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Journal
Journal of Neuroscience Research, 96(1)

ISSN
0360-4012

Authors
Lapato, Andrew S
Tiwari-Woodruff, Seema K

Publication Date
2018

DOI
10.1002/jnr.24088

Peer reviewed

Received: 7 February 2017 | Revised: 8 April 2017 | Accepted: 1 May 2017
DOI: 10.1002/jnr.24088

REVIEW

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Connexins and pannexins: At the junction of neuro-glial homeostasis & disease

Andrew S. Lapato[1,3] | **Seema K. Tiwari-Woodruff**[1,2,3]

[1]Division of Biomedical Sciences, School of Medicine, University of California Riverside, Riverside, CA 92521

[2]Neuroscience Graduate Program, University of California Riverside, Riverside, CA 92521

[3]Center for Glial-Neuronal Interactions, University of California Riverside, Riverside, CA 92521

Correspondence
Seema K. Tiwari-Woodruff, Ph.D., Division of Biomedical Sciences, School of Medicine, University of California Riverside, Rm 205, 311 School of Medicine Research Building, 900 University Ave, Riverside, CA 92521, USA.
Email: seema.tiwari-woodruff@medsch.ucr.edu

Funding information
The National Multiple Sclerosis Society and National Institute of Health generously supported this work, grant numbers: NMSS-RG-4853A3/2 and NIH R01-7R01NS081141.

Abstract

In the central nervous system (CNS), connexin (Cx)s and pannexin (Panx)s are an integral component of homeostatic neuronal excitability and synaptic plasticity. Neuronal Cx gap junctions form electrical synapses across biochemically similar GABAergic networks, allowing rapid and extensive inhibition in response to principle neuron excitation. Glial Cx gap junctions link astrocytes and oligodendrocytes in the pan-glial network that is responsible for removing excitotoxic ions and metabolites. In addition, glial gap junctions help constrain excessive excitatory activity in neurons and facilitate astrocyte Ca^{2+} slow wave propagation. Panxs do not form gap junctions in vivo, but Panx hemichannels participate in autocrine and paracrine gliotransmission, alongside Cx hemichannels. ATP and other gliotransmitters released by Cx and Panx hemichannels maintain physiologic glutamatergic tone by strengthening synapses and mitigating aberrant high frequency bursting. Under pathological depolarizing and inflammatory conditions, gap junctions and hemichannels become dysregulated, resulting in excessive neuronal firing and seizure. In this review, we present known contributions of Cxs and Panxs to physiologic neuronal excitation and explore how the disruption of gap junctions and hemichannels lead to abnormal glutamatergic transmission, purinergic signaling, and seizures.

KEYWORDS

connexin, pannexin, synaptic plasticity, epilepsy, seizure, hemichannel, gap junction, gliotransmission, purinergic signaling, electrical synapse, pan-glial network, neuronal excitability, astrocyte

1 | INTRODUCTION

Accruing evidence indicates that connexin (Cx) and pannexin (Panx) transmembrane channels are crucial for the coordination and maintenance of physiologic CNS activity. In neurons, Cxs electrochemically couple neurons by electrical synapses (Galarreta & Hestrin, 1999), while glial Cxs mediate numerous functions ranging from K^+ buffering to direct modulation of glutamatergic activity (Battefeld, Klooster, & Kole, 2016; Chever, Lee, & Rouach, 2014a; Kamasawa et al., 2005; Kofuji & Newman, 2004). Alone, Cxs and Panxs represent a mechanism for robust autocrine and paracrine signaling through gliotransmitter release, which are essential to synaptic strength and plasticity (Prochnow et al., 2012; Thompson et al., 2008). Dysregulation of Cx and Panx activity is implicated in neurodegenerative disease (Markoullis et al., 2012a) and may be etiologic in some human epilepsy (Bedner et al., 2015). In addition, Cx and Panx sensitivity to inflammatory mediators suggests that neuronal excitability may be altered in a range of disease states. In the following sections, we will describe the structure, function, regulation, and distribution of CNS Cx and Panx molecules. We will also summarize evidence for their functions related to neuronal

Significance

Connexins and pannexins contribute to normal excitatory activity in the central nervous system (CNS). Cells linked by pairs of connexin hemichannels, called gap junctions, regulate levels of potentially toxic metabolites produced during neuronal activity. Unpaired connexin and pannexin hemichannels facilitate learning and memory by providing feedback to neurons through the release of signaling molecules. In this review, we describe how CNS cells utilize connexins and pannexins to perform these tasks. In addition, we discuss how disruption of connexin and pannexin activity leads to abnormal excitation and diseases such as epilepsy.

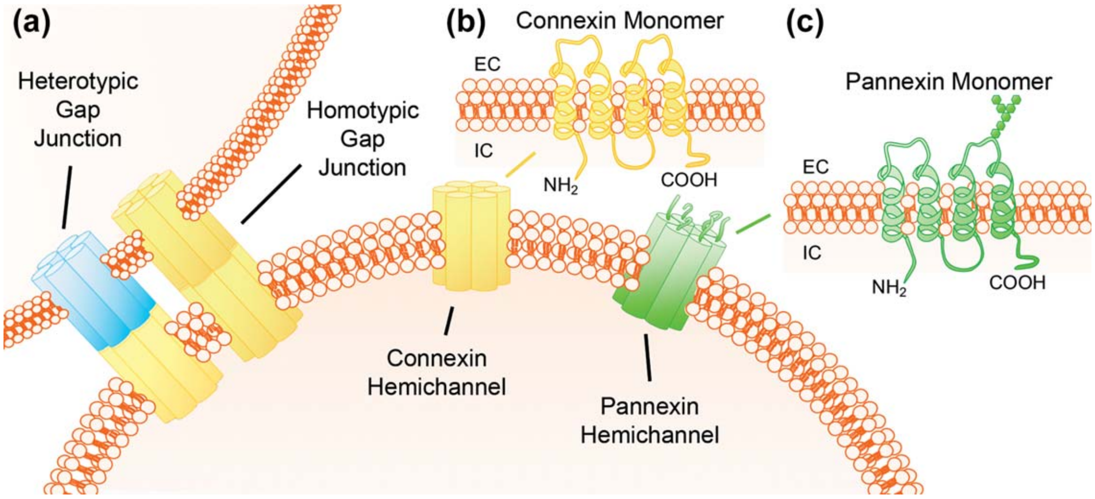

FIGURE 1 Connexin and pannexin structure and organization. (**a**) Connexin hemichannels are transmembrane pores composed of six subunits. Individual hemichannels may be paired with homotypic or heterotypic hemichannels on adjacent cells as gap junctions to allow exchange of cytoplasmic contents up to 1.5 kDa. **(b, c)** Connexins and pannexins are structurally and functionally homologous, but have distinct amino acid sequences. Each subunit possesses four transmembrane domains linked by one intracellular and two extracellular loops. The carboxyl and amine terminals extend into the cytoplasm. The carboxyl tail is the site of regulatory modification and phosphorylation. **(c)** Pannexin monomers are structurally related to connexins but N-linked glycosylation of the second extracellular loop prohibits assembly into functional gap junctions.

excitability under homeostatic conditions and examine their role as effectors of pathological glutamatergic transmission.

