induces membrane disruption to a similar extent as the full-length peptide. However, unlike the full-length IAPP peptide, IAPP1-19 is conformationally stable in a helical conformation when bound to the membrane. In vivo and in vitro measurements of membrane disruption indicate the rat version of IAPP1-19, despite differing from hIAPP1-19 by only by the single substitution of Arg18 for His18, is significantly less toxic than hIAPP1-19, in agreement with the low toxicity of the full-length rat IAPP peptide. To investigate the origin of this difference at the atomic level, we have solved the structures of the human and rat IAPP1-19 peptides in DPC micelles, as well as the completely non-toxic full-length rat and toxic full-length human peptide. While the structures of rat and human IAPP1-19 are similar, the charge at residue 18 plays a key role in controlling the toxicity of the peptide. At pH 7.3, the more toxic hIAPP1-19 peptide is buried deeper within the micelle, while both the less toxic rIAPP1-19 peptide and non-toxic full-length rIAPP peptide are located at the surface of the micelle. Deprotonating H18 in hIAPP1-19 moves the peptide to the surface of the micelle. This change in orientation is accompanied by a corresponding change in toxicity. At pH 6.0, the membrane disruption induced by hIAPP1-19 is significantly decreased and resembles that of the less toxic rIAPP1-19 peptide.

478-Pos Board B357

Amyloidogenic Propensity of ProIAPP and IAPP in the Presence of Negatively Charged Lipid Bilayers

Suman Jha.
TU Dortmund University, Dortmund, Germany.

The islet amyloid polypeptide (IAPP) is synthesized in the β-cells of the pancreas from its precursor, the proislet amyloid polypeptide (ProIAPP). ProIAPP is co-processed in the secretory granules, and then co-secreted to the extracellular matrix together with insulin. As indicated earlier, partially processed N-terminal ProIAPP is able to interact with negatively charged moieties, like heparan sulfate, which may lead to islet amyloid plaque formation. Amyloid plaques have been found both extracellularly and intracellularly in type II diabetic patients. Here, we studied the amyloidogenic propensity of native ProIAPP and compared it with that of IAPP in the absence and presence of negatively charged membranes. Our CD studies show that the secondary structure content of ProIAPP and IAPP is predominantly unordered with small amounts of ordered secondary structure elements as confirmed by ATR-FTIR spectroscopy. However, in the presence of anionic membranes, ProIAPP forms predominantly α-helices and loops that subsequently transform to intermolecular β-sheet structures. For comparison, IAPP forms intermolecular β-sheets largely via unordered and loop structures. The ATR-FTIR and fluorescence spectroscopy studies performed also reveal that ProIAPP has a higher amyloidogenic propensity in the presence of negatively charged membranes, but is still less amyloidogenic than IAPP. AFM studies have also been carried out which show that ProIAPP, at variance to IAPP, does not form long fibrils, but rather protofilaments or short fibrils, only. Hence, both, the presence of a small amount of unprocessed ProIAPP in β-cell secretion, or the interaction with negatively charged surfaces, like negatively charged lipid bilayers, may initiate islet amyloid plaque formation.

479-Pos Board B358

Structural Studies Of Islet Amyloid Polypeptide In The Presence Of Insulin And Lipid Membranes

Shuqiu Han.
Clark University, Worcester, MA, USA.

Previous work by others has shown that insulin inhibits the formation of fibrils from islet amyloid polypeptide. The mechanism for the inhibition is not known. To address this issue, we are studying IAPP in the presence of lipid membranes, with or without insulin. Circular dichroism spectra of IAPP alone in phospholipid membranes show that it undergoes a structural rearrangement from α-helix to a β-sheet conformation. In the presence of insulin, this transition is not observed, that is, IAPP remained a-helical. To explain this, we are using other biophysical methods including solution-state NMR, electron microscopy, SDS-PAGE and limited proteolysis monitored by mass spectrometry. Results from these studies will be presented and discussed in this poster.

480-Pos Board B359

Amyloid-like Misfolding Of Peptides By Membrane Mimicking Environments

Alex Perálvarez-Marín[1], Anna Wahlström[1], Jesper Lind[1], Loïc Hugonin[1], Jüri Jarvet[2], Lena Mäler[1], Andreas Barth[1], Astrid Gräslund[1].
[1]Stockholm University, Stockholm, Sweden, [2]The National Institute of Chemical Physics and Biophysics, Tallin, Estonia.

Sodium dodecyl sulfate has been proven as an amyloid-like misfolding agent [1-3]. Our study comprises the biophysical characterization of human peptides in the presence of submicellar and micellar concentrations of SDS. The prodynorphin derived peptides (Big dynorphin, dynorphin A and dynorphin B) [4], the amyloid β peptide [5], and the proinsulin derived C-peptide are our subject of study. As determined by CD and FTIR spectroscopy, the peptide structural transitions involve different secondary structures, such as random coil, β-sheet and α-helix. By means of NMR, dynamic light scattering, native-PAGE or ThT fluorescence, we have shown that all the peptides transit through a high molecular weight aggregated state at submicellar detergent concentrations. Finally, studies with model membranes with different charge composition have been carried out to relate the structural characterization of these peptides to their possible role in the cell and their action mechanisms in pathology.

