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The Toxic Effects of Kynurenine Metabolites on SH-SY5Y Neuroblastoma Cells

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Abstract : Introduction /Aim: The kynurenine pathway is thought to play an important role in the pathophysiology of numerous neurodegenerative diseases including depression, Alzheimer's disease, and Parkinson's disease. Numerous neuroactive compounds, including the neurotoxic 3-hydroxyanthranilic acid, 3-hydroxykynurenine and quinolinic acid and the neuroprotective kynurenic acid and picolinic acid, are produced through the metabolism of kynurenine and are thought to be the causative agents responsible for neurodegeneration. The toxicity of 3-hydroxykynurenine, 3-hydroxyanthranilic acid and quinolinic acid has been widely evaluated and demonstrated in primary cell cultures but to date only 3-hydroxykynurenine and 3-hydroxyanthranilic acid have been shown to cause toxicity in immortal tumour cells. The aim of this study was to evaluate the toxicity of kynurenine metabolites, both individually and in combination, on SH-SY5Y neuroblastoma cells after 24 and 72 h exposure in order to explore a cost-effective model to study their neurotoxic effects and potential protective agents. Methods: SH-SY5Y neuroblastoma cells were exposed to various concentrations of the neuroactive kynurenine metabolites, both individually and in combination, for 24 and 72 h, and viability was subsequently evaluated using the Resazurin (Alamar blue) proliferation assay. Furthermore, the effects of these compounds, alone and in combination, on specific death pathways including apoptosis, necrosis and free radical production was evaluated using various assays. Results: Consistent with literature, toxicity was shown with short-term 24-hour treatments at 1000 µM concentrations for both 3-hydroxykynurenine and 3-hydroxyanthranilic acid. Combinations of kynurenine metabolites showed modest toxicity towards SH-SY5Y neuroblastoma cells in a concentration-dependent manner. Specific cell death pathways, including apoptosis, necrosis and free radical production were shown to be increased after both 24 and 72 h exposure of SH-SY5Y neuroblastoma cells to 3-hydroxykynurenine and 3-hydroxyanthranilic acid and various combinations of neurotoxic kynurenine metabolites. Conclusion: It is well documented that neurotoxic kynurenine metabolites show toxicity towards primary human neurons in the nanomolar to low micromolar concentration range. Results show that the concentrations required to show significant cell death are in the range of 1000 µM for 3-hydroxykynurenine and 3-hydroxyanthranilic acid and toxicity of quinolinic acid towards SH-SY5Y was unable to be shown. This differs significantly from toxicities observed in primary human neurons. Combinations of the neurotoxic metabolites were shown to have modest toxicity towards these cells with increased toxicity and activation of cell death pathways observed after 72 h exposure. This study suggests that the 24 h model is unsuitable for use in neurotoxicity studies, however, the 72 h model better represents the observations of the studies using primary human neurons and may provide some benefit in providing a cost-effective model to assess possible protective agents against kynurenine metabolite toxicities.

Keywords : kynurenine metabolites, neurotoxicity, quinolinic acid, SH-SY5Y neuroblastoma
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