

Upregulation of γ -glutamate-cysteine ligase as part of the long-term adaptation process to iron accumulation in neuronal SH-SY5Y cells

Aguirre, Pabla

Valdés, Pamela

Aracena-Parks, Paula

Tapia, Victoria

Núñez, Marco T.

Reactive iron is an important prooxidant factor, whereas GSH is a crucial component of a long-term adaptive system that allows cells to function during extended periods of high oxidative stress. In this work, the adaptive response of the GSH system to prolonged iron loads was characterized in human dopaminergic SH-SY5Y neuroblastoma cells. After the initial death of a substantial portion of the cell population, the surviving cells increased their GSH content by up to fivefold. This increase was traced to increased expression of the catalytic and modulatory subunits of γ -glutamate-cysteine ligase. Under conditions of high iron load, cells maintained a low GSSG content through two mechanisms: 1) GSSG reductase-mediated recycling of GSSG to GSH and 2) multidrug resistant protein 1-mediated extrusion of GSSG. Increased GSH synthesis and low GSSG levels contributed to recover the cell reduction potential from -290 mV at the time of cell death to about -320 mV. These results highlight the fu