NOTCH PROTEIN PATHWAY AS NEW PHARMACOLOGICAL TARGET FOR THE PERIPHERAL NEUROPATHIES THERAPY

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Notch proteins are key regulators of the neuronal fate during embryo development, but several results suggest that they also affect neuronal functions in the post natal brain. The exposure of in vitro differentiated SH-SY5Y neuroblastoma cells to the Notch ligand Jagged1 induces a morphological and functional remodelling particularly involving the axonal/presynaptic compartment of the neuron, which includes loss of neurite varicosities, redistribution of presynaptic vesicles and decrease in neurotransmitters release. This phenomenon is rapidly reversible upon removal of the ligand and depends on the activation of the Notch signalling pathway. In fact, it is prevented by the inhibition of γ-secretase or of the transcription machinery and is mimicked by the transfection of the intracellular domain of Notch. Gene array analysis showed that after 1-hour-treatment with Jagged1 a small group of genes are downregulated, and some of them return to normal levels within 1hour after the removal of the peptide from the culture medium. Many of these genes encode for the aminoacyl t-RNA synthetases, known to be involved in the axonal protein synthesis and recently related to the pathogenesis of a group of peripheral neuropathies characterized by axonal degeneration, like Charcot Marie Tooth disease (CMT) and distal spinal muscular atrophy type V. We observed that one of these proteins, the tyrosyl tRNA synthetase (YARS), together with ribosomal components, is present in the axonal termini with a peculiar distribution in the varicosities resulted redistributed all along the neurites upon the Jagged1 treatment.
These data suggest that in adult neurons the activation of the Notch pathway regulates the equilibrium between varicosities formation and varicosities loss in the neuronal presynaptic compartment, through the control on proteins essential for the axonal growth and branching.
In this context, the pharmacological modulation of the Jagged/Notch pathway could influence the axonal trophism and could prevent the axonal degeneration in the peripheral neuropathies.