Cellular Signalling 23 (2011) 305–316

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

Pannexin channels in ATP release and beyond: An unexpected rendezvous at the endoplasmic reticulum

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ARTICLE INFO

Article history:
Received 29 June 2010
Accepted 22 July 2010
Available online 3 August 2010

Keywords:
Pannexin
Hemichannels
Endoplasmic reticulum
Intracellular Ca^{2+} signalling

ABSTRACT

The pannexin (Panx) family of proteins, which is co-expressed with connexins (Cxs) in vertebrates, was found to be a new GJ-forming protein family related to invertebrate innexins. During the past ten years, different studies showed that Panxs mainly form hemichannels in the plasma membrane and mediate paracrine signalling by providing a flux pathway for ions such as Ca^{2+}, for ATP and perhaps for other compounds, in response to physiological and pathological stimuli. Although the physiological role of Panxs as a hemichannel was questioned, there is increasing evidence that Panx play a role in vasodilatation, initiation of inflammatory responses, ischemic death of neurons, epilepsy and in tumor suppression. Moreover, it is intriguing that Panxs may also function at the endoplasmic reticulum (ER) as intracellular Ca^{2+}-leak channel and may be involved in ER-related functions. Although the physiological significance and meaning of such Panx-regulated intracellular Ca^{2+} leak requires further exploration, this functional property places Panx at the centre of many physiological and pathophysiological processes, given the fundamental role of intracellular Ca^{2+} homeostasis and dynamics in a plethora of physiological processes. In this review, we therefore want to focus on Panx as channels at the plasma membrane and at the ER membranes with a particular emphasis on the potential implications of the latter in intracellular Ca^{2+} signalling.

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doi:10.1016/j.cellsig.2010.07.018

1. Introduction

Cells often respond towards extracellular stimuli, like hormones, growth factors, amino acids and purinergic signalling molecules by the generation of an intracellular Ca^{2+} signal [1]. In many cases, extracellular activation generates intracellular signalling molecules, like inositol 1,4,5-trisphosphate (IP_3) [2]. Elevating intracellular IP_3 levels leads to intracellular Ca^{2+} release that originates from the endoplasmic reticulum (ER) by the opening of IP_3-gated channels (IP_3Rs) [3]. The unique spatiotemporal properties of the Ca^{2+} signal controls a variety of downstream cellular and physiological processes, including gene transcription, cell proliferation, cell survival/death, hormone secretion, enzyme release, actin cytoskeletal contraction, neurotransmitter release and according to synaptic plasticity [2].

In many cases, the cells neither function stochastically nor independently from each other, but rather display a coordinated response towards signalling molecules. This coordination is of utmost importance for the physiological outcome of these processes at the tissue or whole-organ level [4,5], and results from intercellular communication and signalling. The most direct way is via the head-to-head docking of hexameric connexin-based gap junctional channels, allowing the passage of small signalling molecules with a molecular weight of less than 1.5 kDa [6–8]. The activity of these gap junctional channels is tightly regulated by intra- and intermolecular protein interactions and a variety of cellular signalling events, including redox modification and phosphorylation [9]. These gap junctions dictate the coordinated response of connected cells, which can be seen as a chemical and electrical syncitium. The latter is very clear in the heart, where the spreading of an action potential across the atrial and ventricular myocytes is based on connexin-based gap junctional channels [10]. In addition to establishing direct cellular connections, connexins have been shown to act as unapposed "hemichannels" that participate in the release of signalling molecules, like ATP in purinergic signalling [11,12]. Besides connexins, a new family of gap junctional-related channels has been identified, the pannexins (Panx) [12–15]. These channels primarily act as ATP-permeable hemichannels rather than gap junctions [16]. Recent findings also indicated the location of Panx in the ER, thereby forming Ca^{2+}-permeable channels [17,18]. Hence, given their potential role at the plasma membrane and the ER, Panx channels may be at the centre of many signalling processes.

