

P064 A β regulates the lysosomal system via p53 in cultured cortical neurons

R.M. McCormack, M.P. Fogarty, V.A. Campbell

Department of Physiology, Trinity College Institute of Neuroscience, Trinity College, Dublin, Ireland

β -amyloid (A β_{1-40}), a hallmark of Alzheimer's disease pathology, mediates its apoptotic effect through the release of lysosomal proteases into the cytosol¹. The aim of this study was to investigate the role of the transcription factor, p53, in A β -mediated regulation of the lysosomal system. Cultured rat cortical neurons were treated with fibrillar A β_{1-40} peptide (2 μ M) \pm the p53 inhibitor, pifithrin- α (100nM). A β_{1-40} significantly increased mean phospho-p53^{ser15} expression at the lysosome from 1637.69 \pm 121.44 (arbitrary units) to 2679.4 \pm 256.91 (p<0.01, AVOVA, n=6) and this was attenuated by pifithrin- α . This correlated with a p53-dependent destabilisation of the lysosomal membrane, as demonstrated by the acridine orange relocalisation assay. Expression of the lysosomal associated membrane protein, LAMP-1, was decreased in A β -treated cells compared with controls at 2, 6 and 24 hours. In addition, A β_{1-40} increased cytosolic activity of the lysosomal enzyme, cathepsin-L, from 29.2 \pm 2.1 pmolAFC/mg/ml to 40 \pm 3.6 pmol/AFC/mg/ml and this effect was reduced by pifithrin- α (p<0.05, ANOVA, n=6).

We suggest a p53-dependent regulation of the lysosomal/cathepsin system which may be pertinent in A β -induced apoptosis.

1: Boland, B and Campbell, V. A. (2004) *Neurobiology of Aging*, 25(1), 83-91.

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