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Exciting and not so exciting roles of pannexins

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Abstract

It is the current view that purinergic signaling regulates many physiological functions. Pannexin1 (Pannx1), a member of the gap junction family of proteins is an ATP releasing channel that plays important physio-pathological roles in various tissues, including the CNS. Upon binding to purinergic receptors expressed in neural cells, ATP triggers cellular responses including increased cell proliferation, cell morphology changes, release of cytokines, and regulation of neuronal excitability via release of glutamate, GABA and ATP itself. Under pathological conditions such as ischemia, trauma, inflammation, epilepsy, extracellular ATP concentrations increases drastically but the consequences of this surge is still difficult to characterize due to its rapid metabolism in ADP and adenosine, the latter having inhibitory action on neuronal activity. For seizures, for instance, the excitatory effect of ATP on neuronal activity is mainly related to its action of P2X receptors, while the inhibitory effects are related to activation of P1, adenosine receptors. Here we provide a mini review on the properties of pannexins with a main focus on Pannx1 and its involvement in seizure activity. Although there are only few studies implicating Pannx1 in seizures, they are illustrative of the dual role that Pannx1 has on neuronal excitability.

Keywords

gap junctions; seizures; purinergic signaling; P2X receptors; Pannx1; epilepsy

Pannexin Genes and Splice Variants

In 2000, while searching vertebrate data bases for homologues to innexins, Yuri Panchin found three cDNAs encoding proteins which were termed “pannexins” [1–3]. Due to their significant but low (~20%) homology to the innexins, the gap junction proteins of invertebrates, and despite their lack of sequence homology with the chordates gap junctions,

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the connexins, the three pannexin (Pannx 1, 2, and 3) were classified as gap junction proteins [1–3].

The three pannexins differ in terms of gene structure and protein sizes. The Pannx1 gene is composed of 5 exons and 4 introns, while the pannexin 2 and 3 genes are each composed of 4 exons [2]. The chromosome locations of pannexin1, 2, and 3 genes in human, mouse and rat are shown in Table 1. Of the three pannexins, Pannx2 is the largest with 633 amino acids, in contrast with Pannx1 (426 amino acids) and Pannx3 (392 amino acids). Several splice variants of pannexins have been described which result in proteins with different sizes (Table 1). For the human *PANX1*, three variants have been reported, two of them resulting from alternatively splicing of exon 5 [2] which generate human Pannx1 proteins with different sizes (hPannx1a: 422; hPannx1b: 426), and the other variant due to the deletion of a single amino acid at position 378 (hPannx1bv: 425; [4]). The rat Pannx1 variants (rPannx1 a, c, d) reported in pituitary cells and male reproductive tract result from alternative splicing in exons 2 and 4 [5, 6]; the shorter rPannx1 isoforms (c and d) result respectively in proteins lacking sequence spanning the second transmembrane domain to part of the intracellular loop (variant c: F108 – G180), and the other variant d lacking the V307 – C426 sequence of the C-terminus [5]. Of the four human *PANX2* splice variants, one was found to be the product of an alternative start codon reducing the length of isoform 1 (633 amino acids) to 509 amino acids in isoform 2 [2]. The mouse Pannx2 gene encoding a 607 amino acid long protein was reported to lack an alternative spliced exon unlike that in the human gene [2]. Other variations reported in pannexin 2 protein lengths (633, 677) could be due to discrepancies in cloning procedures or from predictions based on genomic sequences. There are no reports on *PANX3* splice variants in humans and mice [2].¹

Pannexin Structure and Post-Translational Modifications

Structurally, pannexins bear membrane topology similar to connexin, consisting of 4 transmembrane domains, two extracellular loops, a cytoplasmic loop, and cytosolic N- and C-termini (Fig. 1). Differently from connexins but similarly to innexins, pannexins have 4 conserved cysteines, two in each extracellular loop. In terms of single membrane oligomers (pannexons), Pannx1 has been shown to form hexameric structures like connexins, while Pannx2 oligomerize as octamers [7], as does the innexin-6 (INX6) of *C. elegans* [8, 9]. For Pannx3, however, the stoichiometry has not yet been determined.