We will first present a general overview of the different mechanisms that control intracellular Ca^{2+} homeostasis. In the next paragraphs we describe the role of Panx channels at the plasma membrane as critical mediators of physiological and pathophysiological signalling. Finally, we discuss the possible role of Panx channels in the ER with an emphasis on their potential role as Ca^{2+}-leak channels and function in neurogenesis.

2. Intracellular Ca^{2+} signals: an overview

In cells ranging from bacteria to highly differentiated eukaryotic cells, ionized calcium (Ca^{2+}) is universal and physiologically important intracellular signalling molecule. In all eukaryotic cells, the cytoplasmic concentration of Ca^{2+} ($[Ca^{2+}]_i$) is tightly controlled by complex interplay between Ca^{2+}-pumps, Ca^{2+}-channels, Ca^{2+}-exchangers and Ca^{2+}-binding proteins [19]. Global or local changes in $[Ca^{2+}]_i$ modulate a wide range of intracellular functions. Muscle contraction, secretion, metabolism, neuronal excitability, cell differentiation, cell proliferation and cell death all depend on Ca^{2+} [20]. The large number of diseases caused by mutations and abnormalities in various proteins involved in the cellular Ca^{2+} regulation also emphasize the importance of Ca^{2+} as an intracellular messenger [21].

The cytoplasmic basal Ca^{2+} activity is maintained at about 100 nM, which is much lower than the extracellular Ca^{2+} concentration ($[Ca^{2+}]_o$), which is in the mM range (Fig. 1). Many stimuli can trigger the activation of phospholipase C β/γ (PLC β/γ) and the generation of IP_3, resulting in the release of Ca^{2+} from internal Ca^{2+} stores and a subsequent increase in the cytoplasmic $[Ca^{2+}]$. The increase in $[Ca^{2+}]_i$ depends on the presence and density of cytosolic Ca^{2+}-buffering proteins or Ca^{2+}-buffering organelles such as mitochondria. Furthermore, specialized Ca^{2+} microdomains arise in the close proximity of multi-protein complexes involving Ca^{2+}-channels, which affect local signalling processes or the activity of other proteins, like enzymes and channels [19]. These localized microdomains are established through the formation of Ca^{2+} channel multi-protein complexes, thereby recruiting a variety of effector proteins. Ca^{2+} is delivered from both extracellular space and internal Ca^{2+} stores, such as endoplasmic and sarcoplasmic reticulum (ER and SR), nuclear envelope or Golgi apparatus (Fig. 1). The $[Ca^{2+}]$ in these stores is at least 1000-fold higher than the basal cytoplasmic $[Ca^{2+}]$, creating a high driving force for Ca^{2+} release from the intracellular stores. High

Table 1
Cellular functions of Panx channel.

Functions at the plasma membrane	
Taste bud receptors	Panx1 mediates ATP release to control gustatory afferent nerves during tastant-evoked signalling
Neurons	Panx mediates chemical coupling
Red blood cells	Panx1 mediates ATP release to control microcirculation and micro-environment of the vasculature
Skeletal muscle cells	Panx1 mediates ATP release linked to excitation–transcription regulation during tetanic contractions
Airway epithelial cells	Panx1 mediates ATP release to control mucociliary clearance and maintain proper airway epithelial function during stress
Chondrocytes	Panx1 mediates ATP release (and concomitant decline in intracellular cAMP levels) to control differentiation and proliferation
Keratinocytes	Panx1 causes disorganization, whereas Panx3 channels mediate differentiation
T cells/B cells	Panx1 mediates ATP as co-stimulator for antigenic stimulation
Cells of immune system	Panx1 in "death pore"-complex formation with $P2X_7$
Functions at the ER or other intracellular compartments	
Prostate cancer cells	Panx1 as ER Ca^{2+}-leak channel
Glioma	Panx2 as an inhibitor of cell growth/proliferation
Neuronal progenitor cells	Panx2 neurogenesis and stem-cell like behavior