OPEN

Citation: Cell Death and Disease (2013) 4, e939; doi:10.1038/cddis.2013.492

www.nature.com/cddis

Correspondence

Isomerization of Asp7 leads to increased toxic effect of amyloid-β42 on human neuronal cells

VA Mitkevich[1,2], IY Petrushanko[1,2], YE Yegorov[1], OV Simonenko[1], KS Vishnyakova[1], AA Kulikova[1], PO Tsvetkov[1], AA Makarov*[1] and SA Kozin[1]

Cell Death and Disease (2013) **4,** e939; doi:10.1038/cddis.2013.492; published online 28 November 2013
Subject Category: Neuroscience

Dear Editor,

The generation of toxic oligomers during the aggregation of the 42-residue amyloid-β (Aβ) peptide Aβ42 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 Aβ42 isolated from brain of the patients diagnosed with AD.[2] This modification crucially influences such processes as zinc ion chelation by Aβ,[3] zinc-dependent oligomerization of Aβ,[4] and hydrolysis of Aβ by the angiotensin-converting enzyme.[5] As each of these molecular events is closely related to the aggregation ability of Aβ, we have hypothesized that Aβ42 containing isoaspartate 7 (isoAβ42) might have a role in the development of cerebral β-amyloidosis. Indeed, recently we have shown that when isoAβ42 is administered into blood of transgenic mice used as an animal model of AD, it accelerates the formation of amyloid plaques in contrast to Aβ42, which does not have this effect.[6] Thus, one could rationally suggest that isoAβ42 acts as aggregation seed and/or corruptive template compelling the physiological pool of endogenous Aβ42 to be converted into oligomers and consequently into aggregates. To get a deeper insight into the mechanism of isoAβ42 pathogenicity, in the present study a comparison was made of the cytotoxic effect of isoAβ42 and Aβ42.

Human neural stem cells NSC-hTERT that underwent differentiation have been used.[7] Both isoAβ42 and Aβ42 peptides induce the NSC-hTERT cell death and destruction of the neural network formed by them (Supplementary Figure S1a), however toxic effects of isoAβ42 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 μM of isoAβ42 increased by 37% and 61%, respectively, whereas the increase in the presence of Aβ42 was by 11% and 32%, respectively. The difference in the mechanism of cytotoxic activity of Aβ42 and isoAβ42 is that the effect of isoAβ42 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 Aβ42 the number of cells dying by apoptosis and necrosis is the same (Supplementary Figure S1b). Thus, the isoAβ42 toxic action on neuronal cells is not only more effective but also more specific than that of Aβ42. 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 Aβ42 and isoAβ42 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 Aβ42. Neurotoxic effect of isoAβ42 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 isoAβ42 on human cells, thus, isoAβ42 appears to be a promising drug target in the therapy of AD pathology.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements. This work was supported by the Molecular and Cellular Biology Program and by the Program 'Fundamental sciences to medicine' of the Russian Academy of Sciences, by the Russian Federal Program (contract 14.512.11.0017) and by the Russian Foundation for Basic Research (13-04-40108-comfi).

1. Cohen S *et al. Proc Natl Acad Sci USA* 2013; **110**: 9758–632013.
2. Roher A *et al. J Biol Chem* 1993; **268**: 3072–3083.
3. Tsvetkov P *et al. Biophys J* 2010; **99**: L84–L86.
4. Tsvetkov P *et al. Chembiochem* 2008; **9**: 1564–1567.
5. Toropygin I *et al. Rapid Commun Mass Spectrom* 2008; **22**: 231–239.
6. Kozin S *et al. Neurotox Res* 2013; **24**: 370–376.
7. Dashinimaev E *et al. Electron J Biol* 2008; **4**: 93–97.
8. Mitkevich V *et al. Biochimie* 2013; **95**: 1344–1349.

Supplementary Information accompanies this paper on Cell Death and Disease website (http://www.nature.com/cddis)

[1]Engelhardt 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
[2]These authors contributed equally to this work.