

Title: The pentraxin family regulates neuronal and microglial function in the CNS and is disrupted in phenotypes associated with Alzheimer's disease.

Authors: Cummings, D.M.^{*1}, Benway, T.A.^{*1}, Foster, E.¹, Liu, W.¹, Yasvoina, M.V.¹, Lashley, T.², Murray, C.², Richardson, J.C.³, Edwards, F.A.^{†1}, Salih, D.A.^{†1}

Affiliations: ¹Dept of Neuroscience, Physiology and Pharmacology, UCL, Gower St, London, UK

²Queen Square Brain Bank, London

³Neurosciences Therapeutic Area, GlaxoSmithKline R&D, Stevenage, UK

*Joint first authors, †Joint corresponding authors

Introduction: At synapses, neuronal pentraxin 1 (NPTX1), NPTX2 and NPTX receptor form pentamers, playing a role in plasticity by clustering AMPA receptors (O'Brien et al. 2002 J.Neurosci. 22:4487-98). NPTX1 also mediates amyloid β -induced neurite degeneration and NPTX2 regulates inflammation, a process dysregulated in Alzheimer's disease (AD) (Abad et al. 2006 J.Neurosci. 26:12735-47). The liver also secretes pentraxins, e.g. serum amyloid P component (SAP) that may enter the brain as the blood-brain-barrier breaks down during AD.

Materials and Methods: Models: Transgenic mice (human *APP^{swe}+PSEN1_{M146V}*, or *Tau_{P301L}*). Human AD brain sections. Hippocampal organotypic slice cultures from wild type mice.

Patch clamp recording in organotypic slices.

Immunohistochemistry: antibodies against neuronal pentraxins and SAP; A β 1-40 and A β 1-42 for amyloid pathology; AIF1 and CD68 for microglial number and activation.

Results: We show that NPTX1 and SAP stain amyloid plaques, both in brain sections from AD patients and *APP+PSEN1* mice, indicating that both pentraxins interact with plaques. Interestingly, SAP can form complexes with NPTX family members when they are co-expressed in HEK293 cells, suggesting that SAP could interact with neuronal pentraxins. Application of nanomolar concentrations of each of the human pentraxins over 7 days reduced paired-pulse ratios at CA3-CA1 synapses. This indicates an increase in glutamate release probability, similar to that observed in *APP^{swe}+PSEN1_{M146V}* mice (Cummings et al. 2015 *Brain* 138:1992-2004). Furthermore, our www.mouseac.org database indicates changes in expression of neuronal pentraxins at different ages in mouse models (Matarin et al. 2015 *Cell Reports* 10:633-44).

Finally, we show that NPTX receptor is expressed in BV2 mouse microglial cells and that adding NPTX1 or SAP to organotypic hippocampal slices decreases the number of microglia.

Conclusions: Both neuronal and peripheral pentraxins have effects on release of glutamate and can interact with AD plaques, possibly modulating the plaque-related microglial response. The peripheral pentraxin SAP, when it enters the brain, can form complexes with the neuronal pentraxins.