2 | STRUCTURE AND FUNCTION OF CONNEXINS AND PANNEXINS

Structurally, the Cx and Panx family of proteins comprise a group of hexameric transmembrane pores that are permeable to ions, metabolites, second messengers, and purine signaling mediators up to 1.5 kDa (Loewenstein, 1981) with divergent peptide sequences but homologous topology. Each subunit of the channel-forming complex contains four membrane-spanning domains linked by two extracellular loops that mediate docking with complimentary Cx hexamers (Figure 1). Uncoupled hexamers are termed hemichannels (HCs) and facilitate release of cellular contents into the extracellular space (Simard & Nedergaard, 2004). When HCs are coupled with complementary HCs on adjacent cells, they form gap junctions (GJs), which act in pairs to facilitate direct intercellular communication of cytoplasmic molecules. Of note, Panx1 HCs have not been shown to form GJs in vivo without substantial manipulation (MacVicar & Thompson, 2010; Penuela et al., 2007; Sosinsky et al., 2011), which is thought to be due to post-translational N-linked glycosylation of the second extracellular loop of each Panx subunit (Figure 1). Post-translational modification of Cx monomers largely takes place at the site of the intracellular carboxyl tail (May, Tress, Seifert, & Willecke, 2013) and is thought to regulate non-channel functions of Cxs, including adhesion, migration (Giepmans et al., 2001; Pannasch et al., 2014), and proliferation (Cheng et al., 2004; Santiago et al., 2010). GJ mediated adhesion and migration are of particular importance in the developing CNS, where they facilitate migration of neocortical neurons by providing points of contact with radial glia (Elias, Wang, & Kriegstein, 2007). Similarly, subventricular zone-derived cells utilize adhesive properties of GJs for movement along the rostral migratory stream (Marins et al., 2009). However, Cx and Panx biology may extend beyond these functions into a variety of intracellular regulatory processes (reviewed in Esseltine & Laird [2016]).

Opening of Cx and Panx HCs has traditionally been considered deleterious (Paul, Ebihara, Takemoto, Swenson, & Goodenough, 1991), occurring under pathological conditions such as ischemia and, leading to excitotoxic cell-death (John, Kondo, Wang, Goldhaber, & Weiss, 1999; Kondo, Wang, John, Weiss, & Goldhaber, 2000) and injurious depolarization (Ebihara & Steiner, 1993; Valiunas & Weingart, 2000). More recent evidence, however, has shed light on Cx and Panx HC physiologic activities, including their function as a platform for robust autocrine and paracrine signaling between, and amongst, glia and neurons (Klaassen et al., 2011; Prochnow et al., 2012). Gliotransmission continues to draw attention to Cx and Panx HCs, whereby release of purinergic mediators and other gliotransmitters has proven essential to synaptic strength and plasticity (Cherian et al., 2005; Montero & Orellana, 2015; Stout, Costantin, Naus, & Charles, 2002). When HCs are coupled with complementary HCs on adjacent cells, they form gap junctions (GJs), which act in pairs to facilitate direct intercellular communication of cytoplasmic molecules. Of note, Panx1 HCs have not been shown to form GJs in vivo without substantial manipulation (MacVicar & Thompson, 2010; Penuela et al., 2007; Sosinsky et al., 2011), which is thought to be due to post-translational N-linked glycosylation of the second extracellular loop of each Panx subunit (Figure 1). In neurons, GJs are the substrate of electrical synapses formation (Pereda et al., 2013), while GJs among glia couple cells in the pan-glial network, which participate in buffering excitotoxic metabolites produced by depolarizing activity.

TABLE 1 Cellular distribution of Cx and Panx isoforms expressed by glia and neurons in the adult mammalian CNS

Cell Type	Connexins	Pannexins	References
Astrocytes	Cx26, Cx30, Cx43,	Panx1	Dermietzel et al., 1989, Nagy et al., 2001, Zoidl et al., 2007
Microglia	Cx32a, Cx36, Cx43a	Panx1	Orellana et al., 2015, Dobrenis et al., 2005, Eugenin et al., 2001, Takeuchi et al., 2006
Oligodendrocytes	Cx29, Cx32, Cx47	Panx1	Dermietzel et al., 1989, Domercq et al., 2010, Nagy et al., 2003
Neurons	Cx30.2, Cx31.1, Cx32, Cx36, Cx40, Cx45, Cx50	Panx1, Panx2	Bruzzone et al., 2003, Dere et al., 2008, Kreuzberg et al., 2008, Rash et al., 2000, Rozental et al., 1998, Schutte et al., 1998, Vis et al., 1998, Weickert et al., 2005

[a] expressed by activated microglia

Astrocyte expressed Cx isoforms participate in HC-mediated gliotransmission and astrocyte-oligodendrocyte GJs within the pan-glial network. Cx36 HCs are expressed by microglia under homeostatic conditions, while Cx32 and Cx43 are upregulated in response to inflammation. Oligodendrocyte Cx isoforms contribute to GJ coupling with pan-glial network members and between myelin layers. Neuronal Cx heterogeneity reflects CNS regional specialization. Panx1 HCs are found in all CNS populations listed, but Panx2 is only identified in neurons.

Regulation of GJ and HC open probability is affected by a variety of circumstances. Phosphorylation of the Cx intracellular tail plays a role in gating pore permeability, thereby allowing dynamic opening and closing in response to a variety of stimuli (Zador, Weiczner, & Mihaly, 2008). Under homeostatic conditions, neuronal activity leading to decreased extracellular Ca^{2+} (Thompson et al., 2008; Torres et al., 2012) and increased K^{+} (Santiago et al., 2011) encourages HC opening and adenosine triphosphate (ATP) release (Kawamura, Ruskin, & Masino, 2010). However, pathological environments also open HCs and GJs aberrantly. Neurodegenerative diseases such as experimental autoimmune encephalomyelitis (Markoullis et al., 2012a), multiple sclerosis (Masaki, 2015), and epilepsy (Bedner et al., 2015) cause uncoupling of astrocyte GJs, with the resulting gliotransmitter release contributing to abnormal neuronal activity (Thompson et al., 2008). Inflammatory mediators, including the cytokines interleukin (IL)-1β and tumor necrosis factor (TNF)α, drive HC open probability, with application of either cytokine or the toll-like receptor (TLR) 4 ligand lipopolysaccharide (LPS) causing increased HC-mediated uptake of ethidium bromide in astrocytes in vitro and in slice (Froger et al., 2010; Retamal et al., 2007).

