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Inhibitors of connexin and pannexin channels as potential therapeutics

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Abstract

While gap junctions support the exchange of a number of molecules between neighboring cells, connexin hemichannels provide communication between the cytosol and the extracellular environment of an individual cell. The latter equally holds true for channels composed of pannexin proteins, which display an architecture reminiscent of connexin hemichannels. In physiological conditions, gap junctions are usually open, while connexin hemichannels and, to a lesser extent, pannexin channels are typically closed, yet they can be activated by a number of pathological triggers. Several agents are available to inhibit channels built up by connexin and pannexin proteins, including alcoholic substances, glycyrrhetic acid, anesthetics and fatty acids. These compounds not always strictly distinguish between gap junctions, connexin hemichannels and pannexin channels, and may have effects on other targets as well. An exception lies with mimetic peptides, which reproduce specific amino acid sequences in connexin or pannexin primary protein structure. In this paper, a state-of-the-art overview is provided on inhibitors of cellular channels consisting of connexins and pannexins with specific focus on their mode-of-action and therapeutic potential.

Keywords

Connexin; pannexin; hemichannel; gap junction; inhibitor

1 Introduction

Direct intercellular communication is mediated by gap junctions (GJs), which can exchange a number of small molecules, such as adenosine triphosphate (ATP), glutamate and prostaglandins, as well as ions, including Ca^{2+} , between the cytosolic compartments of adjacent cells (Hertzberg et al., 1981). This flux is called gap junctional intercellular communication (GJIC). GJs arise from the interaction between 2 hemichannels (HCs) of neighboring cells, which in turn are composed of 6 connexin (Cx) proteins (Maes et al., 2014). In recent years, it has become clear that Cx HCs are not merely structural precursors

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Conflict of Interest statement

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of GJs, as they also can provide a circuit for communication, albeit between the cytosol and the extracellular environment (Kar et al., 2012; Vinken et al., 2011). Today, 21 different Cx types have been identified in a myriad of human and mouse cell types (Table 1), all which share a similar structure consisting of 4 transmembrane domains, 2 extracellular loops (EL), 1 cytoplasmic loop (CL), 1 cytoplasmic C-terminal tail (CT) and 1 cytoplasmic N-terminal tail (Figure 1) (Vinken et al., 2008; Willebrords et al., 2015). Since various tissues express more than 1 Cx type, homotypic, heterotypic, homomeric and heteromeric GJs may form between cells. GJs can be regulated by different mechanisms, including pH, transmembrane voltage and Ca^{2+} concentration (Cottrell & Burt, 2005). Posttranslational modifications, such as S-nitrosylation, ubiquitination, sumoylation and phosphorylation, also directly regulate GJ opening (Johnstone et al., 2012). Phosphorylation mainly occurs at the cytoplasmic CT. In fact, all Cxs are phosphoproteins with the exception of Cx26. While GJs are usually open in physiological conditions, Cx HCs are typically closed, yet can be activated by a number of pathological stimuli, such as increases in membrane depolarization, increases in intracellular Ca^{2+} concentration (De Vuyst et al., 2006; Wang et al., 2013) or decreases in extracellular Ca^{2+} concentration (Srinivas et al., 2006), mechanical stimulation (Luckprom et al., 2011), changes in the Cx phosphorylation status (Alstrom et al., 2015), oxidative stress (Riquelme & Jiang, 2013), ischemia/reperfusion insults (Wang et al., 2013), fatty acid overload (Puebla et al., 2017) and inflammatory conditions (Willebrords et al., 2016). In this respect, it has been shown that Cx channels are important players in pathological conditions, such as inflammation (Willebrords et al., 2016), gastrointestinal and liver disease (Maes et al., 2015), wound healing (Wright et al., 2009), brain and spinal cord injury (Tonkin et al., 2014), ischemia/reperfusion injury (Wang et al., 2013), atherosclerosis (Morel et al., 2009) and lung disease (Sariieddine et al., 2009).

