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The Mystery of P2X7 Ionotropic Receptor: From a Small Conductance Channel to a Large Conductance Channel

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1. Introduction

1.1 Ion channels

Ion channels are aqueous pores which allow ions to pass based upon an electrochemical gradient. In order to conduct ions, these channels modify their shape by a process called gating, a shifting between opening and closing states. These channels are gated by various stimuli i.e. applied electric field, chemical transmitters, pH, heat and cold, among others. When an electrical potential is held constant in a cell, the gating process equilibriates rather than reaching an energy-dissipating position (a cyclic steady state). Ions diffuse through open channels very fast, involving an interaction between ions, the pore, and solvent that lead to ionic selectivity, saturation, block and flux coupling (Hille, 1975a; Läuger, 1973a).

The ion channel has generally been viewed as having unchanging selectivity strengthening the argument that there is a degree of specificity between ion and channel. Nevertheless, some classes of ion channels present a more varied selectivity of ions, allowing impermeable ions or molecules to permeate under certain circumstances. However, the there is no a systematic approach to distinguish different ion channels and in most cases, it is necessary to differentiate the channels by their kinetics, molecular sequence, pharmacological properties, and response to ionic substitution.

The diversity of channels continues to pose numerous areas to explore in physiology, molecular biology, pharmacology and biophysics.(Hille, 1991). Ion channels are generally classified into two groups: the channels that allow the passage of ions (Na+, K+, Ca2+) and those that allow the passage of large ions and solutes (ie ATP, glutamate, fluorescent dyes of low molecular weight). This second group is predominantly made up of large conductance ion channels which when activated change the permeability of cell membranes for molecules of up to 1000 Daltons (Ojcius, D. M. & Ding-E Young, J., 1990; Iacovache et al, 2010). These channels are and allow for the secretion of ATP and other intracellular molecules, not to mention implicated in various mechanisms of cell death.

2. Proteins that form large channels in mammal cells

These large channels are distinguished by their proteins which can be classified in accordance with their function, mechanism for membrane penetration, the size of their pores, its pore-forming subunits, and type of pore-forming proteins within the membrane plane (α- or β). By comparing the protein configuration in the plasma membrane it is possible to actually evolutionarily delineate the pore-forming protein of distinct organisms.

Proteins that form large conductance channels in the plasma membrane have been described in virus (Madan et al, 2007), bacteria (Huffman et al, 2004), fungi (Ojcius, D. M. & Young, J. D., 1991) and plantae (Klüsener & Weiler, 1999). Mostly due to these proteins being functionally linked to the mechanism of defense (plantae) or the invasion of the hosts (virus, bacteria, etc). These proteins are often secreted into the extracellular environment as monomers which then oligomerize and form the channel in the host membrane.

In humans and other mammals the secreted proteins, there have been found the antimicrobial peptide families of defensins (Kagan et al 1990) and cathelicidins (Scocchi et al, 1999; Skerlavaj et al, 2001). Other peptides, such as dermicidin (Boman et al 1993; Christensen et al, 1988) and anionic peptides (Brogden et al, 1996,1997,2003) are also found in tissue-specific areas. In the immune system, these pores cause physical damage to invading pathogens. In general, pore-forming proteins are monomeric molecules that interact with each other while they are inserted into membranes, where they continue to polymerize further to form large transmembrane pores, leading to a process of antimicrobial activity and cytotoxicity.

Generally, in vertebrates, more specifically in mammals, these pores are integral membrane proteins that are capable of opening under physiological or pathological condition. They can be found in several parts of the organism and may be associated with organism defense (release of pro-inflammatory agents, destruction of pathogens, cell death) or not (release of neurotransmissor, proliferation etc).

The main large conductance ion channels which are found in mammals, are the connexin hemichannels (Cx43, Cx32 and other), pannexins (pannexin-1), maxi anion channel, voltage-dependent anionic channel (VDAC), maxi-K channel, maitotoxin pore, transient receptor potential vanilloid type-1 (TRPV1), transient receptor potential ankhirin type-1 (TRPA1) and ATP-activated P2X pores (P2X2, P2X4 and P2X7 receptors). All of these permit the passage of mono and divalent ions and the flow of molecules of up to 1000 Da. The majority of these large conductance ion channels are preferentially permeable to cations, while VDAC and maxi anion are permeable to anions. In addition, they are all permeable to the anionic ATP4- molecule (Nagasawa et al, 2009; Pellegatti et al, 2005; Yip et al, 2009) and glutamate (Léon et al, 2008).