Whether or not pannexins form heteromeric channels, as certain connexins do (see [10]) remains a matter of debate. The first reports by Bruzzone et al. [11, 12] suggested that Pannx1 and Pannx2 could form heteromeric channels. By co-expressing Pannx1 and Pannx2 in *Xenopus*

¹**Abbreviations:** AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid); ATP (adenosine 5'-triphosphate); BBG (Brilliant Blue G); BzATP (2'(3')-O-(4-Benzoylbenzoyl)adenosine-5'-triphosphate); CA (Cornu Amonis); CBX (carbenoxolone); CNS (central nervous system); DIDS (4,4'-Diisothiocyano-2,2'-stilbenedisulfonic acid); EGFP (enhanced green fluorescent protein); FFA (flufenamic acid); GABA (gamma-aminobutyric acid); GA (glycylrethnic acid); GFAP (glia fibrillary acidic protein); HEK cell (human embryonic kidney cells); HIV (human immunodeficiency virus); IP₃ (inositol-1,4,5 triphosphate); KA (kainic acid); KN-96 (isoquinoline derivative); MFQ (mefloquine); myc (Myelocytomatosis Viral Oncogene Homolog); NMDA (N-methyl-D-aspartate); NMDG (N-methyl-d-glucamine); NO (nitric oxide); NPC (neural progenitor cell); NPPB (5-nitro-2-(3-phenylpropylamino)benzoic acid); NRK cell (normal rat kidney cell); PKA (protein kinase A); PKC (protein kinase C); Src (sarcoma); Sf9 cell (*Spodoptera frugiperda* cell); SITS (4-acetamido-4'-isothiocyanato-stilbene-2,2'-disulfonic acid); SUR (sulfonyleurea); TLE (temporal lobe epilepsy); PNS (peripheral nervous system).

oocytes the authors found that channel currents displayed properties that differed in terms of amplitude and gating from those composed of Panx1 alone [11], and biochemical analyses revealed that when tagged pannexins (Panx1-myc and Panx2-EGFP) were co-expressed in HEK293 cells, pulldown with either anti-tag antibodies resulted in signals of the other construct [12]. By light microscopy, plasma membrane localization of Panx2 in HEK293T and NRK cells was reported only when co-expressed with Panx1 [13]. However, data from other laboratories indicated that the two pannexins occupy different subcellular domains whether exogenously expressed or in native tissues [7, 14, 15]. Thus, it remains unclear whether the inhibitory effect of Panx2 on Panx1 currents [7, 12] is due to Panx1/Panx2 heteromeric channels being nonfunctional or to Panx1 mistrafficking when co-expressed with Panx2. Interestingly, data obtained from Panx1 and Panx2 purified from baculovirus infected Sf9 cells showed that they formed highly unstable heteromeric channels that disaggregate within few hours after heteromerization [7].

Distinct post-translational modifications (N-glycosylation, palmitoylation, S-nitrosylation, phosphorylation, and caspase cleavage) have been documented for pannexins. In contrast with connexins and innexins, pannexins display glycosylation sites on the extracellular loops with one glycosylation site in the second extracellular loop of Panx1 (amino acid 254) and one on the first extracellular loop of Panx2 (predicted at amino acid 86) and of Panx3 (amino acid 71) [16, 17] (Fig. 1). The degree of N-glycosylation seems to correlate with the subcellular localization of the proteins, with the more complex glycosylation (GLY2) of Panx1 being found at the plasma membrane, while pannexins with lower (GLY1) or no glycosylation (GLY0) modifications being found in intracellular compartments such the endoplasmic reticulum [16, 17]. In addition to the subcellular localization of pannexins, this post-translational modification seems to play a role in the prevention to gap junction formation between two pannexons; deglycosylation of cell surface Panx1 has been shown to significantly enhance functional gap junction formation [18].

Palmitoylation consists in the addition of a saturated C16 fatty acid chain to cytosolic cysteines, which is unique amongst lipid modifications in that it is reversible, thus affecting protein function [19]. Except for the S-palmitoylation of Panx2 (potential palmitoylation consensus site at amino acid 246) observed in stem-like neural progenitor cells [20], no such post-translational modification has been reported for the other 2 pannexins.

