Hemichannels are large pore ion channels that in the traditional view are formed when half a gap connexin junction opens to the extracellular space. It is now evident that other ion channel families, including the newly discovered pannexin family can form channels with all the nascent properties of hemichannels. This suggests that hemichannels should now be defined to include members of non-connexin families. Several connexin, and two pannexins are expressed in neurons and astrocytes where they may function in release of ATP and glutamate. Additionally, pannexin-1 appears to play a role in neuronal death. Hemichannels form a novel and unique class of ion channels that likely have diverse physiological and pathophysiological roles in the nervous system.

**Introduction**

Gap junctions are intercellular connections that allow the exchange of signalling molecules, such as ions and second messengers that are smaller than ~1 kDa. Molecular exchange between two cells was first demonstrated through the pores created by connexin (Cx) channels which are the protein components of gap junctions in vertebrates. Each cell contributes half of the Cx gap junction channel, and these “hemichannels” are assembled in the Golgi complex prior to insertion into the plasma membrane. Insertion occurs extra-junctionally and Cx hemichannels then dock with a corresponding Cx hemichannel in the membrane of the adjacent cell. Several hundred Cx channels can then aggregate into a gap junction plaque and are therefore important for intercellular communication by acting as molecular exchange sites and electrical synapses.

In the traditional view, unapposed connexin hemichannels were kept closed in the plasma membrane until it docked with its partner on the adjacent cell. The tight regulation of the closed state of these hemichannels was thought vital for cell survival because the large pores of the unapposed channels could rapidly deplete ionic gradients and allow the eflux of small molecules. Indeed there is excellent evidence indicating that most unapposed connexin hemichannels remain in the closed state. This is due to binding of calcium to an extracellular domain, phosphorylation on intracellular serine/threonine residues, and a voltage-dependence that is not favorable to hemichannel opening near resting membrane potentials. However, recent evidence suggests that hemichannels can be opened in a regulated manner during physiological events, as well as unregulated (or irreversible) opening during pathological situations but the contributions of Cx hemichannels to physiological events remain contentious.

The field of gap junctional communication was dramatically altered with the recent cloning of pannexins based upon sequence identity to the innexins, the insect gap junction protein. Pannexins have a predicted secondary structure that is similar to the connexins, although sequence homology between the two protein families is low. It is well accepted that connexins form gap junctions in mammals and the evidence that they also form hemichannels remains contentious. In contrast, the opposite is true for the pannexins, whereas there is now ample evidence describing the hemichannel properties of these proteins, their role as gap junctions is far less clear. This review will describe the biophysical properties, physiological and pathophysiological roles of hemichannels in astrocytes and neurons with emphasis on the connexin and pannexin families.

**Hemichannel Defined**

As the debate regarding patent Cx hemichannels was developing, discoveries of structurally and functionally analogous channels support a re-definition of the concept of the “hemichannel”. Where hemichannel was traditionally a literal description for ‘half a gap junction formed by unapposed Cx proteins,’ this concept should now be revised to incorporate new families of large pore ion channels with similar properties. We propose that the hemichannel be more broadly defined as “any channel with a pore large enough to conduct ions and small molecules (~1 kDa).” This definition does not preclude the possibility that opening of the hemichannel can be physiological or pathological, but implies that hemichannels function in physiological processes and are therefore actively and specifically regulated. Although the concept of half-a-channel is a misnomer, it has received significant use in the literature that warrants its continual employment to describe the concept of large pore channels. Although connexins are expressed in most cell types, this review is focussed on hemichannels of neurons and astrocytes to keep the list manageable and because of the critical roles these channels likely play in the central nervous system.