3. P2X7 receptor associated pore

Activation of the purinergic $P2X_7$ receptor (P2X7R) is rather unusual among ion channels. Brief agonist stimulation induces a non-selective cation-dependent pore, permitting the permeation of monovalent and divalent cations that leads to plasma membrane depolarization (Virginio et al, 1999b). By contrast, a prolonged and repetitive agonist application (at concentrations greater than 100 μM) promotes increased membrane

permeability, allowing cellular uptake of fluorescent dyes such as propidium iodide (MW 639) or lucifer yellow (MW 457).

In the last years, some research groups have provided evidence that pannexin-1 (Panx1) hemichannel might be the protein associated with $P2X_7$ receptor pore formation. However, several cells allow the passage of dyes, despite having the pannexin-1 channel blocked (Faria et al, 2005, 2010; Schachter et al 2008; Yan et al 2008). This opens the possibility that other proteins may participate in the formation of the large channel associated with the $P2X_7$ receptor. As mentioned above, there are other proteins capable of forming large pores in plasma membrane.

In keeping with this idea, Faria and collaborators (2009) showed that calcium ionophores may massively increase the intracellular Ca^{2+} and induce dye uptake. They observed a pore with biophysical and pharmacological characteristics similar to $P2X_7$ receptor pore (Figure 1). In addition, Schilling and colleagues (1999) observed the Maitotoxin opening, a pore able to uptake fluorescent dyes. This pore was also biophysically similar to the $P2X_7$ receptor pore. Herein, we will address some questions about the possible protein candidate (or candidates) responsible for the $P2X_7$ receptor pore formation described above. Moreover, we will discuss the possible events which might be occurring to regulate the opening of these pores in mammalian cells.

4. Current methodologies to study large conductance channels

4.1 Patch clamp recordings

In patch-clamp recording, the microelectrode is a micropipette with a relatively large tip diameter. The microelectrode is placed next to a cell and a gentle suction is applied through the microelectrode to draw a piece of the cell membrane (the 'patch') into the microelectrode tip; the glass tip forms a high resistance 'seal' with the cell membrane. The suction causes the cell to form a tight and high-resistance seal around electrode, resulting in a resistance of approximately 10 giga Ohms, which is called a gigaseal. There are several variations of the patch-clamp technique, as depicted in Figure 2.

4.2 Cell permeabilization assays

This technique allows the detection of plasma membrane permeabilization in different cell types, by inducing the activation and opening of large conductance channels. In general, we use low molecular weight fluorescent dyes, such as fluorescein, lucifer yellow, calcein, ethidium bromide, propidium iodide, in order to observe the entrance of these impermeable dyes after the permeabilization phenomenon.

$P2X_7$ receptor pore-formation has been studied by several groups in different cell types. Most experiments associated with pore formation have centered around dye uptake experiments mediated by the $P2X_7$ receptor.

4.3 Flow cytometry assays

This is a technique for counting and examining microscopic particles, such as cells and chromosomes by suspending them in a stream of fluid and passing them through an

