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REVIEW ARTICLE

P2X7 receptors and pannexin1 hemichannels shape presynaptic transmission

Nathalia Vitureira[1] · Alberto Rafael[1] · Verónica Abudara[1]

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Abstract
Over the last decades, since the discovery of ATP as a transmitter, accumulating evidence has been reported about the role of this nucleotide and purinergic receptors, in particular P2X7 receptors, in the modulation of synaptic strength and plasticity. Purinergic signaling has emerged as a crucial player in orchestrating the molecular interaction between the components of the tripartite synapse, and much progress has been made in how this neuron-glia interaction impacts neuronal physiology under basal and pathological conditions. On the other hand, pannexin1 hemichannels, which are functionally linked to P2X7 receptors, have appeared more recently as important modulators of excitatory synaptic function and plasticity under diverse contexts. In this review, we will discuss the contribution of ATP, P2X7 receptors, and pannexin hemichannels to the modulation of presynaptic strength and its impact on motor function, sensory processing, synaptic plasticity, and neuroglial communication, with special focus on the P2X7 receptor/pannexin hemichannel interplay. We also address major hypotheses about the role of this interaction in physiological and pathological circumstances.

Keywords ATP · P2X7Rs · Panx1HCs · Presynaptic function · Tripartite synapse

Nathalia Vitureira graduated in Biology from the University of the Republic (UdelaR, Uruguay). She performed her PhD at the University of Barcelona (Spain), focusing in the role of a novel anti-adhesive protein in central nervous system development. She became passionate about the presynaptic mechanisms underlying synapse function and following this interest performed a postdoctoral training at the Medical Research Council (London, UK), focusing on the role of synaptic adhesion proteins in presynaptic function and plasticity. At present, she is an Assistant Professor at UdelaR (Uruguay). Her lab is interested in understanding how cells in the brain communicate to form functional circuits that maintain stability over time.

Nathalia Vitureira
nvitureira@fmed.edu.uy

Verónica Abudara
abudara@fmed.edu.uy

Alberto Rafael
arafael@fmed.edu.uy

[1] Departamento de Fisiología, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

Introduction

Chemical synapses are specialized junctions through which cells of the nervous system (NS) communicate with each other. At chemical synapses, the transfer of information between two neurons requires the release of neurotransmitter molecules, which act on the postsynaptic neuron by binding to the specific receptor localized at the plasma membrane, in a process known as neurotransmission.

Adenosine triphosphate (ATP) is abundantly present in the cytosol and is classically known to fuel power-consuming reactions. Burnstock and colleagues first highlighted the role of ATP as a physiological modulator of synaptic transmission in the autonomic system, and subsequently, it was identified as a co-transmitter in parasympathetic and sympathetic nerves [1, 2]. At central nervous system (CNS) synapses, it is well-accepted that ATP acts as a transmitter or co-transmitter by being released with other neurotransmitters, such as glutamate or GABA [3]. Interestingly, both spontaneous and evoked ATP release have been described in pyramidal neurons of the mouse cerebral cortex and fast synaptic currents and long-lasting enhancement of the population spikes are induced by ATP release in the hippocampus [4]. The extracellular concentration of ATP in the NS is determined by the balance between its release and enzymatic degradation, and different studies indicate that this nucleotide is released by both neurons and glia [5, 6]. For instance, physiological and high-frequency stimulations modify that balance by increasing ATP release and thus its extracellular availability [7, 8]. In addition to exocytosis and considering that ATP molecules are not able to diffuse across the plasma membrane, the passage of ATP from the intracellular to the extracellular compartment is also mediated by mechanisms involving ATP-permeable channels as connexin or pannexin hemichannels (CxHCs or PanxHCs, respectively) [9, 10].

There are two fundamental classes of receptors for extracellular ATP that work on different time scales. The metabotropic P2Y receptors (P2Y1,2,4,6,11) are G-protein-coupled receptors involved in responses that can last several seconds through changes in gene expression [11–13]. The second class, the ionotropic P2X receptors (P2X1-7), comprises ligand-gated ion channels that mediate fast responses lasting milliseconds. These receptors can assemble as homo- or heterodimers; thus, the different combinations of subunits result in receptors with a wide variety of structural and biophysical properties [11–13].

In this review, we discuss the role of ATP, P2X7 receptor (P2X7Rs) and PanxHC interaction in the modulation of presynaptic strength with a special focus on the participation of the neuron-glia crosstalk in this process. For a detailed view of the structure, expression and pharmacology of P2X7Rs, the following reviews are recommended [14, 1516].