Cxs and Panxs are distributed throughout the CNS (Table 1) where they participate in a variety of functions. In addition to their channel activity which promotes metabolic coupling amongst macroglia (Niu et al., 2016), Cx GJs are critical to glial survival and stabilization of associated Cx HCs (Magnotti, Goodenough, & Paul, 2011; May et al., 2013). Mutations in oligodendrocyte-expressed Cx genes results in phenotypes indistinguishable from inherited hypomyelinating leukodystrophies, which are characterized by impairment of myelin sheath formation, inflammation, and sensorimotor deficits (Magnotti et al., 2011; May et al., 2013; Schiza et al., 2015). For example, a mutation in the Cx47 promoter results in Pelizaeus–Merzbacher-like disease (Gotoh et al., 2014), while altered Cx32 expression leads to symptomology closely resembling Charcot-Marie-Tooth disease (Sargiannidou, Kim, Kyriakoudi, Eun, & Kleopa, 2015).

Further illustrating the importance of glial GJ coupling in maintaining CNS homeostasis, astrocyte-oligodendrocyte coupling is reduced in Cx47-KO mice and is associated with myelin vacuolation (Odermatt et al., 2003). Mice lacking both Cx32 and Cx47 exhibit more pronounced myelin pathology and action tremors in young mice, which, progress into tonic-clonic seizures and mortality by the sixth post-natal week (Menichella, Goodenough, Sirkowski, Scherer, & Paul, 2003; Odermatt et al., 2003). Loss and activation of astrocytes, oligodendrocyte drop out, myelin vacuolation, inflammation, and invasion of phagocytic cells are also common to disorders of GJ coupling (Magnotti et al., 2011; May et al., 2013; Tress et al., 2012), suggesting a role for intact pan-glial network GJ connections in supporting its members' survival. However, while non-channel properties of Cxs have been explored in the context of neuronal differentiation (Cheng et al., 2004; Kunze et al., 2009) and glutamatergic transmission (Chever, Pannasch, Ezan, & Rouach, 2014b), the mechanism whereby Cxs support glial survival remains poorly understood.

3 | CONNEXINS AND PANNEXINS IN SYNAPTIC PLASTICITY

3.1 | Electrical synapses, excitability, and learning

At the forefront of Cx and Panx neurobiology research is their role in neuronal excitability and their ability to modify synaptic activity. Neuronal GJs, which couple cells by electrical synapses, are numerous in the embryonic CNS, but become increasingly limited during development (Belluardo et al., 2000; Bruzzone, Hormuzdi, Barbe, Herb, & Monyer, 2003; Kreuzberg et al., 2008; Rash et al., 2000; Rozental et al., 1998; Schutte, Chen, Buku, & Wolosin, 1998; Swayne & Bennett, 2016; Vis et al., 1998; Weickert, Ray, Zoidl, & Dermietzel, 2005). In the adult mammalian brain, GJs are primarily restricted to inhibitory GABAergic networks and associated principle neurons (Apostolides & Trussell, 2013; Galarreta & Hestrin, 1999), with Cx36 becoming the predominant isoform expressed (Belluardo et al., 2000; Condorelli, Belluardo, Trovato-Salinaro, & Mudo, 2000). Cx36 GJs allow rapid electrochemical transmission and influence synchronization of interconnected neurons (Deans et al., 2001; Landisman et al., 2002). Coupled neurons of the reticular thalamic nucleus and suprachiasmatic nucleus of the thalamus (SCN) display inherent Cx36-dependent desynchronizing properties (Sevetson & Haas, 2015; Wang, Chen, & Wang, 2014). While synchronization of SCN neurons is required for light–dark cycle detection and circadian rhythm, these examples illustrate the overriding strength of inhibitory networks coupled by GJs and hint at their physiologic role in resisting development of epileptiform synchronization.

Traditionally, GJ-mediated electrical synapses have been considered static structures. However, recent research casts doubt on this assumption. Like glutamatergic chemical synapses, GJ-mediated electrical synapses in the rat inferior olive also displayed activity-dependent strengthening (Turecek et al., 2014). In this study, the authors observed that the N-Methyl-D-aspartate receptor (NMDAR) NR1 subunit co-localized with neuropilar Cx36 GJs. Agonism of NMDARs resulted in increased coupled potential upon stimulation that was accompanied by elevated uptake of a tracer dye (Turecek et al., 2014), indicating that GJ-NMDAR complexes are sensitive to synaptic activity and become upregulated or opened in response. As electrical synapses facilitate rapid and widespread inhibition, these data suggest that depolarizing inputs modify GJ strength to set a basal inhibitory tone on excitatory networks.

Unsurprisingly, in addition to their function in limiting excitability, neuronal GJs also play a major role in learning and memory. Knockout of Cx36 resulted in diminished novel object recognition that was exaggerated by environments containing complex stimuli (Frisch et al., 2005). In addition, Cx36-KO mice exhibited impaired short-term and long-term memory in Y-maze testing, and reduced motor learning by rotorod (Frisch et al., 2005). Interestingly, field excitatory post-synaptic potentials (fEPSPs) recorded from cornu ammonis 1 (CA1) hippocampal pyramidal neurons after Schaffer collateral stimulation were also decreased in Cx36-KO mice (Wang & Belousov, 2011), suggesting coordinated GJ-coupled interneuron activity is an essential component of LTP inducing events. This is supported by reports finding that the power of gamma and theta frequencies, which are thought to be mediated by GABAergic inerneurons (Lasztoczi & Klausberger, 2014), are increased in the hippocampus following tetanic stimulation of Schaffer collaterals (Bikbaev & Manahan-Vaughan, 2008).

Similarly, knockout of Cx31.1, which is expressed in dopaminergic neurons of the substantia nigra pars compacta (Vandecasteele, Glowinski, & Venance, 2006) and striatal output neurons (Venance, Glowinski, & Giaume, 2004) that play a role in sensory-motor control and novelty-induced exploration (Leussis & Bolivar, 2006), resulted in elevated exploration of novel environments and impaired performance in novel object recognition tasks (Dere et al., 2008). Together, these studies point to a central role for neuronal coupling via GJs in memory formation and consolidation. This may be attributable to autoinhibition of GABAergic networks by remaining inhibitory chemical synapses and reduced long term potentiation (LTP), which is thought to represent the cellular substrate of learning (Morris et al., 2003).

3.2 | The pan-glial network: beyond buffering

The most abundant source of GJs and HCs in the brain come from the highly interconnected lattice of glial cells interspersed throughout the CNS (Figure 2). Chief among the tasks of this syncytium of astrocytes, oligodendrocytes, and endothelial cells is the modification of neuronal excitation through spatial buffering of ions and metabolites by GJ connected cells (Battefeld et al., 2016; Bedner et al., 2015; Kamasawa et al., 2005; Kofuji & Newman, 2004; Magnotti et al., 2011; Nagy et al., 2001; Wasseff & Scherer, 2011). In this model, inward K^+ currents are generated by active uptake by astrocytes and oligodendrocytes near depolarizing cells and sustained by conduction of buffered K^+ to blood vessels for elimination (Figure 2). Failure to remove sufficient K^+ results in elevated resting membrane potential and more frequent spontaneous action potentials. However, while this activity is critical to physiologic excitatory activity, the pan-glial network exercises additional GJ and HC mediated effects on neuronal excitability both directly and indirectly.