**Connexin Hemichannels**

Several connexins of the ~20 member family (20 in mouse and 21 in human genomes) are expressed in neurons. Each channel has distinct
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Biophysical properties and putative physiological roles. In general, Cx hemichannels are inhibited by carbenoxolone (Cbx) and its derivatives (i.e., 18α-glycyrrhetinic acid), lanthanides (i.e., La3+ and Gd3+), and have differing sensitivity to anion channel blockers like DIDS and niflumic acid. These properties have been extensively reviewed.5

Connexin36. Cx36 is the major gap junction forming protein of GABAergic interneurons in the neocortex and hippocampus (Fig. 1) as well as neurons in the olivary nucleus and cerebellum.15,16

This channel is highly expressed in the retina, with localization in all amacrine cells (the interneurons of the retina),17 cone photoreceptors, and OFF cone bipolar cells.18,19 It is thought that Cx36 gap junctions play critical roles in coordinating network properties such as spike synchronization15 and electrical coupling of hippocampal interneurons.20 amacrine cells,21 and striatal medium spiny neurons.22 The importance of Cx36 as gap junctions of interneurons is well established and has been reviewed elsewhere.23-25

The presence of this gap junction forming protein in interneurons (and pyramidal cells during development) raises the question of whether Cx36 can function as a hemichannel.

In expression systems (PC12 or N2A-neuroblastoma) and cultured hippocampal neurons, Cx36 gap junctions have a small conductance (10-15 pS) and are weakly voltage-sensitive with a half-inactivation voltage of ± 75 mV 26 (Table 1). It would be expected that if Cx36 functioned as a hemichannel the single-channel conductance would be 20-30 pS (i.e., twice the conductance of two channels connected in series), though this has yet to be experimentally established. However, the related Cx35 protein of zebrafish do appear to form functional hemichannels with a conductance of 24 pS (at 0 mV and 0 mM extracellular Ca2+) and are strongly regulated by voltage.8

In oocytes injected with Cx36 mRNA, hemichannel activity was not observed—even in the absence of extracellular Ca2+.27 suggesting that Cx36 does not form patent hemichannels. This notion is contrasted by a recent study using cultured cortical neurons (from E15/16 rats) that suggested that very high K+ (100 mM) or KCN caused spreading depression and opened Cx36 hemichannels to release ATP and induce ischemic tolerance (Fig. 1); Cx36 siRNA treated neurons showed a modest (~25%) reduction in cell death.

![Figure 1. A model of the hemichannels in neurons and astrocytes. A typical pyramidal cell layer is illustrated, with regions in the circles expanded. Although connexin (Cx) based hemichannels have been proposed, more evidence is available to support a role for pannexin based hemichannels in neurons. The opposite appears to be true for astrocytes however, where Cx43 hemichannels seem to predominate. The putative role of the hemichannels are indicated by the boxed text and known mechanisms of activation illustrated with arrows (+).](image-url)
induced by combined KCl/KCN. This interesting study requires confirmation by other techniques, such as electrophysiological demonstration of Cx36 hemichannels and determination if these hemichannels are in interneurons or pyramidal neurons in the cultures. Interneurons express Cx36 into the adult but Cx36 mediated gap junctions between pyramidal neurons of the neocortex are only observed until postnatal day 12. In summary, the high levels of Cx36 expression in interneurons suggest that it may operate as a hemichannel under extreme patho-physiological conditions.

**Connexin45.** Cx45 is a gap junction forming protein of basket and stellate cells. It also appears to be developmentally expressed (up to postnatal day 153) in NeuN positive neurons of the CA3 region of the hippocampus. As a gap junction, Cx45 could form axo-axonal gap junctions in the hippocampus during this period (Fig. 1), but the functional role of Cx45 gap junctions is not yet known. The biophysical properties of the Cx45 hemichannel have been extensively characterized in expression systems. This channel has a unitary conductance of 57 pS (at 0 mV) and its conductance, has a unitary conductance of 57 pS (at 0 mV) and its conductance, was measurable at resting membrane potentials suggesting that the channel is very low (0.06–0.11). Thus, the hemichannel forming ability of Cx45 has to date only been observed during removal of extracellular Ca²⁺. Interestingly, extracellular Ca²⁺ can be depleted during pathological situations such as ischemia and epilepsy. Implicating the putative activation of axonal Cx45 and other Cx hemichannels. However, these conjectures require experimental confirmation.

**Connexin43.** Cx43 is the principle gap junction forming protein of astrocytes. As a gap junction, Cx43 functions in diverse ways, ranging from P2Y receptor-mediated calcium wave propagation to facilitating the spread of ischemic damage and the opposite role of protecting from ischemic injury or inducing preconditioning. There are extensive reviews on the role of Cx43 as a gap junction forming protein in many cell types (to date 148 on PubMed), so this paper will focus on its role as hemichannel in astrocytes. In a few cases, insight in to the regulation of Cx43 will be gained from expression studies or experiments on cardiac myocytes, where it is also highly expressed.

