RECENT ADVANCES IN ATRAZINE-INDUCED NEUROTOXICITY: PERTINENT MECHANISTIC INSIGHT FROM APOPTOTIC REGULATION OF BAX/BCL-2 RATIO AND CASPASE-3-DEPENDENT PATHWAY AND CHEMOPROTECTION

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Abstract: Atrazine (ATZ), a chloro-s-triazine is a well-known herbicide that is frequently detected in ground and surface water at significant levels. It is employed extensively in the US and worldwide for over four decades for the control of grassy weeds and the cultivation of grains and sugar cane. As a persistent environmental contaminant, it has been implicated in the etiology of neurodegenerative diseases such as Parkinson’s disease with underlying mechanism of toxicity involving free radicals. Exploring the molecular events associated with neurological disorders is essential in order to gain mechanistic insight into the therapeutic potential of chemoprotective agents. As such neuroprotection involving the use of naturally occurring phytochemicals may represent important therapeutic strategy for Parkinson’s disease (PD), Alzheimer’s disease, and amyotrophic lateral sclerosis. Our objective was to investigate the toxic effect of ATZ on the human neuroblastoma (SH-SY5Y) cells, and the degree of cytotoxicity and morphological changes during the cell death. Our cytotoxicity bioassays indicate that ATZ (5-50 µg/mL) decreases cell viability in a dose- and time-dependent manner. Evidence that apoptosis occurred was confirmed by an increase in caspase-3 activity, and cell death was blocked when caspase-3 activity was inhibited. Typical apoptotic phenotype that includes nuclear fragmentation, micro nuclei formation, DNA fragmentation and increase in the expressions of apoptosis-associated markers Bax, p53 and p21 and decreased expression of Bcl-2 were observed in treated cells. Furthermore, a dose-dependent increase in reactive oxygen species (ROS) levels in ATZ-treated cells was observed. In order to elucidate the role of chemoprotective agent in ATZ-induced neurotoxicity, Kolaviron from Garcinia kola and Quercetin occurring naturally in onions were tested in SHY-SY5Y cell lines and rats respectively. In SHY-SY5Y cell lines, Kolaviron treatment demonstrates significant restoration in ATZ-induced alterations in the expression of apoptosis markers viz., p53, Bax, Bcl2, caspase-3, caspase-9. In addition, kolaviron prevents ATZ-induced generation of ROS, cell death and inhibited cell proliferation. In vivo, oxidative stress-induced by ATZ in terms of increased lipid peroxidation level and superoxide dismutase (SOD) activity was decreased in the brain of rats treated with quercetin at a dose of 5mg/kg. Overall, the results suggest that ATZ-induces apoptosis and ROS levels in SH-SY5Y cells and oxidative stress in rats and that kolaviron and quercetin elicited chemoprotective effects in these models. The data have added to our present day understanding of the molecular events associated with ATZ-induced neurotoxicity and opened up a new therapeutic window in the possible chemoprevention of human neurodegenerative disorders such as Parkinson disease.

Key words: Atrazine; Apoptosis, ROS, Kolaviron, Quercetin, SHY-SY5Y cells, Rats