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Role of Connexin Hemichannels in Neurodegeneration

Juan A. Orellana^{1,2}, Christian Giaume³ and Juan C. Sáez^{1,4}

¹*Departamento de Fisiología; Facultad de Ciencias Biológicas*

²*Departamento de Neurología; Facultad de Medicina*

Pontificia Universidad Católica de Chile, Santiago,

³*CIRB; UMR CNRS 7241/INSERM U1050, Collège de France, Paris*

⁴*Instituto milenio, Centro Interdisciplinario de Neurociencias de Valparaíso, Valparaíso,*

^{1,2,4}*Chile*

³*France*

1. Introduction

Progressive loss of neuronal structure and function occur in several neurodegenerative diseases. Cellular responses to brain injury depend on properties of the cells (e.g., hormonal nutritional status) and insult (e.g., duration, intensity, and quality), whereas, tissue responses depend on interactions between their constituent cells, including chemical and electrical transmission as well as paracrine and autocrine signaling. In vertebrate cells, autocrine and paracrine communication occur in part via release of chemical signals through connexin hemichannels (Sáez et al. 2010), the precursors of gap junction channels that are formed by two hemichannels provided by one of each apposed cells (Fig. 1). Each hemichannel is composed of six protein subunits termed connexins, which are highly conserved proteins encoded by 21 genes in human and 20 in mouse with orthologs in other vertebrate species (Cruciani and Mikalsen 2005). Connexins are abundantly expressed in cells of the central nervous system (CNS) (Orellana et al. 2009) (Fig. 2), and they are named after their predicted molecular mass expressed in kDa, so that connexin43 (Cx43) has a molecular mass of ~43 kDa.

For a long time the main function attributed to connexin hemichannels was the formation of gap junction channels. Nevertheless, in the last decade, the presence of functional connexin hemichannels in nonjunctional membranes has been demonstrated by several experimental approaches (Sáez et al. 2010). These channels allow cellular release of relevant quantities of autocrine/paracrine signaling molecules (e.g., ATP, glutamate, NAD⁺ and PGE₂) to the extracellular milieu (Bruzzone et al. 2001; Cherian et al. 2005; Stout et al. 2002), as well as uptake of small molecules (e.g., glucose) (Retamal et al. 2007a). Recently, another gene family encoding a set of three membrane proteins, named pannexins (Panxs 1-3), has been identified (Bruzzone et al. 2003). Up to now, only Panx3 has been shown to form gap junctions in osteoblasts (Ishikawa et al. 2011) and further studies will be required to identify pannexin gap junctions in other cell types. Connexins and pannexins present similar membrane topology, with four α -helical transmembrane domains connected by two

extracellular loops, where both N- and C-termini are intracellular. However, there is only 16% overall identity when their full-length amino acid sequences are compared.

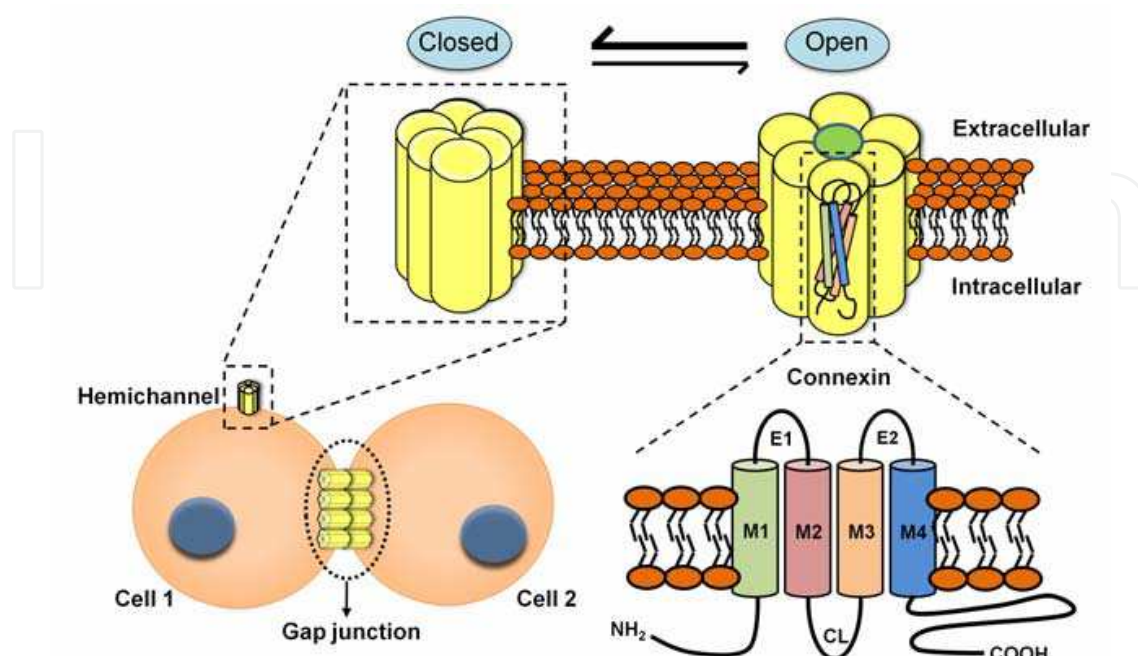


Fig. 1. Diagram illustrating basic structures of connexins and undocked hemichannels present at the cell surface. The membrane topology of a connexin consists of 4 membrane-spanning domains (M1-M4), 2 extracellular loops (E1 and E2) and 1 cytoplasmic loop (CL). The amino (-NH₂) and carboxy (-COOH) terminal tail are intracellular. A hemichannel is formed by six connexins that oligomerize laterally leaving a central pore. In cultured cells under resting conditions hemichannels remain preferentially closed, but they can be activated by diverse physiological and pathological conditions, offering a diffusional transmembrane route between the intra and extracellular milieu. [Modified from Orellana et al. 2011a]

A main role in cellular proliferation and tissue remodelling has been attributed to hemichannels (Burra and Jiang 2009; Schalper et al. 2008), while in the CNS they have been proposed to mediate ischemic tolerance (Lin et al. 2008; Schock et al. 2008) and establish adhesive interactions (Cotrina et al. 2008). To date, most studies suggest that under normal brain conditions hemichannels release physiological molecules relevant for intercellular signalling, including propagation of intercellular Ca²⁺ waves (Orellana et al. 2011a). However, an increasing body of evidence has situated the hemichannels as potential regulators of the beginning and maintenance of homeostatic imbalances present in diverse brain diseases (Orellana et al. 2009). Pioneering findings by Contreras and co-workers (Contreras et al. 2002) showed that astroglial death induced by ischemia-like conditions is accelerated by the opening of Cx43 hemichannels. In this sense, a constant increase of [Ca²⁺]_i mediated by augmented Ca²⁺ entry through hemichannels, which are permeable to Ca²⁺ (Schalper et al. 2010), and deficient or insufficient Ca²⁺ handling by injured cells could lead to cell death. Here, we review and discuss the current evidence about the role of hemichannels in three major neurodegenerative diseases, namely, bacterial meningitis, stroke and Alzheimer's disease.

