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Review

Non-selective cation channels, transient receptor potential channels and ischemic stroke

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Abstract

Several pathways to neural cell death are involved in ischemic stroke, and all require monovalent or divalent cation influx, implicating non-selective cation (NC) channels. NC channels are also likely to be involved in the dysfunction of vascular endothelial cells that leads to formation of edema following cerebral ischemia. Two newly described NC channels have emerged as potential participants in ischemic stroke, the acid sensing ion channel (ASIC), and the sulfonylurea receptor-1 (SUR1)-regulated $NC_{Ca\text{-}ATP}$ channel. Non-specific blockers of NC channels, including pinokalant (LOE 908 MS) and rimonabant (SR141716A), have beneficial effects in rodent models of ischemic stroke. Evidence is accumulating that NC channels formed by members of the transient receptor potential (TRP) family are also up-regulated in ischemic stroke and may play a direct role in calcium-mediated neuronal death. The nascent field of NC channels, including TRP channels, in ischemic stroke is poised to provide novel mechanistic insights and therapeutic strategies for this often devastating human condition.

Keywords: Cation channel; Acid sensing ion channel; $NC_{Ca\text{-}ATP}$ channel; Transient receptor potential; Cerebral ischemia; Stroke

1. Introduction

A number of different mechanisms have been implicated in cell death in CNS ischemia and stroke, including excitotoxicity, oxidative stress, apoptosis, and oncotic (necrotic) cell death. Each of these mechanisms is thought to propagate through largely distinct, mutually exclusive signal transduction pathways [1]. However, in some measure, each of these mechanisms requires cation influx into neural cells. Unchecked influx of Na^+ gives rise to oncotic cell swelling (cytotoxic edema) which predisposes to oncotic cell death (Fig. 1). Unchecked influx of Ca^{2+} can trigger apoptotic as well as necrotic death. Because cation channels are responsible for most cation influx, it is evident that cation channels are key to life–death processes in neural cells during ischemic stroke.

A variety of cation channels have been implicated in neural cell death induced by ischemia/hypoxia. Among them are channels that are highly selective for permeant cations, such as voltage-dependent Na^+ and Ca^{2+} channels, as well as channels that are not selective for any given cation — non-selective cation (NC) channels. In ischemic stroke, much attention has been directed to dihydropyridine-sensitive L-type voltage-dependent Ca^{2+} channels ($Ca_V1.2$), but block of this channel in patients with acute ischemic stroke has shown little benefit [2]. Arguably, the best-studied channels in ischemic stroke belong to the group of receptor operated cation channels opened by glutamate, including *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor channels, which are involved in excitotoxic cell death [3,4]. Again, however, clinical trials with agents targeting these mechanisms have been disappointing [5–7]. Unfavorable experiences with mechanisms involving L-type Ca^{2+} channels and NMDA receptor channels have resulted in redirection of attention to other cation channels, namely, glutamate receptor-independent, NC channels.

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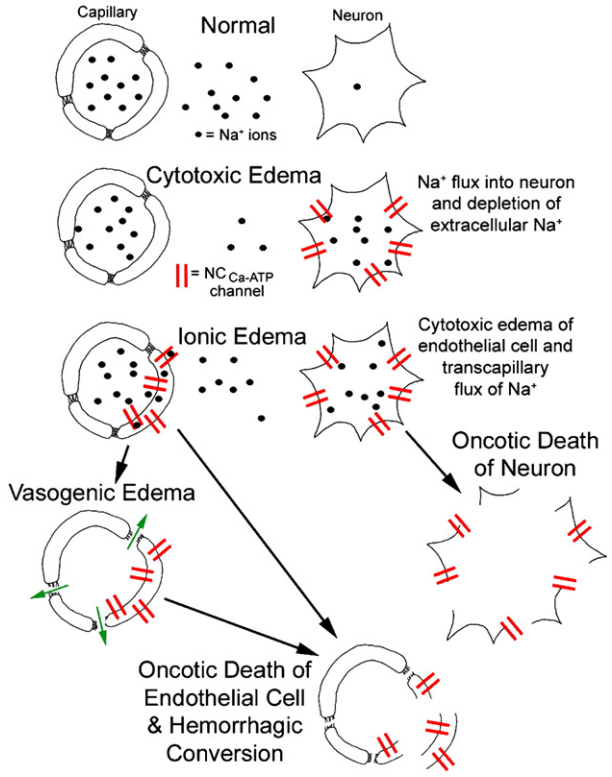