The basic functioning of P2X7Rs

The P2X7Rs are ligand-gated ion channels permeable to Na^+, K^+, and, more significantly, Ca^{2+}, as all P2X receptors. However, they display distinctive properties compared to the other members of the family. Pioneer studies showed that they are the only ones that do not heterodimerize with other P2X subunits, being usually assembled with three to six P2X7 subunits [5, 17]. However, more recent evidence suggests a close association between P2X7 and P2X4 subunits [18, 19]. On the other hand, they have low affinity to ATP, requiring high levels of extracellular ATP (> 100 µm) for activation [17]. Interestingly, P2X7Rs show plasticity, which leads to selective or non-selective currents. In this sense, milliseconds of ATP-dependent activation results in the opening of small cation-selective channels, while a sustained activation—with a high concentration of ATP—increases the permeability to non-selective conductance, including organic cations and small peptides, in a process known as pore formation, which represents an intrinsic property of the channel itself [5, 17, 20–22]. Moreover, repeated stimulation with an agonist results in relevant changes in the amplitude and time course of the current evoked by the following applications [17, 23]. Notably, the C-terminal domain of the P2X7 subunit is suggested to be required for the pore-forming process [24]. However, the molecular mechanism underlying this process remains still unclear and controversial and two main hypotheses, the "pore-dilation" and the "pore-formation," have been raised (reviewed in [21, 25–27]). The first supports that upon sustained or repetitive stimulation, the ion channel intrinsically dilates producing a pore that allows the passage of large molecules (up to ~ 900 Da) [24, 28]. A proposed alternative to this hypothesis is that the channel dilation may involve the successive incorporation of new P2X7 subunits [28, 29]. Notably, a study performed by Karasawa and colleagues suggested that the pore dilation and thus channel permeability could be modulated by the lipid microenvironment in the vicinity of P2X7Rs [27, 30]. Together, these data indicate that the "pore dilation" might be controlled by different cellular pathways. On the other hand, the "pore formation" is supported by different electrophysiology studies evidencing that the increased membrane permeability could be mediated by the interaction of P2X7R with the ATP-permeable channel, Panx1, followed by cytoskeleton rearrangements [24, 31]. We will discuss the interaction of P2X7Rs and Panx1HCs further above in the text. Electrophysiology and dye uptake studies performed in heterologous expression systems reveal that the property of increasing membrane permeability to large molecules is also observed in P2X2 and P2X4 receptors [5, 17, 20–22].

Interestingly, Kim and colleagues showed that P2X7Rs are dephosphorylated upon activation, leading to a negative feedback control of the channel currents [32]. As other members of the family, P2X7Rs have cytoplasmic N- and C-terminal domains and two transmembrane regions separated by an extracellular domain. The C-terminal domain is the longest of the P2X family and mediates several signaling cascades by interacting with the actin cytoskeleton and different intracellular proteins, such as the heat shock proteins (Hsp90, Hsc71, Hsp70), phosphatidylinositol 4-kinase (PI4K), and membrane-associated guanylate kinase (P55) [32, 33]. Interestingly, dephosphorylation of P2X7Rs also reduces the ability to mediate cytoskeletal rearrangements [32]. Thus, activation of P2X7Rs not only opens a cation-permeable channel, but it can participate in different signaling pathways by interacting with downstream components and promoting cytoskeleton rearrangements. In this sense, Armstrong and colleagues showed that bath application of the P2X7R agonist BzATP prevents neurotransmission at the mossy fiber–CA3 synapses. Interestingly, the synaptic depression is blocked by applying 4-(4-fluorophenyl)2-(4-methylsulfinylphenyl)5-(4-pyridyl) imidazole, a strong antagonist of p38/MAP kinase activation. Altogether, these suggest that P2X7Rs modulate mossy fiber synaptic depression through the activation of p38/MAPK in rat hippocampus [34].

Basic functioning of Panx1HCs

The Panx1 protein forms large pore membrane channels permeable to ions and relative large molecules with physiological relevance supporting an autocrine/paracrine signaling. Panx1 is part of a family of membrane glycoproteins comprising three members (pannexins 1, 2, and 3), being Panx1 the most ubiquitously expressed in the nervous system of mammals [35–37]. The protein is mostly detected in neurons but is also found in oligodendrocytes, astrocytes, and microglia [36, 38–41]. Interestingly, neuronal Panx1 could co-localize with the postsynaptic density protein, PSD95, suggesting a role in synaptic transmission [42]. Structurally, pannexins consist of four α-helical transmembrane domains with cytoplasmic amino- and carboxy-termini; two extracellular and one intracellular loops link transmembrane domains [43–45]. Recent studies using single-particle cryo-electron microscopy (cryo-EM) at near-atomic resolution in different heterologous expression systems determined that Panx1 oligomerizes into heptamers in contrast to the hexameric conformation previously reported, forming plasma membrane channels known as pannexons or PanxHCs [46–50].

Despite pannexons sharing some topological and permeability properties with CxHCs or connexons, Cxs and Panxs do not show sequence homologies [44]. PanxHCs, like connexons, exhibit a large central pore allowing interchange of ions and large molecules (up to 1.2 kDa) between the cytosol and the exterior [10]. Classically, Panx1HCs have been known as non-selective high conductance (~500 pS) and permeable channels permitting the passage of transmitters such as ATP and glutamate under diverse physiological and pathological conditions [43, 51–54]. However, current literature associates Panx1HCs with divergent unitary properties [55]. In addition to the high conductance/permeability conformation, recent studies reported an anion-permeable low conductance (~68–74 pS) conformation with no ATP permeability; this channel state shows selectivity for chloride ions and is activated uniquely by voltage [56, 57]. Likewise, dual voltage clamp recordings resolved in HeLa cells expressing human Panx1-YFP and rodent spinal astrocytes described low mean unitary conductance of ~42 and ~48 pS [58]. Discrepancies between unitary conductance and ATP permeation properties may be ascribed to different modes of Panx1 activation; actually, smaller-conductance Panx1HCs (up to ~100 pS) may co-exist with permeation of large molecules [55, 59]. In this line, caspase cleavage of the auto-inhibitory cytoplasmic carboxy-terminus (C-tail) of Panx1 associates with broadening of the central pore; progressive removal of C-tails has been associated with stepwise graded channel activation of multiple discrete open states, each contributed by individual subunits resulting in permeation of ions and large molecules [59]. Combining cryo-EM analysis, ATP release measurements, and electrophysiology, novel studies confirmed the passage of ATP through a heptameric Panx1 channel presenting small single-channel conductance [45–48]. In accordance, a gating mechanism involving two ionic-conducting pathways, a big main pore permeable to large molecules, and seven narrow tunnels located intracellularly and permeable to small anions has been reported. In normal conditions, the main pore is physically blocked by the C-terminal tail and thus anions—but not ATP—can solely pass through the side tunnels. Under pathological conditions, the C-terminal tail is cleaved by caspase, and ATP is released through the main pore [48]. According to cryo-EM reconstructions, the Panx1 permeation pathway is exceptionally wide in the transmembrane and cytoplasmic portions thus supporting permeation of large molecule ATP or ethidium. Constriction sites would take place in the extracellular domains where the conserved tryptophan ring (W74) in the first extracellular loop may act as a putative selective filter [45–48]. Hence, Panx1 seems to have multiple open pore configurations. Finally, the Panx1HC conductance/permeability and kinetics are still a matter of investigation; stimulatory conditions may determine channel properties and conformational states [55, 60].

