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Connexins in neurons and glia: targets for intervention in disease and injury

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Abstract

Both neurons and glia throughout the central nervous system are organized into networks by gap junctions. Among glia, gap junctions facilitate metabolic homeostasis and intercellular communication. Among neurons, gap junctions form electrical synapses that function primarily for communication. However, in neurodegenerative states due to disease or injury gap junctions may be detrimental to survival. Electrical synapses may facilitate hyperactivity and bystander killing among neurons, while gap junction hemichannels in glia may facilitate inflammatory signaling and scar formation. Advances in understanding mechanisms of plasticity of electrical synapses and development of molecular therapeutics to target glial gap junctions and hemichannels offer new hope to pharmacologically limit neuronal degeneration and enhance recovery.

Key Words: *ischemia; retinal degeneration; amacrine cells; astrocytes, dopamine receptors; adenosine receptors, NMDA receptors; connexin mimetic peptides*

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Abundant Gap Junctions in the Central Nervous System (CNS)

The organization of tissues into intricate systems is an essential element of life for multicellular organisms. One of the critical mediators of this organization is the gap junction, which permits direct intercellular communication between neighboring cells. Within the vertebrate central nervous system astrocytes, oligodendrocytes and ependymal cells are independently coupled by gap junctions, with some interconnections. This glial syncytium is critical for support of healthy nervous tissue.

Neurons are also coupled by gap junctions, which form electrical synapses. Electrical synapses permit direct electrical communication between two cells as well as allow passage of some cytoplasmic small molecules (Bennett and Zukin, 2004). Electrical synapses serve unique purposes separate from those of chemical synapses. Electrical synapses between like neurons expand receptive field sizes, dampen non-correlated noise and coordinate activity. Between dissimilar cell types, they establish specialized feed forward synaptic circuits that play prominent known roles in signaling in the retina, hindbrain and spinal cord (Bloomfield and Volgyi, 2009; Pereda et al., 2013). The unexpected abundance of these heterologous electrical synapses in the CNS (Rash et al., 2015) suggests that they play a number of important roles that are not yet known.

Knockout of Connexin36 (*Cx36* or *gjd2*), the most prevalent gap junction gene expressed in neurons, has revealed that electrical coupling is important for learning and memory (Frisch et al., 2005; Van Der Giessen et al., 2008), synapse development (Personius et al., 2007), and scotopic visual signaling (Guldenagel et al., 2001; Abd-El-Barr et al., 2009). Recognition that electrical synapses play a role in a variety of neurological disorders has also been growing in the last decade. Reduced function of electrical synapses has been proposed to underlie autism (Welsh et al., 2005), while their hyper-function may lead to seizure (Traub et al., 2004; Cunningham et al., 2012). These and many other findings highlight the important roles played by electrical synapses and suggest that pharmacological modulation of their activity presents a useful strategy for therapy for some neurological disorders.

The Role of Gap Junctions in Neural Disease and Injury

Cx36 gap junctions are prevalent in neurons throughout the CNS, with increased expression during early development and tapering off in adults (Belousov and Fontes, 2013). Transiently increased levels of gap junctions and electrical coupling are also observed immediately following ischemic injury to the CNS (Oguro et al., 2001; Nakase et al., 2004; Wang et al., 2012), in multiple models of epilepsy (Gajda et al., 2003), and traumatic brain injury (Frantseva et al., 2002;

