09/04 - "Structural biology of human brain CNP, a protein essential for axonal survival" - only abstract available

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Abstract:

Objectives: Structure-function relationships of brain proteins need to be established in order to understand the molecular basis of brain disorders that affect organic health, as well as the psychological well-being.
Methods: Proteins have been prepared and purified, and subjected to structural investigation using spectroscopic and crystallographic methods. Molecular modelling has been used to assess protein-ligand binding.

Results and conclusions: Our study was originally concerned with full-length brain Cyclic Nucleotide Phosphodiesterase (CNP), a member of the 2H phosphodiesterase family, which is found abundantly in the myelin of oligodendrocytes in the central nervous system, and has been shown to be of major importance for axonal survival. As such, CNP is believed to be implicated in diseases such as multiple sclerosis and schizophrenia. The three-dimensional structure of the full-length protein is anticipated to yield new insights into the molecular mechanisms of the protein.
We have developed a protocol for expression and purification of the recombinant full-length protein, verified the integrity of the protein by mass spectrometry, and checked the fold and its stability by circular dichroism and fluorescence spectroscopy. Extensive crystallisation trials did not yield crystals suitable for X-ray diffraction so far. In selected trials, protein self-organisation was observed, probably indicating epitaxy-like formation of nanostructures on the glass plates.
Another family of brain proteins are the Visinin-like Proteins (VILIPs) that are neuronal calcium sensor proteins and an important factor for synaptic plasticity. They are involved in schizophrenia, neurodegenerative diseases such as Alzheimer's and other disorders.
To obtain further insights into the molecular level mechanisms of VILIPs, homology models were generated and modelling techniques were used to elucidate the binding mechanisms of these proteins to specific membrane components (PIPs). We have developed the first three-dimensional model of VILIP:PIP complexes, and propose a mechanism whereby recognition of specific PIP derivatives contributes to the targeting of VILIPs to subcellular locations.

Publications: Braunewell, K.H., Altarche-Xifro, W., Lange, K. & Hofmann, A. (2007) Modelling of VILIP-Phosphatidylinositol Interactions - Implications for Differential Membrane Localisation of NCS proteins. Submitted.; Braunewell, K.H., Brackmann, M. & Hofmann, A. (2006) VILIP-1, A novel regulator of the guanylate cyclase transduction system in neurons. Calcium Binding Proteins 1, 12-15.; Brackmann, M., Hofmann, A. & Braunewell, K.-H. (2006) Structure, function and expression of members of the VILIP (visinin-like protein) subfamily of neuronal Ca2+ sensor proteins in Neuronal calcium sensor proteins (K.-W. Koch, Phillipov, P.), Nova Science Publisher, pp 115-135.

Keywords: Cyclic Nucleotide Phosphodiesterase, Protein Structure-Function Relationships, Visinin-likeProteins