MECHANISMS UNDERLYING THE NEURONAL TOXICITY OF ATRAZINE AND THE CHEMOPROTECTIVE ROLE OF KOLAVIRON IN PC12 CELLS AND HUMAN DOPAMINERGIC SH-SY5Y CELLS

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Abstract: Neurodegenerative diseases are associated with various degrees of behavioral impairments that decrease quality of life. The contribution of environmental contaminants in the etiology of neurodegenerative diseases, such as Parkinson’s disease, has been recognized. Atrazine (2-chloro-4-ethylamino-6-isopropylamino-s-triazine) is a chloro-s-triazine herbicide employed extensively in the US and worldwide for over 40 years for the control of grassy weeds in the cultivation of corn, sorghum and sugar cane has been reported to work as a potential contributory risk factor for Parkinson’s disease and other neurological disorders and free radicals have been implicated. Elucidation of the molecular events associated with free radicals generated by environmental chemicals in neuronal cells is essential in order to gain insight into the pathophysiologic basis for neuronal death. Neuroprotection involving the use of plant-based and phytochemicals may represent important therapeutic strategy for Parkinson’s disease (PD), Alzheimer’s disease, and amyotrophic lateral sclerosis. Kolaviron (KV), a natural biflavonoid obtained from the seeds of Garcinia kola, has been documented for its wide pharmacological window, including anti-apoptotic activities and modulation of a number of molecular events induced by environmental compounds. Using PC12 cells, a rat pheochromocytoma and human neuroblastoma cell line (SHY-SY5Y), we have investigated the neuroprotective effects of KV. We investigated the protective effects of KV on ATZ-induced cell death in the human neuroblastoma cell line (SHY-SY5Y). In both cells KV prevented atrazine-induced levels of markers of oxidative damage and modulated mRNA expression of selected antioxidant enzymes. In both PC12 cells and SHY-SY5Y cell lines, KV treatment also demonstrates significant restoration in ATZ-induced alterations in the expression of apoptosis markers viz., p53, Bax, Bcl2, caspase-3, caspase-9. In SHY-SY5Y, KV prevents ATZ-induced generation of reactive oxygen species (ROS), cell death and inhibited cell proliferation by reduction of cell proliferation. ATZ-mediated nuclear changes associated with apoptosis; including nuclear fragmentation, condensation, DNA laddering, and increased caspase-3 activity were blocked on addition of KV. Furthermore in PC12 cells, KV abolished ATZ induction of cyclooxygenase-2 (COX-2), c-Jun and c-fos. Flow cytometric analysis confirms the involvement of ROS in the mediation of ATZ-induced apoptosis in PC12 cells. Taken together, our data suggest that the toxicity of ATZ in the neuronal cells is mediated by mechanisms involving apoptosis, oxidative stress and dysregulation in the expressions of stress response genes and that KV abolished these molecular events. Hence, these data may open up a new clinical perspective in progressive neurodegenerative diseases such as Parkinson’s disease.

Key words: Atrazine; apoptosis, oxidative stress, PC12 cells; kolaviron; SHY-SY5Y cells