Lipoxygenases and Poly(ADP-ribose) Polymerase-1 in Free Radicals Signalling and Neuronal Death Evoked by Glucose Deprivation. Neuroprotective effect of Sphingosine-1-phosphate

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Mechanism of neuronal cell death evoked by glucose deprivation (GD) followed by glucose reload (GR) is not fully understood. Data suggest that glutamate toxicity, Ca^{2+} and Zn^{2+} influx, production of reactive oxygen (ROS) and mitochondria failure are associated with GD neuronal damage. The increase of intracellular calcium during GD/GR can subsequently leads to activation of cytosolic phospholipase A_2 ($cPLA_2$) and to liberation of free arachidonic acid (AA) which in turn is metabolized by lipoxygenases (LOXs). The increase in the activity of LOXs is connected with liberation of superoxide radicals and oxidative stress. Generation of reactive oxygen species causes DNA damage that activates poly(ADP-ribose) polymerase-1 (PARP-1). Under mild stress PARP-1 is involved in DNA repair but its extensive activation can promote cell death.

The aim of this study was to examine the role of 5-LOX, 12/15-LOX and PARP-1 in ROS signalling and cell death induced by GD/GR in hippocampal cells, HT-22. Our data indicated that about 30% of HT-22 cells died after 6h GD followed by 24h GR. Concomitantly the level of free radicals (FR) was significantly enhanced. The analysis of molecular processes involved in FR cascade indicated that enhanced activity of neuronal isoform of nitric oxide (nNOS) together with activation of 5-LOX may play important role. Inhibitors of nNOS (7-NI), 5-LOX and 12/15-LOX (AA-861, zileuton) protected over 50% of cells exposed to GD/GR. Moreover, our data indicated that NADPH oxidase was significantly involved in oxidative stress mediated neuronal death evoked by GD/GR. The nuclear target for free radical signalling PARP-1 was activated and its specific inhibitor PJ-34 significantly enhanced cells survival. The neuroprotective effect was also exerted by sphingosine-1-phosphate (S1P), an bioactive sphingolipid that protects significant population of cells against death evoked by GD/GR. Summarizing, our data indicate that multiple molecular events are involved in mechanism of neuronal death evoked by oxidative/metabolic stress and suggest that inhibitors of 5-LOX, NADPH oxidase and PARP-1 may have the significant neuroprotective effect. Moreover, S1P seems to offer novel therapeutic strategy.

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