STRESS INDUCIBLE PROTEIN 1 IN NEURITOGENESIS: UNRAVELLING INTRACELULLAR SIGNALING PATHWAYS

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The process of neurite growth occurring in neurons is a crucial step to the correct development of a functional nervous system. We have recently described that Stress Inducible Protein 1 (STI1) promotes neuritogenesis in hippocampal neurons when associated with its cell surface receptor, Cellular Prion Protein (PrPc). Accordingly, in PrPc knockout mice, STI1 does not induce neuritogenesis. In this work we studied the intracellular signaling pathways mediating STI1 neuritogenic activity. By using Phosphatidil-Inositol 3 kinase (PI3K) inhibitors we implicated this kinase in the STI1 neuritogenic cascade. The main target of PI3K, AKT , is activated after 30 minutes of STI1 stimulation. It is a known fact that protein synthesis control is an essential phenomenon to neurite outgrowth and elongation. One of the key regulators of protein synthesis, mammalian Target of Rapamycin (mTOR), promotes the increase of general translation. Since activated AKT directly activates mTOR, we investigated if mTOR could participate in STI1 neuritogenic effects. Rapamycin (5 nM), an mTOR specific inhibitor, completely blocks STI1-induced neurite outgrowth, while does not affect neuritogenesis in unstimulated conditions. These results suggest that the neuritogenic effect of STI1 is mediated by a PrPc-PI3K-AKT-mTOR cascade, and like some neurotrophic factors, STI1 may stimulate the neuronal translational machinery necessary to neurite outgrowth.

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