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INVERTIGATION OF THE MECHANISMS UNDERLYING ACROLEIN-INDUCED TOXICITY IN HUMAN NEURONAL CELL LILNE.

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Acrolein (ACR), a highly toxic α,β-unsaturated aldehyde, is the strongest electrophile compound present commonly in environmental as a pollutant. It is also a metabolite of the anticancer drugs and a by-product of lipid peroxidation. ACR has been shown to be implicated in the pathogenesis of numerous diseases, especially in age related neurodegenerative disorders with higher levels in vulnerable regions of the brain in Alzheimer's disease. Being a highly reactive aldehyde, ACR toxicity is mediated by covalent bounding with nucleophilic molecules in the cells. The aim of our present study was to elucidate the mechanisms of ACR toxicity on SK-N-SH human neuroblastoma cells. We observed that ACR can induce cell death in a dose- and time-dependent manner. Indeed, after a short-term treatment (30min), ACR caused a rapid depletion of GSH, an increase in protein carbonyl levels, an upregulation of p66shc and an activation of the redox sensitive transcription factors (NF-κB). In contrast, after a long-term treatment (24h), the cytotoxicity of ACR implicate different mechanisms with a reduction on protein carbonyl levels while GSH levels were increased with a parallel induction of the expression of the enzyme γ-glutamylcysteine synthetase (γ-GCS). Concomitantly, ACR also led to the up-regulation of heme oxygenase 1, sirt-1 and the activation of the Nrf2 pathway while decreasing the activity of NF-κB as indicated by a decrease in the nuclear level of the subunit P50. Taken together, these data demonstrate that that the mechanisms underlying the ACR-induced toxicity are complex and may vary according to the time of the exposition. This work is supported by NSERC.