Tauroursodeoxycholic Acid (TUDCA): A Promising Neuroprotective Agent Derived from Bile Salts

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Tauroursodeoxycholic acid (TUDCA) is a hydrophilic bile acid synthesized in hepatocytes by the conjugation of ursodeoxycholic acid (UDCA) with the amino acid taurine. UDCA, which is made by gut bacteria, is FDA-approved in the United States for the treatment of certain cholestatic liver diseases. Humans make TUDCA to some extent, but it is found in copious amounts in the bile of bears. It’s fascinating, therefore, to note that bear bile has been used therapeutically in Chinese Medicine for centuries.

Bile acids are important for lipid absorption in the gut, but they can also be absorbed into circulation and have systemic effects. TUDCA is classified as a chemical chaperone. Chemical chaperones are naturally occurring substances that are able to correct inappropriately localized or aggregated proteins in the endoplasmic reticulum (ER) by stabilizing a protein’s structure and facilitating its folding process. If this process becomes deranged, as can happen during oxidative stress, it signals an ER stress response, which is associated with reduced protein synthesis, malfunction of the unfolded protein response, and, finally, cell death. TUDCA attenuates the ER stress response, inhibits cell death, and preserves cellular function.

A growing body of evidence that includes both pre-clinical and clinical studies indicates that TUDCA has extensive therapeutic benefits beyond the hepatobiliary system in, for example, inflammatory metabolic disorders such as atherosclerosis, diabetes, and renal disease. Furthermore, alterations in bile acid-mediated signaling and metabolism appear to play a role in neurodegenerative and neurological disorders. TUDCA has been shown to have neuroprotective effects by inhibiting cell death in several neurodegenerative conditions that are characterized by dysregulations in apoptosis, for example, Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The mechanisms of action that underlie the anti-apoptotic properties of TUDCA include its ability to inhibit mitochondrial pathways of cell death, prevent the production of reactive oxygen species, mitigate endoplasmic reticulum stress, and stabilize the unfolded protein response.

A study published in 2020 found that adult and pediatric patients with multiple sclerosis (MS) had lower levels of circulating bile acid metabolites when compared with controls. Alterations in bile acid metabolite levels were most pronounced in adults with progressive forms of MS. Receptors for bile acids were also noted on immune and glial cells in the white matter brain lesions of post-mortem human tissue samples. In an in vitro experiment, TUDCA was found to prevent expression of the neurotoxic phenotype of astrocytes and the proinflammatory
phenotype of microglia in a dose-dependent manner. Activated astrocytes and microglia are known to play important roles in MS pathophysiology, especially in the progressive phase. It is possible that reduced signaling through bile acid receptors is associated with increased neuroinflammation. Supplementation with TUDCA in an animal model of MS improved signs of neuropathology and reduced disease severity.\textsuperscript{16}

Orally ingested TUDCA is able to cross the blood-brain barrier to reach neuronal tissue and to prevent cell death.\textsuperscript{17} Evidence continues to mount in support of its potential clinical application as part of a therapeutic approach to the treatment of neuroinflammatory and neurodegenerative conditions.

References

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