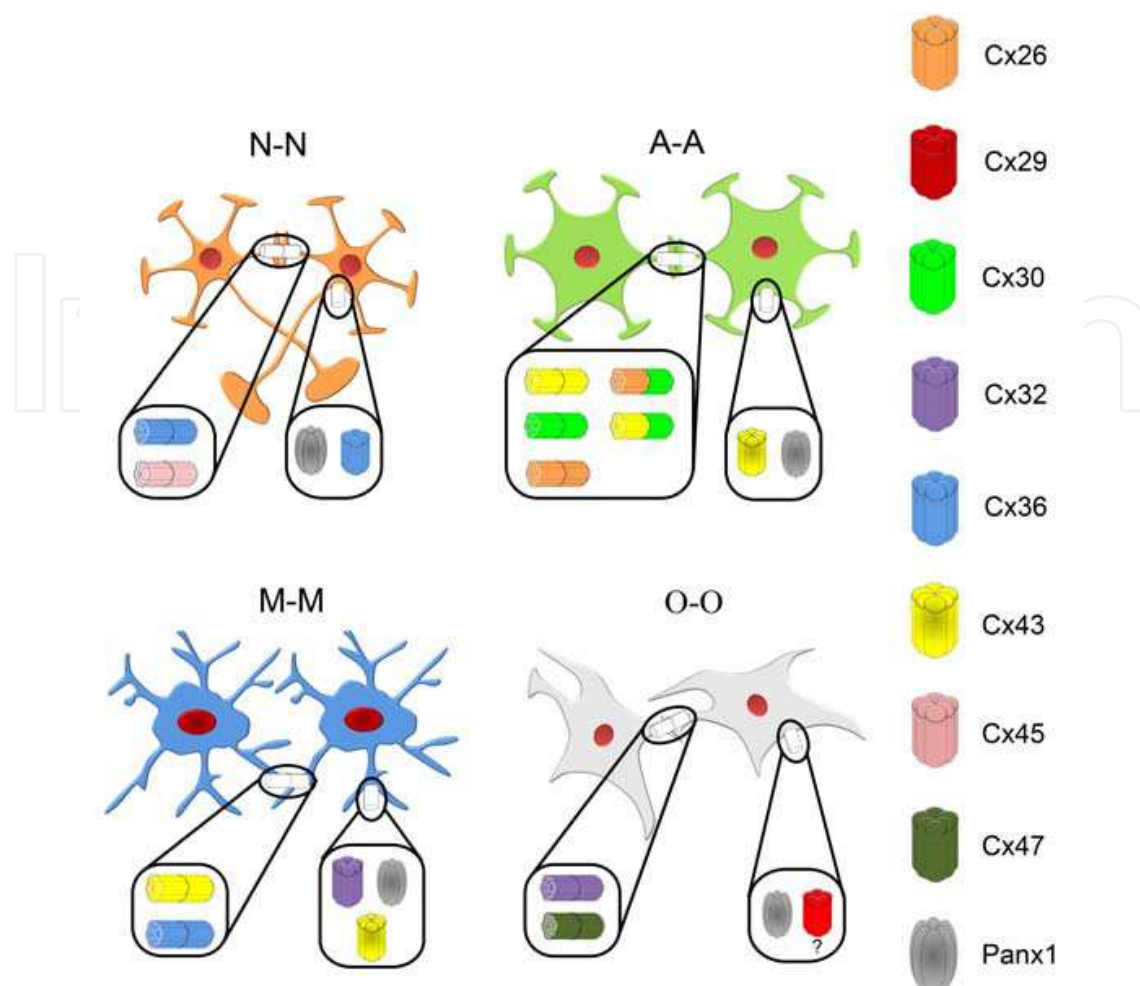


Fig. 2. Cellular distribution of pannexin and connexin hemichannels and connexin gap junctions in brain cells. This figure includes only those cases in which the available information has been obtained *in vivo* and/or *in vitro* with more than one experimental approach. Homocellular connexin gap junction channels and connexin and pannexin hemichannels are indicated within the encircled regions. Neuron (N), astrocyte (A), microglia (M) and oligodendrocyte (O). [Modified from Orellana et al. 2009]

2. What is known about hemichannels in neurological disorders?

2.1 Bacterial meningitis

Despite the advances in the understanding of infectious diseases, including bacterial meningitis, pathogen-host interactions and the widespread use of chemotherapeutic agents, infections are still an important cause of mortality, morbidity and social burden worldwide. Bacterial meningitis promotes inflammation of the pia, arachnoid, and subarachnoid space. Inflammation may also affect the brain parenchyma leading to encephalitis. Bacteria present in the bloodstream induce an innate immune response which produces systemic release of cytokines, mainly $\text{TNF-}\alpha$ (Dietzman et al. 1974; Ring et al. 1998). Then, bacteria colonize and cross the inflamed blood-brain barrier (BBB) and components of their wall, such as lipopolysaccharide (LPS) (Bannerman et al. 1998), peptidoglycan (PGN) (Bannerman et al. 1998), or streptococcal hemolysin/cytolysin (Doran et al. 2003), induce BBB activation and permeabilization (Freyer et al. 1999) (Fig. 3). BBB activation is characterized by numerous