The biophysical properties of Cx43 hemichannels (native or with EGFP tagged to the C-terminus), studied by transfection of HeLa cells (in Ca²⁺-free and depolarized conditions), had a conductance of ~220 pS, with and ~75 pS substrate and a junctional conductance of ~110 pS in paired cells (Table 1). The channel remained closed (electrophysiologically) unless the membrane potential was depolarized beyond about 60 mV, though uptake of ethidium bromide was measurable at resting membrane potentials suggesting that brief openings may occur. Removal of extracellular Ca²⁺ is also reported to open Cx43 hemichannels in Novikoff hepatoma cells and Xenopus oocytes. It is important to note that the majority of studies investigating the electrophysiology or dye flux of Cx43 hemichannels have been performed in nominally zero Ca²⁺ or depolarized conditions to facilitate hemichannel opening. This serves only to underscore the controversy surrounding the proposed role of Cx43 hemichannels in native astrocytes.

It has been suggested that Cx43 hemichannels mediated direct release of glutamatergic transmitter (i.e., glutamate and ATP) from astrocytes and C6 glioma (Fig. 1). Ye et al. suggested that astrocytes release glutamate during exposure to divalent ion-free solutions is independent of exocytosis, reversal of the glutamate transporter and large pore anion channels/purinergic receptors. Additionally, several reports demonstrate that ATP release from C6 gliomas is enhanced by Cx43 expression and zero Ca²⁺ solutions, and inhibited by carbenoxolone and other gap junction/hemichannel blockers. However, recent reports question the role of Cx43 hemichannels in ATP release. It has been suggested that ATP release from astrocytes is mediated by the P2X7 receptor and not by the Cx43 hemichannel because release was absent in P2X7⁻/⁻ spinal cord astrocytes but not those from Cx43⁻/⁻ mice. These reports demonstrate the controversy that

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**Table 1 Biophysical properties of putative neuronal and astrocytic hemichannels**

| Hemichannel | Conductance (pS) | Voltage dependence (mV) | Presence of subconductance states (number) | Cell type | Hemichannel activation mechanism |
|-------------|-----------------|-------------------------|-------------------------------------------|-----------|---------------------------------|
| Cx30        | 179 ± 27        | ±27                     | One 48 pS                                 | Astrocytes | n.d.                            |
| Cx36        | 20–30 ± 75      | ±75                     | n.d.                                      | Aamacrince cells | 100 mM K⁺ Cyanide |
| Cx43        | 220 ~65         | One 75 pS               | Astrocytes                                | Dephosphorylation |
| Cx45        | 57–62 ±11       | ±11                     | Basket cells Stellate cells NeuN positive CA3 neurons | Extracellular Ca²⁺ depletion |
| Px1         | 550 ±11         | Four (25, 140, 165 490 pS) | Pyramidal neurons Interneurons Astocytes* | Intracellular Ca²⁺ Ischemia |
| Px2         | n.d.            | n.d.                    | Pyramidal neurons Astrocytes              | n.d.       |

*Requires in vivo (or brain slice) confirmation. n.d. not determined.
surrounds the role of Cx43 as a hemichannel and route for release of gliotransmitters from astrocytes.

How can these apparently dichotomous data be reconciled? Several possibilities exist including differential regulation of splice variants of Cx43 (of which there are reported to be 2 mRNA species in vascular smooth muscle\(^5\)), regulation by posttranslational modifications, or binding partners. The potential variable properties of Cx43 splice variants have not, to the best of our knowledge, been determined and could therefore account for some of the discrepancies between expression systems and native cells. Cx43 opening in gap junctions are strongly regulated by phosphorylation, and several kinases are involved including PKC, tyrosine kinases and src.\(^5,45,46\) In general, Cx43 (and other connexins) are opened by dephosphorylation during oxidative stress.\(^11,12\) It is not known how these posttranslational modifications interact or predominate in different cell types, or how they affect the propensity for hemichannel formation versus gap junction assembly. Finally, Cx43 (in junctions) is thought to be a hub (or nexus) of protein binding,\(^47,48\) such as the binding of c-src to Cx43 is regulated by the phosphorylation state of the channel.\(^49\) Furthermore, the disruption of debrin binding to Cx43 by siRNA (against debrin) in astrocytes dramatically reduced intercellular coupling.\(^50\) It will be of great interest to determine if these mechanisms that decrease gap junction formation result in a corresponding increase in hemichannel function.