Panx1HCs as dynamic routes for ATP release

Pannexons are typically known as paths for ATP release [10, 51, 61]. Released ATP triggers purinergic signaling either by itself or through its metabolites (adenosine diphosphate or ADP, monophosphate or AMP, and adenosine). This unconventional Panx1-dependent efflux of ATP constitutes a paradigmatic mechanism for non-vesicular transmitter release [43]. In the NS, the release of glio- and neurotransmitters (glutamate, D-serine, and ATP) by neural cells via Panx1HCs has been implicated in synaptic plasticity in health and disease being the subject of an increasing number of publications [41, 62, 63]. Importantly, pannexons open under physiological extracellular Ca^{2+} concentrations and negative resting membrane potentials and show poor voltage dependence [36, 52, 64]. Pannexons can be activated by diverse mechanisms (reviewed in [55, 65–67]) including purinergic (P2X4/7, P2Y1/2/6), alpha1-adrenergic, and glutamatergic (N-Methyl-D-aspartate) receptors [24, 68–70]. When activated by purinergic receptors, Panx1HCs behave as physiological regulators of ATP release; the outcome of this association is the so-called "ATP liberation induced by ATP." Accordingly, ATP released through pannexons opens new pannexons by stimulating purinergic receptors resulting in a positive feedback that reinforces the initial ATP signal [66, 71]. If maintained, this situation is potentially dangerous since channels might be kept in a permanent open state and ensuing exacerbated pannexon activity would be deleterious [72]. Recent reports suggested that physiological activation of Panx1HCs by ATP might be transient in the presence of purinergic P2Y/P2X7 receptors due to the existence of an inhibitory mechanism or internalization of Panx1 [72–76]. While the most studied roles of Panx1HCs rely on their capability to allow the release of ATP and the effects of purinergic signaling, other alternative roles might be ascribed to the non-channel properties of Panx1 [77].

Pannexin1 as subunits of gap junction channels: the debate is open

Pannexins are considered the mammalian orthologs of innexins, the gap junctions of invertebrates, but in contrast to them (and to connexons), whether PanxHCs from opposing cells come together to generate gap junction channels remains controversial. Initial electrophysiological studies carried out by Bruzzone and colleagues in paired oocytes of Xenopus indicated that exogenously expressed Panx1 assembles as intercellular channels forming either homomeric or heteromeric channels with Panx2, having both channel differential properties [36]. Dye coupling assays in C6 glioma cells loaded with sulforhodamine SR101 revealed enhanced dye coupling in Panx1-expressing cells supporting these primary observations [78]. Likewise, overexpression of Panx1 in human cell lines may induce the formation of gap junction channels permeable to Ca^{2+} underlying the propagation of intercellular Ca^{2+} waves [79]. Subsequent investigations questioned the capability of Panx1 to form cell–cell channels in appositional membranes under physiological and in vivo conditions. A main argument is the presence of N-glycosylated asparagine residues on Panx1 second extracellular loop that would prevent docking [73, 80–82]. In agreement with this, electrophysiological and functional studies performed in cell lines carrying different glycosylation patterns of expressed Panx1 showed that lower levels of Panx1 glycosylation associate with higher probabilities to find functional Panx1-formed gap junction channels [83]. Also, combining single-particle cryo-electron microscopy and patch-clamp electrophysiology in a glycosylation-deficient mutant of Panx1 allowed identifying a gap-junction-like structure [48]. Yet, experimental conditions promoting Panx1 glycosylation have been recently discussed [84]. Additional arguments against Panx1-forming gap junctions are that recordings of Panx1-based junction currents require special experimental conditions and may be contaminated with junction currents from connexin-based gap junction channels [81]. A more recent study elegantly performed by Sáez Laboratory using functional/electrophysiological/pharmacological/genetic and in silico assays characterized Panx1-based cell–cell channels in transfected and endogenous human lines [84]. Thus, electrophysiological recordings of exogenous human pannexin1 (hPanx1) cell–cell channels expressed in HeLa cells knocked out for Cx45 showed two states of hPanx1 intercellular channels: O-state with single-channel conductance of ~ 175 pS, a substate of ~ 35 pS and low transjunctional voltage (Vj) sensitivity, and S-state, with single-channel conductance of ~ 35 pS, asymmetry in Vj dependence and permeability to DAPI. Remarkably, S-state hPanx1 intercellular channels were also recognized between TC620 cells, a human oligodendroglioma cell line that endogenously expresses hPanx1 [84]. Importantly, in silico approaches suggested that some arginine residues at the channel pore may be neutralized by hydrophobic interactions permitting DAPI permeability. These novel findings reopen the debate about the possibility that Panx1HCs assemble as functional intercellular channels and, essentially, raise the question about the eventual role of Panx1-gap junction channels as morpho-functional substrates for electrical synapses under defined physiological circumstances [84].