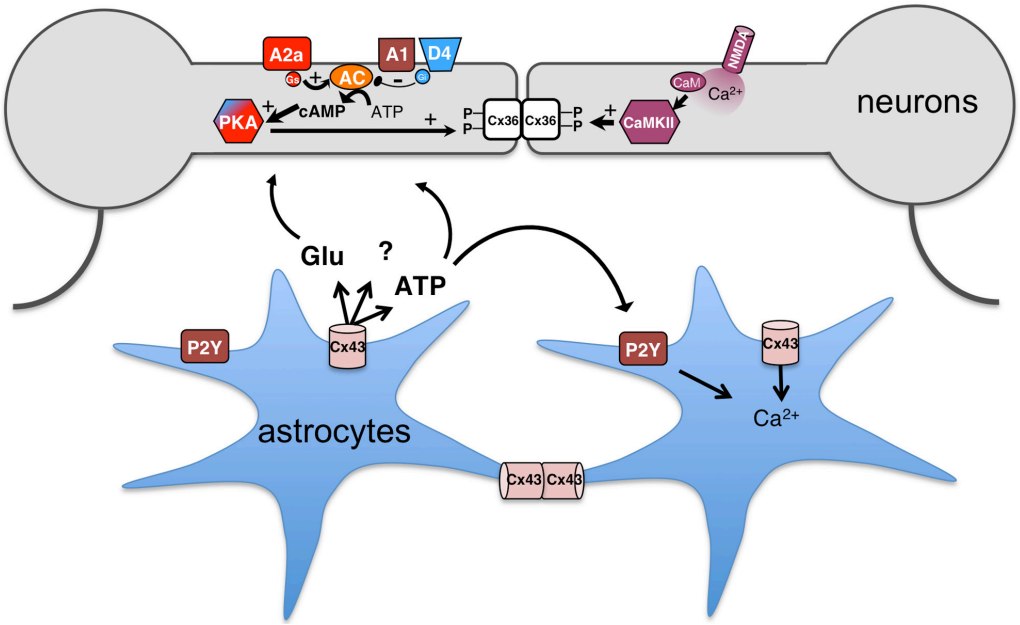

Figure 1 Schematic representation of some of the signaling pathways that control electrical coupling in neurons and contribute to inflammatory signaling by astrocytes.

Protein kinase signaling pathways potentiated by N-methyl-D-aspartate (NMDA) receptors and A2a adenosine receptors are potentially important pathways that increase neuronal coupling and may enhance bystander killing. Note that each signaling mechanism shown is not present on all neurons. See O'Brien, 2014a, b for more detail of electrical synaptic signaling pathways. Connexin hemichannels in activated astrocytes can release substances that cause excitotoxicity and promote inflammation. Adenosine triphosphate (ATP) release also propagates signaling through the network of astrocytes. See Orellana and Stehberg, 2014 for more detailed review of astrocytic hemichannel signaling.

Ohsumi et al., 2006). In models of retinal degeneration, neural network remodeling is accompanied by excessive activity among spiking neurons (Menzler and Zeck, 2011; Trenholm et al., 2012). This activity is strongly dependent on gap junction coupling (Toychiev et al., 2013; Choi et al., 2014). The excessive coupling in damaged neural networks has negative consequences for neuron survival as the extent of death is greatly reduced in Cx36 knockout animals or when gap junction inhibitors are applied (Talhouk et al., 2008; Paschon et al., 2012; Belousov and Fontes, 2013).

Propagation of neural injury to uninjured neighbors is a form of bystander killing. Bystander killing is a well-documented process in which cells that are close neighbors of damaged cells or those undergoing apoptosis are also killed. This effect has been widely exploited in the treatment of tumors with suicide gene therapy or ionizing radiation, and the efficacy of bystander killing has been linked to the presence of gap junctions in the tumor cells (Fick et al., 1995; Mesnil et al., 1996). A bystander killing effect is also evident in experimental models of retinal injury (Cusato et al., 2003; Akopian et al., 2014). Gap junctions are an attractive target for therapeutic intervention, since prevention of bystander killing and aberrant activity can significantly reduce the extent of damage following injury or disease.

