Novel hypoglycemia injury mechanism: N-Methyl-D-Aspartate receptor-mediated white matter damage

With the support by the National Natural Science Foundation of China and the Ministry of Science and Technology of China, Dr. Yang Xin and Prof. Chen Shengdi's laboratory at the Department of Neurology, Ruijin Hospital, affiliated with Shanghai Jiaotong University School of Medicine, reported that the hypoglycemia injury is caused, in part, by excitotoxicity mediated by N-Methyl-D-Aspartate receptor (NMDARs), most likely activated by aspartate released into the extracellular space. This result was published in *Annals of Neurology* (2014, 75: 492—507).

By the use of an acutely isolated mouse optic nerve as a model white matter structure, Yang et al. showed that in hypoglycemia, WM function could be significantly preserved by NMDA receptor blockers, while non-NMDA receptor blockers did not. This is unexpected, because a related insult, ischemia, injures WM via non-NMDA glutamate receptors, and NMDARs are not involved in producing irreversible loss of WM excitability. Further study indicated that hypoglycemia reduced glutamate levels, and instead increased extracellular aspartate, which could alternatively activate NMDARs. Meanwhile, Yang et al. found the contrasting effects of ischemia and hypoglycemia on tissue pH. Ischemia produced acidosis, which attenuated NMDARs-mediated neuronal injury, whereas hypoglycemia produced alkalinization, which could contribute the participation of NMDARs in hypoglycemic WM injury. The results have important implications for the fundamental differences between hypoglycemia and ischemia, as well as the new clinical management of severe hypoglycemia, i. e. antagonist of NMDARs.

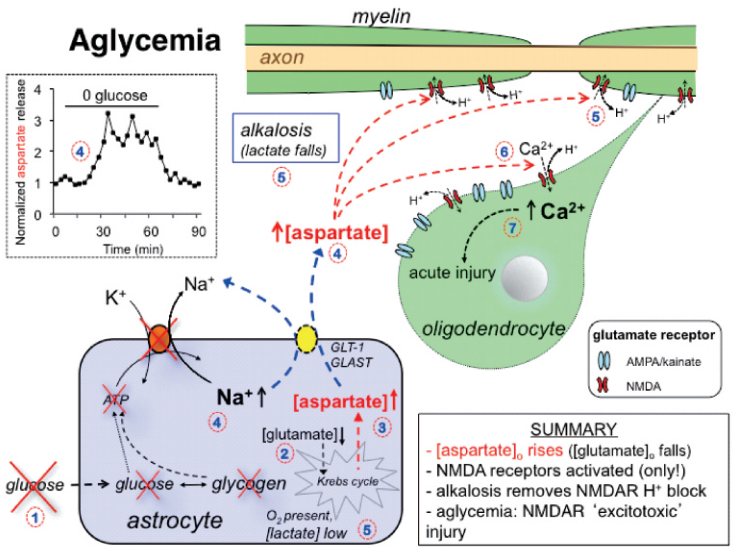

Figure WM during hypoglycemia. With severe hypoglycemia, or aglycemia, energy metabolism persists until glycogen and other substrates, such as glutamate, are exhausted (#1). In the absence of glucose, glutamate is consumed in the Krebs cycle as a short-term substrate and its intracellular concentration falls (#2). The Krebs cycle now produces aspartate (from accumulating oxaloacetate), and the intracellular concentration of aspartate increases 4-fold (#3; see text). As ATP falls, the Na^+ pump fails and $[Na^+]_i$ increases, leading to reversal of Na^+-dependent glutamate/aspartate transport (#4). Because intracellular glutamate is decreased, and aspartate is increased, it is aspartate that is transported into the extracellular space (#4). The $[lactate]_o$ falls, pH_o increases, and the proton block of NMDARs is relieved (see text; #5). Aspartate is a high-affinity agonist for NMDARs and activates these, causing toxic ion fluxes, especially Ca^{2+} influx (#6), and damage to oligodendrocytes and myelin (#7).