ERK 1/2 AND PROTEASOME SIGNALING ARE INVOLVED IN TAU PROTEOLYSIS INDUCED BY SORBITOL

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Maintenance of protein homeostasis is a critical process to assure cellular viability and alterations at this level are widely involved in neurodegenerative disorders. Tau is a microtubule-associated protein and its primary function in neurons is to regulate microtubule dynamics and consequently cytoskeleton stability. The interaction of Tau with tubuline is regulated by phosphorylation, thus hyperphosphorylation targets Tau to dissociate from microtubules and makes this protein more prone to self-assemble into paired helical filaments (PHF), which precedes the formation of neurofibrillary tangles (NFT), one of the pathological hallmarks of Alzheimer's Disease. Tau may also undergo fragmentation, which leads to the appearance of neurotoxic protein fragments.

The aim of this work was to study Tau cleavage in response to hyperosmotic stress. To perform this, we used the neuroblastoma cell line SH-SY5Y. Contribution of both MAPKs and cellular proteolytic systems were analysed by Western Blotting using pharmacological inhibitors (SB203580, PD98059, PD184352, U0126, MG-132, Lactacystin and Caspase inhibitor II).

Sorbitol treatment induces a time-dependent degradation of Tau which is partially prevented by MG-132, suggesting a role for proteasome in this process. In addition, sorbitol increases both calpain and caspase-3 activity and p38 MAPKs and ERK1/2 phosphorylation. Pre-treatment of cells with p38 MAPKs inhibitors (SB203580 and BIRB0796) does not prevent Tau degradation. However, this effect is partially prevented by ERKs inhibitors (PD98059, PD184352 and U0126), which indicate the involvement of ERK pathway in sorbitol-induced Tau degradation. Work supported by grants: PRIS0933, BFU2007-67577-C02-02/BMC. MOSC and MCB are recipients of Junta de Extremadura- FSE fellowships.