Pathophysiological changes of progranulin in active microglia after cerebral ischemia

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Progranulin (PGRN) is implicated in neuronal protection and anti-inflammation. On the other hand, granulin (GRN), which is cleaved from PGRN by neutrophil elastase, has pro-inflammatory effects. However, pathophysiological roles of PGRN and GRN after cerebral ischemia have not been fully determined. In this study, we examined time-course of changes in the levels of PGRN and GRN and their cellular sources after cerebral ischemia using a rat microsphere-embolism (ME) model and rat primary cultured microglia. Protein and mRNA levels of PGRN in activated microglia were increased in the ischemic region of cerebral cortex on day 3 after ME. Elastase activity was increased on day 1 after ME. GRN was increased on days 1 and 3 after ME. Next, we examined effect of sivelestat, a selective neutrophil elastase inhibitor, on the levels of PGRN and GRN after ME. The level of PGRN was increased in the cerebral cortex, whereas elastase activity and GRN level were decreased in sivelestat-treated rats on day 1 after ME compared with those of vehicle-treated rats. Thus, the increase in PGRN level and inhibition of GRN production after ME caused by siverestat treatment would prevent ischemic brain injury.