Panx1HC association with P2X7Rs

Panx1HCs functionally associate with ionotropic purinergic P2X7Rs. In addition to operating as a cationic channel, prolonged stimulation (up to 20 min) of the ligand-gated ion P2X7R leads to the permeation of large molecules (up to 1 kDa) such as ATP [5, 85]. As we commented above, the mechanisms underlying the permeation of P2X7Rs to large molecules are subject of intense debate. In one possible scenario, pioneering studies done in macrophages suggested that Panx1HCs could function as the large pore of the P2X7R under prolonged activation [24]. In these cells, ATP gates P2X7Rs and opens a large transmembrane route allowing ethidium uptake and the release of the pro-inflammatory cytokine interleukin-1beta (IL-1β), being these effects prevented by Panx1 block. By using small interference RNA (siRNA) directed to Panx1 and a Panx1-mimetic inhibitory peptide, the authors inhibited the dye uptake elicited by P2X7Rs without affecting the ionic current and Ca^{2+} entry associated with P2X7R stimulation [24]. Some studies then reported that large plasma membrane pore opening upon P2X7R activation could occur in the absence of Panx1 [86, 87]. The biphasic permeation properties of P2X7Rs were reported in systems not expressing Panx1 and under high agonist concentrations; intracellular residues of the channel pore seemed to be required for the pore dilatation under those circumstances [86].

What mechanisms link P2X7Rs and Panx1HCs? Increases in cytosolic Ca^{2+} activate pannexons and ATP release; thus, opening of Panx1HCs would be triggered by the increase in intracellular Ca^{2+} downstream P2X7R stimulation [9, 73, 88, 89]. Conversely, it has been reported that Panx1HC opening might be independent from extracellular Ca^{2+} and direct protein–protein interaction could underlie Panx1HC activation as suggested by the fact that Panx1 co-immunoprecipitates with the P2X7R [24, 72]. A Src tyrosine kinase-dependent process might couple Panx1HC and P2X7R activation, while the carboxy-terminal region of P2X7Rs would be required to open Panx1HCs [53, 90]. To add more intricacy to the P2X7R/Panx1 interaction, a recent study performed in heterologous expression systems revealed that Panx1 attenuates the P2X7R-dependent Ca^{2+} entry. This P2X7R inhibition appears to be mediated by the C-terminal domain of Panx1 [91]. Interestingly, whether Panx1 attenuates or potentiates P2X7R-dependent signaling pathways seems to depend on the degree of P2X7R activation [92]. Hence, solid evidence supports the idea that Panx1 and P2X7R exert a modulatory influence on each other; however, the accurate mechanisms underlying the physical interaction between them remain to be clarified.

In this review, we will focus on pannexons expressed in neural cells and their acting in conjunction with P2X7Rs to contribute to the shaping of presynaptic neurotransmission.

P2X7Rs and Panx1HCs as modulators of presynaptic strength

Different studies described the presence of P2X7Rs in presynaptic terminals and functional data support a pivotal role of these receptors in presynaptic neuronal function [34, 93–99]. Presynaptic P2X7Rs promote a wide range of effects on synapse functionality, including facilitation and/or inhibition. For instance, activation of P2X7Rs with the receptor agonist BzATP promotes neurotransmitter release in glutamatergic synapses in the cortex, hippocampus, cerebellum, spinal cord, and neuromuscular junction [93, 94, 100–102]. In isolated presynaptic terminals, pulses of ATP or BzATP induce an increase in presynaptic Ca^{2+} availability, which is sensitive to P2X7R antagonists, suggesting that functional P2X7Rs are present in presynaptic terminals [100, 101, 103]. Interestingly, the P2X7R permeability to Ca^{2+} is lower at depolarized membrane potentials compared to negative potentials. In this sense, it has been suggested that neurotransmitter release could be initiated through P2X7R activation, without presynaptic depolarization and voltage-gated Ca^{2+} channel opening, thus, also contributing to neurotransmitter release at resting membrane potentials [94, 104]. Furthermore, the P2X7R- mediated Ca^{2+} currents are not desensitized and potentiated when the extracellular concentration of Ca^{2+} or Mg^{2+} is decreased. The high conductivity to Ca^{2+} ions under physiological conditions provides P2X7Rs the alternative to act as presynaptic sources of Ca^{2+} [100, 105, 106]. Either presynaptic P2X7R-mediated Ca^{2+} signaling or P2X7R-activated intraterminal Ca^{2+}-dependent signaling messengers modulate neurotransmitter release in central and peripheral synapses [100, 102, 107, 108]. During the last years, Panx1 has emerged as an important modulator of synaptic function. In the adult brain, the absence of Panx1 leads to changes in the dendritic arbor and excitability of hippocampal neurons, preserving spontaneous activity [77]. Moreover, Panx1HCs, which are reported to open under resting membrane potential, are also essential regulators of synaptic plasticity in hippocampal synapses. For instance, the absence or blockade of Panx1HCs in adult mice favors LTP by modifying the threshold of synaptic plasticity induction and increases excitatory synaptic transmission [109, 110]. Accordingly, a recent report showed that blocking Panx1HCs in hippocampal slices increases the synaptic level of endocannabinoids and the activation of CB1 receptors; as a consequence, GABAergic efficacy decreases. This effect shifts the excitatory/inhibitory balance toward excitation and facilitates the induction of LTP in CA3-CA1 synapses [111]. The functional significance of Panx1HCs in hippocampal synapses is suggested to be mediated by both pre- and postsynaptic mechanisms [109]. More recently, evidence suggests that neurotransmitter release probability (pr) and the size of the readily releasable pool (RRP) are affected in Panx1-knockout (Panx1KO) mice and thus glutamate release [77]. In this line, we have recently reported that, in hippocampal dissociated cultures, neuronal Panx1HCs and P2X7Rs are required for the compensatory adjustment of presynaptic strength upon chronic inactivity [99]. In the ensuing paragraphs, we review recent advances regarding the role of ATP, P2X7Rs, and Panx1HCs in the modulation of presynaptic strength at central and peripheral synapses and address major research gaps that require more study.

