Review of: "Somatostatin and the pathophysiology of Alzheimer's disease"

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Potential competing interests: No potential competing interests to declare.

Thank you for inviting me to review the manuscript entitled "Somatostatin and the pathophysiology of Alzheimer's disease". Alzheimer's disease is among the most severe and burdensome medical conditions worldwide [World Health Organization, Dementia, 2019. https://www.who.int/news-room/fact-sheets/detail/dementia (Accessed July 2020).]. The author of the paper provides a current examination of a theory regarding the role of somatostatin in Alzheimer's disease. The author provides a comprehensive review of the literature on SST alterations in AD and proposes a model based on SST-IN hyperactivity and hypofunction. The article is structured well and provides a concise overview of the proposed model. I think this article makes a valuable contribution to the field of AD research.

There are some suggestions, please find them here below:

1) list of abbreviations should be added

2) please note that many AD hypotheses have been revised and supplemented and this should be noted in the introduction. The author cites Solarski, M et al (2018) [Solarski, M., Wang, H., Wille, H., & Schmitt-Ulms, G. (2018). Somatostatin in Alzheimer's disease: A new Role for an Old Player. Prion, 12(1), 1-8.], but does not cite the critical approach noted there. I advise you to convey the following thoughts from this article in the introduction « As so often, a first round of experiments may not yet be conclusive. A rigorous evaluation of the scenario painted in this perspective is needed to determine its broader significance for neurodegenerative diseases.»

3) Known association between vascular risk factors and GABA disturbances [I. Gacsalyi, K. Moricz, G. Gigler, K. Megyeri, P. Machado, F.A. Antoni, Persistent therapeutic effect of a novel α5-GABA(A) receptor antagonist in rodent preclinical models of vascular cognitive impairment, Eur. J. Pharm. 834 (2018) 118–125]. I propose to also note the role of somatostatin as vascular risk factors [Holm H, Nägga K, Nilsson ED, Ricci F, Cinosi E, Melander O, Hansson O, Bachus E, Magnusson M, Fedorowski A. N-Terminal Prosomatostatin and Risk of Vascular Dementia. Cerebrovasc Dis. 2017;44(5-6):259-265. doi: 10.1159/000479940. Epub 2017 Aug 31. PMID: 28854435.]

4) GABA may be the linchpin in a complex system of factors that eventually leads to the principal clinical hallmark of AD [Joan Jim´ enez-Balado, Teal S. Eich GABAergic dysfunction, neural network hyperactivity and memory impairments in human aging and Alzheimer's disease. Seminars in Cell and Developmental Biology 116 (2021) 146–159]. Defective GABAergic neuronal functions may lead to cortical network hyperactivity and aberrant neuronal oscillations and in consequence, generate a detrimental alteration in memory processes. «two major and non-overlapping groups of

inhibitory interneurons (SOM-cells and PV-cells) displayed distinct vulnerability in the perirhinal cortex of APP/PS1 mice and AD patients. Therefore, disrupted functional connectivity of this cortical region, as a result of the early SOM and PV neurodegeneration, might contribute to the altered brain rhythms and cognitive failures observed in the initial clinical phase of AD patients. Finally, these findings highlight the failure of amyloidogenic AD models to fully recapitulate the selective neuronal degeneration occurring in humans.». By noting these data, the author can emphasize the advantage of the somatostatin model.

5) Although it has been shown that binding of the SST ligand triggers an intracellular event cascade that modulates the expression of neprilysin, a membrane metallo-endopeptidase involved in Aβ degradation [Saito T, Iwata N, Tsubuki S, et al.. Somatostatin regulates brain amyloid beta peptide Abeta42 through modulation of proteolytic degradation. *Nat Med*. 2005;11(4):434–9.]. However, there is other data. The possibility that SST may modulate Aβ plaque formation directly is heightened by the fact that this molecule spontaneously forms amyloid fibrils in vitro [van Grondelle W, Iglesias CL, Coll E, Artzner F, Paternostre M, Lacombe F, et al. Spontaneous fibrillation of the native neuropeptide hormone Somatostatin-14. J Struct Biol. 2007;160(2):211-23.33] and is, in fact, stored prior to its synaptic release in dense granules as a natural amyloid [Maji SK, Perrin MH, Sawaya MR, Jessberger S, Vadodaria K, Rissman RA, et al. Functional amyloids as natural storage of peptide hormones in pituitary secretory granules. Science. 2009;325(5938):328-32.].. In particular in Latest data [Williams, D., Yan, B.Q., Wang, H. *et al.* Somatostatin slows Aβ plaque deposition in aged $APP^{NL\text{-}F/NL\text{-}F}$ mice by blocking Aβ aggregation. *Sci Rep* 13, 2337 (2023). https://doi.org/10.1038/s41598-023-29559-z] « Follow-on western blot analyses of whole brain extracts indicated that Sst interferes with early steps of Aβ assembly that manifest in the appearance of SDS-stable smears of 55–150 kDa in *Sst* null brain samples. As expected, no effect of Sst on tau steady-state levels or its phosphorylation were observed. Results from this study are easier reconciled with an emerging body of data that point toward Sst affecting Aβ amyloid plaque formation through direct interference with Aβ aggregation rather than through its effects on neprilysin expression». I think that the author should also provide these data and put a question mark in Figure 1 neprilysin expression.

6)A critical point of view is needed at the end and a series of challenges/tasks perspective for therapy are raise. For example, the author can write such a conclusion - «Proposed somatostatin model could be diagnostic biomarkers and therapeutic targets for AD» ? There is no final conclusion in the article, where it is desirable to note the limitations of this model.