MEMANTINE COUNTERACTS NEURONAL B-AMYLOID PRODUCTION BY SELECTIVELY INHIBITING EXTRASYNAPTIC NMDA RECEPTOR-INDUCED KPI-APP EXPRESSION

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Introduction: A dysregulation of neuronal calcium homeostasis was shown to affect metabolism of amyloid precursor protein (APP), leading to increased production of β-amyloid and contributing to the initiation of Alzheimer’s disease. If a linkage between excessive glutamate receptor activation and neuronal Aβ release was established, synaptic and extrasynaptic NMDA receptor (NMDAR) may have distinct role in this process.

Aim: In the present work, we studied the ability of memantine, the only clinically approved NMDAR antagonist for the treatment of AD, to modulate the consequences of a chronic and selective stimulation of each NMDAR pool.

Methods: Neuron cultures were exposed to either synaptic or extrasynaptic NMDAR activation. Expression of the amyloidogenic isoform KPI-APP was evaluated by immunocytochemistry, PCR and Western-blot analysis. Neuronal Aβ release was measured by ELISA in the presence or not of memantine.

Results: Chronic activation of extrasynaptic NMDAR increased neuronal production of Aβ. This effect was preceded by a shift from APP695 to KPI-APPs, isoforms exhibiting an important amyloidogenic potential. Conversely, synaptic NMDAR activation did not trigger any KPI-APP expression or neuronal Aβ production. Calcium imaging data showed that intracellular calcium concentration after extrasynaptic NMDAR stimulation was lower than after synaptic activation. This suggests distinct signalling pathways for each pool of receptors. Memantine dose-dependently inhibited extrasynaptic NMDAR-induced KPI-APPs expression as well as neuronal Aβ release.

Conclusions: These data show that Memantine preferentially targets extrasynaptic NMDAR without altering normal synaptic functions. This provides new arguments in favour of its use to antagonize neurodegenerative pathways such as in AD.