Microsc. Microanal. 8 (Suppl. 2), 2002
DOI 10.1017.S1431927602107446

Zwitterionic Detergents Promote the Formation of Atypical Aß$_{40}$ Fibrils

Richard W. McLaughlin*, Robert J. Chalifour*, Xianqi Kong*, Louis Lavoie*, Philippe Sarazin*, Dino Stéa*, Hojatollah Vali**, Xinfu Wu*, Patrick Tremblay*, and Francine Gervais*.

*Neurochem Inc., 7220 Frederick-Banting St., Bureau 100, Saint-Laurent, Quebec, H4S 2A1 Canada.
**McGill University, Dept. of Anatomy and Cell Biology, 3640 University St., Montreal, Quebec, H3A 2B2 Canada.
E-mail: abstracts@neurochem.com

Alzheimer's disease is characterized by the presence in the brain of distinctive extracellular amyloid plaques. The major constituent of these deposits is the beta amyloid (Aß) peptide, which self-associates *in vitro* to form amyloid-like fibrils [1]. The mechanism of fibrillization has been extensively studied in hopes of developing anti-amyloid therapeutic agents [2]. We have studied a family of compounds that promote Aß$_{40}$ assembly as a means to explore the process of fibril formation. Using circular dichroism (CD) to test their effect on Aß$_{40}$ assembly, zwitterionic detergents with 14 or 16 carbon chain lengths, 3-(N, N-dimethyltetradecylammonio) propanesulfonate (**III**) and 3-(N, N-dimethylhexadecylammonio)propanesulfonate (**IV**) were identified as promoters of Aß$_{40}$ fibrillogenesis based on their induction of ß-sheet structure. Interestingly, two related compounds with chain lengths of 10 and 12 carbons respectively, 3-(N, N-dimethyldecylammonio)propanesulfonate (**I**) and 3-(N, N-dimethyldodecylammonio) propanesulfonate (**II**) were found not to have this effect. CD only indirectly infers the assembly state of Aß, based on the appearance of ß-structure [3]. Transmission electron microscopy (TEM) was therefore used to directly visualize the appearance of the Aß$_{40}$ fibrils in the presence of these compounds. EM confirmed the CD findings and revealed the presence of a unique fibril morphology [4, 5]. TEM images of high-resolution platinum/carbon replicas showed that the Aß$_{40}$ in the presence of compounds **III** and **IV** assembled into a network of highly bundled and cross-linked fibrils not observed with Aß$_{40}$ alone. Compounds **I** and **II** did not have this effect, indicating that the promotion and morphological changes are dependent on the length of the hydrophobic chain. Preliminary 2-D-NOESY experiments clearly indicate that these detergents interact with the Aß molecules. Studies are currently ongoing to better characterize the interactions between Aß$_{40}$ and **III** and **IV**.

REFERENCES

[1] D.J. Selkoe, Physiol. Rev. 81 (2001) 741.
[2] J.D. Harper and P.T. Jr. Lansbury, Annu. Rev. Biochem. 66 (1997) 385.
[3] J.W. Kelly, Curr. Opin. Struct. Biol. 6 (1996) 11.
[4] D.M. Walsh et al., J. Biol. Chem. 274 (1999) 25945.
[5] E.H. Nielsen et al., Methods in Enzymol. 309 (1999) 491.

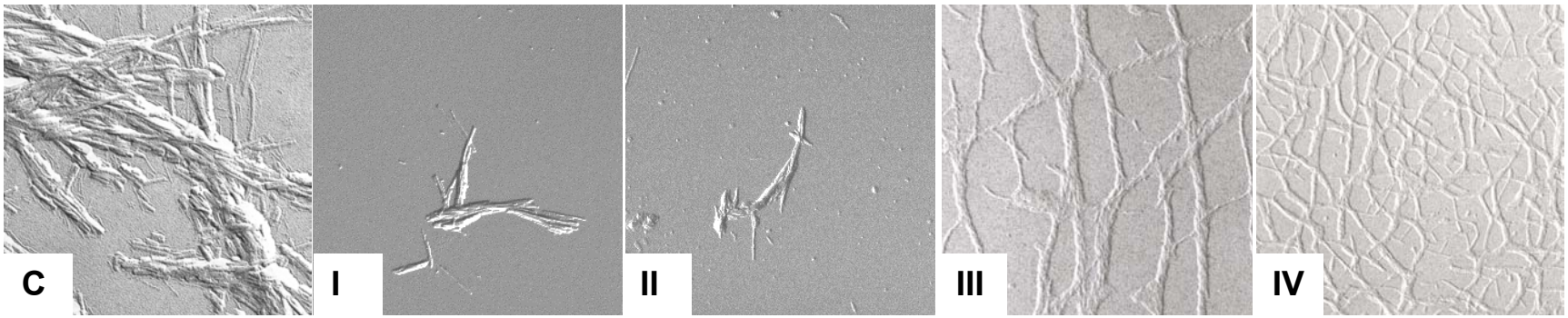

Figure 1. Electron micrographs of platinum/carbon replicas showing Aß fibril structures in the presence of compounds I, II, III, and IV compared to control. Magnification = X 21 000. Typical amyloid fibrils are formed by Aß control (C). Identical fibril morphology is visualized in the presence of compounds **I** and **II.** A network of cross-linked fibrils is visualized in the presence of compounds **III** and **IV**.

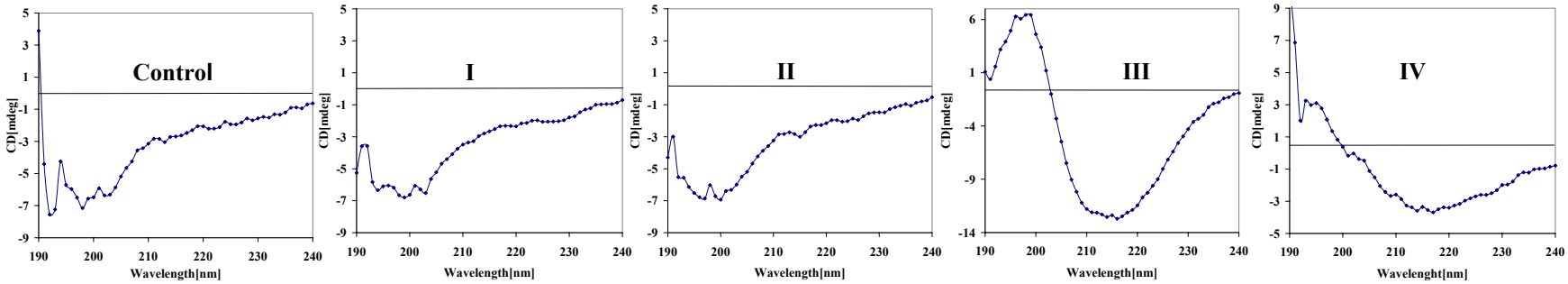

Figure 2. Circular dichroism analysis of compounds **I, II**, **III**, **IV**, and control after a 4-h incubation. Compounds **III** and **IV** are potent promoters of ß-sheet formation.