]. However, biliverdin treatment without prior aflatoxin B_1 exposure, did not stimulate cell growth, was not mutagenic and did not cause DNA strand breaks [15]. Although the *in vivo* relevance of these findings is questionable due to the non-physiological biliverdin concentrations applied to the cells, the findings must be considered carefully in the context of events that may occur after liver transplantation and where prior exposure to oncogenic agents occur [17,18].