The modification of cysteine thiols by nitric oxide has emerged as a key process in protein regulation and increasing evidence suggests that the pannexin family may serve as downstream targets for S-nitrosylation. Indeed, Panx1 was recently demonstrated to be modified by S-nitrosylation at 2 specific cysteine residues (C40 and C346; Fig. 1), resulting in functional inhibition of channel currents and ATP release into the extracellular milieu [21]. Panx3 has also been shown to be modified by S-nitrosylation, while Panx2 appears to be resistant to NO-mediated modification [22].

There are several predicted phosphorylation sites on S, T or Y residues, including putative sites for PKC and PKA (<http://www.cbs.dtu.dk/services/NetPhos/>). However, except for the study by the Saez group [23] indicating a change in phosphor-serine and phosphor-threonine levels of Panx1, direct demonstration that a specific kinase phosphorylates a specific residue

on Panx1 has not yet been provided. Most evidence for the regulation of pannexin channels by phosphorylation is largely indirect, based on the use of pharmacological antagonists of kinases that alter Panx1 activation.

Recently, human Panx1 was shown to have two potential caspase cleavage sites (Fig. 1) of which one was shown to be cleaved by caspases 3 and 7 [24]. Cleavage at these sites, which are located on the C-terminal render the human Panx1 channels constitutively open, leading to apoptotic cell death [24].

Distribution of Pannexins in the Nervous System

Of the three pannexins, only Panx3 is not present in the nervous system. The distribution of Panx1 is widespread, being present in most types of cells and tissues [2, 11, 25]. In the nervous system, Panx1 is prominently expressed in the CNS (cerebellum, hippocampus, olfactory bulb, and thalamus: [26–28]) and in the PNS (sensory ganglia: [25, 29, 30]). In the hippocampus, high Panx1 expression was found in GABAergic and glutamatergic neurons within the dentate gyrus and all CA regions, stratum oriens, stratum radiatum, and stratum lacunosum-moleculare [28]. Although the initial studies showed no overlap of Panx1 with the astrocyte marker GFAP in the brain, recent work by the Sosinsky group reported Panx1 staining in astrocytes using a variety of different Panx1 antibodies thus far developed [31]; this study corroborates other *in vivo* and *in vitro* evidence for Panx1 expression in astrocytes [32–36].

Panx2 transcript is predominant in the CNS and very weak signals are detected in non-neural tissues. The expression of Panx2 mRNA obtained from CNS tissues extracts indicated the presence of Panx2 in forebrain, cerebellum, brain stem, and spinal cord [2, 11, 27, 28, 37]. Using real-time PCR and western blot analysis with newly developed Panx2 antibodies, a recent study by Naus' group [38] indicated that Panx2 protein expression is surprisingly higher in non-CNS tissues while at the transcription level, results were consistent with previous reports indicating Panx2 expression in the CNS. In the rat brain, cells stained for Panx2 were identified, based on their antigenic markers, as being neuronal cells [20]. Conversely, glial cells were found not to express Panx2, as was shown by the lack of Panx2 labeling of cells immuno-labeled for GFAP [20]. Panx2 has been shown to be dynamically expressed over the course of postnatal hippocampal neurogenesis, and two Panx2 isoforms were shown to be present in stem-like Type I and IIa NPCs, but not in neuronally committed Type IIb and III progeny or in immature neurons [20]. The authors proposed that the two species of Panx2 represent S-palmitoylated and unpalmitoylated forms, with the S-palmitoylated Panx2 being uniquely expressed in pluripotent NPCs [20].

Biophysics and Pharmacology of Pannexins

In contrast with connexins, pannexins do not form gap junction channels but form plasma membrane channels [39]. Of the three pannexins, Panx1 is best characterized. Whole cell recording performed in a variety of cell types expressing endogenous or exogenous Panx1 channels have indicated that Panx1 provides outwardly rectifying currents activated at voltages more positive than $\sim +10$ mV [11, 40, 41]. Single channel conductance of Panx1 has

been reported to vary from 60 to a maximal of 500 pS, suggesting that Panx1 exhibits multi subconductance states [4, 42].