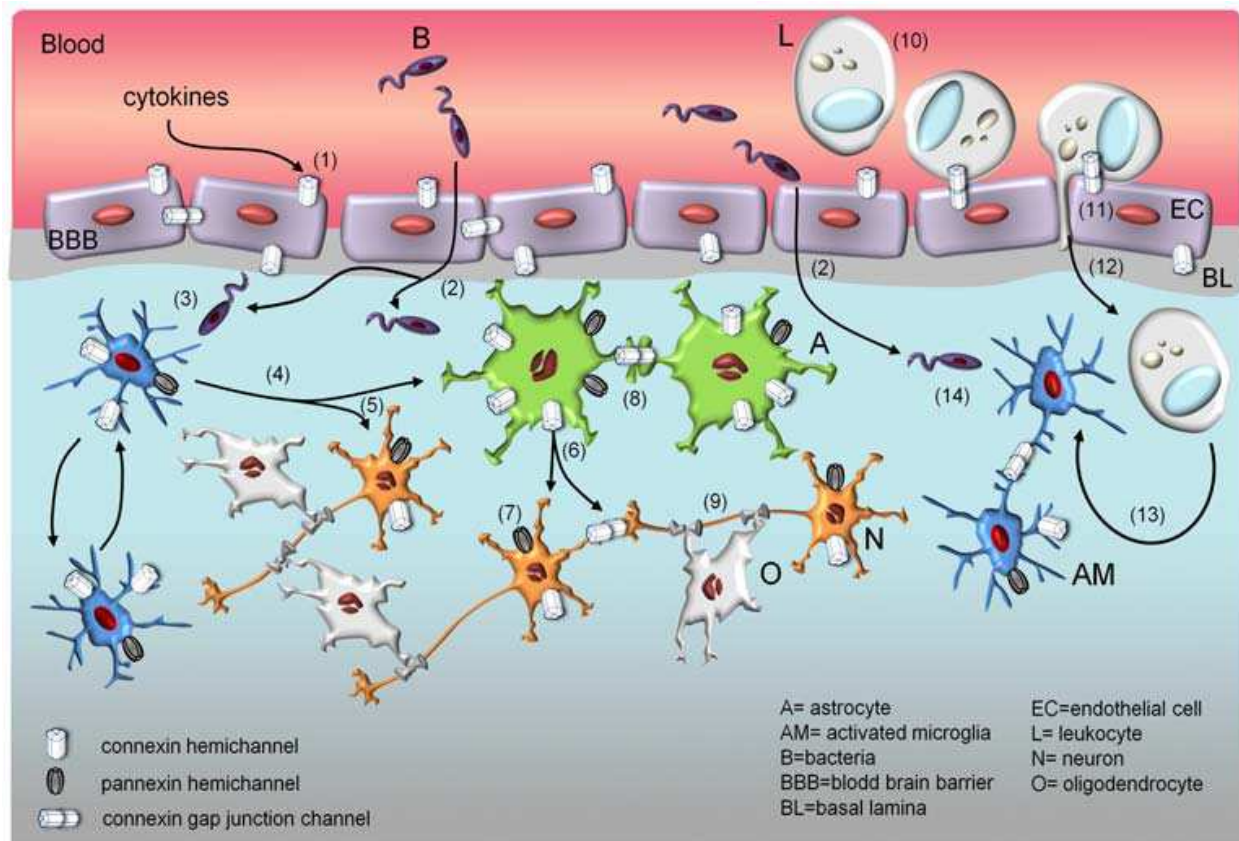


Fig. 3. Connexin based channels in brain cells during bacterial meningitis. During bacterial infection blood levels of cytokine (e.g., $\text{TNF-}\alpha$ and $\text{IL-1}\beta$) are elevated. Both, $\text{TNF-}\alpha$ and $\text{IL-1}\beta$ enhance the hemichannel activity (1) of brain endothelial cells. Furthermore, these cytokines induce BBB discontinuity favoring bacterial extravasation (2). Once in the interstitium, bacteria and their extracellular wall components such as LPS and PGN are recognized by microglia (3), which are activated and release cytokines that further activate them (reciprocal arrows). ATP released via hemichannels from microglia (4) promotes microglial migration from less affected regions. Activated microglia can also release glutamate through hemichannels and oxygen and nitrogen derived free radicals that are neurotoxic (5). The enhanced hemichannel activity of activated astrocytes induces neuronal damage through the release of neurotoxic and/or inflammatory compounds such glutamate and PGE_2 (6). These compounds may also increase the activity of neuronal connexin/pannexin hemichannels (7) causing electrochemical imbalance and Ca^{2+} overload in neurons. In contrast to increased opening of hemichannels, astroglial gap junction communication is reduced (8), impairing glutamate and K^+ spatial buffering that enhances neuronal susceptibility to insults. Bacterial meningitis can also induce demyelination (9), possibly via microglial cytokine release. Severe inflammation induces recruitment of leukocytes (10) to the infected loci. Gap junction communication between leukocytes and endothelial cells (11) may contribute to strength heterocellular adhesion and allow transfer of signals that regulate leukocyte diapedesis across the endothelium (12). Activated microglia may perform antigen cross-presentation interaction with infiltrating leukocytes in which gap junctions between them may play an important role (13). Direct microglial interaction with LPS or PGN induces gap junction communication between microglia, which can coordinate microglial function (14). [Modified from Orellana et al. 2009]

changes including cytokine production, overexpression of cell adhesion molecules and NO synthesis (Freyer et al. 1999). Recently, hemichannels have been implicated in the pathogenesis of bacterial meningitis. Using a model of bacterial brain abscess, Karpuk and co-workers (Karpuk et al. 2011) showed that a transient hemichannel activity is induced in astrocytes within close proximity to the abscess border, which dissipates with increasing distance from the inflammatory site. Moreover, this transient hemichannel opening was blocked with the Cx43 mimetic peptide Gap26, carbenoxolone, the Panx1 mimetic peptide ¹⁰panx1, and probenecid (Karpuk et al. 2011), indicating the involvement of both Cx43 and Panx1 hemichannels in this response. In addition, astroglial gap junction coupling was significantly reduced in areas immediately surrounding the abscess margins, while regions far from abscess presented normal coupling (Karpuk et al. 2011). These data are consistent with previous studies showing opposite regulation of gap junction channels versus hemichannels in astrocytes subjected to pro-inflammatory conditions (Froger et al. 2010; Froger et al. 2009; Orellana et al. 2011b; Orellana et al. 2010; Retamal et al. 2007a).

Pioneering findings by Retamal and co-workers (Retamal et al. 2007a) showed that TNF- α and IL-1 β released from LPS-treated microglia induce an increase and decrease in astroglial hemichannel and gap junction channel activity, respectively (Retamal et al. 2007a).

The consequence of this opposite regulation on the homeostasis of the infected and uninfected brain parenchyma and how they may influence CNS function remain to be elucidated. A possible consequence of increased astroglial hemichannel opening could be an enhanced glucose uptake, which might explain the observed changes in the metabolic status of astrocytes under inflammatory conditions (Retamal et al. 2007a). Moreover, hemichannel-mediated astroglial release of neurotoxic and/or inflammatory compounds such as glutamate and ATP could promote paracrine neuronal damage (Iglesias et al. 2009; Jiang et al. 2011; Kang et al. 2008; Orellana et al. 2011b; Orellana et al. 2011c; Ye et al. 2003).

Since the BBB critically regulates the passage of molecules into the CNS, the possibility of defective hemichannels in cells of the BBB during bacterial meningitis may be relevant. In this regard, TNF- α blocks the ATP release induced by photoliberation of InsP₃ or zero [Ca²⁺]_o, but increases the basal ATP release and hemichannel-mediated dye uptake in brain cortical endothelium derived cell lines, RBE4 and GP8 (Vandamme et al. 2004). Since the increase in basal ATP release induced by TNF- α is not affected by the mimetic peptide Gap26, a prominent blocker of InsP₃- and zero Ca²⁺-triggered connexin-dependent ATP release (Braet et al. 2003), it was concluded that the InsP₃- and zero Ca²⁺-induced ATP release would involve a mechanism distinct from the one involved in the TNF- α induced elevation of basal ATP release (Vandamme et al. 2004). However, the authors did not rule out the involvement of other type of hemichannels (connexin/pannexins), including hemichannels formed by Cx40, which is highly expressed in brain endothelial cells (Nagasawa et al. 2006). Thus, the rise in basal activity induced by TNF- α could be related to Cx40 and/or pannexin hemichannels. At least in peripheral endothelial cells, the ATP release induced by brief exposure to PGN depends exclusively on Cx43 hemichannels (Robertson et al. 2010).

