MICROGLIA BLOCKADE WITH GLIBENCLAMIDE, A THERAPEUTIC TARGET FOR STROKE

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A retrospective study showed that patients with diabetes mellitus taking glibenclamide (Gbc) have a better neurological outcome. Gbc blocks SUR, which forms the regulatory subunit of the KATP and the NCCa-ATP channels. The astroglial NCCa-ATP channel mediates the Gbc-induced prevention of cerebral edema, reduce infarct volume and decreases mortality in experimental stroke models. We previously showed that reactive microglia express SUR1 after brain injury, while in vitro overexpressed KATP channels components and microglial behavior was modified in presence of Gbc. Microglia has a key role in fostering cerebral ischemia newly formed SVZ neuroblasts migration towards the injury. We hence hypothesized that early blockade of microglial KATP channel would provide neuroprotection and enhance ischemia-induced neurogenesis in the SVZ, leading to an improved functional outcome. Microglial specific Gbc-binding was confirmed in rat primary cultures. Also, 90 min tMCAO was performed to Wistar rats and Gbc administrated i.v. at 6, 12 and 24 hours after reperfusion. The lesion progression as well as the cellular response was studied 3- and 30-days after reperfusion. Histopathologycal analysis did not show Gbc effect in terms of gliosis reaction. However, Gbc cause neuroprotection in the peri-infarct region in both time-points studied. Neurogenesis was enhanced in Gbc-treated rats 3-days after ischemia and this effect was still observed at 30-days, when increased number of NeuN/BrdU-positive neurons were found in the peri-infarct cortex, the intact cortex and the hippocampus. As a consequence, performance in the behavioral tests showed a slight outcome of the Gbc-treated rats at 3-days, whereas this outcome was even more notorious 30-days after ischemia. Therefore, microglial KATP channel should be considered as a therapeutic target for stroke.

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