Astrocyte Ca^{2+} waves are associated with neuronal activity and are conducted through GJs and HCs (Torres et al., 2012). Accompanied by rapid elevation of intracellular Ca^{2+} in both astrocytes and neurons, glutamatergic activity induces a decline in extracellular Ca^{2+}. After a delay, astrocytes then exhibit a secondary "slow" intracellular Ca^{2+} wave initiated by ATP release via Panx1 HCs acting in an autocrine fashion (Torres et al., 2012). These waves are not attributable to glutamate signaling and require Cx30 and Cx43 GJs to travel between neighboring astrocytes (Torres et al. 2012). Importantly, astrocyte slow waves are associated with activation of the metabotropic purine receptor P2Y1 on nearby inhibitory interneurons, leading to increased inhibitory post synaptic currents (IPSCs; Torres et al., 2012). This suggests that Ca^{2+} slow waves may be involved in augmenting feedback inhibition through purinergic signaling, expanding the ways that astrocytes modify glutamatergic and GABAergic transmission.

Additional modulation of excitatory activity is exerted by astrocytes through Cx isoform-dependent regulation of synaptic glutamate release. Cx43 sets basal quantal release of glutamate at excitatory synapses without altering the threshold for depolarization or the activity of excitatory amino acid transporters (Chever et al., 2014b). Instead, postsynaptic glutamate release is augmented by purinergic signaling through astrocyte HCs (Chever et al., 2014a). In contrast, Cx30 influences synaptic glutamate buffering indirectly through non-GJ mediated activities (Pannasch et al., 2014). Organotypic slices from Cx30-KO mice exhibit decreased glutamatergic activity independent of presynaptic quantal release or postsynaptic glutamate sensitivity. Instead, Cx30 regulates astrocyte migration and glutamate transporter 1 (GLT-1) efficacy. In a 2014 study, Pannasch et al. (2014) observed that Cx30-KO astrocyte processes enriched in GLT-1 invade excitatory synapses deeper than wild type astrocytes, thereby reducing glutamate within the synaptic cleft. This activity is independent of Cx30's GJ function, possibly relying on regulation by proteins complexed to Cx30 GJs.

Oligodendrocytes are commonly overlooked in the composition of the pan-glial network, often thought of as merely myelinating projection axons. However, emerging evidence indicates that oligodendrocytes are also essential to maintaining physiologic generation of action potentials independent of their myelinating function (Nagy, Ionescu, Lynn, & Rash, 2003). Oligodendrocytes comprise a varying fraction of

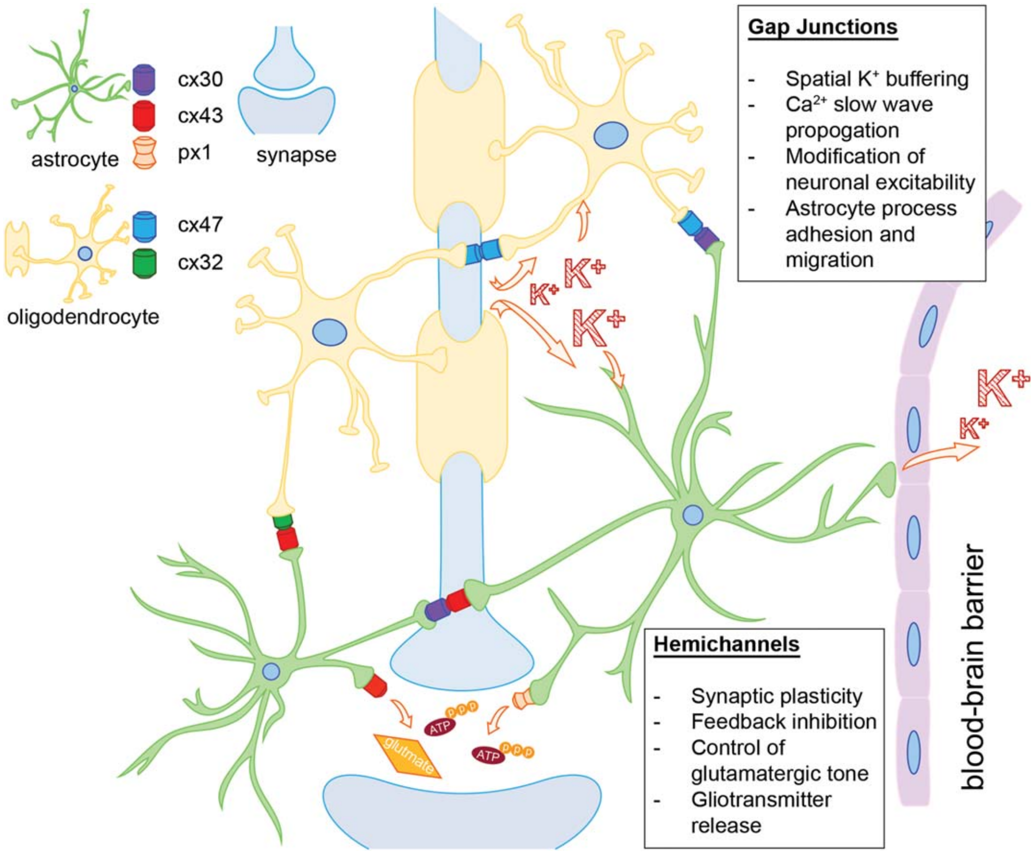

FIGURE 2 The pan-glial network participates in regulating excitatory neuronal transmission through gap junction and hemichannel-mediated functions. Connexin gap junctions control glutamatergic activity indirectly through generation of inward K^+ currents & spatial K^+ buffering, activity-dependent astrocyte Ca^{2+} slow wave propagation, and regulation of synaptic invasion by GLT-1 enriched astrocyte process. Model depicts coupling partners for homotypic and heterotypic glial GJs and their cellular expression. Cx43 and Panx1 HCs contribute to synaptic plasticity, inhibitory feedback, and glutamatergic tone by autocrine and paracrine release of synaptic gliotransmitters, including glutamate and ATP.

pan-glial network participants. In addition to forming biocytin-permeable homotypic GJs with other oligodendrocytes and $NG2^+$/$Olig2^+$CNPase$^-$ oligodendrocyte precursors (Maglione et al., 2010), oligodendrocytes also make heterotypic GJs with astrocytes throughout the CNS (Griemsmann et al., 2015).