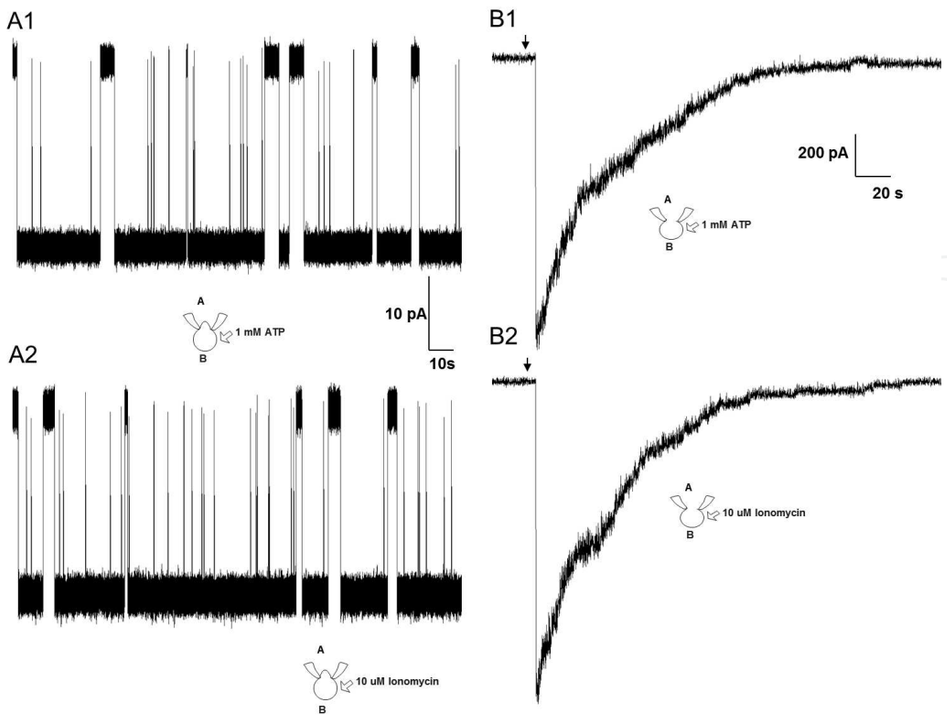

Fig. 1. Single channel and macroscopic currents in mouse peritoneal macrophages. The ionic currents were recorded at 37ºC and holding potential of -60mV using the cell attached configuration. A1- Single channel activity recorded after stimulation with 1mM ATP in the bath. A2- Single channel activity recorded after stimulation with 10uM Ionomycin in the bath. A3- Macroscopic current recorded after stimulation with 1mM ATP in the bath. A4- Macroscopic current recorded after stimulation with 10uM ioniomycin in the bath. Arrows in figure B represent the moment of application of the agonists. Under each recording there is a schematic representing the electrophysiological configuration, the localization and the agonist concentration used. A- Intracellular saline: 150mM KCl, 5mM NaCl, 0.1mM EGTA, 10mM HEPES, pH 7.4. B- Extracellular saline: 150mM NaCl, 5mM NaCl, 1mM MgCl2+, 1mM CaCl2+, 10mM Hepes, pH 7.4.

electron detection apparatus. It allows the simultaneous multiparametric analysis of the physical and chemical characteristics of thousands of particles per second. Clinical and research laboratories uses flow cytometry , to analyze multiple cell parameters such as cell cycle, cell membrane alterations and cell phenotype. Several studies have used flow cytometry in dye uptake assays stimulating the pore forming protein to open and permit the entry of fluorescent dyes.

4.4 Colorimetric assays

The measurement most commonly used to detect effects of P2X7 activation is colorimetric assays which are based on the absorbance of light. In according to Beer's Law, a solute absorbs light of a particular wavelength, and the absorbance is directly proportional to the substance concentration in solution. The measurement is done by a spectrophotometer, displaying and recording absorbance in quantifiable units. In general, the substance of

