Cleavage of LRP1 and increase in LRP1-ICD in ischemic brain and excitotoxic neuronal injury

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Low-density lipoprotein receptor-related protein-1 (LRP1), a member of the LDL receptor family, plays important roles in endocytosis and intracellular signaling. LRP1 is processed by furin in the trans-Golgi network (TGN), becomes mature LRP1 and moves to the cell surface. Previous studies have shown that LRP1 suppresses glutamate excitotoxicity in primary cultured retinal ganglion cells. However, the pathophysiological role of LRP1 in the brain after cerebral ischemia is unclear. The purpose of this study was to investigate the pathophysiological role of LRP1 after cerebral ischemia and *N*-methyl-D-aspartate (NMDA)-induced neuronal injury. First, we demonstrated that LRP1 was significantly cleaved after cerebral ischemia and in NMDA-induced neuronal injury. The LRP1-intracellular domain (ICD) produced by neuronal injury was co-localized with TGN and furin. In addition, we found that furin inhibitors inhibited LRP1 cleavage and suppressed co-localization with TGN or furin. Theses findings suggest that furin-mediated LRP1 cleavage and LRP1-ICD localization are involved in ischemic neuronal injury.