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Structural insights into neurotoxic Alzheimer's $A\beta_{(1-42)}CC$ oligomers using solid-state NMR

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Small intermediate aggregates (oligomers and protofibrils) of amyloidogenic peptides and proteins have been shown to be neurotoxic *in vitro* and are believed to be the principal toxic species for brain neurons causing Alzheimer's and other neurodegenerative diseases.[1] However, cell toxicity and structural studies of oligomers and protofibrils of Aβ using solid-state NMR and microscopy (TEM, STEM and AFM) are challenging, because of the transient nature and structural diversity of oligomers and a high level of polymorphism of protofibrils and amyloid fibrils, usually all coexisting in the same macroscopic sample. Recently, β-sheet rich oligomers and protofibrils of a model Alzheimer's $A\beta_{(1-42)}$ peptide, $A\beta_{(1-42)}CC$, were stabilized by the specific double mutation (A21C and A30C) followed by intramolecular cysteine-cysteine cross-linking.2 $A\beta_{(1-42)}CC$ forms only oligomers and protofibrils, which exhibit ca 100-fold higher apoptotic caspase-3/7 activity (neurotoxicity to SH-SY5Y human neuroblastoma cells) compared with $A\beta_{(1-42)}$ amyloid fibrils.2

We report on a variety of important structural constraints in oligomers of uniformly (^{13}C,^{15}N) and selectively (^{13}C,^{15}N and ^{17}O) labelled $A\beta_{(1-42)}CC$ using multi-dimensional correlation ^{13}C-^{13}C and ^{13}C-^{15}N solid-state NMR experiments. Structural constraints obtained from 2D ^{13}C-^{13}C and ^{13}C-^{15}N NMR on hydrated oligomers of recombinant U-^{13}C,^{15}N-$A\beta_{(1-42)}C_{21}C_{30}$ reveal β-sheet secondary structure features and intermolecular packing of the C-terminal regions in oligomers. Using 2D ^{13}C-^{13}C DARR NMR, V24Cγ-K28Cε and V36Cγ-K16Cε cross-peaks were detected in different selectively (^{13}C,^{15}N) labelled $A\beta_{(1-42)}CC$ samples of oligomers suggesting spatial proximities between side-chains of these amino acid residues. These constraints together with the Cα and Cβ ^{13}C having chemical shifts characteristic of β-sheet structures in proteins are consistent with a β-hairpin structure in the V24-K28 structural fragment and with a specific packing of the central (K16) and the C-terminal (V36) regions in $A\beta_{(1-42)}$ CC oligomers, respectively. In addition, we also explore implementation of $^{15}N\{^{17}O\}$ REAPDOR NMR on selectively (^{13}C,^{15}N and ^{17}O) labelled $A\beta_{(1-42)}CC$ for the direct probing of hydrogen bonding in oligomers: The method has successfully been validated on Aβ amyloid fibrils.

Biography

Oleg N. Antzutkin is Professor in Chemistry of Interfaces at LTU (since 2006) and also Professorial Fellow (since 2008) at the University of Warwick, UK. After B.Sc.(Hon) and M.Sc. degrees in Chemical Physics at Novosibirsk State University, Russia, in 1990 he moved to Sweden as a research fellow. He received his licentiate of technology degree (in 1992) in the field of ESR spectroscopy under supervision of Prof. Anders Lund at University of Linköping. He has received Ph.D. in Physical Chemistry in 1996, solid-state MAS NMR spectroscopy, under supervision of Prof. Malcolm H. Levitt. He spent one-year sabbatical (1998-1999) at NIH, USA (host Robert Tycko). During this time he engaged a new highly successful project at NIH and together with Tycko and co-workers have solved supramolecular-level structure of Alzheimer's amyloid fibrils using novel solid-state NMR methods. Only five papers from this period were already cited more than 2000 times. One of recent achievements of his group at LTU in collaboration with Warwick University is the development of novel 15N{17O}-REAPDOR NMR methodology to probe hydrogen bonding in amyloid fibrils and other biologically important systems: These results were reported in Angewandte Chemie International Edition in 2012. He has published >125 articles in refereed scientific journals, a few chapters in books and received a number of prizes. 'h'-index>25, number of citations > 3462 (2013-05-22) (ISI web of sciences), conference contributions: 61 (28 invited talks).

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