

**P020** Calmodulin binding to APP and the APLPs

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The calcium hypothesis in Alzheimers disease (AD) suggests that the neurodegenerative process is a result of impaired  $\text{Ca}^{2+}$  signalling. The intracellular  $\text{Ca}^{2+}$ -sensor protein calmodulin (CaM) interacts with a large number of proteins to regulate their biological activity in response to  $\text{Ca}^{2+}$  flux. The molecular interaction of CaM with a number of target proteins typically requires a motif that is based upon variations on the basic amphiphilic  $\alpha$ -helix involving conserved hydrophobic residues at positions 1-10, 1-14 or 1-16. Sequence analysis of proteins associated with AD (PS1, PS2, PEN-2 and nicastrin) found that they contain one or more putative  $\text{Ca}^{2+}$ -dependent CaM-binding domains. In keeping with this, we analysed APP, APLP1 and APLP2 for the presence of putative CaM-binding domains. Here we show that APP and the APLP's each contain putative  $\text{Ca}^{2+}$ -dependent motifs of the 1-14 class. Interestingly, the predicted domain is found between residues 712-732 of APP which also includes sites targeted for  $\gamma$ - cleavage and ICD generation. Full-length APP and the APP CTF from stably transfected CHO cells were retained on CaM-agarose in a  $\text{Ca}^{2+}$ -dependent manner. Current studies are aimed at assessing whether the interaction of CaM with APP/APLPs modulates their processing by  $\gamma$ -secretase and/or the generation of ICD fragments.