In myelinated fiber tracts, oligodendrocytes participate in spatial K^+ buffering at the level of periaxonal myelin, which conducts ions through reflexive Cx32 GJs within myelin layers closest to the axolemma and strings of Cx32 GJs connecting adjacent paranodal loops (Kamasawa et al., 2005). Nearby astrocyte processes then siphon K^+ from myelin and oligodendrocyte somata for elimination through heterotypic Cx47-43 and Cx32-30 GJs (Kamasawa et al., 2005). In genetic ablation studies, mice lacking both Cx32 and Cx47 exhibit periaxonal myelin vacuolation in the optic nerve that is worsened by retinal ganglion activity (Menichella et al., 2006). Interestingly, the authors of this study also found that mice lacking the inward rectifier K^+ channel Kir4.1 exhibited myelin vacuolation in spinal cord grey matter (Menichella et al., 2006), possibly due to osmotic damage arising from failure to disperse rising K^+ concentration within the myelin sheath.

In a recent study from Battefeld et al. (2016), satellite oligodendrocytes (sOLs) associated with the axon initial segment of somatosensory cortex layer V pyramidal neurons were predicted to dampen neuronal bursting by computational modeling. Their model suggested this phenomenon was mediated by activity dependent inward rectifying K^+ (Kir) currents in sOLs, which was validated experimentally. Furthermore, GJ blockade using the non-specific Cx/Panx inhibitor carbenoxolone (CBX) abolished Kir currents and reduced voltage coupling between sOLs and adjacent astrocytes (Battefeld et al., 2016). These findings support the importance of oligodendrocytes in maintaining homeostatic extracellular ion concentrations, with implications for disease states involving white matter injury, including MS.

3.3 | Hemichannels and purinergic signaling in synaptic plasticity, learning, and memory

Purinergic signaling molecules released by Cx and Panx HCs acting on neuronal and glial P2X and P2Y receptors comprise a fundamental component of synaptic plasticity (Kim & Kang, 2011; Prochnow et al., 2012; Thompson et al., 2008; Zoidl et al., 2007). Measurement of CA1 fEPSPs after CA3 Schaffer collateral tetanic stimulation shows that LTP is abnormally increased in mice lacking Panx1 HCs (Panx1-KO; Ardiles et al., 2014; Prochnow et al., 2012). Interestingly, in addition to elevated fEPSPs, stimulation of Panx1-KO Schaffer collateral projections results in absent long term depression (LTD) in CA1 pyramidal neurons (Ardiles et al., 2014; Prochnow et al., 2012). Behaviorally, Panx1-KO mice also perform worse at novel object recognition and spatial recall tasks (Prochnow et al., 2012). Thus, purines released by Panx1 HCs represent a negative feedback mechanism dampening exaggerated LTP, which has been shown to impair spatial learning (Moser, Krobert, Moser, & Morris, 1998). Remarkably, physiologic LTP is restored in Panx1-KO mice when Schaffer collateral stimulation is accompanied by a mix of gliotransmitters including adenosine and ATP, possibly reflecting hyperpolarization through ATP-dependent K^+ channels (Kawamura, Gachet, Inoue, & Kato, 2004) or adenosine mediated inhibition through A_1 and A_2 receptors (Boison & Aronica, 2015; Diogenes et al., 2014).

Astrocyte HCs also participate in purinergic signaling and learning. In a study from Chever et al. (2014a), blockade of Cx43 HCs with the Cx43 HC-specific inhibitor gap26 resulted in reduced fEPSPs recorded in CA1 neurons after Schaffer collateral stimulation (Chever et al., 2014a). These results were replicated when Cx43 HCs were left intact, but P2 receptors were blocked using the P2 antagonists RB2 and PPADS (Chever et al., 2014a), suggesting purinergic signaling molecules released by Cx43 HCs were responsible for modifying glutamatergic activity after stimulation.

A similar in vivo study examining the role of Cx43 HCs in fear-conditioning supports these findings. In a study by Stehberg et al. (2012), a microinjection of the Cx43 HC-specific blocking peptide TAT-Cx43L2 or gap27 into the basolateral amygdala resulted in amnesia to fear-conditioning training (Stehberg et al., 2012). Interestingly, co-administration of these blocking peptides with a gliotransmitter cocktail including glutamate, glutamine, lactate, D-serine, glycine, and ATP restored fear-conditioning memory. This effect was not observed when either peptide was injected several hours after training, indicating that Cx43 HCs participated in short term fear-memory consolidation (Stehberg et al., 2012). While this study did not implicate a specific gliotransmitter in mediating the observed effects, it bolsters slice-recording findings that implicate HCs in learning and memory.

4 | A LITTLE TOO EXCITED: CONNEXIN AND PANNEXIN DYSREGULATION AND SEIZURES

4.1 | Electrical synapses in seizures

Seizures are characterized by aberrant hypersynchronous excitatory activity that may be localized to a specific population of neurons or generalized throughout several brain regions. Classically, seizure development is thought to occur when inhibitory GABAergic transmission is compromised or overwhelmed by glutamatergic activity. Under homeostatic conditions, a range of mechanisms exist that confer resistance to seizures, including principal cell inhibition and desynchronizing activity of GABAergic networks (Apostolides & Trussell, 2013; Deans, Gibson, Sellitto, Connors, & Paul, 2001; Landisman et al., 2002). Damage to or dysfunction of these networks may be involved in seizure initiation and propagation (Schwaller et al., 2004; Toyoda, Fujita, Thamattoor, & Buckmaster, 2015).

As the primary Cx isoform expressed in the adult CNS, Cx36 GJ-coupled GABAergic populations are critical for setting basal inhibitory tone in several brain regions (Belluardo et al., 2000; Deans et al., 2001; Turecek et al., 2014; Vandecasteele et al., 2006; Venance et al., 2004), and may be indispensable to maintaining physiologic resistance to epileptiform activity. However, the contribution of Cx36-coupling to seizures remains uncertain due to disparate, and occasionally contrary, reporting. Studies utilizing global ablation of Cx36 GJs have yielded data indicating an anti-epileptogenic (Jacobson et al., 2010), pro-epileptogenic (Maier et al., 2002), and bystander (Beaumont & Maccaferri, 2011; Voss et al., 2010b) role for these molecules.

