PROTECTIVE EFFECT OF *LEVETIRACETAM* VERSUS OXYGEN STRESS – INDUCED CELL DEATH IN PC12 AND IN SH-SY5Y CELL LINES

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Results of several studies suggest the possible use of antiepileptic drugs (AEDs) for neuroprotection owing to a possible role of AEDs in the modification of neurological diseases. Different mechanisms have been proposed to explain the neuroprotective effect of several AEDs. However, no information is available at the moment on the mechanism by which Levetiracetam (LEV) exerts its neuroprotective activity. In the present study we have investigated the effect of LEV versus apoptotic cell death induced by oxygen-stress in PC12 and in SH-SY5Y cell lines. The experimental scheme encompassed the treatment of the cells with LEV at a concentration of 10, 100 and 1000 µM, before and after induction of apoptosis by hydrogen peroxide (H_20_2). Cell death was evaluated as percentage of hypodiploid nuclei detected by cytometry analysis The results showed that LEV was able to protect both PC12 and SH-SY5Y cells in a range of 20-30% and 30-45%, respectively. To understand mechanisms underlying this protective effect, we investigated whether LEV was able to inhibit caspases activation in H_20_2 treated cells. Both the pro-caspase and the cleaved forms were evaluated by means of immunoblot analysis and by assaying the enzymatic specific activity. The results showed that LEV inhibited both the pro-caspase form and the cleaved forms of caspase 3, 6, 8 and 9 in SH-SY5Y and in PC12 cells. Moreover, LEV exerted the highest inhibitory effect toward caspase 6 (from 45% to 68% inhibition) in SH-SY5Y cells, while caspase 9 was preferentially inhibited (68%) in PC12. The preferential inhibition of caspase 6 is of potential interest since caspase 6 seems to exert an important function in the epileptogenic process. For comparison, experiments with valproic acid (VPA) as a reference compound were carried on in parallel with those with LEV. Results showed that in above described experimental conditions, VPA was unable to protect cells from oxygen stress induced cell death.