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Understanding regulation of nerve cell death by mGluRs as a method for development of successful neuroprotective strategies

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Abstract

A common cause of nerve cell death often leading to vascular dementia is ischemic stroke. Attempts to develop clinically effective stroke treatment and prevention strategies based on pharmacological manipulations of a single mechanism have not led to clinical success. Analysis of clinical neuroprotection trials suggests that combination treatments may be more effective. To identify optimal components for such treatment, *N*-methyl-D-aspartate receptor (NMDAR) activation-induced cell death in organotypic hippocampal preparations was studied as a model of neurodegeneration that occurs in association with stroke or vascular dementia. Pharmacological manipulation of metabotropic glutamate receptors mGluR1 and 5 resulted in significant reduction of nerve cell susceptibility to NMDA-induced injury, suggesting that these receptors may function as physiological regulators of neuronal vulnerability. cDNA microarray analysis of over 1000 brain-related genes performed after the neuroprotective activation of group I metabotropic glutamate receptors (mGluRs) revealed a complex pattern of activation and inactivation of seemingly unrelated genes responsible for regulation of neuronal excitability, inflammation, cell death pathways, cell adhesion and transcriptional activation. Combined pharmacological targeting of these processes may provide basis for clinical trials of effective neuroprotective compounds.

Keywords: mGluR; Vascular dementia; Cell death

In an adult brain, nerve cell death can be caused by a variety of insults, most common of which is the sudden interruption of blood flow to the brain or ischemia. Brain tissue ischemia is commonly associated with such events as stroke. In most cases, stroke is the outcome of arteriosclerosis set in motion decades earlier and is associated with several risk factors that include cigarette smoking, and alcohol consumption. It has been estimated that there are 400,000 strokes in the United States each year and approximately 150,000 deaths are attributable to cerebrovascular disease [1]. Those who survive suffer from long-term physical, emotional, and cognitive disabilities, a treatment of which carries a great financial burden.

There have been numerous attempts to develop drugs that prevent ischemic brain tissue death, most of them unsuccessful. For example, out of 178 controlled clinical trials of acute stroke therapies reported in English language literature in 20th century only four produced positive results. Among them clot dissolving treatments were more likely to be successful. In contrast, out of 49 neuroprotective drugs tested in 114 stroke studies none was successful [2]. The numerous reasons for this failure range from clinical trial design issues to failure to fully appreciate the complexity of regulations controlling nerve cell death and survival [2].

Ischemic nerve cell death is thought to occur via excitotoxicity. This excitotoxicity appears to be mediated primarily by excessive release of glutamate, which overactivates the *N*-methyl-D-aspartate receptor/channel complex (NMDAR), allowing the influx of toxic levels of Ca^{2+} into nerve cells [3,4]. This knowledge has, however, not yet

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resulted in effective treatment or prevention strategies. Although blockade of NMDARs is very effective in reducing ischemic cell death in experimental models [5–7], the clinical use of this approach has been negligible mainly due to psychotogenic side effects [8] of NMDAR antagonists.

Recent evidence suggests that nerve cell susceptibility to injury is regulated by built-in physiological mechanisms. One of these mechanisms involves metabotropic glutamate receptor (mGluR)-mediated regulation of nerve cell susceptibility to injury discussed in this article. It can be hoped that a thorough understanding of these mechanisms could help to develop pharmacological tools or "neuroprotective" compounds that could eventually lead to improved outcomes for patients at risk for strokes.

