

Correspondence

Isomerization of Asp7 leads to increased toxic effect of amyloid- β 42 on human neuronal cells

VA Mitkevich^{1,2}, IY Petrushanko^{1,2}, YE Yegorov¹, OV Simonenko¹, KS Vishnyakova¹, AA Kulikova¹, PO Tsvetkov¹, AA Makarov^{*1} and SA Kozin¹

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Dear Editor,

The generation of toxic oligomers during the aggregation of the 42-residue amyloid- β (A β) peptide A β 42 into amyloid fibrils and plaques has emerged as a central feature of the onset and progression of Alzheimer's disease (AD).¹ Isomerization of an aspartic acid residue at position 7 is a common chemical modification of A β 42 isolated from brain of the patients diagnosed with AD.² This modification crucially influences such processes as zinc ion chelation by A β ,³ zinc-dependent oligomerization of A β ,⁴ and hydrolysis of A β by the angiotensin-converting enzyme.⁵ As each of these molecular events is closely related to the aggregation ability of A β , we have hypothesized that A β 42 containing isoaspartate 7 (isoA β 42) might have a role in the development of cerebral β -amyloidosis. Indeed, recently we have shown that when isoA β 42 is administered into blood of transgenic mice used as an animal model of AD, it accelerates the formation of amyloid plaques in contrast to A β 42, which does not have this effect.⁶ Thus, one could rationally suggest that isoA β 42 acts as aggregation seed and/or corruptive template compelling the physiological pool of endogenous A β 42 to be converted into oligomers and consequently into aggregates. To get a deeper insight into the mechanism of isoA β 42 pathogenicity, in the present study a comparison was made of the cytotoxic effect of isoA β 42 and A β 42.

Human neural stem cells NSC-hTERT that underwent differentiation have been used.⁷ Both isoA β 42 and A β 42 peptides induce the NSC-hTERT cell death and destruction of the neural network formed by them (Supplementary Figure S1a), however toxic effects of isoA β 42 are manifested to a greater extent (Supplementary Figure S1b). Percentage of the dying cells, relative to control in the population in the presence of 10 and 15 μ M of isoA β 42 increased by 37% and 61%, respectively, whereas the increase in the presence of A β 42 was by 11% and 32%, respectively. The difference in the mechanism of cytotoxic activity of A β 42 and isoA β 42 is that the effect of isoA β 42 is by three quarters caused by the induction of apoptosis, and only one-fourth of the cells dies via necrosis path, whereas in the case of A β 42 the number of cells dying by apoptosis and necrosis is the same (Supplementary Figure S1b). Thus, the

isoA β 42 toxic action on neuronal cells is not only more effective but also more specific than that of A β 42. Apoptotic effect of both peptides is associated with reduced mitochondrial potential of cells (Supplementary Figure S1c), which indicates the start of the mitochondrial apoptosis pathway.⁸ The action of peptides A β 42 and isoA β 42 leads to a decrease in intracellular glutathione level (Supplementary Figure S1c). Depletion of intracellular glutathione is also one of the causes of cell death.

In summary, it has been established for the first time that isomerization of the Asp7 residue leads to a significant increase of cytotoxic properties of A β 42. Neurotoxic effect of isoA β 42 is due to the induction of apoptosis and not damage of the cytoplasmic membrane. According to our data, the mechanism of the pathological development of AD may include direct neurotoxic effect of isoA β 42 on human cells, thus, isoA β 42 appears to be a promising drug target in the therapy of AD pathology.

Conflict of Interest

The authors declare no conflict of interest.

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¹Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Vavilov Street 32, Moscow 119991, Russia

*Corresponding author: AA Makarov, Laboratory of Conformational Stability of Proteins and Physical Methods of Analysis, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Vavilov Street 32, Moscow 119991, Russia. Tel: +7 499 1359824; Fax: +7 495 1351405; E-mail: aamakarov@eimb.ru

²These authors contributed equally to this work.