ATP, P2X7Rs, and Panx1HCs regulate the presynaptic release of acetylcholine (ACh) at the neuromuscular synapse

During neuromuscular transmission, in addition to released ACh, ATP originating from both nerve terminals and muscle fibers accumulates at the synaptic cleft [112, 113]. Endogenous ATP and its hydrolysis products regulate the presynaptic release of ACh [107, 108, 113–115]. Recent reports propose Panx1HCs as sources of synaptic ATP involved in purinergic regulation of neuromuscular junctions (NMJs). According to these studies, stimulation of P2X7Rs by the specific agonist BzATP in isolated hemidiaphragm neuromuscular preparations of Panx1KO mice enhances evoked ACh release through presynaptic activation of calmodulin, Ca^{2+}/calmodulin-dependent kinase II, and L-type of voltage-dependent Ca^{2+} channels. Effects induced by P2X7R stimulation, i.e., increased quantal content of evoked endplate potentials (EPPs) and increased size of the readily releasable ACh pool, were not observed in wild-type mice yielding to the suggestion that Panx1 normally inhibits the tonic enhancement of P2X7-evoked release of ACh [107]. This is counterintuitive since activated Panx1HCs boost neurosecretion in other systems through a process involving P2X7R and amplification of cytosolic Ca^{2+} signals [116, 117]. However, other purinergic receptors would come into play; at the frog neuromuscular junction, ATP co-released with ACh inhibits quantal ACh release from motor nerve terminals via metabotropic P2Y receptors [118]. At mouse NMJs, the inhibitory actions of presynaptic purinergic P2Y13 and adenosine A1 receptors activated by Panx1HC-released ATP and adenosine would override the stimulatory effects of P2X7R, resulting in net inhibition of ACh release by Panx1HCs [107, 113]. Noteworthily, the global Panx1KO mice used in mammalian NMJs studies do not discriminate the cellular origin of the Panx1HCs involved in the control of presynaptic ACh release. Interestingly, at the postsynapse, Panx1 activation enhances muscle contraction; in adult skeletal muscles, Panx1HC opening mediates ATP efflux and influx of Ca^{2+} and glucose, necessary for potentiation of contraction [119, 120]. Hence, the final effects of the P2X7Rs/Panx1HC interplay on muscle function (stimulatory or inhibitory) will depend on the cellular localization of Panx1HCs as well as on the actions of purinergic receptors other than P2X7Rs, also activated during the Panx1HC-mediated ATP discharge. What would be the physiological role of the tonic inhibition of ACh release by Panx1HCs in mouse NMJs? As proposed by others, Panx1HCs might be part of a feedback control mechanism through which transmitters could adjust the gain of synaptic strength [63, 121]. We speculate that, at mouse motor synapses, inhibition of ACh release by the Panx1HCs during high neuronal activity might avoid synaptic fatigue. According to this idea, the resultant effects on presynaptic ACh release, due to the stimulatory (P2X7R) and inhibitory (P2YR) actions of Panx1HC-released ATP, would contribute setting the moment-to-moment dynamic range of ACh synaptic levels, within the NMJ which would efficiently perform in physiological conditions. However, further studies will be required to resolve this issue.

The neuroglial crosstalk in the modulation of synaptic strength

Different sources of evidence showed that the fine-tuned modulation of neurotransmission, that has been previously thought to only require the signaling between two neuronal cells, involves an intimate communication between glial cells and neurons. Thus, currently it is well-recognized that glial cells are not only passive support cells for neurons but also active players in neuronal network development and information processing. At synapses, neuronal and non-neuronal cells are closely associated by the fine processes of both astrocytes and microglia that modulate synapse formation and function [122–124]. Added to their proximity to synapses, astrocytes secrete a wide variety of chemical signals that control synaptic transmission. This led to the concept of "tripartite synapse," a synapse composed of one presynaptic neuron, one postsynaptic neuron, and an astrocyte, shaping together a functional unit [124–128]. A tripartite synapse displays an intimate communication between the different cellular players through a bidirectional signaling pathway; neurons release neurotransmitters that bind to postsynaptic receptors and receptors on the adjacent astrocyte process, activating signaling pathways in the astrocytes which finally fine-tune synaptic function [127, 128]. Thus, brain function depends on the communication between neurons and glial cells that can activate a wide variety of molecular interactions leading to the modulation of synaptic strength. In this scenario, we next discuss recent findings that shed light on the role of P2X7Rs and their interaction with pannexons in the modulation of presynaptic strength in both central and peripheral nervous systems.