Enhanced endothelial hemichannel activity could elevate the ATP release, which would recruit microglia to the injury site (Davalos et al. 2005). In agreement with a role of hemichannels in ATP release during inflammatory conditions triggered by bacterial

infections, *Shigella* infection of epithelial cells promote ATP release through Cx26 hemichannels, resulting in the activation of purinergic receptors on neighboring cells and bacterial dissemination (Tran Van Nhieu et al. 2003). In the same way, normal calcium signaling between astrocytes could be affected under pro-inflammatory conditions, eliciting one of the two calcium waves reported (Orellana et al. 2011a) (Fig. 4). In one of them, Ca^{2+} waves propagate by diffusion of cytoplasmic inositol (1,4,5)-trisphosphate (IP_3) through gap junctions between astrocytes, after phospholipase C (PLC) activation (Fig. 4). Evidence for this mechanism includes: (i) the waves are dependent on gap junctional communication; (ii) the waves are not blocked by extracellular apyrase, which is an ATPase; (iii) are not blocked by purine-receptor antagonists such as suramin; and (iv) do not jump a gap between cells (Orellana et al. 2011a). Other possible mechanism for astroglial Ca^{2+} waves is through the ATP released by Cx43 and/or Pannx1 hemichannels after ATP-mediated P2 receptor activation (Fig. 4). Evidence for this mechanism include: (i) the waves require Cx43 and/or Pannx1 expression (ii) hemichannel blockers prevent the waves; (iii) ATP is released by the

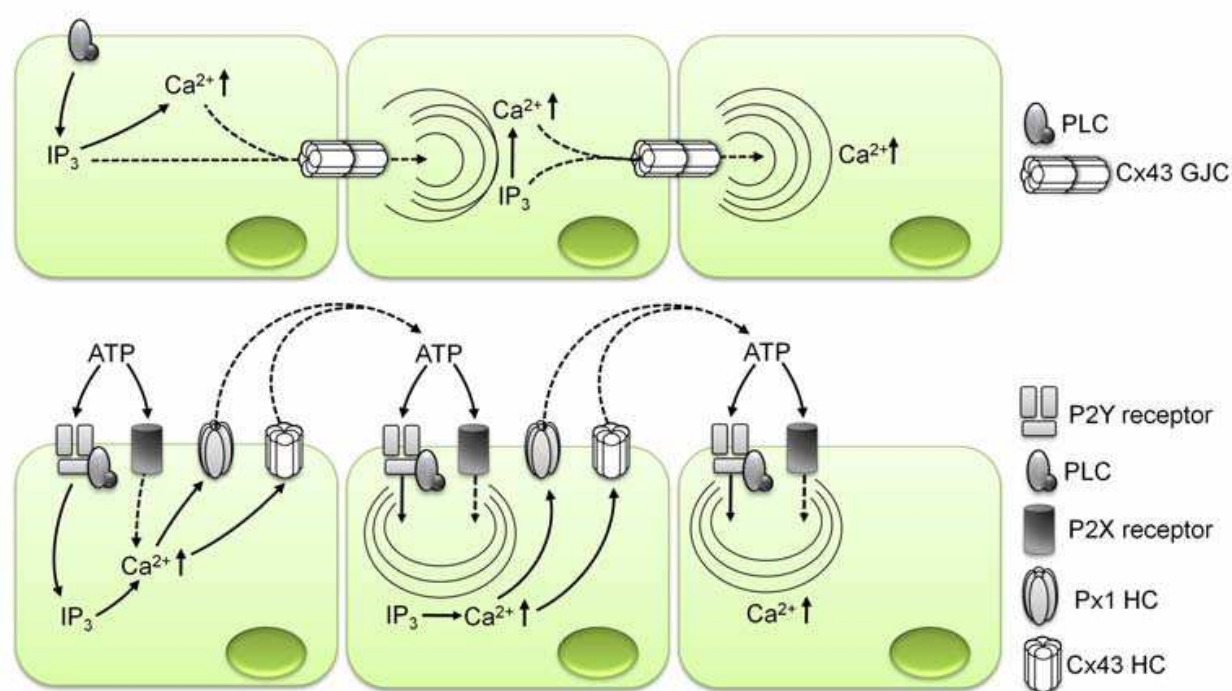


Fig. 4. Two models for conduction of Ca^{2+} waves in astrocytes. (Top panel) Upstream receptor stimulation leads to activation of phospholipase C (PLC) and formation of cytoplasmic inositol (1,4,5)-trisphosphate (IP_3), which promote the release of Ca^{2+} stored in the endoplasmic reticulum. Both IP_3 and Ca^{2+} diffuse to neighboring cells through gap junction channels generating waves of rises in intracellular Ca^{2+} concentration $[\text{Ca}^{2+}]_i$. (Bottom panel) ATP released from vesicles and/or ion channels diffuses through the extracellular space and activates membrane purinergic (P2) receptors. Stimulation of metabotropic P2Y receptors leads to activation of phospholipase C (PLC) and formation of IP_3 . Whereas, activation of ionotropic P2X receptors leads to Ca^{2+} influx. The increase in free $[\text{Ca}^{2+}]_i$ induced by IP_3 and P2X receptor opening could promote ATP release through Cx43 and Pannx1 hemichannels, extending the Ca^{2+} wave to neighboring cells. [Modified from Orellana et al. 2011a]

initiator cell, and the Ca^{2+} waves extend as far as the ATP diffuses; (iv) the waves are blocked by extracellular apyrase; (v) are blocked by suramin (P2 receptor blocker); and (vi) jump cell-free gaps and are deflected by flow of medium (Orellana et al. 2011a). Probably, *in vivo* these two mechanisms coexist and are subjected to regulation by neuro- and gliotransmitters, playing a key role in the functional synchronization of neurovascular coupling.

As mentioned before, in the brain parenchyma, bacteria may undergo lysis and thus, they release pro-inflammatory and toxic factors such as PGN and LPS (Stuertz et al. 1998; Stuertz et al. 1999), while microglia interact directly with intact bacteria (Kim 2003). Bacterial derived pro-inflammatory factors such as LPS induce neurodegeneration (Qin et al. 2007). PGN and LPS stimulate microglial Toll-like receptors (TLRs), induce translocation of nuclear factor (NF) κB (Schwandner et al. 1999), and activation of MAPK signaling and transcription of genes encoding inflammatory cytokines (Laflamme and Rivest 2001; Nau and Bruck 2002). Moreover, PGN increases microglial Cx43 mRNA and protein expression, which correlates with development of gap junction communication *in vitro* (Garg et al. 2005). Similarly, treatment with LPS plus IFN- γ increases Cx43 expression in rat microglia and induces gap junction communication (Eugenín et al. 2001). In addition, brain stab wounds induce recruitment of Cx43 immunoreactive microglia to the injured foci, suggesting that Cx43 is important for coordinating microglial responses (Eugenín et al. 2001). However, up to now, the functional state of hemichannels in microglia has been not examined in model of bacterial brain infection.