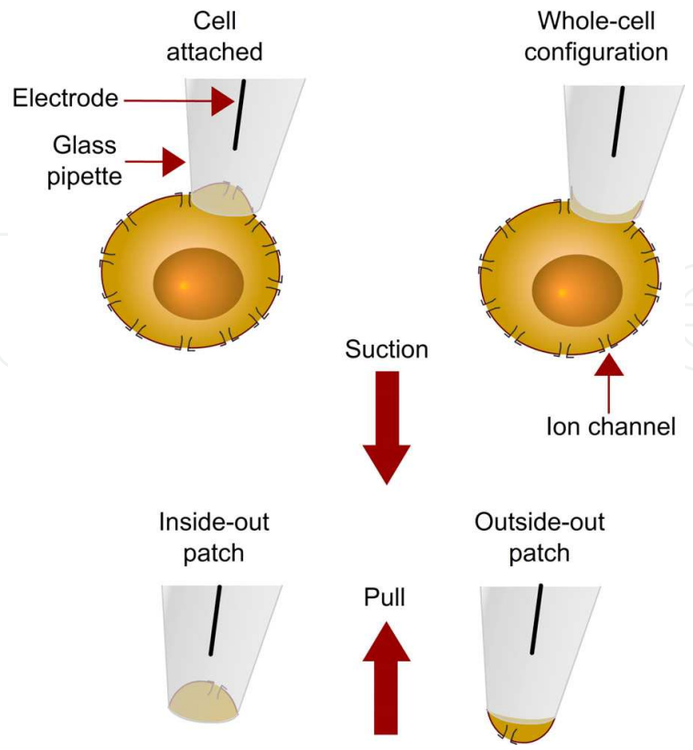

Fig. 2. Illustration of the different modes and configurations of the patch-clamp technique. In the cell-attached mode, the patch electrode remains sealed to the cell membrane, permitting the recording of currents through single-ion channels from the patch of membrane surrounded by the tip of the electrode. This configuration can be used for studying the activity of ion channels present in the membrane patch. In the whole cell mode, in the initial cell-attached configuration, additional suction is applied to rupture the cell membrane, thus providing access to the intracellular space. The larger opening at the tip of the patch electrode, compared with the sharp microelectrode, provides lower resistance and better electrical access to the cell- because the volume of the patch electrode is much bigger than the cell, cellular soluble contents will slowly be replaced by contents of the electrode, referred to as "dialyzing" the cell contents. Whole-cell mode records currents through all channels from the entire cell membrane at once. In the Inside-out patch mode, after the gigaseal are formed, the micropipette is quickly withdrawn from the cell, pulling off a patch of membrane from the cell, leaving the membrane patch attached to the micropipette, and exposing the intracellular surface of the membrane to the external media. This is useful when an experimenter wishes to pharmacologically manipulate the intracellular side of the ion channels. In the outside-out mode, after the whole-cell patch is formed, the electrode can be slowly withdrawn from the cell, allowing a bulb of membrane to bleb out from the cell. After the electrode to be pulled far enough away, this bleb will detach from the cell and reform as a convex membrane at the electrode end (like a ball open at the electrode tip), with the original outside of the membrane facing outward from the electrode. Single channel recordings are possible in this form if the membrane bleb is small enough. Outside-out patching gives the experimenter the opportunity to examine the properties of an ion channel when it is isolated from the cell, and exposed to different solutions on the extracellular membrane surface.

interest, by itself, does not absorb light in the wavelength used. We have to apply one or more reagents to produce colored compounds which are proportional to the substance concentration of the unknown. These methodologies may be used to measure cell death (LDH release, MTT assay), release of substances (neurotransmissors, cytokines and others), uptake of substances (fluorescent dyes) and enzymatic activity.

5. Electrophysiological studies of $P2X_7$

The first group which published a unitary current associated with the $P2X_7$ pore was Coutinho-Silva and coworkers in 1997. They used a cell attached configuration in mouse macrophages to show that the $P2X_7$ receptor when activated by ATP (in milimolar concentrations), is able to activate a large conductance channel with unitary conductance of about 400 pS (Coutinho-Silva et al, 1997). These pores were voltage dependent and had properties similar to P2Z permeabilization, such as uptake of large cations (N-methyl-D-glucamine) and anions (glutamate). Their opening is favored at temperatures higher than 30 degree Celsius and is blocked by oxidized ATP and Mg^{2+}. These authors did not record this conductance in excised patches which was the first clue for the participation of secondary messengers and cytoskeletal proteins.

After this discovery, other groups used cell attached configuration however only in low currents (~8pS) was the $P2X_7$ receptor recorded (Jiang et al, 2005; Ugur et al, 1997; Virginio et al, 1997). The large conductance activity was detected in dye uptake assays (Jiang et al, 2005; Hibell et al, 2000; Virginio et al, 1997;) or in whole cell experiments. In the whole cell, the macroscopic current induced by ATP or BzATP (a synthetic analog more potent than ATP) could be divided, according to some reports, into two distinct conductance (or components). The first component are the small channels opening and the second component is related to the large conductance of the $P2X_7$ receptor (Jiang et al, 2005; Virginio et al, 1999).