The P2X7R/Panx1 complex mediates astroglial D-serine release: possible impact on presynaptic strength

Astrocytes synthesize and release D-serine, an endogenous neurotransmitter that acts as a co-agonist with glutamate at N-methyl-D-aspartate receptors (NMDARs) [129, 130]. In the brain, astrocyte D-serine controls NMDAR-mediated synaptic activity, long-term potentiation (LTP), long-term depression (LTD), and cognition [131–134]. Studies reveal that the rate of supply of D-serine to neurons controls the firing rate of these cells. Neurological (i.e., Alzheimer, epilepsy, stroke) and psychiatric (i.e., schizophrenia) disorders typically exhibit alterations of extracellular D-serine. Then, the adequate function of NMDAR requires the fine adjustment of extracellular levels of this molecule [135]. Several molecular and cellular mechanisms mediate the D-serine efflux [136]. In particular, astrocytes secrete this neurotransmitter through a Ca^{2+}-independent activation of P2X7Rs that involves Panx1; additional releasing pathways include Ca^{2+}/SNARE-dependent exocytosis and Cx43HCs [137–139]. In cultured cortical astrocytes, stimulation of glial P2X7Rs by ATP elicits D-serine discharge via Panx1HCs through a Ca^{2+}-independent PKC isozyme [137]. Formation of the P2X7R-Panx1 complex is essential for this effect, as pharmacological inhibition of the Panx1HCs and downregulation of Panx1 expression by shRNAs prevent the release of astrocyte D-serine triggered by the P2X7R agonist BzATP [137]. Whereas Ca^{2+}-dependent exocytosis of astrocyte D-serine controls synaptic plasticity in the hippocampus and Cx43HC-mediated astrocyte-released D-serine potentiates NMDAR-synaptic currents at the prefrontal cortex, the contribution of glial D-serine and P2X7R/Panx1HCs in neurotransmission and particularly in the presynapse is unknown [134, 138]. An eventual effect of glial D-serine on presynaptic NMDARs could be a possibility. In other brain regions, electrophysiological studies have shown that D-serine promotes glutamate release from nerve terminals acting through presynaptic NMDARs [140, 141]. Besides, cortical astrocytes may provide D-serine to activate presynaptic NMDARs facilitating glutamate release [142]. Currently, future studies are required to unravel the role for astroglial D-serine and P2X7R/Panx1HC in neurotransmission, as well as to discriminate whether the different molecular mechanisms involving its release (Cx43HCs, Panx1HCs, P2X7Rs, or exocytosis) operate under specific circumstances (i.e., health or disease) and trigger precise modulatory mechanisms (i.e., pre or postsynaptically), alone or concurrently.

Paracrine signaling by Panx1HCs and P2X7Rs sustains bidirectional interactions between neurons and satellite glial cells (SGCs) in peripheral sensory ganglia: implications for nociceptive afferent transmission