Bacterial meningitis also causes axonal damage and demyelination (Nau et al. 2004). These effects may be related to microglial cytokine release, which could promote opening of oligodendrocyte hemichannels, possibly composed of Panx1, Cx32 or Cx29 [Cx29 does not form gap junctions and faces the periaxonal space (Li et al. 2002)] and, thus, promoting ion gradient imbalance and Ca^{2+} overload.

Adhesion between leukocytes and endothelial cells could result in part from leuko-endothelial gap junction formation (Veliz et al. 2008). In fact, treatment with diverse gap junction channel blockers reduces leukocyte adhesion to venular endothelium *in vivo* (Veliz et al. 2008) as well as transmigration across a BBB model (Eugenín et al. 2003). Gap junctions between lymphoma and endothelial cells have also been demonstrated, and $\alpha\text{-GA}$ attenuates the transmigration of lymphoma cells across an endothelial barrier (Haddad et al. 2008). However, it is important to keep in mind that most gap junction blockers will also block hemichannels and that connexin knockout animals will also have impaired transmembrane diffusional transport mediated by hemichannels. Indeed, the autocrine release of ATP through Cx37 hemichannels in monocyte/macrophages limits their adhesion to the endothelial wall and recruitment to the subendothelial compartment (Wong et al. 2006). Recent findings also suggest that connexin and pannexin hemichannels participate in acute and chronic inflammatory responses mediated by macrophagic cells. In fact, LPS or TNF- α promote microglial release of neurotoxic glutamate concentrations via Cx32 hemichannels (Takeuchi et al. 2006). Panx1 hemichannel opening occur in primary macrophages, macrophage cell lines and microglia exposed to pro-inflammatory conditions (Orellana et al. 2011c; Pelegrin and Surprenant 2006; Pelegrin and Surprenant 2007). In addition, caspase-1/inflammasome-mediated release of members of the IL-1 family including IL-1 β from mouse peritoneal macrophages requires hemichannel activation through P2X $_7$ purinergic receptors (Pelegrin and Surprenant 2006).

2.2 Stroke

Stroke is a major cause of death in industrialized countries and results from a transient or permanent reduction in cerebral blood flow produced, in most cases, by cerebral artery occlusion by an embolus or local thrombosis, i.e., focal ischemia (Dirnagl et al. 1999). Severe and/or prolonged reduction in cerebral blood flow leads to deprivation of oxygen and glucose as well as build-up of potentially toxic substances. During stroke, decreased cellular oxygen levels, loss of oxidative phosphorylation and reduced ATP synthesis are the initial steps leading to cell death (Dirnagl et al. 1999). The ATP depletion may induce a rapid decrease in ATPase activity, leading to imbalanced electrochemical gradients across the plasma membrane. Notably, increased pannexin and/or connexin hemichannel activity occur in cortical astrocytes (Contreras et al. 2002; Orellana et al. 2011b; Orellana et al. 2010; Retamal et al. 2006), oligodendrocytes (Domercq et al. 2010) and hippocampal neurons (Lin et al. 2008; Schock et al. 2008; Thompson et al. 2006) subjected to ischemic like conditions. The enhanced hemichannel activity induced by ischemic like conditions accelerates cell death, at least in cultured rat astrocytes (Contreras et al. 2002; Orellana et al. 2010) (Fig. 5). Possibly, sustained hemichannel opening contribute to increased $[Ca^{2+}]_i$, which in turn may favour even more the connexin hemichannel activity (De Vuyst et al. 2007; Schalper et al. 2008), inducing Ca^{2+} and Na^+ intracellular overload (Fig. 5). The ionic (or electrolyte) imbalance leads to an osmotic imbalance that results in cell swelling and plasma membrane phospholipase A_2 , with the subsequent generation of arachidonic acid and activation of

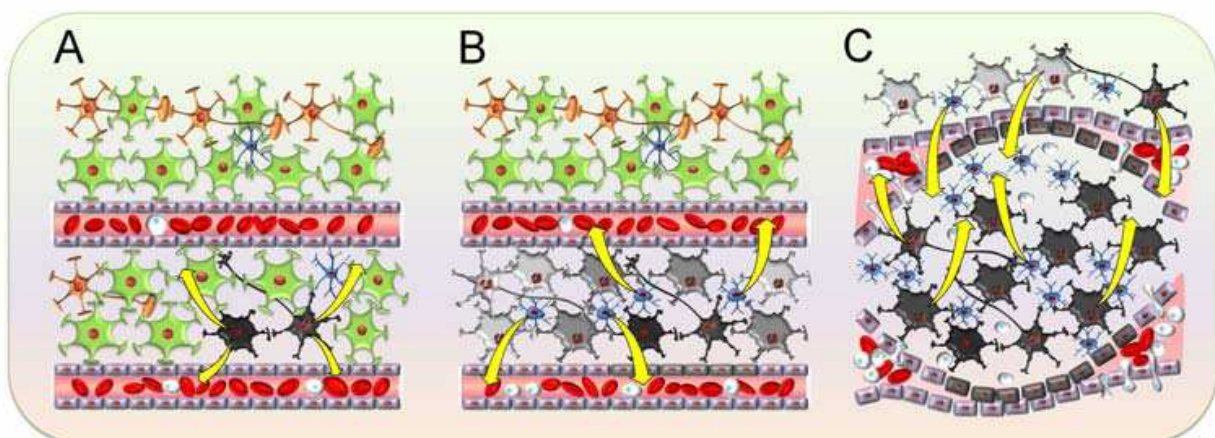


Fig. 5. Three mechanisms of death amplification. (A) Initially, a brain injury produced by ischemia, infection or necrosis affecting astrocytes (green), neurons (orange) or resting microglia (blue), could start a wave of death propagated (yellow arrows) and amplified through diffusible toxins and molecules (e.g., Ca^{2+} , NO, superoxide ion, peroxynitrite, glutamate, and NAD^+) present in high concentration in injured cells (depicted in the figure as dark colored cells). These molecules could be transferred through connexin gap junctions and connexin and pannexin hemichannels from injured cells (less and more affected cells in gray and black, respectively) to healthier cells. (B) Later, a second wave of death (yellow arrows) may be mediated by microglial cells overactivated by ATP and cytokines released by injured cells. (C) Still later inflammation-induced edema that reduces tissue perfusion could worsen the inflammatory response, recruiting leucocytes and increasing the extent of the lesion. [Modified from Orellana et al. 2009]

breakdown as observed in astrocytes exposed to ischemic conditions (Kimmelberg 2005) (Fig. 5). Calcium overload induced in part by hemichannel opening may also activate cyclooxygenase/lipoxygenase pathways leading to increased free radicals, lipid peroxidation and further plasma membrane damage. It is noteworthy that arachidonic acid and decrease in the intracellular redox potential also activates Cx43 hemichannels, which may exacerbate cell damage (De Vuyst et al. 2009; Retamal et al. 2007b).