In support of an anti-epileptogenic function, Cx36-KO mice exhibit increased susceptibility to seizure induction in the pentylenetetrazol (PTZ) model of epilepsy (Jacobson et al., 2010). Consistent with these findings, pharmacological GJ blockade by CBX or quinine, which preferentially inhibits Cx36 and Cx50 (Srinivas, Hopperstad, & Spray, 2001), resulted in increased cortical epileptiform activity in organotypic slice culture using the low-Mg^{2+} model of seizure induction (Voss, Jacobson, Sleigh, Steyn-Ross, A., & Steyn-Ross, 2009). Jacobson et al. (2010) hypothesize that this phenomenon may be the result of autoinhibition of GABAergic Cx36-coupled neurons. In this study, the authors suggest that although the electrical synapses responsible for excitation of linked inhibitory networks would be absent in Cx36-KO animals, GABAergic chemical synapses on nearby inhibitory interneurons would remain. The resulting inhibition of inhibitory cells could feasibly give rise to aberrant excitatory activity by failing to suppress collateral excitation of surrounding pyramidal neurons or providing feedback inhibition (Jacobson et al., 2010). This hypothesis is supported by lines of evidence that indicate that in Cx36-KO mice, hippocampal epileptiform activity induced by kainate exposure may be partially attributable to reduced $GABA_A$ receptor activity (Pais et al., 2003).

In contrast, Maier et al. (2002) found that Cx36-KO hippocampi were less susceptible to seizures induced by the K^+ channel inhibitor 4-aminopyridine (4-AP). Their recordings from Cx36-KO slices showed less frequent spontaneous sharp wave events than wild type hippocampi with fewer and slower ripples. These data suggest that Cx36 GJs help coordinate the excitatory hypersynchronization thought to generate sharp wave-ripple complexes (Schlingloff, Kali, Freund, Hajos, & Gulyas, 2014), with their activity becoming pathologic after 4-AP exposure. Surprisingly, while ongoing seizure-like events were reduced in Cx36-KO mice, a portion of the slices recorded from failed to exhibit any activity whatsoever in response to 100 μM 4-AP, indicating that Cx36 blockade could represent an effective method of managing seizures. Corroborating this, relatively selective Cx36 GJ inhibition by quinine or widespread inhibition by CBX application after 4-AP-induced seizures suppressed the amplitude of epileptiform activity and reduced involvement of the contralateral cortex in vivo (Gajda, Szupera, Blazso, & Szente, 2005). However, to qualify these results, although their summed ictal activity was lower than control animals, quinine treated rats displayed more frequent, yet shorter seizures.

Additional complication in understanding Cx36-mediated activity in seizures comes from studies that find it dispensable to seizure initiation and resistance. Mefloquine, a quinine derivative inhibitor of Cx36 and Cx50 GJs at low doses (Cruikshank et al., 2004), failed to elicit any change in seizure-like event amplitude, frequency, or duration in low Mg^{2+}– and aconitine-treated neocortical slice preparations from wild type mice, compared to control treated and Cx36-KOs (Voss et al., 2010b). Similarly, in a 2011 study, Beaumont & Maccaferri (2011) found that 4-AP treated CA1 interneurons of Cx36-KO mice exhibited no difference in epileptiform GABAergic currents relative to wild type nice despite uncoupling of interneurons across hippocampal strata. Furthermore, the authors demonstrated that CBX, but not mefloquine, inhibits $GABA_A$ receptors independently of the allosteric regulatory site of benzodiazepines, calling into question the use of CBX to study Cx contributions to seizures.

The use of Cx36-KO mice also presents an important limitation in the study of epilepsy. In the low Mg^{2+} model of seizure, slices from these mice exhibit a GJ-independent increase in picrotoxin-sensitive GABAergic augmentation (Voss, Melin, Jacobson, & Sleigh, 2010a). Wild type slices, treated with mefloquine prior to seizure induction, did not exhibit picrotoxin or etomidate-sensitive augmentation, indicating these effects were the result of compensatory changes in Cx36-KO animals. While differences in choice of model may underlie the variegated findings in these reports, they also highlight the need for selective Cx36 inhibitors in the study of electrical synapse dysregulation and its contribution to neuronal hyperexcitability.

4.2 | Inflammation, seizure, and pan-glial network gap junction dysregulation

Panglial network maintenance of a sufficiently high-seizure threshold in the normal CNS relies on various GJ and non-GJ dependent functions (Chever et al., 2014b; Pannasch et al., 2014). Spatial buffering of K^+ and other metabolites released during periods of increased neuronal depolarization is critical to constraining hypersynchronous excitatory activity and reducing generalization of epileptiform bursting when initiated (Battefeld et al., 2016; Bedner et al., 2015; Kamasawa et al., 2005; Kofuji & Newman, 2004; Magnotti et al., 2011; Wasseff & Scherer, 2011). Astrocytes are central to the panglial network's ability to carry out this function and recent evidence illustrates that dysregulation of astrocyte Cx43 GJs may drive the pathogenesis of some acquired human temporal lobe epilepsies.

In a 2015 study from Bedner et al. (2015), hippocampal astrocytes from surgical specimens of sclerotic hippocampi from epileptic patients anomalously expressed ionotropic glutamate receptors, but not glutamate transporters. In addition, dye-loading experiments in these astrocytes revealed severely restricted diffusion of biocytin into neighboring cells, suggesting they had become uncoupled from the pan-glial network (Bedner et al., 2015). These results were replicated in vivo using the 3-month, post-intrahippocampal kainate (KA) injection mouse model of epileptogenesis (Bedner et al. 2015).

In the same study, Cx43-eYFP labeled astrocyte uncoupling was induced by a single injection of KA and persisted for at least 6 months and preceded neuronal apoptosis (Bedner et al., 2015). Astrocyte uncoupling was recapitulated in organotypic slice and in vivo by application of tumor necrosis factor α (TNFα), and interleukin (IL)-1β (Bedner et al., 2015), which are elevated in serum and cerebrospinal fluid of epileptic patients (Vezzani, French, Bartfai, & Baram, 2011). Interestingly, another study using a 7 day, post-intrahippocampal KA injection model showed an increase in dye coupling of hippocampal reactive astrocytes and increased expression of Cx43 (Takahashi, Vargas, & Wilcox, 2010), indicating time-dependent changes in coupling of astrocyte GJs after seizure.

Seizure activity could also arise as a result of loss of oligodendrocyte Cxs and reduction of Cx43 expression as observed in immune-mediated mouse models of MS (Brand-Schieber et al., 2005; Markoullis et al., 2012a). Furthermore, demyelinating MS lesions show evidence of GJ dysregulation, where inflamed white matter tracts and adjacent normal appearing tissue exhibit decreased Cx43 expression and oligodendrocyte uncoupling from reactive astrocytes (Markoullis et al., 2012b; Markoullis et al., 2014). In addition, MS patients are three to six times more likely to develop epilepsy than the overall population (Poser & Brinar, 2003). While the mechanism that predisposes a subset of these patients to seizures remains unclear, a recent study identified altered expression of the astrocytic water channel implicated in epileptogenesis, aquaporin (AQP)4 (Binder, Nagelhus, & Ottersen, 2012), and extensive infiltration of microglia/macrophages into the CA1 of mice that experienced seizures following chronic cuprizone (CPZ)-induced demyelination (Lapato et al., 2017). However, although Cx47 redistribution has been noted in CPZ demyelination (Parenti et al., 2010), whether GJ dysfunction is etiologic to seizure development in this model is still unknown.