1. Rangachari, V., Moore, B.D., Reed, D.K., Sonoda, L.K., Bridges, A.W., Conboy, E., Hartigan, D., and Rosenberry, T.L. (2007). Biochemistry *46*, 12451-12462.
2. Rangachari, V., Reed, D.K., Moore, B.D., and Rosenberry, T.L. (2006). Biochemistry *45*, 8639-8648.
3. Tew, D.J., Bottomley, S.P., Smith, D.P., Ciccotosto, G.D., Babon, J., Hinds, M.G., Masters, C.L., Cappai, R., and Barnham, K.J. (2008). Biophys J *94*, 2752-2766.
4. Hugonin, L., Barth, A., Graslund, A., and Peralvarez-Marin, A. (2008). Biochim Biophys Acta. *in press.*
5. Wahlstrom, A., Hugonin, L., Peralvarez-Marin, A., Jarvet, J., and Graslund, A. (2008). FEBS J. *in press.*

481-Pos Board B360

Modeling amyloid toxic ion channels

Hyunbum Jang[1], Ratnesh Lal[2], Ruth Nussinov[1].
[1]NCI-Frederick / SAIC-Frederick, Inc., Frederick, MD, USA, [2]University of Chicago, Chicago, IL, USA.

Non-amyloidogenic beta peptides, p3 ($A\beta_{17-42}$) and $A\beta_{11-42}$, resulting from α-secretase and BACE cleavage are often found in amyloid plaques. However, the biophysical properties and functional role of these non-amyloidogenic peptides are not understood. We present molecular dynamics (MD) simulations of channels consisting of the U-shaped *beta-strand-turn-beta-strand* peptides using available NMR-based coordinates of p3 and $A\beta_{9-42}$. Our results show that non-amyloidogenic p3 and $A\beta_{9-42}$ peptides form ion channel-like structures with loosely attached subunits. These channels are dynamic and are made of small peptide oligomers. The channels can conduct calcium and obtain shapes and dimensions consistent with Atomic Force Microscopy (AFM) images. All channels break into mobile subunits suggesting that membranes do not support intact β-sheet channels. We shall further present results of modeling both PG-1 and k3-β_2m channels, presenting a consistent general picture of toxic beta-sheet based channels. Funded in part by DHHS #N01-CO-12400.

482-Pos Board B361

Probing Tau-Vesicle Interactions

Shana Elbaum, Jocelyn Traina, David Eliezer, Elizabeth Rhoades.
Yale University, New Haven, CT, USA.

Tau is the major protein component of the neurofibrillary tangles that characterize a group of neurodegenerative diseases, including Alzheimers Disease. The transformation of tau from its native state where it functions as a microtubule-associated protein (MAP), to its pathological state as is found in patients suffering from any of the various associated diseases, is not well understood. Studies have shown that tau aggregation can be induced by anionic lipid vesicles, and that detergent micelles can induce folding of the microtubule binding domain of tau. Here we use fluorescence correlation spectroscopy (FCS) to monitor the interaction of tau with synthetic lipid vesicles, in order to investigate vesicle binding and aggregation. Studying several isoforms of tau, we find that solution pH plays a strong role in such interactions.

483-Pos Board B362

An α-Helical Conformation of the SEVI Peptide, a Dramatic Enhancer of HIV Infectivity, Promotes Lipid Aggregation and Fusion

Jeffrey Brender, Kevin Hartman, Ravi P.R. Nanga, Stephanie V. Le Clair, Lindsey M. Gottler, Ayyalusamy Ramamoorthy.
University of Michigan, Ann Arbor, MI, USA.

A peptide ubiquitous in human seminal fluid has been recently described that dramatically enhances the infectivity of the HIV virus (3-5 orders of magnitude by some measures). Previous studies have shown that this peptide, a fragment of human Prostatic Acid Phosphatase ($PAP_{248-286}$) referred to as SEVI (Semen-derived Enhancer of Viral Infection), is amyloidogenic and the enhancement of viral infectivity is dependent on the aggregation state of the peptide. To complement these previous in vivo studies we have performed in vitro assays to investigate the physical mechanisms by which the $PAP_{248-286}$ promotes the interaction with lipid bilayers. Our results indicate a strong interaction of freshly dissolved $PAP_{248-286}$ with lipid bilayers but a weaker interaction with the amyloid form of $PAP_{248-286}$, as measured by the tendency of freshly dissolved $PAP_{248-286}$ to induce aggregation of lipid vesicles and membrane fusion. The