Connexins in glia also play critical and somewhat complicated roles in neural injury and disease. Connexin 43 (Cx43 or Gja1), the primary connexin forming gap junctions among astrocytes in most of the CNS, also efficiently forms gap junction hemichannels under some conditions (Contreras et al., 2002) (**Figure 1**). Astrocytic gap junctions and hemichannels seem to play very different roles in neural injury. Gap junctions among astrocytes appear to enhance neuron viability during the initial phase of an ischemic injury. In a middle cerebral artery ischemia model, knock-out of Cx43 in astrocytes resulted in increased stroke volume, apoptosis and inflammatory signaling compared to controls (Nakase et al., 2004). However, substantial evidence suggests that gap junction hemichannels also contribute to inflammatory signaling and the spread of ischemic brain injury (Davidson et al., 2013b; Orellana and Stehberg, 2014). An increase in gap junctions and gap junction hemichannels is also a characteristic component of reactive gliosis in Alzheimer's disease (Koulakoff et al., 2012) and potentially other progressive neurodegenerative diseases, contributing to inflammatory signaling. Thus strategies to mitigate neuronal degeneration in injury and neurodegenerative diseases could be refined through knowledge of the different forms of signaling regulating gap junctions and hemichannels in neurons and glia.

Physiological Regulation of Gap Junctions in the CNS

A potentially useful strategy to minimize neuronal degeneration during injury or degenerative diseases is to specifically

target neuronal gap junctions and glial gap junction hemichannels during critical periods. Gap junction inhibitors are fairly non-specific and systemic administration is complicated due to the critical role of gap junctions in cardiac function. However, interventions can be designed to reduce neuronal electrical coupling by targeting signaling pathways that control physiological plasticity, potentially reducing the damage caused by ischemic events, seizures, or traumatic brain injuries.

Research in retinal neurons has revealed that many electrical synapses display a high degree of plasticity (O'Brien, 2014a). This plasticity is observed in response to light adaptation and is regulated by a variety of signaling pathways. Coupling among retinal AII amacrine cells is regulated by light in a biphasic pattern, with very low coupling under conditions of prolonged complete dark adaptation or bright light adaptation, and maximal coupling at intermediate light levels (Bloomfield and Volgyi, 2004). Kothmann et al. (2009) found that these changes in coupling were directly correlated to phosphorylation of Cx36 at certain regulatory sites, with the phosphorylation state of Cx36 linearly correlated with coupling over more than an order of magnitude dynamic range in coupling. The light-induced increase in coupling resulted from Calcium-Calmodulin-dependent kinase II (CamKII) phosphorylation of Cx36 driven by Ca^{2+} influx through non-synaptic N-methyl-D-aspartate (NMDA) receptors (**Figure 1**) activated by glutamatergic bipolar cells (Kothmann et al., 2012). In brighter light conditions, stimulation of dopamine release in the retina activates a complex signaling pathway that dephosphorylates Cx36. Dopamine activates D1 dopamine receptors on AII amacrine cells that in turn activate protein kinase A (PKA) (Hampson et al., 1992; Mills and Massey, 1995). PKA activity in turn activates protein phosphatase 2A, resulting in net dephosphorylation of Cx36 (Kothmann et al., 2009; O'Brien, 2014b). While the signaling is best described in retinal neurons, there are many examples of similar electrical synaptic plasticity elsewhere in the brain, including activity- and CamKII-dependent increases in coupling (Pereda et al., 1998; Turecek et al., 2014) and dopamine-dependent decreases in coupling (Rorig et al., 1995).

In contrast to retinal AII amacrine cells, retinal photoreceptors use a somewhat different mechanism to control coupling (Li and O'Brien, 2012; O'Brien, 2014a). Photoreceptor coupling changes profoundly under control of a circadian rhythm (Ribelayga et al., 2008), with extensive coupling at night and low coupling in the day and in bright light adapted states. This coupling is also controlled by phosphorylation of Cx36 at the same sites, but depends directly and positively on PKA activity, in contrast to the negative regulation by PKA in AII amacrine cells (Li et al., 2009, 2013). Cx36 phosphorylation and PKA activity are controlled in photoreceptors by bidirectional signaling from G-protein coupled dopamine and adenosine receptors to adenylyl cyclase (AC) (Li et al., 2013, 2014) (**Figure 1**). High levels of dopamine in the daytime activate D4 dopamine receptors to inhibit AC while high levels of adenosine at night activate A2a adenosine receptors to activate the cyclase (Li et al., 2013). While retinal adenosine levels are lower in the daytime and in bright light-adapted conditions, the daytime level of adenosine does activate A1 adenosine receptors that inhibit AC, reinforcing the dopamine effect (Li et al., 2014). Thus photoreceptor coupling is controlled very precisely by a balance of extracellular signaling cues reported by G-protein coupled receptors.

