BILIRUBIN MODULATES NEUROTROPHIN REDOX SIGNALING

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Until twenty years ago, bilirubin (BR) was merely considered as a by-product of heme metabolism. Only in 1987, Stocker et al. demonstrated that BR is an endogenous molecule with a strong antioxidant activity (1). Following this first evidence, several studies corroborated the main role of BR in counteracting both oxidative and nitrosative stress conditions (2). Unfortunately, if produced in excess, BR becomes neurotoxic and is responsible for the development of *kernicterus* in the newborn. Here we report that exposure of rat pheochromocytoma cells (PC12) and primary rat cerebellar granule neurons to BR (10 μM) for 2 hours decreased the neurotrophin (NGF and BDNF)-induced overexpression of both Akt and extracellular-signals regulated kinases (ERKs), indicating a direct interference of the bile pigment with crucial pro-survival signaling pathways. This effect seems to involve the scavenging capacity of BR, this latter being able to inhibit, in PC12 cells, accumulation of intracellular reactive oxygen species and phosphorylation of Akt and ERKs in response to extracellular hydrogen peroxide. Interestingly, in the absence of exogenous growth factor, BR (1-10 μM) elicited the phosphorylation of ERKs and of the cAMP Responsive Element Binding (CREB) transcription factor, a signature of NGF-dependent survival signaling. These growth factor-like signaling effects were paralleled by the induction of the neuronal nitric oxide synthase (nNOS) and generation of nitric oxide (NO). Pharmacological dissection of the signaling cascade triggered by BR revealed that phosphorylation of ERKs requires NO signaling through soluble guanylyl cyclase and, at a further upstream level, influx of extracellular calcium is necessary for nNOS induction and NO release, likely through calcium dependent phosphorylation of CREB. Interestingly, the cascade elicited by BR through NO and ERKs reduced, at least in part, BR neurotoxic effect, as revealed by exacerbated BR toxicity in cultures treated by either NOS or MEK inhibitors. Taken together these observations indicate an important action of BR on redox signaling by neurotrophins, with either inhibitory or agonistic effects based on growth factor availability.

Stocker R., Yamamoto Y., McDonagh A.F., Glazer A.N. and Ames B.N. (1987) Science. 235: 1043-1046.

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