

ABSTRACT

Phototherapy (PT) with blue-green light (420-490 nm) is the standard treatment for severe neonatal jaundice to prevent infants from toxic bilirubin (BR). Upon blue-green light exposure, BR is converted to more polar photoisomer (PI) lumirubin (LR) and the other oxidation products (mono-, di-, tripyrrols) which can be more easily disposed of the body via urine and/or bile. Although generally considered to be safe, PT is accompanied by an increased risk of various pathophysiological conditions (inflammatory processes, allergies, diabetes, and some types of cancer), in extremely low-birth-weight newborns. Thus, to account for these consequences, our study aimed to understand the mechanism of BR secretion in different tissues and cell lines and investigate the bioactive properties of BR and its main photooxidation product LR.

At first, we focused on the detection of BR in the bile and feces of hyperbilirubinemic Gunn rats. Simultaneously, we tested the antioxidant and pro-oxidant effects of unconjugated BR in human hepatoblastoma (HepG2), proximal tubular (HK2), neuroblastoma (SH-SY5Y), and murine endothelial (H5V) cells by exposing them to progressively increasing concentrations of BR. To compare the BR and LR effects on metabolic and oxidative stress markers, the biological activities were investigated in vitro on human hepatoblastoma (HepG2), fibroblast (MRC5), and murine macrophage (RAW 264.7) cells. We also focused on proliferation, morphology, expression of specific genes and proteins, and differentiation of neural stem cells (NSC).

Our experiments confirmed no link between the regulation of transintestinal cholesterol excretion and plasma concentrations of unconjugated BR in Gunn rats. We observed in all studied cell lines, that low concentrations of BR exhibit antioxidant effects, whereas higher concentrations exhibit a prooxidant or cytotoxic effect, confirming that each cell type has a different threshold for BR. When compared to LR, significantly lower toxicity and maintenance of antioxidant capacity in serum were observed. LR also suppressed the activity leading to mitochondrial superoxide production but was less effective in preventing lipoperoxidation. Our data also confirmed the effect of BR and LR on the early phase of NCS differentiation and the ability of LR to influence the polarity and identity of NSCs during early human neuronal development, which may have clinical relevance since cell polarity has an important role during CNS development.

Key words: Haem metabolism, bilirubin, photo-oxidation products, neonatal jaundice