A variety of other signaling mechanisms have been described that regulate electrical synapses in different parts of the brain. These include plasticity controlled by nitric oxide (Mills and Massey, 1995; Patel et al., 2006), histamine receptors (Hatton and Yang, 2001; Yang and Hatton, 2002), cannabinoid receptors (Cachope et al., 2007), and metabotropic glutamate receptors (Haas et al., 2011). The latter are also critical for the post-injury increase in expression of Cx36 in CNS tissues (Park et al., 2011). The host of different mechanisms that regulate coupling in different neural circuits underscores the fact that the mechanisms of plasticity are specific to each type of neuron. However, there is ample evidence that certain regulatory behaviors, which we might refer to as 'regulatory modules,' recur in many types of neurons in many areas of the CNS (O'Brien, 2014b). These modules represent attractive targets for pharmacological intervention and require the development of an adequate understanding of their prevalence and distribution in the CNS to develop targeted therapies for diseases and injuries.

Therapeutic Targeting of Gap Junctions in CNS Disorders

Knowledge of signaling pathways that control plasticity of electrical synapses is expanding rapidly, and it is now possible to consider therapeutic strategies that target these pathways in treatments for neurological diseases and injuries. NMDA receptor antagonists, widely studied for their neuroprotective potential to reduce excitotoxicity, are also important targets to reduce electrical coupling and bystander killing. Linkage of non-synaptic NMDA receptor activation to potentiation of electrical synapses is likely to be very widespread in the CNS (O'Brien, 2014b). Inhibition of adenosine A2a receptors, useful targets to suppress inflammatory signaling, should also suppress coupling in some neuronal networks.

The use of connexin mimetic peptides has shown promise in therapeutic treatment for a number of disease and injury models. The vast majority of these peptides focus on Cx43, which is found in most mammalian tissues. A Cx43 mimetic αCT1, mimicking the carboxy terminus of Cx43, was shown to significantly increase corneal wound healing in a traumatic wound injury model *in vivo* for both WT and STZ diabetic rat models when applied in a microencapsulated form (Moore et al., 2013, 2014). Retinal reperfusion and ischemia models testing a Cx43 mimetic targeting an

extracellular loop transiently blocked Cx43 activity, leading to a reduction in vascular leaking and ganglion cell death post injury (Danesh-Meyer et al., 2012; Kerr et al., 2012). The therapeutic actions of the peptide are thought to center on blockage of Cx43 hemichannel activity, as revealed by a reduction in inflammatory signaling. This hypothesis was examined further in an optic neuropathy model by Chen et al. (2013), using mimetic peptides stabilized with lipoamino acid groups to create long term blockage of hemichannels, and thus curtailing retinal cell death. Using a similar blockade of Cx43 with mimetics in a fetal sheep global cerebral ischemia model led to reduction of seizures, increased cell survival, and improvements in sleep state cycle (Davidson et al., 2012, 2013a). Cx43 mimetics also reduced long term developmental defects, increased cell recovery, and reduced neuronal damage *in vivo* using models of epilepsy and preterm asphyxia associated with cerebral palsy (Samoilova et al., 2008; Davidson et al., 2014; Mylvaganam et al., 2014). The therapeutic applications of connexin mimetic peptides have so far been limited to connexins that would be present in glia and vascular tissues in the CNS. It is reasonable to expect that strategies combining mimetic peptides to target glial and endothelial gap junction hemichannels with drugs targeting electrical synaptic signaling pathways may further improve survival of neurons in neurodegenerative diseases and injuries.

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