NEUROTENSIN RECEPTOR INVOLVEMENT IN THE RISE OF EXTRACELLULAR GLUTAMATE LEVELS AND APOPTOTIC NERVE CELL DEATH IN PRIMARY CORTICAL CULTURES AFTER OXYGEN AND GLUCOSE DEPRIVATION

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In view of the ability of neurotensin to increase glutamate release, the role of neurotensin receptor mechanisms in oxygen-glucose deprivation (OGD) induced neuronal death in cortical cultures has been evaluated by measuring lactate dehydrogenase levels (LDH), mitochondrial dehydrogenase activity with 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide levels (MTT), apoptotic nerve cell death with Hoechst 33258 and microtubule-associated protein 2 (MAP2) immunoreactivity. Furthermore, the involvement of glutamate excitotoxicity in the neurodegeneration enhancing actions of neurotensin was analyzed by measurement of endogenous extracellular glutamate levels.

Exogenous neurotensin enhanced the OGD-induced increase of LDH, endogenous extracellular glutamate levels, apoptotic nerve cell death. In addition the peptide enhanced the OGD-induced loss of mitochondrial functionality and MAP2 immunoreactivity . These effects were blocked by the neurotensin receptor 1 (NTR1) antagonist SR48692. Unexpectedly, the antagonist at 100 nM counteracted not only the neurotensin effects, but also the OGD-induced biochemical and morphological alterations.

These results suggest that NTR1 receptors may participate in neurodegenerative events induced by OGD in cortical cultures, used as an *in vitro* model of cortical ischemia. The NTR1 receptor antagonists could provide a new tool to explore the clinical possibilities and thus to move from chemical compound to effective drug.