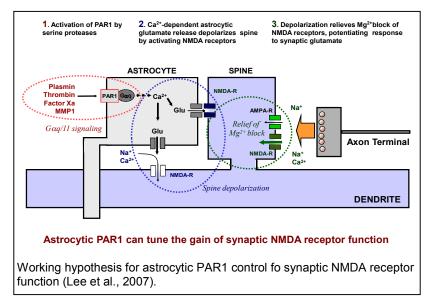
## Functional roles of protease receptors in central nervous system

Protease activated receptors (PAR-1,2,3,4) are G-protein coupled receptors that are activated by cleavage of the N-terminal by serine proteases such as thrombin or plasmin, which reveals a new N-terminal that acts as a tethered ligand. The new N-terminal binds to an extracellular pocket to initiate intracellular signaling, typically through multiple G-protein classes (e.g.  $G_{q/11}, G_{i/o}, G_{12/13}$ ). Protease receptors are best known for their actions in the cardiovascular system, platelet aggregation, and peripheral wound healing. However, they are extensively expressed in the central nervous system, and



apparently activated by a highly regulated serine protease system in the brain and spinal cord. PAR-1 appears to control neuronal function, synaptic strength, and set the threshold for stimulus induced long-term increases in synaptic strength. The mechanisms by which protease receptors control neuronal function remain elusive, but one candidate is PAR-1-mediated astrocytic release of glutamate, which subsequently acts on neurons to induce dendritic depolarization and relieve Mg<sup>2+</sup> blockade of NMDA receptors. In addition, preliminary data suggest PAR-1 activation can alter the time course of glutamate in the synaptic cleft. In pathological situations, blood-brain barrier breakdown allows multiple serine proteases circulating in the blood stream to enter the CNS, and a wide range of studies support the idea that these serine proteases produce aberrant activation of PAR-1 and other protease activated receptors, leading to harmful effects that contribute to neuropathology.