In 2005, our group, using cell attached configuration, recorded a unitary conductance of approximately 400 pS in murine macrophages and 2BH4 cells (Faria et al, 2005). We observed a linear response in positive and negative holding potential however this large conductance channel was never observed in excised patch, supporting that there is a dependence of intracellular signals as previously suggested by Coutinho-Silva's studies (Faria et al, 2005). In addition it was found that blockers of the $P2X_7$ receptor reduced the conductance and were modulated by the intracellular Ca^{2+} and MAPK. On the otherhand, Riedel's group in 2007, using the patch-clamp technique, studied the influence of external alkali and organic monovalent cations on the single-channel properties of the human $P2X_7$ receptor. In cell attached and excised patches, they observed activity only of the small conductance channel. Interestingly, they also reported an increased probability of $P2X_7$ small channel opening when extracellular Na^+ was substituted for other monovalent cations (Riedel et al, 2007a). This same group used human $P2X_7$ receptors expressed in *Xenopus laevis* oocytes and recorded single channels using the patch-clamp technique in the outside-out configuration. The result observed was similar to the previous paper as the large conductance channel was not observed (Riedel et al 2007b).

In 2008, Schachter and coworkers compared the $P2X_7$ receptor pore formation of macrophages and HEK-293 cells transfected with $P2X_7$ (HEK-P2X(7)) receptors using patch-

clamp recordings. They did not record a unitary conductance activity in transfected HEK-293 cells. A pore with conductance of approximately 400 pS was recorded only in mouse peritoneal macrophages. Using dye uptake experiments, they also observed the differential uptake of cations and anions between the endogenous $P2X_7$ receptor pore formation in macrophages. The anionic pathways associated with the large conductance channel and the cationic pathway were unidentified (Schachter et al, 2008).

In 2009, based on previous data reporting that increasing intracellular Ca^{2+} is able to induce the opening of a pore biophysically similar to the $P2X_7$ receptor pore. Investigating this channel we found that calcium ionophores at micromolar concentrations induced dye uptake and ionic currents presented a unitary conductance of 400 pS, in the attached cell. This pore was unaffected by $P2X_7$ receptor blockers, but it had intracellular signaling components similar to the $P2X_7$ receptor large conductance channel and not observed in excised patches. However, we did not identify the entity responsible for inducing intracellular Ca^{2+} pore opening in mouse macrophages and 2BH4 cells (Faria et al, 2009).

In 2010, Yan and collaborators performed experiments to understand how the three binding site occupation for the ATP may affect the $P2X_7$ receptor gating. They showed that ATP concentrations in the milimolar range were able to biphasically activate and deactivate native receptors while micromolar concentrations responded monophasically. Both phases of response were abolished by the application of Az10606120, a $P2X_7$R-specific antagonist. This slow secondary growth of current in the biphasic response coincided temporally with pore dilation. This pore current was insensitive to Na^+ and Ca^{2+} influx and fully reestablished the initial gating properties after 30 min of washout. The complex pattern of gating exhibited by wild-type channels can be accounted for by the Markov state model that includes the negative cooperativity of agonist binding to unsensitized receptors caused by the occupancy of one or two binding sites, thus opening the channel pore to a low conductance state when the two sites are bound, and when three sites are occupied, triggering a high conductance state (pore dilation) (Yan et al, 2010). In contrast, Flittiger and collaborators while investigating the participation of protons in the activation of $hP2X_7$Rs observed that human $P2X_7$ receptors expressed in *Xenopus laevis* oocytes were activated by ATP or BzATP at different pH values. The unitary currents were blocked by protonation and the large conductance channel not recorded (Flittiger et al, 2010).

In 2010, Roger and coworkers, used a whole cell configuration to characterize the functional properties of the biphasic ionic conductance recorded in human and rat $P2X_7$ receptors. They observed that in humans there was a Ca^{2+}/calmodulin independence of the secondary conductance (pore), while in rats there was dependency (Roger et al, 2010)

6. The search of large channels associated with $P2X_7$

In search of the $P2X_7$ receptor protein responsible for large unitary conductance and the pore that is induced rising intracellular Ca^{2+} (Faria et al, 2009) we compared the main biophysical properties of the other large conductance channels with these types of pores.

In cultured cells under resting conditions, hemichannels have a low open probability at negative membrane potentials, and the open probability is increased at positive potentials (Bukauskas & Verselis, 2004). Increases in hemichannel levels have been clearly associated

with rises in intracellular-free Ca^{2+} concentration ($[Ca^{2+}]_i$) (Schalper et al, 2008, Sánchez et al, 2009). Normally, positive membrane potentials activate the fast gating, which corresponds to fast transitions between the fully open state and a substate. At negative membrane potentials, the loop gating activates slow transitions, perhaps involving multiple substates between the fully open state, substates and the fully closed state (Bukauskas & Verselis, 2004). Unitary conductance of the connexin hemichannel recorded in a cell attached configuration exhibited conductance values of approximately 300 pS for connexin 56 (Ebihara et al, 1999), for connexin 43 approximately of 200 pS (Contreras et al, 2003a, 2003b; Kang et al, 2008; Retamal et al, 2007b), 250 pS for connexin 46 (Ma & Dahl, 2006) and 200 pS for connexin 50 hemichannel (Liu et al, 2011).