Transcriptome analysis of Cx and Panx expression following seizure induction using a Co^{2+} model of seizure demonstrated significant upregulation of Panx1, Panx2, and Cx43 mRNAs and post-translational phosphorylation of Cx43 (Mylvaganam et al., 2010), which is associated with increased GJ open probability and seizure (Zador et al., 2008). Protein and mRNA changes were independent of Co^{2+} administration and required epileptiform discharges, since Co^{2+} application in the presence of tetrodotoxin, a voltage gated Na^+ channel blocker, ablated transcriptome changes (Mylvaganam et al., 2010).

Intracellular Ca^{2+} slow wave propagation and HC mediated purinergic signaling amongst GJ coupled astrocytes also influences seizure development (Kekesi, Ioja, Szabo, Kardos, & Heja, 2015; Torres et al., 2012). In the low Mg^{2+} model of seizure, slow Ca^{2+} waves become synchronized across nearby astrocytes, which become paired to synchronized neurons during seizure-like events (Kekesi et al., 2015). This aberrant neuron-glial synchrony is GJ dependent, as CBX and anti-Cx43 antibodies reduce epileptiform activity-induced Ca^{2+} slow wave coordination, increased interictal periods, and completely ablated seizures in a number of trials (Kekesi et al. 2015). However, this study does not distinguish between Cx43 GJs and HCs, so whether the observed anti-epileptic effects of these molecules is due to inhibited Ca^{2+} second messenger exchange across coupled astrocytes or impaired gliotransmitter release remains to be demonstrated.

TABLE 2 Genetic and pharmacologic manipulations to examine connexin & pannexin function

Manipulation		Mechanism	Outcomes	References
Cx30	KO	genetic ablation	↓ CA1 fEPSPs after Schaffer collateral stimulation, ↓ LTP; ↓ astrocyte/astrocyte dye coupling	Abudara et al., 2015, Pannasch et al., 2014
Cx31.1	KO	genetic ablation	↓ novel object recognition, ↑ novel environment exploration	Dere et al., 2008
Cx36	KO	genetic ablation	absent interneuron voltage coupling, ↓ IPSP amplitude; ↓ novel object recognition, ↓ short-term memory by Y-maze, ↓ motor learning by Rotarod; ↑ seizures w/ PTZ induction; ↓ CA1 fEPSPs after Schaffer collateral stimulation	Apostolides, 2013, Deans et al., 2001 Frisch et al., 2005, Jacobson et al., 2010, Wang and Belousov, 2011
Cx43	Astrocyte KO	GFAP:Cre $Cx43^{fl/fl}$	↓ dye coupling, hypertrophic astrocytes, ↓ vesicular glutamate release	Chever et al., 2014b
	gap26/27	EC loop mimetic peptide; HC inhibitor	↓ Ethidium bromide uptake, ↓ excitatory post synaptic current amplitude, ↓ ATP release; ↑ fEPSP amplitude after LPS	Abudara et al., 2015, Chever et al., 2014a
	TAT-Cx43L2	tail mimetic peptide; HC inhibitor	↓ fear conditioning memory with intra-amygdala injection	Stehberg et al., 2012
	anti-Cx43 antibodies	HC blockade	↓ Ca2 + slow wave synchronization, ↓ seizure number & frequency	Kekesi et al., 2015
Cx30 + Cx43	Cx30 + astrocyte Cx43 DKO	Cx30—KO + GFAP:Cre $Cx43^{fl/fl}$	↑ astrocyte intracellular Ca^{2+} after LPS, ↓ dye uptake after LPS; ↓ Ca^{2+} slow waves	Abudara et al., 2015, Torres et al., 2012
Panx1	KO	genetic ablation	absent LTD; ↑ CA1 fEPSPs after Schaffer collateral stimulation, ↑ LTP, ↓ novel object recognition, ↓ spatial memory recall	Ardiles et al., 2014, Prochnow et al., 2012
	^{10}panx1	EC loop mimetic peptide; Panx1 HC inhibitor	After chronic restraint stress: ↓ ethidium bromide uptake, ↓ glutamate release, ↓ ATP release	Orellana et al., 2015

Summary of genetic and pharmacologic manipulations used to identify the function of specific Cx and Panx isoforms. Key results are indicated beside manipulation. Note that selective inhibitors are only available for HCs, but many will also block GJs over time (Samoilova et al., 2008).

4.3 | Microglia, hemichannels, and inflammation

Microglia express Cx32 and Cx36 under homeostatic conditions, but because they do not form GJs (Wasseff & Scherer, 2014), their physiologic role remains unclear in these cells (Dobrenis et al., 2005; Maezawa & Jin, 2010). Research investigating microglial Cx and Panx HC function often occurs in the context of disease, where they have been implicated in excitotoxic glutamatergic signaling (Abudara et al., 2015; Eugenin et al., 2001; Mandolesi et al., 2013; Takaki et al., 2012; Takeuchi et al., 2006). Using organotypic slices, Adubara et al. (2015) demonstrated that LPS application augments astrocyte Cx43 HC opening, resulting in enhanced synaptic glutamate. The authors identified TLR4 activation by LPS, which triggers secretion of inflammatory mediators such as TNFα, inducible nitric oxide synthase, and IL-1β (Akira & Takeda, 2004), was required for HC dependent glutamate release. Interestingly, fEPSP amplitude was suppressed in LPS treated slices despite increased synaptic glutamate, but was restored by blockade of Cx43 by gap26 or TNFα/IL-1β inhibitors IL-1RA and sTNF-αR1 (Abudara et al., 2015). While decreased glutamatergic transmission and its recovery following IL-1RA administration may partially be explained by IL-1β's dampening effect on post-synaptic glutamate sensitivity (Mandolesi et al., 2013), this study illustrates how microglia modify neuronal activity in pathology.

Microglial Panx1 and Cx HCs also release purinergic-signaling molecules under inflammatory conditions. In a report by Orellana et al. (2015), restraint stress increased hippocampal microglial, astrocyte, and neuronal ethidium bromide uptake, which was abrogated by application of the Panx1 HC blocking peptide ^{10}panx1 but not Cx43 HC blockers (Orellana et al., 2015). These changes in dye uptake were abolished by application of ionotropic purinergic receptor $P2X_7$ and NMDAR antagonists, but not metabotropic purinergic $P2Y_1$ receptor blockade, and were accompanied by increased extracellular glutamate and ATP (Orellana et al., 2015). This suggests that ionotropic purinergic signaling downstream of Panx1-mediated gliotransmitter release may be a vehicle of microglial HC dysfunction during inflammatory conditions, such as those generated by chronic stress (Walker, Nilsson, & Jones, 2013).