The first *in vivo* evidence for the involvement of connexin-based channels in the spread of death signals came from experiments in which octanol, a non-selective gap junction and hemichannel blocker, reduced the infarct size after focal cerebral ischemia (Rawanduzy et al. 1997). However, these observations disagree with the findings obtained in heterozygous Cx43 knockout mice or mouse astrocytes lacking Cx43 expression, in which focal ischemia causes larger lesions (Nakase et al. 2003; Nakase et al. 2004; Siushansian et al. 2001). In a rat model of transient global ischemia, pretreatment with compounds that block both hemichannels and gap junction channels (i.e. CBX, α -GA and endothelin) reduces the number of apoptotic neurons as compared to the contralateral hippocampus treated with saline (Perez Velazquez et al. 2006). In addition, hemichannels present in surrounding cells or in the stromal component of diverse organs may also participate in the ischemic responses. For example, the CA1 region of Cx32- deficient mice show increased sensitivity to global ischemia (Oguro et al. 2001). Since Cx32 forms hemichannels in activated microglia (Takeuchi et al. 2006), it is possible that Cx32 knockout animals may show attenuated microglial release of regulatory paracrine signals. When acute diseases like stroke have the presence of other pro-inflammatory components (e.g. high glucose produced by diabetes mellitus), brain damage and cognitive functions in patients is worse (Pasquier et al. 2006). Indeed, it has long been known that hyperglycemia worsens the outcome of acute brain ischemia by increasing the extent of tissue injury in animals and humans (Kagansky et al. 2001). Recently, we showed in astrocytes that high levels of extracellular glucose increase hemichannel activity and decrease gap junction permeability induced by hypoxia (Orellana et al. 2010). These changes are transient after 3 hours of hypoxia in high glucose. However, they are more prominent after 6 hours of hypoxia and last for over 3 hours followed by death of numerous astrocytes (Orellana et al. 2010). Because high glucose worsens the effect on ischemia-induced cell damage in endothelial cells, neurons, and microglia (Kagansky et al. 2001; Lin et al. 1998a; Tsuruta et al. ; Wang et al. 2001), it would be of interest to study if elevated hemichannel activity plays a relevant role as in astrocytes. Importantly, we also demonstrated that microglia treated with amyloid β peptide ($A\beta$) potentiate the increase in astroglial hemichannel activity and reduction in gap junctional communication induced by hypoxia in high glucose, suggesting that these changes are a common denominator of inflamed or activated astrocytes (Orellana et al. 2011b) (Fig. 6).

In addition, the extracellular media of activated astrocytes was neurotoxic due to its glutamate and ATP content that activate neuronal Panx1 hemichannels via NMDA/P2X receptors leading to neuronal death (Orellana et al. 2011b). Therefore, in a more integrated system (e.g., brain or brain slices) neurons could be efficiently protected from ischemia and neurotoxicity by blocking NMDA and P2X receptors as already proposed (Dirnagl et al. 1999), but also by targeting either glial or neuronal hemichannels composed by Cx43 and Panx1, respectively.

Hemichannels may also be involved in tissue response to stroke through their participation in a phenomenon known as ischemic preconditioning, in which a sublethal ischemic insult induces resistance to a subsequent more severe insult (Gidday 2006). It was recently shown

