

Gerd Multhaup



Ligand associated conformational changes of the amyloid precursor protein APP

Current Research

APP is suggested to be involved in maintaining the Cu-homeostasis within the CNS, together with the prion protein (PrP) that also binds copper very specifically. Apart from their action to monomerize APP dimers, copper ions facilitate the non-amyloidogenic cleavage and attenuate the amyloidogenic cleavage of APP. Thus, we conclude that dimeric forms of APP inside the cell are the preferred targets of the β -secretase that initiates amyloid formation.

We would like to understand how the homophilic interaction domains and the copper binding site of APP regulate the complex formation between APP and β -secretase and in which cellular compartments the proteolytic cleavage event can occur which is required for amyloid formation.

Projects for a doctoral thesis

How APP mutants (affecting copper binding and/or dimerization) are transported and processed within hippocampal neurons from APP knock-out mice. Our goal is to study the physiological function of APP dimerization and its conformational requirement for APP/ β -secretase interactions.

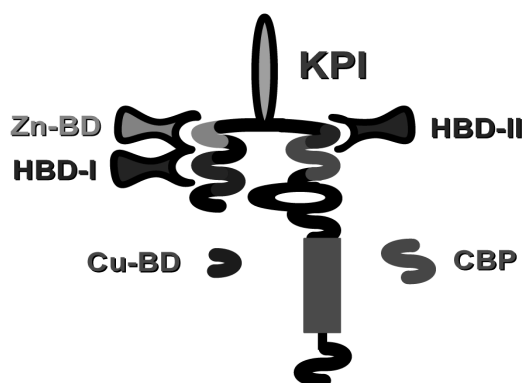
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Selected Publications

- 1) Multhaup, G., Schlicksupp, A., Hesse, L., Beher, D., Ruppert, T., Masters, C. L. and Beyreuther, K. (1996). The amyloid precursor protein of Alzheimer's disease in the reduction of copper(II) to copper(I). *Science*, 271, 1406-1409.
- 2) Multhaup, G., Ruppert, T., Schlicksupp, A., Hesse, L., Bill, E., Pipkorn, R., Masters, C.L. and Beyreuther, K. (1998). APP-copper complexes undergo site-specific fragmentation in the reduction of hydrogen peroxide. *Biochemistry*, 37, 7224-7230.
- 3) Borchardt, T., Camakaris, J., Cappai, R., Masters, C. L., Beyreuther, K., and Multhaup, G. (1999). Copper inhibits β -amyloid production and stimulates the non-amyloidogenic pathway of amyloid precursor protein (APP) secretion. *Biochem J* 344, 461-467.
- 4) Strausak, D., Mercer, J.F.B., Dieter, H.H., Stremmel, W. and Multhaup, G. (2001). Copper in disorders with neurological symptoms: Alzheimer's disease, Menkes and Wilson disease. *Brain Res Bull*, in press.
- 5) Bodendorf, U., Fischer, F., Bodian, D., Multhaup, G. and Paganetti, P. (2001). A splice variant of β -secretase deficient in the amyloidogenic processing of the amyloid precursor protein. *J Biol Chem*, in press.



Structural domains and binding motifs of APP. CBD, collagen binding domain; CuBD, copper binding domain; HBD-I and HBD-II, heparin binding domains I and II; ZnBD, zinc binding domain; KPI, Kunitz-type protease inhibitor.