Ganglia primary neurons are the first relay in the sensory pathways transmitting afferent information from the periphery (skin, muscles, organs, etc.) to the CNS (spinal cord and brainstem). The soma of these sensory neurons localizes in the peripheral dorsal root ganglion (DRG) or ganglia of sensory cranial nerves. The sensory neurons are pseudounipolar and their cell body gives origin to a short axon, which divides into two branches yielding a t-shaped bifurcation. One branch innervates the periphery while the other enters the CNS where it synapses with central neurons (second relay) localized in the posterior horn (for spinal nerve) or the medulla oblongata (for cranial nerves) [143]. Although action potential conduction from the periphery to axon terminals innervating the postsynaptic second relay might bypass the perikaryon without distortion of the sensory information, the ganglia neuronal soma provides the unique possibility for regulating the afferent sensory transmission to the CNS [144]. Moreover, notably, there is no current morphological or functional evidence indicating that neurons within the peripheral ganglia chemically synapse between each other, and sensory neurons principally rely on satellite glial cells (SGCs), the chief ganglia glial cells, to modulate their excitability through gliotransmission. Actually, cell bodies of sensory ganglia neurons are typically enwrapped by surrounding SGCs forming a “neuroglial unit” [145, 146]. Recent reports indicate that interaction mediated by purinergic signaling and Panx1HCs sustains paracrine communication between sensory neurons and SGCs contributing to regulate nociception [147–153]. In murine visceral nodose-petrosal-jugular (NPJ) complexes, the SGCs Cx43HCs act together with P2X7Rs and Panx1HCs to mediate a paracrine neuroglial communication [149]. In this case, the pharmacological opening of glial CxHCs increases the frequency discharge in vagal axons projecting from the NPJ sensory neurons to the medulla, being this effect inhibited in Panx1KO mice. Single application of BzATP, a P2X7R agonist, to the NPJ complexes, also increases the electrical activity in sensory neurons. The oxidized ATP (oATP), an irreversible P2X7R antagonist, and probenecid, a Panx1 blocker, reduce the increased sensory discharge elicited by pharmacological CxHC opening. Panx1 is found in both sensory neurons and SGCs [149, 154–156] whereas P2X7Rs are selectively expressed by satellite glial cells [147, 148, 153, 157, 158]. Since Panx1HC activation associates with P2X7R function, authors proposed that interactions between neuronal Panx1HCs, glial Cx43HCs, and P2X7Rs orchestrate the increase of NPJ sensory neuron activity [149]. In the dorsal root ganglia (DRG), stimulation of P2X7Rs by BzATP triggers cytosolic Ca^{2+} increases in SGCs and neurons in vivo being these responses blocked by antagonists of P2X7Rs, $P2X_3Rs$, and Panx1 [153]. Then, in DRG, activated P2X7Rs could induce the paracrine release of glial ATP through opening Panx1HCs, which increases neuron excitability in vivo through $P2X_3Rs$ that are mainly expressed by sensory neurons [5, 157]. In turn, released ATP may result in the opening of neuronal Panx1HCs that would contribute to further ATP release [153]. Interestingly, the study by Chen and colleagues also evaluated the impact of the SGC–neuron interaction in the modulation of afferent transmission [153]. In this regard, ganglionic application of BzATP increases the number of activated DRG neurons that respond to brush stimulation of the ipsilateral hind paw. In addition, the response of C-fibers to the electrical stimulation of the sciatic nerve increases after BzATP application to the L4 DRG and the ganglionic application of carbenoxolone (CBX), a Panx1 and Cx general blocker, decreases the number of DRG neurons activated by peripheral high-intensity electrical stimulation. Hence, this work provides clear evidence that DRG neuron activation triggered by P2X7R stimulation and Panx-1HCs sensitizes sensory neurons to subsequent peripheral stimulation enhancing the nociceptive transmission from the periphery to central pathways [153]. In chronic pathological pain, the initial injury induces hyperexcitability of primary afferent neurons from the ganglia (peripheral sensitization), leading to central hypersensitivity that persists after the original injury. In pathological pain, Panx1 is up-regulated as reported in murine trigeminal ganglia in a chronic orofacial pain model and in DRG after nerve injury [151, 156]. The Panx1 contribution to orofacial pain depends on the cell-type expressing the protein; targeted deletion of Panx1 in satellite glia completely blunts hypersensitivity, while silencing Panx1 expression in sensory neurons reduces baseline sensitivity and hypersensitivity duration. The role of Panx1HCs in pathological orofacial pain might involve the increased release of the algogenic mediator ATP and cytokines [151]. Since as discussed, the interaction between P2X7Rs and Panx1HCs amplifies the nociceptive entry, we might speculate that this could represent a defense mechanism to enhance alert about the presence of a noxa. Finally, the contribution of Panx1HCs in nociceptive processing and pathological chronic pain points at this protein as a promising target for new therapeutic strategies [152].

Homeostatic role of the purinergic ATP/P2X7R pathway and Panx1HCs: modulation of presynaptic strength under chronic inactivity

Homeostatic synaptic plasticity (HSP) is a form of plasticity displayed with the aim to stabilize the activity of neural circuits in response to chronic perturbations that can lead to irreversible damage. Compensatory mechanisms involve changes in pre- and postsynaptic strength and/or intrinsic neuronal excitability [159–161]. Consistent with a role of gliotransmission in modulating basal synaptic strength, molecular mechanisms underlying neuron-glia bidirectional communication in PSH have been also described. Indeed, studies in hippocampal dissociated and entorhino-hippocampal slice cultures showed that tumor necrosis factor alpha (TNFα) is required for a postsynaptic form of HSP known as synaptic scaling [162–165]. Moreover, the role of TNFα in postsynaptic homeostatic plasticity has been described for different neural functions including developmental plasticity, diverse addiction models, and response to psychiatric drugs [166].

