Neuroprotection against Aminochrome Neurotoxicity: Glutathione Transferase M2-2 and DT-Diaphorase

- Segura-Aguilar J.[a]
- Muñoz P.[b]
- Inzunza J.[c]
- Varshney M.[c]
- Nalvarte I.[c]
- Mannervik B.[d]

Abstract

Glutathione is an important antioxidant that plays a crucial role in the cellular protection against oxidative stress and detoxification of electrophilic mutagens, and carcinogens. Glutathione transferases are enzymes catalyzing glutathione-dependent reactions that lead to inactivation and conjugation of toxic compounds, processes followed by subsequent excretion of the detoxified prod-ucts. Degeneration and loss of neuromelanin-containing dopaminergic neurons in the nigrostriatal neurons generally involves oxidative stress, neuroinflammation, alpha-synuclein aggregation to neurotoxic oligomers, mitochondrial dysfunction, protein degradation dysfunction, and endoplas-mic reticulum stress. However, it is still unclear what triggers these neurodegenerative processes. It has been reported that aminochrome may elicit all of these mechanisms and, interestingly, ami-nochrome is formed inside neuromelanin-containing dopaminergic neurons during neuromelanin synthesis. Aminochrome is a neurotoxic ortho-quinone formed in neuromelanin synthesis. How-ever, it seems paradoxical that the neurotoxin aminochrome is generated during neuromelanin syn-thesis, even though healthy seniors have these neurons intact when they die. The explanation of this paradox is the existence of protective tools against aminochrome neurotoxicity composed of the enzymes DT-diaphorase, expressed in these neurons, and glutathione transferase M2-2, expressed in astrocytes. Recently, it has been reported that dopaminergic neurons can be protected by gluta-thione transferase M2-2 from astrocytes, which secrete exosomes containing the protective enzyme. © 2022 by the authors. Licensee MDPI, Basel, Switzerland.

Author keywords

Aminochrome; Astrocytes; Dopamine; Glutathione; Glutathione transferase; Neuron; Neuroprotection; Parkinson’s disease