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Excitotoxicity and stroke: Identifying novel targets for neuroprotection

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ABSTRACT

Excitotoxicity, the specific type of neurotoxicity mediated by glutamate, may be the missing link between ischemia and neuronal death, and intervening the mechanistic steps that lead to excitotoxicity can prevent stroke damage. Interest in excitotoxicity began fifty years ago when monosodium glutamate was found to be neurotoxic. Evidence soon demonstrated that glutamate is not only the primary excitatory neurotransmitter in the adult brain, but also a critical transmitter for signaling neurons to degenerate following stroke. The finding led to a number of clinical trials that tested inhibitors of excitotoxicity in stroke patients. Glutamate exerts its function in large by activating the calcium-permeable ionotropic NMDA receptor (NMDAR), and different subpopulations of the NMDAR may generate different functional outputs, depending on the signaling proteins directly bound or indirectly coupled to its large cytoplasmic tail. Synaptic activity activates the GluN2A subunit-containing NMDAR, leading to activation of the pro-survival signaling proteins Akt, ERK, and CREB. During a brief episode of ischemia, the extracellular glutamate concentration rises abruptly, and stimulation of the GluN2B-containing NMDAR in the extrasynaptic sites triggers excitotoxic neuronal death via PTEN, cdk5, and DAPK1, which are directly bound to the NMDAR, nNOS, which is indirectly coupled to the NMDAR via PSD95, and calpain, p25, STEP, p38, JNK, and SREBP1, which are further downstream. This review aims to provide a comprehensive summary of the literature on excitotoxicity and our perspectives on how the new generation of excitotoxicity inhibitors may succeed despite the failure of the previous generation of drugs.

Abbreviations: ADD1, adipocyte determination and differentiation-dependent factor 1; AIF, apoptosis-inducing factor; BDNF, brain-derived neurotrophic factor; CaM-KK, calcium–calmodulin dependent protein kinase kinase; CAPON, carboxyl-terminal PDZ ligand of nNOS; cdk5, cyclin-dependent kinase 5; CRE, cyclic adenosine monophosphate response element; CREB, CRE binding protein; CSAID, cytokine-suppressive anti-inflammatory drug; CSBP, CSAID-binding protein; DAPK1, death-associated protein kinase 1; DL-TBOA, DL-threo-benzyloxyaspartic acid; Drp1, dynamin-related protein 1; ERK, extracellular signal-regulated kinase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GluN2AR, GluN2A subunit-containing NMDA receptor; GluN2BR, GluN2B subunit-containing NMDA receptor; GSK3, glycogen-synthase kinase 3; INPP4A, inositol polyphosphate phosphatase 4A; insig1, protein encoded by insulin-induced gene 1; IRS-1, insulin receptor substrate-1; JBD, JNK-binding domain of JIP; JIP, JNK-interacting protein; JNK, c-Jun N-terminal kinase; JNK-1, JNK inhibitor 1; LTD, long-term depression; LTP, long-term potentiation; MAGUK, membrane-associated guanylate kinase; MAPK, mitogen-activated protein kinase; MCU, mitochondrial calcium uniporter; mGluR, metabotropic glutamate receptor; MMAC1, mutated in multiple advanced cancers 1; MMP-9, matrix metalloprotease-9; mNCX, mitochondrial sodium–calcium exchanger; NFI-A, nuclear factor I-A; NCX, sodium–calcium exchanger; NMDA, N-methyl-D-aspartate; NMDAR, NMDA-type of glutamate receptor; nNOS, neuronal nitric oxide synthase; NOS1AP, nitric oxide synthase 1 adaptor protein; p35, the 35-kDa regulatory activator of cdk5; PARP-1, poly(ADP-ribose) polymerase 1; PKB, protein kinase B; PI3K, phosphatidylinositol 3-kinase; PIKE-L, long form of phosphoinositide 3 kinase enhancer; PSD95, postsynaptic density protein 95; PtdIns(3,4)P2, phosphatidylinositol (3,4)-bisphosphate; PtdIns(3,4,5)P3, phosphatidylinositol (3,4,5)-triphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome ten; rac, protein kinase related to the A and C kinases; RK, MAPK-activated protein kinase-2 reactivating kinase; ROS, reactive oxygen species; SAPK, stress-activated protein kinase; SCAP, SREBP cleavage-activating protein; SREBP1, sterol response element binding protein 1; STEP, striatal-enriched protein tyrosine phosphatase; TEP1, TGF-beta-regulated and epithelial cell-enriched phosphatase 1; TRPM7, transient receptor potential cation channel M7; TTX, tetrodotoxin; UCPs, uncoupling proteins.

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Contents

1. Introduction

In the past several decades, excitotoxicity, a type of neurotoxicity mediated by glutamate, has been at the center stage of stroke research. Glutamate is the principle neurotransmitter in the adult central nervous system. In addition to being required for the rapid synaptic transmission that is critical for neuron-to-neuron communication, glutamate plays important roles in neuronal growth and axon guidance, brain development and maturation, and synaptic plasticity in health and disease. Among the ionotropic and metabotropic glutamate receptors in the adult central nervous system, the N-methyl-D-aspartate (NMDA) type of glutamate receptor (the NMDAR) acts as a hub, by detecting and processing extracellular glutamate signals into diverse intracellular signaling outputs. With the emergence of cellular and molecular biology, scientists are unraveling the mechanisms by which glutamate-mediated activation of the NMDAR in health and disease transmits so many different functional outputs, at both the microscopic neuron level and the macroscopic behavior level. These mechanisms have important implications for research concerning excitotoxicity and its role in ischemic neuronal death. The identification of distinct intracellular pathways linking NMDAR activation to neuronal death allows scientists to develop novel treatments that target specific death signaling pathways without affecting all the signaling pathways downstream of the receptor. This increased specificity not only translates into reduced side effects but also increases the therapeutic window in which the drug can be efficaciously administered.

2. Stroke and the NMDAR

Compared to other tissues and organs in the body, the brain is particularly prone to ischemic damage. Unlike the immediate ischemic damage that is observed in other tissues, a transient period of cerebral ischemia (approximately 10 min) can produce profound neuronal damage that only becomes evident 3d post-ictus and continues progressively for months. As relief of vascular occlusion is the primary method by which tissue ischemia is treated in the clinic, the propensity for ischemic damage to occur regardless of the recovery of blood flow highlights the need for an alternative method for treating cerebral ischemia. Importantly, the delayed and progressive nature of neuronal damage following cerebral ischemia points to a wide time window for therapeutic intervention and emphasizes the importance of understanding the nature of ischemic neuronal death. An improved understanding of the processes that translate cerebral ischemia into neuronal damage would highlight new therapeutic targets for stopping the seemingly inevitable progression from ischemia to neuronal death. One explanation for the peculiar susceptibility of the brain to ischemic damage is that brain tissue contains high levels of the neurotoxic excitatory neurotransmitter glutamate, and many neurons in the brain contain receptors that actively respond to