Panx1 channels have been reported with different voltage dependence. In some cases, Panx1-mediated currents are outwardly rectifying and require a depolarization for activation (R. Bruzzone et al, 2003, Pelegrin et al, 2006). This observation is at odds with currents recorded in pyramidal neurons following Panx1 activation by ischemia or NMDAR stimulatio, where the current-voltage (I-V) relationship is clearly linear (Thompson et al, 2006, 2008a, 2008b) similar to Panx1 when it is conducting ATP (Bao et al, 2004). Upon activation, pannexons open into large non-selective pores, which are insensitive to physiological levels of extracellular Ca^{2+} but they are permeable to ions and small molecules as well as metabolites of up to 1000 Da and a wide range of membrane depolarization levels (S. Bruzzone et al, 2004). In addition, some groups have measured the unitary conductance of this large conductance channel, which is approximately 500 pS (Bao et al, 2004; Locovei et al, 2006; Thompson et al, 2006) which suggests that depolarization activates rectifying Panx1 currents and that other mechanisms lead to currents that are not significantly rectifying.

The presence of VDAC in the plasma membrane (pl-VDAC) would be expected to be lethal to the cell (Yu and Forte, 1996). However, considering the resting membrane potential across the plasma membrane of about -30 to -60 mV (Dermietzel et al, 1994), VDAC1 in the plasma membrane would be in a closed state most of the time (Mannella, 1997). Current events were recorded from excised patches of plasma membranes of a rat astrocytic cell line (RGCN)where it was found that the underlying channels exhibited a conductance from 401 to 250 pS. Open probability was the highest between 210 mV, and gradually approached zero beyond 225 mV. Activity induced by voltage ramps between 240 mV appeared after a several minute delay.

Several authors have reported the single-channel opening of the Maxi-anion with larger unitary conductance (300–400 pS) recorded in the cell-attached mode after cell swelling (Dutta et al, 2004; Liu et al, 2006, 2008a). Most authors noted that the maxi-anion channel has multiple subconductance states of various levels, such as 15, 50, 100, 150 and 200 pS (Dutta et al, 2004; Olesen & Bundgaard, 1992; Schwarze & Kolb, 1984; Akanda et al, 2008). When the extracellular Cl^- concentration varied, the single-channel conductance saturated at 640 pS with Km = 112 mM in L6 myoblasts (Hurnák & Zachar, 1994), at 581 pS with Km = 120 mM in T lymphocytes (Schlichter et al, 1990) and at 617 pS with Km = 77 mM in frog skeletal muscle ‘‘sarcoballs’’ (Hals et al, 1989). The maxi-anion channel presents roughly uniform behavior in different cell types. The current–voltage relationship of the fully open state is usually symmetrical and linear with no rectification when it is recorded by cell attached configuration. The channel has a maximal open channel probability at around 0 mV, but it readily closes when the voltage exceeds a range of ±15 to ± 30 mV. The macroscopic currents

exhibit a time dependent inactivation at large positive and negative potentials over ±15 to +30 mV. The voltage dependence of open probability (Popen) remains bell-shaped with maximum at a voltage near 0 mV. These results indicate that the channel is highly selective to anions (Mitchell et al, 1997; Schlichter et al, 1990) but that the degree of anion selectivity may vary (Bajnath et al, 1993, Kemp et al, 1993) not only with cell types but also with the experimental conditions.

TRPV1 is a nonselective cation channel which is structurally related to the voltage-activated potassium (Kv) channels. The TRPV1 expressed alone in human embryonic kidney-derived HEK293 cells or *Xenopus* oocytes can account for the majority of the electrophysiological properties exhibited by native capsaicin receptors in sensory neurons, including ligand affinity, permeability sequence, current/voltage (I/V) relationship, conductance and open probability at both single-channel and whole-cell levels.

