ACADEMIA | Letters

A Novel Treatment Approach in Alzheimer's Disease: sAPPα

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Alzheimer's disease (AD) is the most common cause of age-related dementia and the number of patients with AD is increasing worldwide. The amyloid cascade hypothesis(ACH) provides a fundamental perspective for the pathogenesis of AD. It is also strongly criticized due to the failure of the clinical trials that experimented with anti-amyloid drugs. Dar et al. brilliantly pointed out that sAPPα could be developed as a novel therapeutic agent in treatment of AD(1).

In the ACH model amyloid precursor protein(APP) is cleaved either by β-secretase followed by γ-secretase(amyloidogenic pathway) or α-secretase followed by γ-secretase(non-amyloidogenic pathway). It is the amyloidogenic pathway that ACH mostly focuses on as many studies showed the neurotoxic effects of β-amyloid.

However, there is growing evidence showing non-amyloidogenic pathway products have essential roles in several significant physiological processes including neurite growth, learning and memory, neural progenitor cell proliferation, and neural survival(2,3,4,5). Studies by Small et al. and Allinqu ant et al. demonstrate that sAPPα promotes neurite outgrowth(6,7). sAPPα also plays a role in synaptogenesis(8). Zheng et al. showed that APP KO mice display neurological deficits that can be explained by effects on synaptogenesis(9). Zou et al. found that sAPPα is important in maintaining constitutive and adaptive plasticity of dendritic spines in the adult brain(10). sAPPα also demonstrates neuroprotective properties(11). Obregon et al. demonstrated that sAPPα decreases βamyloid by modulating APP processing via BACE1(12). The study showed that while blocking sAPPα increases Aβ production, overexpression of sAPPα decreases amyloid plaques and soluble Aβ.

sAPPα also stimulates the proliferation of embryonic neural stem cells(NSCs)(13,14). Studies by Caillé et al. showed that infusion of APP antisense oligonucleotides reduces prolif-

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eration of neural progenitor cells and this could be reversed by APPα infusion(4). On the other hand, a study by Berna beu-Zornoza et al. proved that Aβ42 increases apoptotic cell death at high concentrations and increases the pool of proliferating glial precursors(15). EHT-0202 is a modulator of the GABA type A (GABAA) receptor and an inhibitor of phosphodiesterase 4, developed as a treatment in AD, stimulates α-secretase via elevating sAPPα levels. Preclinical studies show that EHT-0202 protects neurons against Aβ42 toxicity and that the provided neuroprotection is due to elevated levels of sAPPα. Studies in guinea pigs and rats show that chronic treatment with EHT-0202 decreases Aβ42 levels in cerebrospinal fluid(16).

To briefly summarize the non-amyloidogenic alpha pathway promotes learning, neurite outgrowth, synaptogenesis as well as neural survival and repair; and the amyloidogenic beta pathway triggers neural destruction and glial proliferation. Taken altogether one can propose that alpha and beta pathways constitute a system where the alpha pathway is the anabolic pathway responsible for survival and development of the neurons whereas the beta pathway is the destructive pathway that triggers apoptosis and cell death perhaps for remodeling.

This point of view is also supported by data from two fields other than Alzheimer's Disease. Recently several studies proved that APP and sAPPα are linked to increased tumor cell proliferation, migration, and invasion which endorses the view that sAPPα is part of an anabolic pathway(17). Another group of data comes from the autism studies where several groups showed increased levels of sAPPα and decreased levels of sAPPβ and βamyloid in patients with autism(18).

Alzheimer's disease (AD) is the most common cause of age-related dementia worldwide and the number of patients with AD is increasing. Although the amyloid cascade hypothesis provides a fundamental perspective for the pathogenesis of AD, anti-amyloid treatment strategies failed to demonstrate significant clinical benefits in trials. However, neuroprotective, synaptogenesis, neural growth and neural progenitor stimulating and BACE1 inhibitor properties of sAPPα supports that this APP fragment could provide a new treatment strategy in curing AD.

