Introduction: Neurexins (NRXNs) are synaptic cell adhesion molecules having essential roles in the assembly and maturation of synapses into fully functional units. γ-Secretase is an intra-membrane cleaving protease complex and mutations in Presenilin-1 (PS1), the catalytic subunit of the protease, cause early-onset familial Alzheimer's disease (FAD). Known γ-secretase substrates are cleavage products of the α-secretase TACE or β-secretase BACE1.

Aims: We investigated whether neurexin-3β (NRXN3β), the most widely expressed variant of β-neurexin, can be processed by α- and/or β and γ-secretases.

Methods: We first detected by western blot analysis NRXN cleavage products in cell lines overexpressing NRXN3β, as well as in primary cortical neurons (PCN). To confirm NRXN processing by γ-secretase, cell-free activity assays and a cell-based luciferase assay were used. In addition, the effects of PS1 FAD on NRXN3β processing were assessed. PCN were stimulated with KCl or L-Glutamate to study the effect of neuronal activity on NRXN processing.

Results: TACE and γ-secretase can sequentially process NRXN3β, leading to the formation of two final products: a ~80 kDa N-terminal extracellular domain (sNRXN3β) and ~12 kDa C-terminal domain (NRXN3β-ICD). This processing was altered by several PS1 FAD mutations. In addition, cleavage of endogenous neuronal neurexins by TACE and γ-secretase could be modulated by neuronal activity.

Conclusion: Cleavage of NRXNs by α- and γ-secretases likely has functional implications beyond the mere clearance of NRXNs in the context of protein turnover. Therefore, we can speculate that NRXN3β processing by α-secretase and γ-secretase can modulate synaptic transmission.