In addition to TLR4 ligands, microglial HCs open in response to inflammatory cytokines. Application of LPS or TNFα to primary microglial cultures results in upregulation of glutaminase and glutamate release (Takeuchi et al., 2006). Furthermore, supernatant from glutamate-releasing microglial cultures induces downregulation of the astrocyte glutamate aspartate transporter, GLAST (Takaki et al., 2012). Together, these results indicate that microglial HCs alter extracellular glutamate concentration and astrocyte-dependent glutamate buffering in pathology. However, because in vitro models often lack the complex regulatory environment of the CNS, in vivo studies are required to validate these findings.

4.4 | Purinergic signaling in epilepsy

Like Cx and Panx HCs, the $P2X_7$ ionotropic purinergic receptor is a relatively large, ATP-gated transmembrane channel permeable to molecules 800 kDa or smaller, including low to medium weight cations such as K^+ and Ca^{2+} (Sperlagh & Illes, 2014) and cytokines (i.e., IL-1β; Monif et al., 2016). Activation of NMDARs results in a burst of ATP release by synaptic and astrocyte-derived Panx1 and Cx43 HCs, respectively, amplifying depolarization (Kim & Kang, 2011; Prochnow et al., 2012; Thompson et al., 2008). Activity-dependent ATP signaling is facilitated by Panx1 coupling to $P2X_7$ in membrane complexes (Bravo, Maturana, Pelissier, Hernandez, & Constandil, 2015; Pan, Chou, & Sun, 2015), thereby ensuring that NMDAR activation is augmented by the ensuing purinergic drive.

Dysregulation of this interaction has been implicated in the pathogenesis of seizure, but evidence is highly model dependent. Increased Panx1 protein expression was detected in lobectomy specimens from epileptic patients, while Panx2 was decreased (Jiang et al., 2013), indicating that purinergic signaling dysregulation may occur in these patients. Organotypic slice studies support this finding; in the low Mg^{2+} model of seizure, blockade of Panx1 by CBX and NMDAR antagonism attenuated epileptiform burst frequency and amplitude (Thompson et al., 2008). This suggests that feed-forward augmentation of NMDAR currents can initiate runaway seizure like activity. However, while the putative mechanism of epileptiform bursting is NMDAR activation in this model, synchronization of principle neurons by GABAergic interneuron populations may have contributed to neuronal hyper synchronization through low Mg^{2+} sensitive Cx36 GJs (Palacios-Prado et al., 2013). Thus, selective inhibition of Panx1 HCs may be required to untangle specific contribution of Panx1 to seizures in this model.

Alternatively, $P2X_7$-KO mice display augmented seizure susceptibility when challenged with the muscarinic agonist pilocarpine that is not attributable to changes in glutamatergic or GABAergic transmission (Kim & Kang, 2011). $P2X_7$ or Panx1 blockade in wild type mice reproduced the decreased seizure threshold observed in knockout animals (Kim & Kang, 2011). Physiologic seizure resistance was restored in $P2X_7$-KO mice by inhibition of intracellular Ca^{2+} release by the ryanodine receptor antagonist dantrolene (Kim & Kang, 2011). In contrast, $P2X_7$ antagonism by JNJ-42253432 resulted in a less severe seizure profile in the kainate model of epilepsy, with decreased seizure severity, but not frequency, in Sprague-Dawley rats (Amhaoul et al., 2016). These studies suggest that purinergic signaling in epilepsy may be complicated by the choice of model and potentially species examined. Further research is required to fully illuminate how Panx1 function in seizures relates to the complex neuropathology observed in the epileptic CNS.

5 | CONCLUDING REMARKS

Evidence increasingly indicates that Cx and Panx GJs and HCs are critical to maintaining physiologic neuronal excitability, resistance to seizures, and may be central to hippocampus and amygdala based learning (Apostolides & Trussell, 2013; Battefeld et al., 2016; Prochnow et al., 2012; Stehberg et al., 2012). In GABAergic interneurons, Cx36 GJs allow for rapid and expansive inhibition via electrically coupled inhibitory syncytia that are calibrated to depolarizing activity (Apostolides & Trussell, 2013; Deans et al., 2001; Turecek et al., 2014). In glia, GJs link participants in the pan-glial network, which supports physiologic resting membrane potential through spatial buffering of K^+ and constrain of epileptiform bursting (Battefeld et al., 2016; Bedner et al., 2015; Kamasawa et al., 2005; Kofuji & Newman, 2004; Magnotti et al., 2011; Wasseff & Scherer, 2011). Purinergic and glutamatergic gliotransmission, which continues to accrue attention for its role in modifying neuronal activity, relies heavily on autocrine and paracrine signaling by Cx and Panx HCs (Kim & Kang, 2011; Prochnow et al., 2012; Thompson et al., 2008).

Inflammation-induced dysregulation of Cx GJs not only impacts glutamatergic neurotransmission (Abudara et al., 2015; Mandolesi et al., 2013; Schwaller et al., 2004; Takaki et al., 2012; Takeuchi et al., 2006; Toyoda et al., 2015), but also underlies disorders of excitation, such as epilepsy (Bedner et al., 2015). However, the role of Cx and Panx HCs in purinergic signaling and excitotoxicity remains conflicted, exhibiting a model-dependent effect on the result of ionotropic purinergic receptor activation (Amhaoul et al., 2016; Kim & Kang, 2011; Thompson et al., 2008). Furthermore, the contribution of microglial Cxs and Panxs to both homeostatic and disease processes remains largely unknown. Apart from a handful of studies (Abudara et al., 2015; Orellana et al., 2015), existing evidence regarding microglial HC and GJ function in pathology is restricted to in vitro work and focuses on TLR4 signaling (Takaki et al., 2012; Takeuchi et al., 2006), which may produce artifacts not seen in vivo (Wasseff & Scherer, 2014).

An important limitation to many studies of individual Cx and Panx function is the lack of selective and specific GJ and HC inhibitors. Mimetic peptides and antibodies that inhibit Panx1 (^{10}panx1) and Cx43 (gap26, gap27, and TAT-Cx43L2) HCs with relatively high selectivity are now available (Table 2). Importantly, many of these peptides also inhibit GJs, making blockade of HCs or GJs alone difficult in situ (Giaume et al., 2013). Additionally, peptides targeting other Cx and Panx isoforms are not widely available, making their study more arduous and reliant on knockout models. However, as the tools available for their study become more varied and accessible, the study of Cxs and Panxs is likely to more easily uncover the homeostatic and pathological properties of HCs and GJs.

CONFLICT OF INTEREST

The authors have no conflicts of interest, including any financial, personal, or other relationships with people or organizations that could influence the present article.

AUTHOR CONTRIBUTIONS

Conducted the literature review, prepared the manuscript, and composed figures: A.S.L. and S.K.T-W.

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How to cite this article: Lapato AS, Tiwari-Woodruff SK. Connexins and pannexins: At the junction of neuro-glial homeostasis & disease. *J Neuro Res*. 2017;00:1–14. https://doi.org/10.1002/jnr.24088