**Connexin30.** Cx30 is expressed in astrocytes\(^51\) and the cochlea\(^52\) where it forms gap junctions. Mutations in Cx30 are associated with deafness.\(^53\) In HeLa cells, expressed Cx30 gap junctions had properties expected of members of this family of proteins. There were two conductance states (179 and 48 pS) and a strong dependence upon junctional voltage with a half-voltage of inactivation of ±27 mV\(^7\) (Table 1). Cx30 hemichannels have also been studied in the oocyte expression system and wild type channels did not form functional hemichannels at depolarized potentials; however the effect of removing extracellular divalent ions on channel activation was not tested.\(^54\) Interestingly, two mutations in Cx30 (A88V and G11R) formed functional, ATP permeable hemichannels.\(^54\) To date, there is not strong evidence to support a role for Cx30 based hemichannels in astrocytes. It is however, important to determine if Cx30 hemichannel function is altered in the Cx43 knockout mouse, which could explain some of the controversial data on the role of Cx43 as a hemichannel (see above).

In summary, the evidence for Cx-based hemichannels in neurons is weak, and is controversial in astrocytes. Where neurons do express some connexins (particularly interneurons) the best available evidence indicates that these function primarily in gap junctions, though a hemichannel role cannot be ruled out and requires an increased understanding of how these channels are gated. While it is clear that Cx43 hemichannels open in astrocytes when concentrations of extracellular divalent cations are quite low, it is less clear when this occurs in vivo. Furthermore, alternative explanations still exist that could explain the hemichannel behaviour seen in astrocytes, including the involvement of other large-pore channels (i.e., P2X7).

**Pannexin Hemichannels**

A three member family of novel gap-junction channel-like proteins has been identified based upon sequence homology to the invertebrate innexin family.\(^13,55\) This unique group, the pannexins (Px) appear to function in neurons and other tissues as a hemichannel. Px1 and Px2 are expressed in the brain, whereas Px3 appears exclusive to skin and osteoblasts.\(^13,55\) Within the brain, Px1 and Px2 are highly expressed in the hippocampus, neocortex, cerebellum, thalamus and hypothalamus.\(^56\) At the cellular level, Px1 has been reported in hippocampal and neocortical pyramidal neurons, parvalbumin positive interneurons, motoneurons and purkinje cells.\(^21,23\) Expression of Px1 and Px2 has also been reported in horizontal cells, retinal ganglion cells and amacrine cells of the retina.\(^57\) Interestingly, Px1 has been demonstrated to colocalize with postsynaptic density protein, PSD95, suggesting that this hemichannel may have a role in synaptic function.\(^58\) Px1 expression has been reported in cultured astrocytes, oligodendrocytes and neurons,\(^59\) but is absent in C6 glioma cells.\(^60\) It has not been determined to date if Px1 is expressed in astrocytes in vivo or in brain slices. However in situ hybridization signals in vivo show high levels of mRNA expression in neurons but little expression in astrocytes.\(^61\) Px2 is reported to be expressed in neurons but not astrocytes; however ischemia/reperfusion increased Px2 levels in astrocytes.\(^62\) The expression patters of Px1 and Px2 overlap in neurons, but appear to be inversely related. When Px1 is high near birth Px2 is low and vice versa, but both channels are expressed at all ages tested.\(^56,61\)

