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Progress in neuroprotective strategies for preventing epilepsy

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Abstract

Neuroprotection is increasingly considered as a promising therapy for preventing and treating temporal lobe epilepsy (TLE). The development of chronic TLE, also termed as epileptogenesis, is a dynamic process. An initial precipitating injury (IPI) such as the status epilepticus (SE) leads to neurodegeneration, abnormal reorganization of the brain circuitry and a significant loss of functional inhibition. All of these changes likely contribute to the development of chronic epilepsy, characterized by spontaneous recurrent motor seizures (SRMS) and learning and memory deficits. The purpose of this review is to discuss the current state of knowledge pertaining to neuroprotection in epileptic conditions, and to highlight the efficacy of distinct neuroprotective strategies for preventing or treating chronic TLE. Although the administration of certain conventional and new generation anti-epileptic drugs is effective for primary neuroprotection such as reduced neurodegeneration after acute seizures or the SE, their competence for preventing the development of chronic epilepsy after an IPI is either unknown or not promising. On the other hand, alternative strategies such as the ketogenic diet therapy, administration of distinct neurotrophic factors, hormones or antioxidants seem useful for preventing and treating chronic TLE. However, long-term studies on the efficacy of these approaches introduced at different time-points after the SE or an IPI are lacking. Additionally, grafting of fetal hippocampal cells at early time-points after an IPI holds considerable promise for preventing TLE, though issues regarding availability of donor cells, ethical concerns, timing of grafting after SE, and durability of graft-mediated seizure suppression need to be resolved for further advances with this approach. Overall, from the studies performed so far, there is consensus that neuroprotective strategies need to be employed as quickly as possible after the onset of the SE or an IPI for considerable beneficial effects. Nevertheless, ideal strategies that are capable of facilitating repair and functional recovery of the brain after an IPI and preventing the evolution of IPI into chronic epilepsy are still hard to pin down.

Keywords: Aberrant synaptic reorganization; Anti-epileptic drugs; Antioxidants; Dentate gyrus; Dentate neurogenesis; GABA-ergic interneurons; Head injury; Hippocampus; Hippocampal cell grafts; Hormones; Ketogenic diet; Learning and memory deficits; Mossy fiber sprouting; Neural cell transplants; Neural stem cells; Neurodegeneration; Neurotrophic factors; Spontaneous seizures; Status epilepticus; Synaptic plasticity; Temporal lobe epilepsy

Abbreviations: AAT, aspartate aminotransferase; AACOT, acetoacetyl-CoA thiolase; Ad-GDNF, adenoviral vector derived glial cell line derived neurotrophic factor; AED, anti-epileptic drug; AKG, alpha keto glutarate; aFGF, acidic fibroblast growth factor; BBB, blood brain barrier; BDA, biotinylated dextran amine; BDNF, brain derived neurotrophic factor; bFGF (FGF-2), basic fibroblast growth factor or fibroblast growth factor-2; BHB, beta hydroxy butyrate; cAMP, cyclic adenosine mono phosphate; CNS, central nervous system; CR, calorie restricted; CS, citrate synthetase; CREB, cAMP responsive element binding protein; Cyt c, cytochrome c; DCX, doublecortin; DG, dentate gyrus; DH, dentate hilus; DHEA, dehydroepiandrosterone; DSGL, dentate supragranular layer; EEG, electro-encephalogram; EPO, erythropoietin; EPSP, excitatory post-synaptic potential; ERK, extracellular-signal-regulated kinase; FBM, felbamate; GABA, gamma amino butyric acid; $GABA_A$, GABA receptor A subtype; GAD, glutamic acid decarboxylase; GAT-1, GABA transporter type 1; GBP, gabapentin; GCL, granule cell layer; GDNF, glial cell derived neurotrophic factor; Gln, glutamine; ICV KA, intracerebroventricular kainic acid; IPI, initial precipitating injury; IP KA, intraperitoneal kainic acid; IPSP, inhibitory post-synaptic potential; KA, kainic acid; KD, ketogenic diet; LDH, lactate dehydrogenase; LEV, levetiracetam; LDL, low density lipoprotein; LPS, lipopolysaccharide; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; MPT, mitochondrial permeability transition pore; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NPY, neuropeptide Y; NSC, neural stem/progenitor cells; NTF, neurotrophic factor; NT-3, neurotrophin-3; OAA, oxaloacetate; OGD, oxygen-glucose deprivation; PHB, Phenobarbital; PI3K, Phosohatidylinositol-3-kinase; PNS, Peripheral nervous system; PROG, progesterone; PREG, pregnenolone; PREGS, pregnenolone sulfate; PTZ, pentelenetetrazole; PDH, pyruvate dehydrogenase; rhGDNF, recombinant human GDNF; ROS, reactive oxygen species; SCOT, succinyl-CoA transferase; SE, status epilepticus; SGZ, subgranular zone; SLM, stratum lacunosum moleculare; SO, stratum oriens; SP, stratum pyramidale; SR, stratum radiatum; SRMS, spontaneous recurrent motor seizures; TCA, tricarboxylic acid; TGB, tiagabine; TGF-β, transforming growth factor beta; TLE, temporal lobe epilepsy; TPM, topiramate; UCP, uncoupling protein; VEGF, vascular endothelial growth factor; VGB, vigabatrin; VPA, valproic acid; 3-OH-butyrate, 3-hydroxy-butyrate.

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