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Differential Contributions of GluN2A- and GluN2B- containing NMDA Receptors to Tissue Recovery after SD

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Abstract (300)

Spreading depolarizations (SDs) are now recognized as a principal source of excessive glutamate accumulation in stroke. It is not yet known whether different NMDA receptor (NMDAR) subtypes contribute to progression of SD or damaging effects of SD in vulnerable tissues. We examined possible contributions of GluN2A- and GluN2B-containing NMDARs to SDs in healthy and vulnerable tissues. Focal microinjection of KCl was used to initiate SDs in the hippocampal CA1 subregion of murine brain slices. Intrinsic optical signals (iOS) monitored SD propagation and tissue swelling. Extracellular potential changes ("DC shifts") were used to examine prolonged depolarizations previously linked to neuronal injury. Field excitatory postsynaptic potentials (fEPSPs) provided an additional measure of functional recovery. DC shifts, iOS, and fEPSPs were fully recoverable after SD in healthy recording conditions, but are persistently suppressed in vulnerable tissues where metabolic substrate supply was reduced by flow restriction. Non-selective inhibition of NMDARs (MK801 or APV) caused concentration-dependent inhibition of SD initiation/propagation and reduced the duration of DC shifts. Selective inhibition of GluN2A-containing NMDARs (NVP-AAM077, 300nM) slowed SD propagation (4.2±0.8 vs. 3.4±0.8 mm/min, control vs NVP-AAM077, $P<0.05$, n=7), while GluN2B inhibition (Ro 25-6981, 1μM) was without effect. Neither GluN2A- nor GluN2B- antagonism affected fEPSP recovery rate in healthy tissues (n=4-6, $P=0.38$). In vulnerable tissues, GluN2B-antagonism did not protect tissues from SD induced injury, but GluN2A-antagonism significantly improved fEPSP recovery rate (24.3±9.8 vs 101.4±51.2% baseline, control vs NVP-AAM077, $P< 0.05$, n=7) and iOS recovery (110.9±6.3 vs 127.9±6.1, control vs NVP-AAM077, $P< 0.05$, n=6) after SD. While previous work has often implicated GluN2B-containing receptors in damaging excitotoxicity, these results suggest instead that GluN2A-contining NMDARs activated by SD-induced increases in extracellular glutamate is more likely to contribute to tissue detriment. Selective targeting of these receptor subtypes during SD events may provide an adjunct approach to limiting progression of stroke.

Non-expert summary (75)

In the days following stroke, the area of injury often grows. This infarct growth is caused by brain events called spreading depolarizations (SDs). Our laboratory's work focuses on SDs, with the hope to discover the foundational knowledge required to limit injury expansion. I found that blocking a specific type of receptor, GluN2A-containing NMDA receptors, can prevent harmful consequences of SD. This work suggests targeting GluN2A-containing NMDARs could help to protect our brains after stroke.