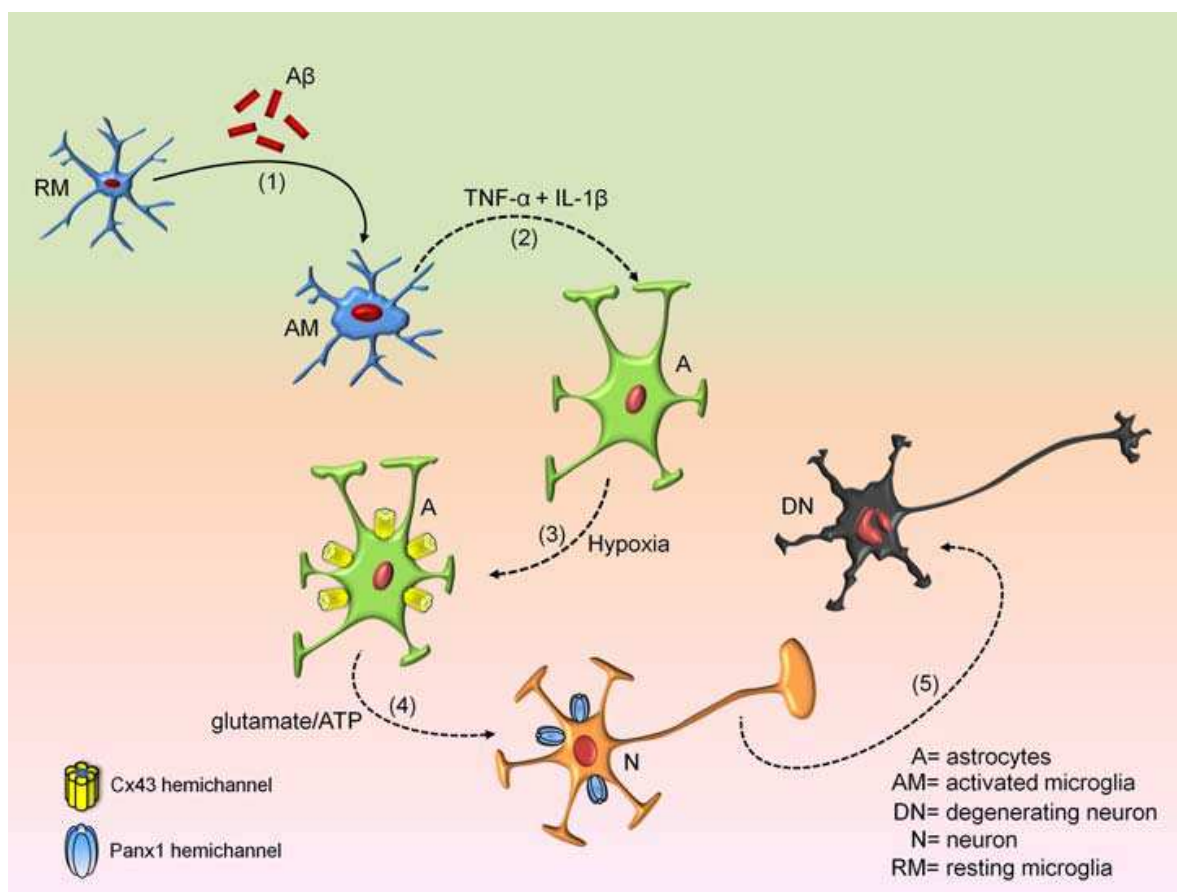


Fig. 6. Involvement of extracellular signals released by inflamed glial cells in neuronal death. Activated microglia (by for example $A\beta$) release pro-inflammatory cytokines (e.g., $TNF-\alpha$ / $IL-1\beta$), which increase astroglial hemichannel activity when another pro-inflammatory agent is involved (e.g., hypoxia). Then, astrocytes release glutamate and ATP via Cx43 hemichannels, which can activate more microglia and could promote activation of neuronal NMDA and P2X receptors and further opening of Panx1 hemichannels in neurons. ATP released as a result of Panx1 hemichannel opening could contribute to the progression of neuronal death by a vicious cycle since it will activate more P2X receptors leading to more Ca^{2+} entry and activation of intracellular neurotoxic cascades. Moreover, dead neurons can activate more microglia and thus, can either restart or potentiate the toxic circuit. [Modified from Orellana et al. 2011b]

that preconditioning reduces degradation of Cx43 in astrocytes, leading to a marked increase in the amount of surface Cx43 hemichannels (Lin et al. 2008). In agreement with the possible involvement of hemichannels in preconditioning responses, Cx43 null mice are insensitive to hypoxic preconditioning whereas wild-type littermates mice exhibit a prominent reduction in infarct volume after induction of preconditioning through occlusion of the middle cerebral artery (Lin et al. 2008). The mechanism of neuroprotection in this model involves the release of ATP through Cx43 hemichannels to the extracellular milieu, where it becomes hydrolyzed to adenosine, a potent neuroprotective molecule. The involvement of Cx36 hemichannels in the preconditioning response of cultured cerebellar granule neurons has been also recently demonstrated (Schock et al. 2008). The possible involvement of pannexin based hemichannels in brain preconditioning responses remains

unknown. Final demonstration of the relative importance of enhanced hemichannel activity on cell viability during ischemia *in vivo* will require new approaches including better controlled experimental models and molecules that selectively block connexin- or pannexin-based hemichannels.

2.3 Alzheimer's Disease

Alzheimer's Disease (AD) is an age-related neurodegenerative disease that results in memory loss, behaviour and personality changes, among other symptoms. This disorder is characterized by the accumulation of the A β into amyloid plaques in the extracellular brain parenchyma, formation of tangles inside neurons as a result of abnormal phosphorylation of the microtubule associated protein tau, dendritic atrophy, and changes in neurotransmission in specific brain regions (Parihar and Hemnani 2004). A β is generated by proteolytic cleavage of the amyloid precursor protein (APP), which plays a role in neuronal adhesion, synaptogenesis, and axonal growth (Parihar and Hemnani 2004). High concentrations of A β are toxic to several neuronal types (Loo et al. 1993; Parihar and Hemnani 2004; Pike et al. 1995). The mechanisms underlying A β -neurotoxicity are complex but involve activation of NMDA receptors, sustained elevations of $[Ca^{2+}]_i$, and oxidative stress (Ekinici et al. 2000; Forloni et al. 1993), which are effects common to those induced by ischemia-reperfusion but on a different time scale.

In addition to the above, the cerebral cortex of individuals with AD present activated microglia and astroglia closely associated with amyloid plaques (Kalara 1999; Wisniewski and Wegiel 1991). Notably, increased Cx43 immunoreactivity is detected in about 80% of A β plaques in postmortem human samples from AD patients (Nagy et al. 1996). Accordingly, a recent study performed in a murine model of AD showed that the immunoreactivity for Cxs 30 and 43 is increased at the proximity of most A β plaques (Mei et al. 2010). Imbalance in brain homeostasis may explain the increase expression of Cxs 30 and 43 close to amyloid plaques as compensatory mechanism to ensure normal brain function (Mei et al. 2010)(Nagy et al. 1996). Alternatively, increased astroglial gap junctions may serve as a pathway for the propagation of neuronal damage, transferring death signals generated in the microenvironment of amyloid plaques to distant neurons, as death signals can propagate from C6 glioma cells injured with calcium ionophore (Lin et al. 1998b). In agreement with this interpretation, inhibition of gap junctions with octanol abolishes the ability of A β to enhance the velocity and extent of propagation of astroglial calcium waves (Haughey and Mattson 2003). However, octanol also blocks P2X₇ receptors expressed by spinal astrocytes that also show calcium waves (Suadicani et al. 2006). In support of P2 receptor mediation of the A β -induced increase of calcium wave velocity in cortical astrocytes is the fact that suramin, a P2Y and P2X receptors blocker, reduces this response (Haughey and Mattson 2003).

Recently, it was shown that the treatment with the neurotoxic fragment of A β , 25-35 (A β_{25-35}) increases hemichannel opening in microglia, astrocytes and neurons monitored by single-channel recordings and by time-lapse ethidium uptake (Orellana et al. 2011c). The hemichannel forming proteins responsible of this activity were Cx43 and Panx1 in the case of microglia, Cx43 in the case of astrocytes and Panx1 and possibly Cx36 in neurons (Orellana et al. 2011c). Moreover, A β_{25-35} increased the surface level of Cx43 in microglia and astrocytes and for the first time it was detected an increase in surface Panx1 in A β_{25-35} - treated microglia (Orellana et al. 2011c). Panx1 was also detected in astrocytes, but not at

their surface, either in the absence or presence of $A\beta_{25-35}$, which is in disagreement with a recent study in which astroglial Panx1 hemichannels were activated by extracellular ATP (Iglesias et al. 2009). Importantly, conditioned media harvested either from $A\beta_{25-35}$ -treated microglia or astrocytes, increased neuronal ethidium uptake and mortality, an effect prevented by inhibitors of P2X/NMDA receptors and Panx1 hemichannels, indicating that ATP and glutamate contribute to these changes (Orellana et al. 2011c). The contribution of these two molecules in neurotoxicity is well known (Lipton and Rosenberg 1994) and the involvement of hemichannels in glutamate and ATP release has also been documented