Panx1 channels have been shown to be permeable to anions (Cl^- , NO_3^- , F^- , I^- , Br^-), to moderate sized negatively charged molecules, (glutamate, aspartate, ATP) [4, 43] and to anionic (Lucifer Yellow, calcein) and cationic (ethidium bromide, YoPro-1, sulforhodamine B) fluorescent dyes: [13, 34, 40, 44–46]) but interestingly not to the organic cation NMDG⁺ [4]. Importantly, the permeability profile of Panx1 channels to ions and small molecules is dependent on the mode of activation; voltage activation of Panx1 channels results in small channel conductance that is permeable to chloride but not to ATP [4, 47], while other forms of activation (see below) results in large channel conductance that is permeable to ATP and fluorescent dyes (reviewed in [48]). In contrast to hemichannels formed by certain connexins (e.g., Cx46, Cx26), Panx1 currents are insensitive to extracellular calcium but sensitive to intracellular calcium concentrations in the micromolar range [12, 49]. In addition to the activation by voltage, Panx1 channel activity can be modulated by mechanical stretch, by extracellular ATP and K^+ directly [35, 36, 43, 50]. Panx1 currents are also modulated by caspases and following activation of membrane receptors (P2X and P2Y, α 1-adrenergic, glutamatergic (NMDA), and thromboxane receptors) via signaling mechanisms that lead to elevation of cytosolic calcium levels and/or to kinases activation (PKA, tyrosine kinases) [40, 41, 43, 49, 51–56].

Since their discovery, the number of compounds reported to block Panx1 channels has increased enormously spanning beyond those known to affect the gap junction family members (innexins and connexins). Panx1 currents are sensitive to a variety of compounds known to block gap junction channels formed by different connexins such as CBX, FFA, α -, β -GA, MFQ and by other compounds to which gap junction channels are insensitive such as the organic anion transporter blocker (probenecid), the chloride channel blockers (DIDS, SITS, NPPB), the SUR subunit of ATP-regulated potassium (K_{ATP}) channel inhibitor (glibenclamide), P2X7 agonists (ATP, BzATP) and antagonists (BBG, suramin, KN62, A438079) (reviewed in [57]), and some food dyes, such as Brilliant Blue G (BBG) and the food dye FD&C Blue No. 1 (BB-FCF) [57–59].

Pannexin1 and Epileptic Seizure Activity

Because Panx1 channels are permeable to ATP [43, 60] they contribute to purinergic signaling including that involved in the propagation of intercellular calcium waves between astrocytes [34, 61], communication between satellite glia and sensory neurons [29, 62], neutrophil activation and immune defense [63, 64], and vascular tone [54]. Several studies indicate the involvement of Panx1 in certain pathophysiological conditions (ischemia, seizures, innate immune response, cell death, HIV infection, neuropathic and inflammatory pain, spinal cord injury and cardiac arrhythmias) [65–71].

Evidence that pannexins play a role in seizures comes from clinical studies as well as from pre-clinical *in vivo* and *in vitro* models of epileptic seizure activity. Clinical evidence that pannexins are associated with epilepsy was provided in two recent studies of tissue samples from patients with TLE [72] and children with intractable epilepsy due to focal cortical

dysplasia (FCD) [73]. In the first study, increased expression of Panx1 but not of Panx2 protein was found in temporal lobe cortex surgically removed from patients with TLE compared to samples from subjects without epilepsy [72]. In addition, these authors found that Panx1 tissue distribution differed among control and TLE patients. In non-epileptic tissues, obtained from patients with traumatic brain injury, Panx1 expression was found to be confined to the temporal lobe cortical layers II and III, while a more widespread Panx1 expression was found in samples of patients with TLE which also included ectopic expression in layers IV–VI besides the layers II and III [72]. In the second study, the authors found that although both Panx1 and Panx2 mRNA and protein levels were increased in FDC epileptic lesions, their cellular distribution differed [73]. While enhanced expression of Panx1 was found in all dysplastic cells including dysmorphic neurons, balloon cells, microcolumn neurons and in reactive astrocytes, upregulation of Panx2 was detected only in balloon cells [73]. Whether the changes in Panx1 expression levels reported in TLE patients [72] were or were not associated with the disease duration (2 – 37 years) and or the type of seizures (e.g., simple partial seizures, generalized tonic-clonic seizures, etc.) that the subjects experienced has yet to be determined. However, for patients with focal cortical dysplasia lesions, the authors found a positive correlation between Panx1 expression levels and the frequency of seizures that the patients had before surgery [73], suggesting the involvement of Panx1 in the epileptogenic process. Similar upregulation of Panx1 expression levels were obtained using mouse hippocampal slices subjected to Co^{2+} [74], an *in vitro* model of epileptiform-like activity [75]. In this *in vitro* study, the authors found a two-fold increase in the glycosylated form of Panx1 and no change in Panx2 expression levels within 2 hours after Co^{2+} exposure [74].