REFERENCES:

1. Dar NJ, Glazner GW. Deciphering the neuroprotective and neurogenic potential of soluble amyloid precursor protein alpha (sAPPα). *Cell Mol Life Sci.* 2020 Jun;77(12):2315-2330. doi: 10.1007/s00018-019-03404-x. Epub 2020 Jan 20. PMID: 31960113.

2. M Xiong et al, Secreted amyloid precursor protein-alpha can restore novel object location memory and hippocampal LTP in aged rats. *Neurobiol Learn Mem.* **138**, 291-299

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(2017).

3. PR Turner et al, Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory. *Prog Neurobiol.* **70**, 1-32 (2013).

4. Caille I et al, Soluble form of amyloid precursor protein regulates proliferation of progenitors in the adult subventricular zone. *Development* **131**, 2173–2181 (2004).

5. E Thornton et al, Soluble amyloid precursor protein alpha reduces neuronal injury and improves functional outcome following diffuse traumatic brain injury in rats. *Brain Res.* **1094**, 38–46 (2006).

6. DH Small et al, A heparin-binding domain in the amyloid protein precursor of Alzheimer's disease is involved in the regulation of neurite outgrowth.*J Neurosci.* **14,** 2117-27 (1994).

7. B Allinquant et al, Downregulation of amyloid precursor protein inhibits neurite outgrowth in vitro. *J Cell Biol.* **128**, 919-27 (1995).

8. Z Wang et al, Presynaptic and postsynaptic interaction of the amyloid precursor protein promotes peripheral and central synaptogenesis. *J Neurosci.* **29,** 10788-801 (2009)

9. H Zheng et al, Beta-Amyloid precursor protein-deficient mice show reactive gliosis and decreased locomotor activity. *Cell* **81**, 525–531(1995).

10. C Zou et al, Amyloid precursor protein maintains constitutive and adaptive plasticity of dendritic spines in the adult brain by regulating D-serine homeostasis. *EMBO J.* **17***, 2213-2222 (*2016).

11. 11. UC Müller, T Deller, M Korte, Not just amyloid: physiological functions of the amyloid precursor protein family. *Nat Rev Neurosci.* **18**, 281-298 (2017)

12. D Obregon et al, Soluble amyloid precursor protein-α modulates β secretase activity and amyloid-β generation. *Nat Commun.* **10**, 777 (2012)

13. Y Hayashi et al, Alzheimer amyloid protein precursor enhances proliferation of neural stem cells from fetal rat brain. *Biochem Biophys Res Commun.* **205**, 936-943 (1994)

14. I Ohsawa I et al, Amino-terminal region of secreted form of amyloid precursor protein stimulates proliferation of neural stem cells. *Eur J Neurosci.* **11**, 1907-1913 (1999)

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Citation: Topcular, B., Turkmen, C. (2021). A Novel Treatment Approach in Alzheimer's Disease: sAPPα. *Academia Letters*, Article 1189. https://doi.org/10.20935/AL1189.

15. A Bernabeu-Zornoza et al, Aβ42 Peptide Promotes Proliferation and Gliogenesis in Human Neural Stem Cells. *Mol Neurobiol.* doi: 10.1007/s12035-018-1355-7 (2018).

16. Uddin MS, Kabir MT, Jeandet P, Mathew B, Ashraf GM, Perveen A, Bin-Jumah MN, Mousa SA, Abdel-Daim MM. Novel Anti-Alzheimer's Therapeutic Molecules Targeting Amyloid Precursor Protein Processing. *Oxid Med Cell Longev.* 2020 Apr 29;2020:7039138. doi: 10.1155/2020/7039138.

17. P Pandey et al, Amyloid precursor protein and amyloid precursor-like protein 2 in cancer. *On cotarget.* **12**, 19439-19444 (2016).

18. CJ Westmark et al, Novel roles of amyloid-beta precursor protein metabolites in fragile X syndrome and autism. *Mol Psychiatry.* **21**, 1333-1341 (2016).

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