1. Excitotoxicity

Olney [9] initially described excitotoxicity in 1969 when he found that treatment of mice with monosodium glutamate caused brain lesions. L-Glutamate is a high affinity agonist on at least four major subtypes of neuronal glutamate receptors. Three of these subtypes, named according to their preferred agonists kainate, AMPA and NMDA, implicated in cell death, are classified as ionotropic, being directly linked to neuronal ion channels. It is generally believed that excessive stimulation of ionotropic glutamate receptors triggers an influx of Na^+ and Ca^{2+} through the receptor-controlled channels and subsequently leads to cell death. It has been proposed that Ca^{2+} entering through NMDAR may be especially lethal due to co-localization of these channels with particularly sensitive intracellular targets (e.g., calpain-induced cytoskeletal breakdown, phospholipase-A2-induced formation of arachidonic acid and metabolites, membrane translocation of PKC, Ca^{2+}-activated endonuclease destruction of cellular DNA, and other Ca^{2+}-dependent processes). There have been numerous reports on glutamate toxicity in a variety of preparations [10–13] and several excellent reviews have been published on this topic [14–16] recognizing the critical role of NMDAR in pathophysiology of ischemic nerve cell death. The nature of cell death (necrosis vs. apoptosis) remains a subject of debate (as perhaps is the definition of the term "apoptosis" (e.g., see Ref. [17]). Morphological and other features of both apoptotic and necrotic cell death have been reported following ischemic damage [18,19]. A diagram illustrating these and other steps involved in excitotoxicity is shown in Fig. 1.

2. Neuroprotection by glutamate involves mGluRs

Glutamate can be both an excitotoxin and neuroprotectant. It has been well established that moderate levels of glutamate agonists protect neurons from damage caused by their subsequent exposure to glutamate at excitotoxic concentrations [21–26]. Recent evidence suggests that

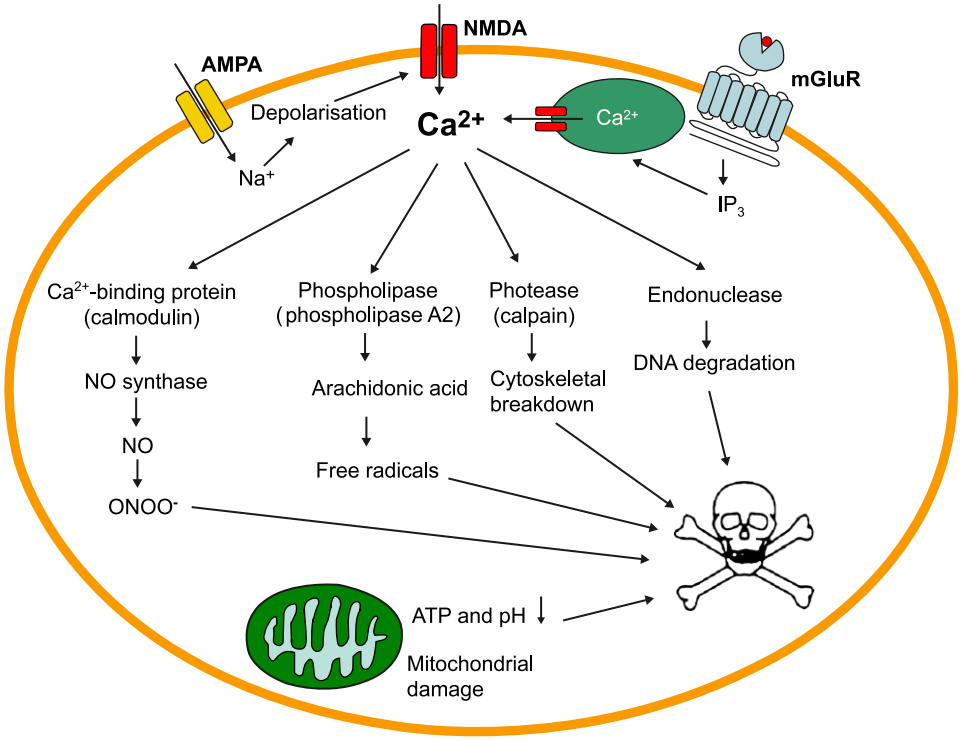

Fig. 1. Schematic drawing of the devastating consequences of an increase in intracellar Ca^{2+} above a toxic threshold. IP_3; inositol-1,4,5-bisphosphate, NO; nitric oxide, $ONOO^-$; peroxynitrite. Modified from Ref. [20].