In whole cell configuration, I/V relationships have reversal potentials close to 0 mV, indicating the opening of non-selective cationic channels, and a substantial outwards rectification with a region of negative slope conductance at potentials negative to +70 mV (Gunthorpe et al, 2000).

In cell attached configuration, the single-channel amplitude histogram showed two well separated peaks representing open and closed states, without sub-conductance levels observed at +60 mV. The single-channel amplitude at +60 mV was 5.3 pA, corresponding to a conductance of 88.3 pS. Open probability depends on membrane potential as it has been shown in single-channel and whole-cell recordings (Premkumar *et al.* 2002; Voets *et al.* 2004b). At the molecular level, an extracellular Ca^{2+}-dependent reduction of TRPV1 responsiveness upon continuous vanilloid exposure (electrophysiological desensitization) may underlie this phenomenon, at least in part (Caterina et al, 1997; Szallasi & Blumberg, 1999). In relation to TRPV1 large conductance formation, some papers have published that this channel may mediate fluorescent dye uptake, however they did not characterize the biophysical properties related to this phenomenon (Blumberg, 2007; Hellwig et al, 2004; Myrdal & Steeiger, 2005). Since 2008, other research groups have now characterized this second stage of conductance of the TRPV1 channel.

MTX may initially induce the activation of a NSCC, which is permeable to Na+ and K+, but it has a low permeability to Ca2+ (Schilling et al., 1999; de la Rosa et al., 2007). MTX may also increase [Ca2+]i via various Ca^{2+} entry pathways following depolarization, including L-type voltage-sensitive Ca^{2+} channels (VSCCs), which are the predominant Ca^{2+} channel type in vascular smooth muscle (Sanders, 2001). The unitary conductance was 12 pS in the presence of 50 mM Ba^{2+}. Within a burst, the distribution of opening times was a single exponential with a mean open time of 10.4 ms (Kobayashi et al, 1987-Br J Pharmacol). GH4C1 rat pituitary cells were stimulated with independent currents of an MTX-induced steady-state voltage of nearly 400 pS/pF within seconds of addition to the bath. Ion substitution experiments demonstrated that these ionic currents are consistent with the conductance of sodium and chloride, but not calcium ions (Young et al, 1995).

7. Conclusion

In summary, Maxi anion and pl-VDAC had unitary conductance of 400 pS, but were voltage-dependent and anionic. In relation to Maitotoxin and TRPV1 pores which were not

recorded in cell attached configuration yet their whole cell characteristics are similar. In addition, pannexin-1 hemichannels had unitary conductance of approximately 500 pS and could be activated by intracellular Ca^{2+}, though when this channel is activated by voltage its biophysical properties change. Altogether, these data show how complex and difficult is to characterize or rule out the participation of these proteins in the $P2X_7$ receptor large conductance.

A better understanding of the molecular mechanism for P2X7 pore formation might open new therapeutic strategies since this receptor is involved in several processes such as the killing of intracellular pathogens, chronic inflammation, neuropathic pain and rheumatoid arthritis.

So, despite the important efforts carried out in the studies of P2X7 receptor, the pore opening mechanism (large channel) is still unknown.

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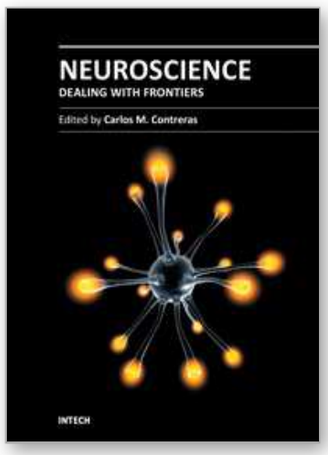

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The Neuronal Doctrine recently reached its 100th year and together with the development of psychopharmacology by the middle of 20th century promoted spectacular developments in the knowledge of the biological bases of behavior. The overwhelming amount of data accumulated, forced the division of neuroscience into several subdisciplines, but this division needs to dissolve in the 21st century and focus on specific processes that involve diverse methodological and theoretical approaches. The chapters contained in this book illustrate that neuroscience converges in the search for sound answers to several questions, including the pathways followed by cells, how individuals communicate with each other, inflammation, learning and memory, the development of drug dependence, and approaches to explaining the processes that underlie two highly incapacitating chronic degenerative illnesses.

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