JNK- AND MINERALOCORTICOID RECEPTOR-MEDIATED INSULIN RESISTANCE IN AGED MICE SUBJECTED TO CHRONIC MILD STRESS

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Introduction: There is much interest in understanding the molecular mechanisms underlying interactions among stress, ageing, memory and Alzheimer´s disease (AD).

Methods: We studied the effects of chronic mild stress (CMS) on the ageing process and development of AD pathology.

Results: CMS aged mice showed learning impairment in the novel object recognition test and insulin resistance. The synaptic markers synaptophysin and β-catenin were decreased whereas the stress-activated protein kinase pJNK was increased in CMS aged mice, which also exhibited decreased hippocampal levels of pIRS, pAkt, GSK3β and pERK1/2 and increased levels of pTau. A genetic (ob/ob mice) and an environmental (high fat diet, HFD) model of insulin resistance, showed JNK-independent increases in pTau levels and concomitant cognition impairment. Therefore, insulin resistance and cognitive impairment in CMS aged mice, but not in ob/ob or HFD animals, were mediated by JNK. This was further confirmed in primary cell neurons in which an inhibitor of JNK reversed the short time decreases in GSK3β, pERK1/2 and β-catenin and increases in pTau levels induced by dexamethasone. Significant decreases in glucocorticoid receptor (GR) and increases in mineralocorticoid receptor (MR) expression were found in CMS aged mice. Interestingly, dexamethasone effects were reversed by spironolactone, a MR antagonist, but not by mifepristone, a GR antagonist.

Conclusions: Overall the results suggest that the effects of chronic stress in aged mice result from an alteration of the JNK-mediated pathways involved in tau-related cognition deficits. The primary event triggering the effects seems to be an exacerbation of non-genomic MR pathways.