Functional expression in *Xenopus* oocytes revealed that Px1 formed functional hemichannels and gap junctions, whereas Px2 did not form channels when expressed alone, but modified the properties of Px1 channels during coexpression; Px1 junctional conductance between paired oocytes (~18 μS) was reduced by about half during coexpression with Px2.\(^14\) At the single-channel level, Px1 hemichannels have a very large conductance, -550 pS in symmetrical KCl and 475 pS in Kgluconate;\(^63,64\) this is at least 200 pS larger than any Cx based hemichannel conductance observed to date (Table 1). The hemichannels have multiple sub-conductance states and flux large molecules such as ATP.\(^63,64\) Px1 appears to have little voltage dependence compared to the Cx counterparts.\(^14\) In oocytes and acutely isolated hippocampal neurons, the current-voltage (I–V) relationship is linear over the range ±80 mV.\(^26,27,29,30\) In contrast, Px1 in macrophages and taste buds, or those expressed in HEK 293 cells with the P2X7 receptor display an outwardly rectifying I–V.\(^65,66\) It is unclear if these differences represent splice variants of the channel, the influences of posttranslational modifications or binding partners (i.e., P2X7), or different mechanisms of activation that modify the biophysical properties of the hemichannel. In support of the latter concept, we observed that during ischemia the activation of Px1 proceeds as an apparent loss of rectification, leading to time dependent increases in inward currents carried by the hemichannel (Thompson RJ and MacVicar BA, unpublished).

Px1 hemichannels are reported to have several physiological and patho-physiological functions. In non-neuronal cells, Px1 may mediate ATP release. In taste cells, Px1 opening by a voltage-dependent but Ca\(^2+\)-independent mechanism suggests that release occurs independently of exocytosis,\(^66\) and that the hemichannel itself may be the conduit for ATP efflux.\(^63\) In erythrocytes, P2Y receptor stimulation increases intracellular Ca\(^2+\) and this may be directly coupled to ATP efflux through Px1. They studies raise the intriguing possibility that ATP release from neurons may also involve Px1.
A role for Px1 hemichannels in cell death has been suggested. This occurs, so far, under two different death-inducing paradigms. Prolonged P2X7 receptor activation by ATP in Px1/P2X7 expressing astrocytoma (1321N1 cells) activated an ionic current that was partially blocked by carbeneoxalone (a Px1 blocker).67 In macrophages, P2X7 receptor stimulation with 3 mM ATP induced cell death and activated a dye uptake pathway that was sensitive to macrophages, P2X7 receptor stimulation with 3 mM ATP induced cell death and becomes irreversible after about 10 minutes.69,70 These depolarization, which typically happens within 1–2 minutes of ischemia and becomes irreversible after about 10 minutes,69,70 These data suggest that Px1 hemichannel opening is not directly responsible for the anoxic depolarization, but may be a consequence of it. An alternative explanation is that Px1 opening during ischemia occurs independently of the anoxic depolarization by a parallel pathway.

In summary, there is ample evidence that Px1 functions as a hemichannel in neurons, and less that it functions as a gap junction (reviewed in refs. 59 and 60). How Px1 hemichannels are regulated during physiological and pathological conditions is not yet known, though intracellular Ca2+ or nitric oxide may be involved.64,71 It is of great importance to understand how this channel is regulated and what its roles in neuronal (and possibly astrocytic) physiology are.

Conclusions

Both astrocytes and neurons express the proteins necessary for formation of hemichannels. These connexin and pannexin channels are rapidly becoming highly appreciated members of the central nervous system's extensive repertoire of ion channels. The majority of cell types in the central nervous system (including microglia and components of the vasculature that were not discussed here) have the potential to express hemichannel activity. It will be of great importance to determine the roles of these large pore channels in the physiology and pathophysiology of the nervous system. Furthermore, it is interesting to speculate that hemichannels from one cell type (i.e., neurons) could release signalling molecules (i.e., ATP) that affect hemichannels on nearby cells (i.e., astrocytes or other neurons).

It is noteworthy that the ionic conductance of hemichannels (especially members of the Cx family) is not necessarily large, despite the observation that the pores are permeable to large molecules. This implies the presence of interesting gating mechanisms or features of the conduction pathway (energy barriers?) that differentially regulate ionic and metabolite fluxes. This combination of differential conductance and small molecule permeation (i.e., fluorescent dyes) between hemichannel types is however a very powerful tool for identifying the involvement of specific hemichannels in biological processes, of which the list continues to grow.

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