

NEW TARGETS FOR PHARMACOLOGICAL INTERVENTION IN THE GLUTAMATERGIC SYNAPSE

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NMDA receptors in the glutamatergic synapse have been implicated as a mediator of neuronal injury associated with many neurological disorders including ischemia, epilepsy, brain trauma, dementia, and other neurodegenerative disorders.

Among others, the glutamatergic synapse has been shown to be implicated in the early phases of Alzheimer Disease (AD), and this is reflected in a loss of synaptic plasticity. The glutamatergic synapse is characterized by a complex network of protein-protein interactions defining both the pre-synaptic cytomatrix and the post-synaptic density (PSD). The PSD is a highly organized biochemical organelle which segregates, in a highly ordered array, membrane receptors and signaling elements clustered through a family of linker proteins, i.e. the membrane associated guanylate kinase (MAGUK). Among MAGUKs, SAP97 has been described to be involved in ionotropic glutamate receptors trafficking and a deficiency in SAP97 functioning in AD pathogenesis has been reported. Thus, we checked for a link between SAP97, involved in the dynamic trafficking of key elements to the excitatory postsynaptic membrane, and the elements of the amyloid cascade as the primary pathogenic event in AD. The results obtained demonstrate a clear interaction between ADAM10 and SAP97, which is instrumental for the intracellular localization and the activity of ADAM10 as alpha-secretase. Our data indicate SAP97 as a bridge between key elements of the primary pathogenic events of AD, such as ADAM10, and key elements of the secondary pathogenic events such as the glutamatergic synaptic dysfunction adding new pieces to the puzzle in the understanding of the complex and coordinated events leading to AD pathogenesis.

In addition, abnormal function of the glutamatergic synapse has been suggested to be correlated with the pathogenesis of Parkinson's disease (PD) as well as with the development of L-DOPA-induced dyskinesia. In particular, dyskinetic animals have profound modifications of NMDA receptor subunit association with MAGUK protein proteins such as SAP97 and SAP102. Of relevance, treatment of non-dyskinetic animals with synthetic peptides able to affect NMDA receptor binding to MAGUK proteins as well as synaptic localization of NMDA receptor subunits is sufficient to induce a shift of treated rats towards a dyskinetic motor behaviour. These findings may allow the identification of specific molecular targets whose pharmacological or genetic manipulation might lead to innovative therapies for specific neurodegenerative disorders.