

P046 Activation of p75NTR is linked to functional impairment in the rat hippocampus

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The neurotrophins play key roles in determining neuronal fate. Nerve growth factor (NGF) and other neurotrophins signal via two receptor subtypes; the high-affinity Trks, associated with cell survival and plasticity, and p75NTR, associated with cell death and damage via the stress-activated protein kinase, JNK. Here we have examined the role of p75 in neuronal degeneration using an *in vivo* model, kainic acid (KA)-induced excitotoxicity. All experiments conformed to local and national ethical regulations.

Urethane-anaesthetised rats were injected intracerebroventricularly with saline (0.9%) or KA (100 μ M) and long-term potentiation (LTP) was induced by tetanic stimulation of the perforant path. LTP was sustained in the saline-treated, but not the KA-treated group; this KA-induced synaptic impairment was associated with increased p75 ($p < 0.05$) and phosphoJNK ($p < 0.05$) expression. Tissue from dentate gyrus of saline and KA-treated rats was incubated with NGF (50ng/ml) in the presence and absence of the Trk inhibitor tyrphostin (1mM) and analysed for JNK activation. The results of these experiments suggest that the increased JNK activation associated with these impairments is due to binding of NGF to p75.

These data are consistent with the hypothesis that activation of p75 leads to impairment in neuronal function in the dentate gyrus of the rat via phosphorylation of JNK.