Thus, these studies [72–74] indicate that the seizure activity is accompanied by Panx1 upregulation; whether Panx1 contribute to hyper-excitability was not investigated. Nevertheless, the close proximity of Panx1 channels with AMPA and NMDA receptors expressed on principal hippocampal neurons as well as on interneurons especially at the postsynaptic density [33, 76, 77] suggests that the glutamatergic receptors may regulate Panx1 channel opening.

The first evidence that Panx1 channel regulates neuronal activity came from MacVicar's group [78]. This group demonstrated that in cultured hippocampal slices the activation of NMDA receptors by application of exogenous NMDA led to Panx1 channel opening which was associated with increased amplitude and frequency of inter-ictal spiking in the zero extracellular Mg^{2+} model of epileptiform-like activity [78]. The study also showed that changes in intracellular Ca^{2+} did not play a role in NMDA receptor-mediated activation of Panx1 channel opening; instead, the NMDA receptor-mediated activation of Panx1 channels involved the metabotropic NMDA receptor - Src kinase Panx1 complex signaling, independently of the classical Ca^{2+} -permeable NMDA receptors [52, 53]. Figure 2A illustrates the signaling pathway by which Panx1 may regulate neuronal excitability according to these studies [52, 53, 78].

The first *in vivo* evidence that Panx1 plays a role in the maintenance of the epileptiform activity came from Scemes' group using mice with global deletion of Panx1 [33]. Using KA-induced seizures in 2 weeks-old mice, the group demonstrated that opening of Panx1

channels contributes to the development of a state of prolonged seizures called status epilepticus but has no effect on seizure initiation. In mutant mice lacking Panx1 or in wild type mice after pharmacological inhibition by a Panx1 channel blocker, the duration of KA-induced status epilepticus was significantly reduced, while the onset of KA-induced seizures was not affected by blocking the Panx1 activity in wild-type mice or in mice lacking Panx1 [33]. The authors also showed that Panx1 channels were activated during status epilepticus and contributed to increase in the levels of extracellular ATP; the amount of ATP released from hippocampal slices derived from wild type mice sacrificed during continuous KA-induced seizures lasting 2 hours, was 2 fold higher than the ATP levels recorded from slices of KA-treated Panx1 null and from those of saline-treated wild type mice [33]. Our study suggests that Panx1 channels are not involved in seizure initiation but rather participate in the self-sustaining nature of seizures, likely by releasing the excitatory transmitter ATP [33]. Figure 2B illustrates a mechanism by which Panx1 may sustain neuronal excitability, according to this study.

There is evidence, however, that depending on the interactions of Panx1 with specific neurotransmitter system the effect of Panx1 channels on seizure may lead to opposite outcomes. An example is the sensitivity to seizures induced by pilocarpine, a non-selective muscarinic (M) receptor agonist. Mice in which Panx1 gene was silenced by intraventricular infusion of specific siRNA were shown to display increased sensitivity to pilocarpine-induced seizures compared to mice with functional Panx1 channels [77]. This suggests that the muscarinic M1 receptor-Panx1 interaction controls the seizure initiation process [77], which is in contrast to the KA-seizure model that has been shown to affect seizure maintenance but not seizure initiation [33]. Also, in contrast to the NMDA receptor-mediated activation of Panx1 channels, which does not involve Ca^{2+} rises [78], intracellular Ca^{2+} elevation seems to play an important role in Panx1 channel opening associated with the cholinergic receptor activity. Kang's group [77] proposed a cascade of events to explain how the opening of Panx1 channels controls the sensitivity to pilocarpine-induced seizures. According to these authors, activation of muscarinic M1 receptors by pilocarpine results in mobilization of IP_3 leading to release of intracellular Ca^{2+} . Increased intracellular Ca^{2+} levels lead to opening of Panx1 channels and release of ATP, which activates the purinergic P2X7 receptors; activation of P2X7 receptors then lead to desensitization of the M1 receptors (see Fig. 2C), as has been shown in periphery [79]. Thus in this case, Panx1 increases the threshold for the pilocarpine-induced seizures.

