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Calcium-sensing receptor antagonist (calcilytic) NPS 2143 prevents the increased secretion of endogenous Aβ$_{42}$ prompted by exogenous Aβ$_{25-35}$ in human cortical astrocytes and neurons

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Previously we showed that adding fibrillar (f)Aβ$_{25–35}$, a proxy retaining the main physical and biological features of Aβ$_{42}$, stimulated untransformed astrocytes isolated from fragments of the adult human temporal lobe cerebral cortex to synthesize and accumulate large amounts of endogenous Aβ$_{42}$ and its oligomers, while releasing excess amounts of nitric oxide (NO) and of vascular endothelial growth factor (VEGF-A) [1,2]. Here, we investigated the effects of fAβ$_{25-35}$ and soluble (s)Aβ$_{25-35}$ on Aβ$_{42}$ and Aβ$_{40}$ accumulation/secretion by human cortical astrocytes and HCN-1A neurons. And since the calcium-sensing receptor (CaSR) binds Aβs, we studied whether calcium-CaSR signaling plays any role in such Aβ$_{25-35}$-elicited effects and their modulation by NPS 2143, a CaSR allosteric antagonist (calcilytic). The fAβ$_{25-35}$-exposed astrocytes and neurons produced, accumulated, and secreted increased amounts of Aβ$_{42}$, while Aβ$_{40}$ also accrued but its secretion was unchanged. Accordingly, secreted Aβ$_{42}$/Aβ$_{40}$ ratio values rose for astrocytes and neurons but NPS 2143 addition specifically suppressed the fAβ25-35-elicited surges of endogenous Aβ$_{42}$ secretion by both cell types. Therefore, NPS 2143 addition always kept Aβ$_{42}$/Aβ$_{40}$ values to baseline or lower levels. Compared to fAβ$_{25-35}$, sAβ$_{25-35}$ also stimulated Aβ$_{42}$ secretion by astrocytes and neurons and NPS 2143 specifically and wholly suppressed this effect. Therefore, since NPS 2143 prevents any Aβ/CaSR-induced surplus secretion of endogenous Aβ$_{42}$ and hence further vicious cycles of Aβ self-induction/secretion/spreading, the CaSR antagonists like NPS 2143 might be novel therapeutic drugs for Alzheimer's disease.

References

[1] Chiarini et al. (2010) Amyloid-β(25-35), an amyloid-β(1-42) surrogate, and proinflammatory cytokines stimulate VEGF-A secretion by cultured, early passage, normoxic adult human cerebral astrocytes. J Alzheimer's Dis 21(3): 915-926.

[2] Dal Prà et al. (2011) The amyloid-β42 proxy, amyloid-β(25-35), induces normal human cerebral astrocytes to produce amyloid-β(42). J Alzheimer's Dis 24(2): 335-347.

Key words

Human cerebral cortex, astrocytes, neurons, calcium sensing receptor, amyloid-ß, Alzheimer's disease.