A recent study using hippocampal dissociated cultures has identified a pivotal role for gliotransmission in the compensatory adjustment of presynaptic strength upon chronic TTX exposure [99]. Evidence showed that the compensatory increase in the abundance of synaptic vGlut1 requires glial-derived ATP, astrocytic Cx43HCs, neuronal Panx1HCs, and presynaptic P2X7Rs, as suggested by blocking experiments using specific antagonists. How may this homeostatic modulation occur? The precise relationship between these molecular players is the aim of future work, but one possible scenario is that, upon chronic activity blockade, neurons reduce the release of glutamate, which is sensed by astrocytes, leading to a sustained opening of Cx43HCs and thus enhancing ATP release. Acting as a gliotransmitter, ATP activates presynaptic P2X7Rs, which are Ca^{2+}-permeable channels in a voltage-independent manner [101, 167, 168]. Interestingly, by using a Ca^{2+} reporter targeted to presynaptic terminals of hippocampal dissociated neurons, Zhao and colleagues showed that adaptation to chronic inactivity involves an increase in presynaptic Ca^{2+} in response to an action potential [169]. In this sense, another study performed in cortical dissociated neurons showed an extensive molecular remodeling of the presynapse upon chronic inactivity, with significant changes in the amount of different presynaptic proteins, such as Cav2.1 and P/Q-type Ca^{2+} channels [170], suggesting that the increase in presynaptic Ca^{2+} upon inactivity could be due to the rise in the abundance of these channels. Interestingly, a more recent study found that low voltage–threshold T-type Ca^{2+} channels participate in the homeostatic modulation of excitability and integrative properties in hippocampal dissociated and organotypic slice cultures upon chronic TTX application [171]. On the other hand, the data shown by Rafael and colleagues opens up the possibility that the increase in presynaptic Ca^{2+} upon chronic inactivity could be, at least in part, mediated by P2X7Rs. This seems to be due more to an enhanced activation and prolonged P2X7 channel opening, than to an increase in the presynaptic amount of these receptors upon chronic inactivity [99]. This is suggested by immunocytochemistry studies where the distribution and abundance of presynaptic P2X7Rs were not affected upon chronic TTX treatment, suggesting that the availability of these channels is not modified due to HSP [99]. Interestingly, neuronal Panx1HCs are suggested to cooperate with presynaptic P2X7Rs in the compensatory adjustment of presynaptic strength [99]. Again, the abundance of Panx1HCs seems not to be affected upon chronic inactivity. In agreement with this and taking into account the documented interaction between P2X7Rs and Panx1HCs, it is tempting to hypothesize that chronic inactivity triggers the release of ATP by astrocytes, activating presynaptic P2X7Rs, increasing the entrance of Ca^{2+} to the presynaptic terminal, and activating presynaptic Panx1HCs. These channels may cooperate with P2X7Rs by increasing both the release of ATP (and potentiated P2X7R activation) and the entrance of Ca^{2+} to the presynaptic terminal by a positive feed-forward loop (Fig. 1). The precise functional crosstalk between these molecular components upon chronic inactivity awaits further studies. Thus, understanding the cell-specific mechanisms that control presynaptic P2X7Rs and Panx1HC function and interactions will enrich our knowledge about synaptic transmission.

Concluding remarks

Since the discovery of ATP as a transmitter, our knowledge about the role of this nucleotide and the purinergic receptors, particularly P2X7Rs, in the modulation of synaptic strength and plasticity has increased significantly. Purinergic signaling has a crucial role in coordinating the molecular interaction between the components of the tripartite synapse and thus modulating presynaptic strength, and much progress has been made in how this interaction impacts neuronal physiology under basal and pathological conditions. On the other hand, Panx1HCs have emerged as important modulators of synaptic function under basal and activity-dependent conditions. Thus, we may speculate that the strong influence of P2X7Rs and pannexons in presynaptic function could rely on their functional interaction, which could be based on specific features that both channels share. For instance, P2X7Rs and Panx1HCs are both active under resting membrane potentials and after presynaptic depolarization. Also, the extracellular concentration of ATP fine-tunes their activation and thus membrane permeability. However, the precise mechanisms underlying their interaction need to be elucidated. Hence, deciphering the cell- and tissue-specific mechanisms sustaining the linking between P2X7Rs and Panx1HCs under certain conditions will be relevant to go deep in understanding synapse physiology in both health and disease.

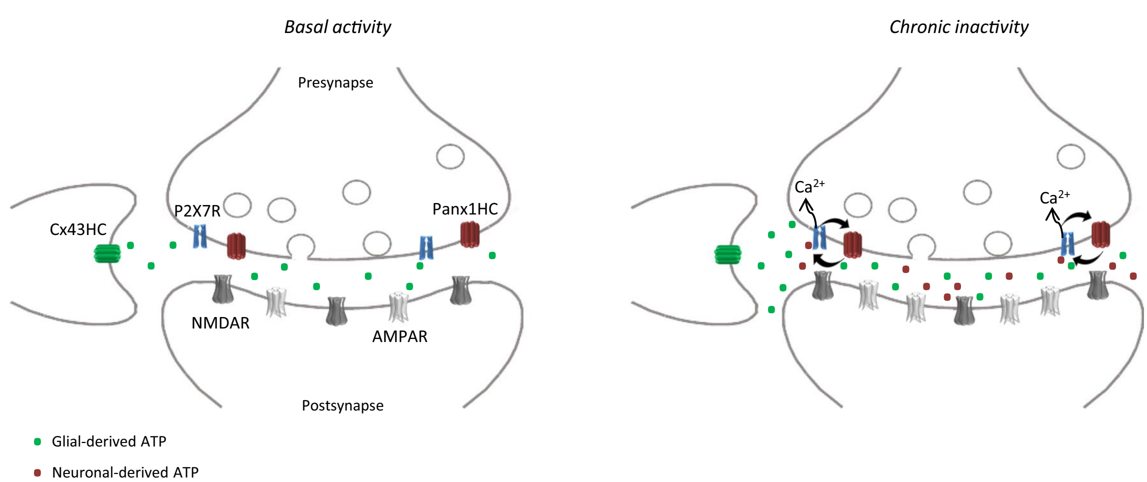

Fig. 1 P2X7Rs and Panx1HCs modulate presynaptic homeostatic plasticity: hypothetical pathway. Upon chronic inactivity, astrocytes sense the reduction of glutamate concentration at the synaptic cleft and, consequently, increase the amount of ATP released by Cx43HCs. Glial-released ATP activates presynaptic P2X7Rs, enhancing the amount of Ca^{2+} entering to the terminal and neurotransmitter release probability. Concomitantly, the increase in presynaptic Ca^{2+} activates neuronal Panx1HCs and thus ATP release, strengthening the activation of P2X7Rs by a positive feedback loop and promoting the compensatory increase in presynaptic function upon synaptic activity blockade

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