Ceramides in Molecular Mechanisms of Neuronal Cell Death. Effect of Selected Cytoprotective compounds

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Ceramides, bioactive members of the sphingolipids are produced via *de novo* synthesis, hydrolysis of sphingomyelin by sphingomyelinases and acylation of sphingosine. Ceramides are important second messengers and are involved in proliferation, differentiation, cell death and senescence. An increase in cellular concentration of ceramides occurs in several pathological conditions such as brain ischemia, hypoglycemia, inflammation and in neurodegenerative disorders.

The aim of this study was to investigate the molecular mechanisms of neuronal cells death evoked by ceramides. The neuroblastoma cell line (SH-SY5Y) was exposed for 24 h to cell-permeable C2-ceramide. Ceramide decreased the viability of SH-SY5Y cells in concentration dependent manner. The intracellular free radical generation after ceramide treatment was by about 3-fold higher comparing to control. Concomitantly our study indicated that ceramide induced poly(ADP-ribose) polymerase-1 (PARP-1) activation and accumulation of poly(ADP-ribose) PAR, a signalling molecule involved in mitochondria-nucleus cross-talk and mitochondria integrity. The ceramide treatment significantly decreased the level of apoptosis inducing factor (AIF) in mitochondria. The PARP-1 inhibitors (PJ-34 and 3-AB) prevented the AIF release from mitochondria and its translocation into nucleus. Ceramide decreased also the level of anti-apoptotic Bcl-2 protein. PARP-1 inhibitors increased the level of Bcl-2 protein and enhanced cells survival by about 30%. Summarizing, our data present that ceramide in SH-SY5Y cells induces caspase-3 independent death regulated by PARP/PAR/AIF. PARP-1 inhibitors through modulation of anti-apoptotic proteins protect mitochondria and neuronal cells against death evoked by ceramide. Inhibition of PARP-1 activity may offer a promising neuroprotective effect in several pathological conditions in which ceramide is accumulated.

Supported NCN Grant 5870/PO1/2011/40