Another inhibitory action of Panx1 on neuronal excitability has been proposed that links Panx1 channel activation to A1 adenosine receptor mediated activation of the ATP-sensitive-inward-rectifying potassium channels (K_{ATP}), one of the mechanisms that may underlie the anticonvulsant effects of fasting and low carbohydrate/high fat (ketogenic) diet therapy [80]. Using acute hippocampal slices of rodents bathed in solution with different glucose concentrations (reducing from 11 to 3 mM) and manipulated intracellular ATP levels (0.5 to 5 mM), Masimo's group [81] recorded spontaneous postsynaptic currents (sPSCs) from CA3 pyramidal neurons. Under the condition of low extracellular glucose (3 mM) and sufficient intracellular ATP concentration (1 mM), the authors detected significant hyperpolarization associated with an outward current and decreased frequency of sPSCs. Because pharmacological blockade or deletion of adenosine A1 receptors prevented the

hyperpolarization as well as the decreased frequency of sPSCs in CA3 neurons, the authors proposed that the increased adenosine levels resulted from ecto-nucleotidases action on ATP released from Panx1 channels. Indeed, Panx1-mediated outward currents, sensitive to carbenoxolone and the ¹⁰Panx1 peptide, were found to be maximal in reduced extracellular glucose and high intracellular ATP concentration (2 mM) [81]. Using tolbutamide as a blocker of K_{ATP} channels, the authors provided evidence that under low glucose, autocrine activation of A1R leads to opening of K_{ATP} channels. Based on these results, the following model was proposed [81]: under moderate hypoglycemia, opening of Panx1 channels leads to the release of intracellular ATP to the extracellular space where it is rapidly dephosphorylated to adenosine. Increased adenosine concentration activates, via adenosine A1 receptor, the K_{ATP} channels leading to rapid hyperpolarization and subsequent neuronal silencing (Fig. 2D).

These four proposed mechanisms by which Panx1 channels may influence seizures are likely not mutually exclusive. For instance, given that the maintenance of self-sustaining seizures irrespective of seizure origin is associated with NMDA receptor trafficking to the post-synaptic density and NMDA receptor activation [82], the contribution of Panx1 and P2X receptor interaction to the self-sustaining nature of seizures that we reported [33] may also involve Panx1 interactions with the NMDA receptors as described by MacVicar's and Thompson's groups [52, 53, 78]. Also, given the fact that pilocarpine administration stimulates the release of insulin by activating pancreatic muscarinic M1 receptors, thus leading to hypoglycemia [83], it is possible that the hypoglycemia-induced activation of K_{ATP} channels leading to neuronal activity silencing as described by Masimo's group [81] may also participate in the decreased sensitivity to pilocarpine-induced seizures reported by Kang's group [77].

CONCLUSIONS

It is well established that Panx1, unlike the other two pannexins, forms plasma membrane channels that are activated under physiological and pathological conditions. These channels by allowing the flux of ions and relatively large molecules have a profound impact on cell and tissue physiology. In particular, ATP, a powerful signaling molecule, can be released through these channels and promote cell death, proliferation and migration, and affect cell excitability, etc. The diverse modes of Panx1 channel activation, its complex pharmacology, its association with diverse signaling molecules, and its broad cellular and tissue distribution have certainly promoted interest in disease relevant research. Indeed, in the last decade Panx1 has been implicated in HIV infection, cardiac arrhythmias, colitis, Crohn's disease, ischemia and stroke, migraine, encephalomyelitis, and epilepsy, among others. With regard to epileptic activity, studies reviewed here suggest that Panx1 channels have a complex and dual role in seizure activity. On one hand, activation of neuronal Panx1 channels seems to be involved in the maintenance of NMDA- and KA-induced seizure activity, either by promoting depolarization through the flux of ions through Panx1 channels or by the activation of ionotropic P2X receptors following Panx1-mediated release of ATP. On the other hand, under metabolic stress (e.g., ketogenic diet) or in the pilocarpine model, Panx1 channel opening has seizure preventing effects due either to activation of adenosine receptors or to activation of intracellular signaling pathways that desensitize the muscarinic

receptors. Adding to this complexity is the fact that Panx1 is also expressed in glial cells. Whether or not the activation of glia Panx1 channels contribute to hyperexcitability or to distinct functional outcomes remains to be determined.