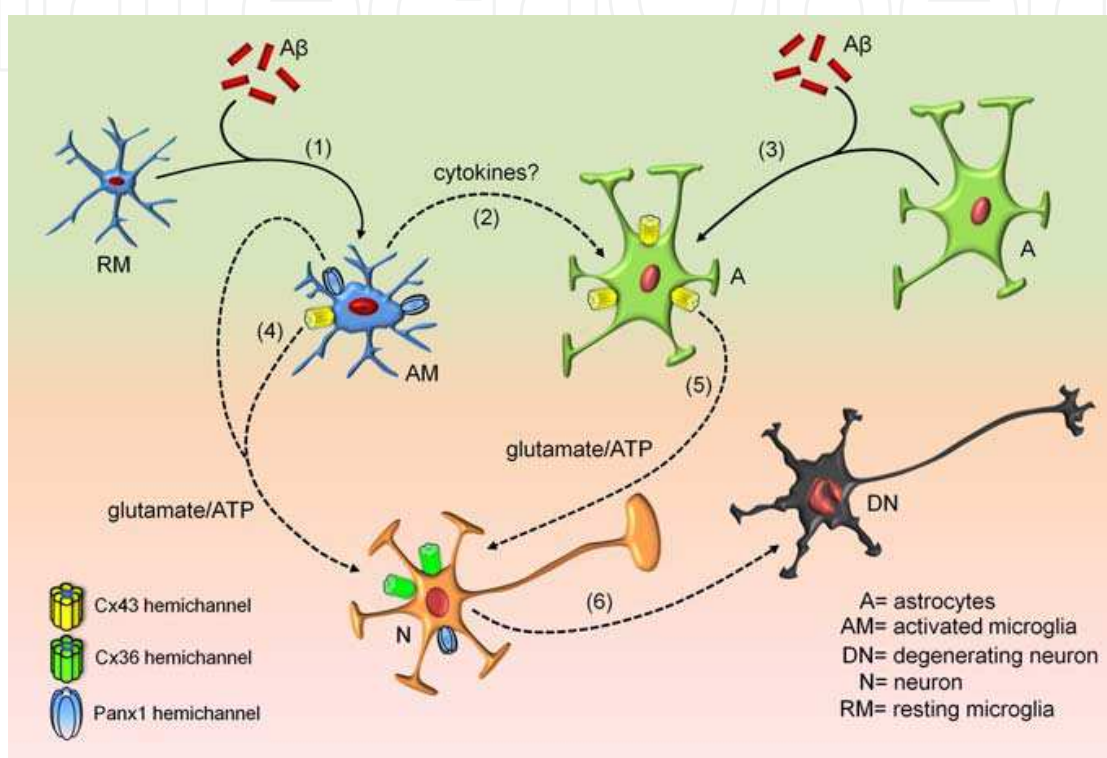


Fig. 7. Model of $A\beta$ -induced cascade resulting in glial and neuronal hemichannel activation that leads to neuronal death. Microglia exposed to the amyloid β ($A\beta$) peptide become first activated (1), enhancing the opening of Cx43 and Panx1 hemichannels. Under these conditions, they release pro-inflammatory cytokines (2) that contribute to the $A\beta$ -induced Cx43 hemichannel opening in astrocytes (3). Activated microglia might release glutamate and ATP through hemichannels (4), while astrocytes could release the same molecules through Cx43 hemichannels (5). This gliotransmission activates neuronal purinergic and NMDA receptors, resulting in an elevation of the intracellular free Ca^{2+} concentration that might trigger massive Cx36 and Panx1 hemichannel opening and further neuronal death (6). [Modified from Orellana et al. 2011c]

(Iglesias et al. 2009; Jiang et al.; Kang et al. 2008; Orellana et al. 2011b; Orellana et al. 2011c; Takeuchi et al. 2006; Ye et al. 2003). Moreover, these two molecules were shown to induce neuronal death via activation of Panx1 hemichannels in neurons (Orellana et al. 2011b). Their effect on neuronal death may proceed according to at least two mechanisms: 1) through the stimulation of NMDA and/or P2X receptors or 2) through Cx36 and Panx1 hemichannels themselves that could evoke large Ca^{2+} influxes resulting in neuronal death (Orellana et al. 2009) (Fig. 7).

Moreover, these two mechanisms could also be linked since transient activation of NMDA receptors induced a nonselective cationic current that develops slowly and mediates Ca^{2+} influx directly linked to neuronal death. Interestingly, this secondary current was reported recently to be mediated by neuronal Panx1 hemichannels (Thompson et al. 2008). Moreover, activation of Panx1 hemichannels might be triggered by protein-protein interaction with activated P2 receptors (Iglesias et al. 2008). Alternatively, Panx1 hemichannels could be activated by the rise in $[\text{Ca}^{2+}]_i$ caused by opening of NMDA and P2X receptors (Locovei et al. 2006). In this mechanism, neuronal ATP released as a result of Panx1 hemichannel opening is also likely to contribute in the progression of neuronal death by a vicious cycle since it will activate more ionotropic P2 receptors enhancing the Ca^{2+} entry and activation of intracellular neurotoxic cascades (Fig. 7). Studies in AD models will help to confirm or reject the above interpretations.

3. Conclusions

In the last decade, connexin hemichannels have been implicated in paracrine and autocrine cellular communication in several normal and pathologic conditions (Sáez et al. 2010). Currently, most of the available data regarding hemichannel involvement in brain pathologic events are from cultured cells and animal models of diseases. However, the current knowledge of human brain disease processes and the documented presence of hemichannels forming proteins in most studied human CNS tissues allows to speculate about the involvement of hemichannels in neurodegenerative processes. The role of glial cells in mediating nervous tissue inflammation has been recognized previously as leading to neuronal death; these cells can be bad neighbours for neurons (Block et al. 2007). Dysfunction of astroglial and microglial hemichannels, as well as gap junction channels, are likely mechanisms commonly elicited in all brain diseases associated with inflammatory responses. Therefore, normalization of connexin- and pannexin-based channel dysfunctions should confer tissue protection, improve quality of life, and extend survival of patients suffering acute or chronic brain inflammatory responses. Thus, it is proposed that chronic or acute processes of neurodegeneration might be prevented by blocking glial and neuronal hemichannels. Prevention might also be accomplished by reducing the effects of soluble factors (i.e., glutamate, ATP, prostaglandins, and cytokines) accumulated in the microenvironment of the inflamed CNS.

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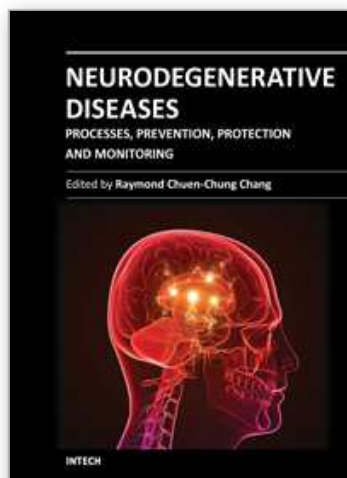
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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring focuses on biological mechanisms, prevention, neuroprotection and even monitoring of disease progression. This book emphasizes the general biological processes of neurodegeneration in different neurodegenerative diseases. Although the primary etiology for different neurodegenerative diseases is different, there is a high level of similarity in the disease processes. The first three sections introduce how toxic proteins, intracellular calcium and oxidative stress affect different biological signaling pathways or molecular machineries to inform neurons to undergo degeneration. A section discusses how neighboring glial cells modulate or promote neurodegeneration. In the next section an evaluation is given of how hormonal and metabolic control modulate disease progression, which is followed by a section exploring some preventive methods using natural products and new pharmacological targets. We also explore how medical devices facilitate patient monitoring. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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