NOVEL MECHANISMS OF STRESS-INDUCED MOOD AND COGNITIVE IMPAIRMENT - THE PATH FROM DEPRESSION TO ALZHEIMER’S DISEASE

I. Sotiropoulos1,2, V. Pinto1, A. Takashima3, O.F.X. Almeida2, N. Sousa1

1ICVS Institute, Health and Life Sciences School, University of Minho, Braga, Portugal, 2Neuroadaptation Group, Max Planck Institute of Psychiatry, Munich, Germany, 3Laboratory for Alzheimer’s Disease, RIKEN Brain Science Institute, Wako, Japan

Introduction: Current lifestyle places individuals under increasingly greater loads of psychological and physical stress. Although the mechanisms that are triggered by stress are primarily adaptive to facilitate homeostasis, chronic stress can become maladaptive. Specifically, stress and its primary manifestation, glucocorticoid (GC) secretion is strongly associated with neuronal atrophy/dysfunction, impaired cognition, and mood and affective disorders such as depression. A causal role of chronic stress in the etiopathology of Alzheimer’s disease (AD) has been also suggested.

Aims: Although cumulative evidence suggests a continuum between depression and AD, and stress is suggested to play a detrimental role in both diseases, considerably less attention has been given to the suggested role of stress as a connecting risk factor.

Methods: Using both transgenic and non-transgenic animals, we investigate the sequential inter-relationships between these various pathogenic elements, in particular with respect to the mechanisms through which stress might precipitate brain pathology.

Results: Our studies show that stress and GC trigger APP misprocessing towards the production of neurotoxic amyloid-β (Aβ) as well as abnormal tau hyperphosphorylation and aggregation resulting in associated impairments of cognitive and emotional status. Furthermore, we show that the presence of tau predisposes to GC and/or stress exposure as well as tau protein is essential for excitotoxicity providing molecular, electrophysiological and behavioural evidence.

Conclusions: These studies suggest an essential role of tau in a critical mechanism through which stress and GC exert their neuro-remodelling and neurodegenerative effects upon the substrates of cognition and emotion.