Fig. 1. Schematic diagram illustrating various types of edema progressing to hemorrhagic conversion. Normally, Na^+ concentrations in serum and in extracellular space are the same, and much higher than inside the neuron. Cytotoxic edema of neurons is due to entry of Na^+ into ischemic neurons via pathways such as $NC_{Ca\text{-}ATP}$ channels, depleting extracellular Na^+ and thereby setting up a concentration gradient between intravascular and extracellular compartments. Ionic edema results from cytotoxic edema of endothelial cells, due to expression of cation channels on both the luminal and abluminal side, allowing Na^+ from the intravascular compartment to traverse the capillary wall and replenish Na^+ in the extracellular space. Vasogenic edema results from degradation of tight junctions between endothelial cells, transforming capillaries into "fenestrated" capillaries that allow extravasation (outward filtration) of proteinatious fluid. Oncotic death of neuron is the ultimate consequence of cytotoxic edema. Oncotic death of endothelial cells results in complete loss of capillary integrity and in extravasation of blood. i.e., hemorrhagic conversion. (from Simard et al. [8], with permission).

Apart from neural cell death, other critically important pathophysiological processes that contribute to adverse outcome in ischemic stroke include formation of ionic edema, vasogenic edema and hemorrhagic conversion — all processes involving capillary endothelial cells [8] (Fig. 1). Molecular mechanisms involved in these processes are only beginning to be elucidated. In the case of ionic edema formation, transcapillary flux of Na^+ constitutes the seminal process that drives inflow of H_2O into brain parenchyma, resulting in edema and swelling. It is likely that NC channels play a crucial role in this process. Thus, NC channels may be implicated not only in primary neural cell death but in secondary neural cell death caused by endothelial dysfunction.

In recent years, study of ischemia/hypoxia-induced cell death has been dominated by discussion of apoptosis, a form of "delayed" programmed cell death that involves transcriptional up-regulation of death-related gene products such as caspases. However, in stroke, only a fraction of cells undergo apoptotic death, with the majority of cells dying by oncotic/necrotic death [9]. The lesson from studies on apoptosis is that death, like so many other cellular events, is driven by gene expression and synthesis of new gene products, a concept that has not been fully embraced in studies on oncotic/necrotic death. Comprehensive understanding of the pathophysiology of ischemic stroke requires a focus not only on constitutively expressed NC channels in neurons, astrocytes and endothelial cells, but perhaps more importantly, on newly expressed NC channels whose transcription is driven by mechanisms involved in ischemic stroke, namely, hypoxia and oxidative stress.

The purpose of this review is to examine evidence that NC channels, including TRP channels, are involved in CNS ischemia and ischemic stroke. In reviewing this literature, it becomes apparent that for stroke, the potential contribution of NC channels including TRP is far less well understood than for many other normal and pathological conditions. The relative dearth of hard data forces consideration of somewhat weaker evidence, including indirect or suggestive data. First, we review potential involvement of two important, recently identified NC channels that are up-regulated in ischemic stroke, ASIC and the SUR1-regulated $NC_{Ca\text{-}ATP}$ channel. Next, we consider studies using non-specific NC channel blockers, specifically pinokalant (LOE 908 MS), the fenamates, SKF 96365 and rimonabant (SR141716A). Finally, we consider evidence for involvement of NC channels of the TRP family, reviewing not only data documenting their role in neuronal death and their up-regulation in cerebral ischemia, but also data that would predict potential involvement based on the transcriptional drivers, hypoxia and oxidative stress.

2. NC channels in ischemic stroke

2.1. Acid sensing ion channel (ASIC)

Acid sensing ion channels (ASIC) are not members of the TRP family, but are included here because they are NC channels relevant to ischemic stroke. ASIC are members of the epithelial Na^+ channel/degenerin family of ion channels, and they are expressed throughout the mammalian nervous system [10,11]. Six different ASIC subunits have been cloned to date, which are encoded by four genes (ASIC1–ASIC4) [12]. Members of this supergene family are permeable to Na^+(P_{Na}/P_K: 8–40) and, to a lesser degree, to Ca^{2+}, and they are blocked by amiloride (IC_{50}, 0.2–10 μM).

ASIC were first described a quarter of a century ago in sensory neurons by Krishtal and coworkers [13–15]. Recently, ASIC have enjoyed renewed interest in the context of neural cell death and ischemic stroke. It is well known that ischemia results in a marked reduction in tissue pH, and that acidosis is an important determinant of neurological injury [16,17]. Oxygen depletion necessitates a switch from aerobic metabolism to anaerobic glycolysis, leading to generation of lactic acid as well as protons, resulting in acidification of tissues.