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

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Previously we showed that adding fibrillar (f)\(A\beta_{25-35}\), a proxy retaining the main physical and biological features of \(A\beta_{42}\), stimulated untransformed astrocytes isolated from fragments of the adult human temporal lobe cerebral cortex to synthesize and accumulate large amounts of endogenous \(A\beta_{42}\) 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 f\(A\beta_{25-35}\) and soluble (s)\(A\beta_{25-35}\) on \(A\beta_{42}\) and \(A\beta_{40}\) accumulation/secretion by human cortical astrocytes and HCN-1A neurons. And since the calcium-sensing receptor (CaSR) binds A\(\beta\)s, we studied whether calcium-CaSR signaling plays any role in such \(A\beta_{25-35}\)-elicited effects and their modulation by NPS 2143, a CaSR allosteric antagonist (calcilytic). The f\(A\beta_{25-35}\)-exposed astrocytes and neurons produced, accumulated, and secreted increased amounts of \(A\beta_{42}\), while \(A\beta_{40}\) also accrued but its secretion was unchanged. Accordingly, secreted \(A\beta_{42}/A\beta_{40}\) ratio values rose for astrocytes and neurons but NPS 2143 addition specifically suppressed the f\(A\beta_{25-35}\)-elicited surges of endogenous \(A\beta_{42}\) secretion by both cell types. Therefore, NPS 2143 addition always kept \(A\beta_{42}/A\beta_{40}\) values to baseline or lower levels. Compared to f\(A\beta_{25-35}\), s\(A\beta_{25-35}\) also stimulated \(A\beta_{42}\) secretion by astrocytes and neurons and NPS 2143 specifically and wholly suppressed this effect. Therefore, since NPS 2143 prevents any \(A\beta/\)CaSR-induced surplus secretion of endogenous \(A\beta_{42}\) and hence further vicious cycles of \(A\beta\) self-induction/secretion/spreading, the CaSR antagonists like NPS 2143 might be novel therapeutic drugs for Alzheimer’s disease.

References


Key words

Human cerebral cortex, astrocytes, neurons, calcium sensing receptor, amyloid-\(\beta\), Alzheimer’s disease.

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