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Highlights

- A mini review on the properties of pannexins with a main focus on Panx1 and its involvement in epileptic seizure activity is provided.
- Studies suggest that Panx1 channels have a dual role in epileptic seizure activity: activation of neuronal Panx1 channels maintains NMDA- and KA-induced seizure activity, while under metabolic stress or in the pilocarpine model, Panx1 channel opening leads to neuronal silencing.
- Four mechanisms by which Panx1 channels may influence seizures are presented.

Figure 1. Schematics of pannexins' membrane topologies and post-translational modification sites

The three pannexins (Panx1, Panx2, and Panx3) are tetraspan membrane proteins with cytosolic N- and C-termini and two extracellular and one intracellular loops. N-glycosylation sites (green circles) are shown on the second extracellular loop of Panx1 and on the first extracellular loop of Panx2 and Panx3. Two nitrosylation (red circles) and one caspase cleavage (yellow circle) sites are shown for Panx1.

Figure 2. Schematics of hypothesized excitatory and inhibitory roles of Panx1 in regulating neuronal excitability

Excitatory (A, B) and inhibitory (C, D) roles of Panx1. (A) Activation of NMDA receptors (1) leads via a Src tyrosine kinase (2) to the opening of Panx1 channels (3) which generate the NMDA receptor secondary currents and thus contribute to epileptiform activity [52, 53, 78]. (B) Elevated extracellular K⁺ concentration (1), resultant from KA-induced seizures, activates Panx1 channels directly; ATP released from Panx1 channels (2) activates P2X7 receptors (3) which via a Src tyrosine kinase (4), further promote the opening of Panx1 channels in a positive feedback loop that sustain and prolong seizure activity [33, 34, 51]. (C) Activation of muscarinic M1 receptors (1) leads, via elevation of intracellular Ca²⁺, to the opening of Panx1 channels (2) and subsequent release of ATP; activation of P2X7 receptors (3) then leads, via PKC (4), to M1 desensitization and consequent reduction of seizure activity [77]. (D) Moderate hypoglycemia (1) leads to opening of Panx1 channels (2) and release of ATP. Ecto-nucleotidases (CD39/CD73) then dephosphorylate ATP into adenosine (3) which activates adenosine A1 receptors (4) that are linked to K_{ATP} channels (5) leading to the efflux of K⁺ and consequent silencing of neurons [81].

Table 1
Gene symbol, protein sizes, chromosome location and gene ID of human, mouse, and rat pannexins

The size of pannexin proteins displayed below in italic were obtained from published studies mentioned in text (sizes in italics: [2, 4–6]) and from NCBI (sizes not italicized: <https://www.ncbi.nlm.nih.gov/protein/?term=pannexin>).

Gene symbol	Protein (size: aa)	Chromosome	Gene ID
<i>PANX1</i>	Human pannexin 1(<i>422, 425, 426</i>)	11q21	24145
<i>Panx1</i>	Mouse pannexin 1(<i>426</i>)	9 A2	55991
<i>Panx1</i>	Rat pannexin 1 (<i>309, 356, 426</i>)	8q12	315435
<i>PANX2</i>	Human pannexin 2(<i>509, 633, 643, 677</i>)	22q13.33	56666
<i>Panx2</i>	Mouse pannexin 2(<i>607, 677, 678</i>)	15 E3	406218
<i>Panx2</i>	Rat pannexin 2 (664, 674)	7q34	362979
<i>PANX3</i>	Human pannexin 3(<i>392</i>)	11q24.2	116337
<i>Panx3</i>	Mouse pannexin 3(<i>392</i>)	9 A4	208098
<i>Panx3</i>	Rat pannexin 3 (392)	8q21	315567