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Connexins and Pannexins in cerebral ischemia☆

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ABSTRACT

A common cause of mortality and long-term adult disability, cerebral ischemia or brain ischemia imposes a significant health and financial burden on communities worldwide. Cerebral ischemia is a condition that arises from a sudden loss of blood flow and consequent failure to meet the high metabolic demands of the brain. The lack of blood flow initiates a sequelae of cell death mechanisms, including the activation of the inflammatory pathway, which can ultimately result in irreversible brain tissue damage. In particular, Connexins and Pannexins are non-selective channels with a large pore that have shown to play time-dependent roles in the perpetuation of ischaemic injury. This review highlights the roles of Connexin and Pannexin channels in cell death mechanisms as a promising therapeutic target in cerebral ischemia, and in particular connexin hemichannels which may contribute most of the ATP release as a result of ischemia as well as during reperfusion. This article is part of a Special Issue entitled: Gap Junction Proteins edited by Jean Claude Herve.

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1. Introduction

Cerebral ischemia contributes significantly to morbidity and mortality in a wide range of pathologies, including stroke, trauma, cardiac arrest and perinatal hypoxic-ischaemic encephalopathy. Ischemia is caused by a reduction in blood flow to a tissue resulting in insufficient delivery of both oxygen and glucose to support metabolic requirements. Stroke can result from cerebral ischemia and is the third leading cause of death in the Western world. In the United States alone, 3.5 million survivors are living with the long-term disabilities caused by stroke, resulting in a devastating health and economic impact to the society [81]. Current treatment options for cerebral ischemia are limited, and the development of rationally derived therapeutics is imperative. The aim of this review is to outline the underlying pathophysiology of cerebral ischemia and identify the roles of connexin and pannexin channels that are the primary targets for therapeutic intervention.

Connexin channels are often referred to as 'non-selective' channels based on their large pore size [86] and indiscriminate permeability to biological molecules [62]. There is a general consensus that connexin channels allow the passage of molecules of up to ~1 kDa in size [116] which provides further evidenceto support connexins as non-selective channels. Across connexin isoforms, however, there is a variation in unitary conductance and permeability characteristics [62], and this is likely to have evolved according to the requirements of the tissue in which each is expressed [136]. As connexin channels are gatekeepers of many signalling molecules implicated in both physiology and disease, deciphering a role for gap junction channels and hemichannels in cell survival and cell death mechanisms has been controversial. The following paragraphs discuss connexin channel roles in physiology and pathology to support a rationale for targeting hemichannels in cerebral ischemia. The reader is referred to other chapters in this special themed edition for more information on connexin and pannexin structure, modulation of activity, and their functions in other tissues.

1.1. Gap junction channels in the brain

Gap junction channels facilitate the passive diffusion of ions (e.g. Na^+, K^+ Cl^-) and metabolites between adjacent cells to regulate electrical [135,138] and chemical transmission [128]. A consensus for the physiological significance of gap junction channels is evident in morphogenesis [44,145], development [89], and tissue synchronization [56]. In contrast, a role for gap junction channels in cell death is supported by two opposing hypotheses. The "Bystander death" mechanism as termed by Freeman et al. [52] describes the induction of apoptosis by Ganciclovir-sensitive tumour cells in a co-culture of Ganciclovir-insensitive tumour cells via gap junction channels [52]. The transfer of viral peptides [93] and caspase–derived apoptotic peptides through gap junction channels in an interconnected network of cells [102] also supports the innocent 'Bystander death' mechanism [80].

In contrast, a 'Good-Samaritan' role has been suggested of gap junction communication in injury. Connexin43 gene knockout studies were used to demonstrate that a loss of connexin43 is associated with a larger stroke lesion size [92,117], amplified apoptosis, and inflammation [92]. Furthermore, inhibiting gap junction channels following injury has been correlated to glutamate cytotoxicity and increased neuronal injury arising from a lack of functional syncytium between astrocytes [101]. The 'Good-Samaritan' role suggests that gap junction communication in injury is required for transmission of rescue signals (e.g. the free radical scavenger glutathione) [25] and dilution of metabolites to prevent toxic accumulation [92]. The timing of the signal transmitted through the gap junction channels may be crucial for determining a cell's fate. For example, molecules that are involved in the early induction of apoptosis, such as cytochrome C, apoptotic protease activating factor (APAF-1) and caspases, are too large to directly permeate through gap junction channels [41]. However, downstream of cytochrome C is the activation of IP_3 and Ca^{2+} signalling molecules that have been shown to amplify apoptosis [14]. A study based on apoptotic cell death in C6 glioma cells has shown that connexin43 gap junction channels induce cell death directly in neighbouring cells, but hemichannels propagate secondary injury as far as 100 μm away from the initial damage site [41].

1.2. Hemichannels

For some time, hemichannels were considered to be nothing more than precursors to gap junction channels, remaining closed until docking with an adjacent hemichannel. However, there is substantial evidence to suggest that hemichannels possess a function of their own by regulating the exchange between the cytoplasm and the extracellular space. Hemichannels are often portrayed as 'pathological pores' owing to their low opening probability under normal conditions [24] but they are stimulated to open in response to cellular stress [32,36,55,99]. Indeed, unregulated opening of hemichannels has been correlated with cell death by facilitating i) loss of osmoregulation [109,113], ii) excitotoxicity [53], iii) spread of secondary injury [41], and iv) inflammation [17]. As an example, Connexin43 hemichannel mediated ATP release has been shown to activate the purinergic inflammatory pathway by binding to the purinergic receptor, P2RX7, in the peri-traumatic regions of a spinal cord injury [17,26,65], while post-traumatic ATP release is not seen in Connexin43 knockout mice providing further support for Connexin43 dependent ATP release [65].

Normal physiological roles for hemichannels have also been reported, particularly in the retina where they are involved in the regulation of neural progenitor proliferation [149] and integration of input into horizontal cells [150,151,152,153]. In the brain, hippocampal astroglial Connexin43 hemichannels have been suggested to modulate basal synaptic transmission [154]. To what extent hemichannels play a physiological role is debatable considering that hemichannel gating mechanisms are tuned to open in response to conditions that are present in cellular stress. In such cases, the opposing regulation of gating mechanisms would suggest that gap junction channels uncouple in injury but hemichannel activity is heightened.

1.3. Pannexin channels

A layer of complexity was added with the discovery of pannexin channels, the vertebrate counterpart of invertebrate connexins analogues (innexins) [3,105]. Pannexin1 [3] and Pannexin2 [120] are highly expressed in the central nervous system, and Pannexin3 expression is reported in synovial fibroblasts and osteoblasts [3].

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