Print this Page for Your Records Close Window

Control/Tracking Number: 2007-A-39378-SfN
Activity: Scientific Abstract
Current Date/Time: 5/14/2007 7:51:50 PM

C-terminal fragments inhibit amyloid β-protein oligomerization and neurotoxicity

AUTHOR BLOCK
: *E. A. FRADINGER[1], M. TAN[2], S. M. SPRING[1], A. LOMAKIN[3], B. H. MONIEN[1], G. B. BENEDEK[3], C.-W. XIE[2], G. BITAN[1];
[1]Dept Neurol, [2]Semel Neuropsychiatric Inst., David Geffen Sch. Med. UCLA, Los Angeles, CA; [3]Physics, MIT, Cambridge, MA

Abstract: Self-association of amyloid β-protein (Aβ) into toxic oligomers is a seminal event in Alzheimer's disease (AD). Aβ exists in two predominant forms, Aβ40 and Aβ42. The oligomers formed by Aβ42 are significantly more toxic than those formed by Aβ40. Previously, it was shown that the C-terminus of Aβ42 is critical for the formation of higher order oligomers. We hypothesized that molecules with a high affinity for the C-terminus of Aβ42 may inhibit Aβ42-induced neurotoxicity. We prepared a series of Aβ(x-42) C-terminal fragments (CTFs) and tested their ability to inhibit Aβ42 oligomerization and neurotoxicity. The formation of neurotoxic Aβ42 hexamers was attenuated by CTFs and correlated roughly with peptide length. Aβ(29-42) inhibited hexamer formation at submicromolar concentrations. Surprisingly, inhibition of toxicity did not correlate with inhibition of oligomerization. Aβ(31-42) was the strongest inhibitor of toxicity and significant inhibition was found for Aβ(39-42). Aβ(31-42) inhibited Aβ42 induced neurotoxicity completely and fully rescued cells from Aβ42-induced inhibition of mini excitatory postsynaptic currents. Additionally, dynamic light scattering revealed that Aβ(31-42) significantly decreased the rate of Aβ42 aggregation. The ability of both short and long CTFs to inhibit Aβ42 toxicity suggests the existence of two classes of CTFs that act through different mechanisms. Preliminary data suggest that Aβ(31-42) interacts with Aβ42 to form large heterooligomers that precipitate out of solution, whereas, Aβ(39-42) may interact with the N-terminus of Aβ42 modifying the biological properties of the oligomers.
:

Theme and Topic (Complete): C.01.d. Alzheimer's disease: Abeta toxicity ; C.01.c. Alzheimer's

disease: Abeta assembly and deposition
Keyword (Complete): ALZHEIMER'S DISEASE ; BETA AMYLOID ; NEUROTOXICITY ; PEPTIDE ; IN VITRO
Presentation Preference (Complete): Slide Preferred
Support (Complete):
Support : Yes
Grant/Other Support: : NIH/NIA grant AG027818
Grant/Other Support: : Larry L. Hillblom Foundation grant 2005/2E
Grant/Other Support: : American Federation for Aging Research grant A04084
Grant/Other Support: : Generous gift from the Turken Family

Linking Group (Complete): CaribbeanFuchsia
Special Requests (Complete):
Religious Conflict? : No Religious Conflict
Additional Conflict? : No

Status: Complete