In 2000, a novel class of Cx-like proteins, the pannexin (Panx) proteins, has been identified. They assemble in Cx HC-like configuration and do not form GJs (Figure 1) (Wang et al., 2013). The Panx family consists of 3 members, namely Panx1, Panx2 and Panx3, of which 1 or more have been detected in every mammalian organ (Table 1). Moreover, it has been reported that heteromeric channels consisting of Panx1 and Panx2 can be formed at the plasma membrane of *X. laevis* oocytes (Bruzzone et al., 2005) with an attenuated functional activity as observed by a decreased dye uptake and currents (Bruzzone et al., 2003). Posttranslational modifications, including phosphorylation, N-glycosylation and S-nitrosylation, are known to affect Panx trafficking and channel gating (Boyce et al., 2017). Panx channels can be activated in both physiological and pathological conditions. Although Panx1 channels open at positive potential, a number of triggers have been identified that promote their opening at membrane resting potential. These include the elevation of intracellular Ca^{2+} concentration (Locovei et al., 2006), ATP binding to purinergic P_2 receptors, such as P_2Y receptors (Locovei et al., 2006) as well as ionotropic receptors, like P_2X_7 receptors (Pelegriin & Surprenant, 2006), oxygen deprivation (Weilinger et al., 2012) and mechanical stress (Locovei et al., 2006). The role of Panx channels in cell death (Chekeni et al., 2010; Cisneros-Mejorado et al., 2015; Sandilos et al., 2012; Xiao et al., 2012) and inflammation (Brough et al., 2009; Crespo Yanguas et al., 2017; Csak et al., 2011; Ganz et al., 2011; Marina-García et al., 2008) has been well documented.

In this review, an overview of chemical-based inhibitors of Cx and Panx channels is provided, including glycyrrhetic acid, carbenoxolone, alcohols, fenamates and quinine, RNA-based inhibitors, antibodies and peptide-based blockers.

2 Chemical-based inhibitors

2.1 Glycyrrhetic acid and derivatives

Historically, 18 α -glycyrrhetic acid (GA) and 18 β -GA were among the first compounds found to inhibit GJs. These pentacyclic triterpenoid saponins are molecular constituents of *Glycyrrhiza glabra*, also named licorice, which is known to perform anti-inflammatory, anti-ulcerous, hepatoprotective and immunomodulatory effects (Amagaya et al., 1984; Capasso et al., 1983; Nose et al., 1994). These properties are partly due to GA's mineralocorticoid and glucocorticoid receptor binding capacity as well as to 11 β -hydroxysteroid dehydrogenase inhibition (Armanini et al., 1983). Furthermore, GA blocks Ca²⁺ currents in rat mesenteric small arteries (10 μ M) (Matchkov et al., 2004), Cl⁻ conductance in primary rat hepatocytes (40 μ M) (Böhmer et al., 2001), delayed rectified K⁺ currents in guinea pig ventricular myocytes (1, 5 and 10 μ M) (Wu et al., 2013), Cx50 and Cx46 HCs (2 μ M) (Bruzzone et al., 2005; Eskandari et al., 2002) as well as Panx1 channels and P₂X₇ receptors (half maximal inhibitory concentration (IC₅₀) 50 μ M) in *X. laevis* oocytes (Bruzzone et al., 2005; Locovei et al., 2007) (Table 2). GA affects many different GJs without being Cx subtype specific (Bodendiek & Raman, 2010), but detailed selectivity studies are lacking.

The mode of inhibitory action of GA is still not completely understood. Direct interaction between GA and GJs is possible when the former is inserted into the plasma membrane, thereby binding to GJs and causing a conformational alteration (Davidson & Baumgarten, 1988; Davidson et al., 1986). This mechanism has been suggested based on the observation of rapid onset and reversal of inhibition (Davidson et al., 1986), yet the reproducibility of this effect has been questioned (Spray et al., 2002). Other possibilities include changes in the Cx phosphorylation status, which lead to a reduction in Cx expression (Goldberg et al., 1996; Guan et al., 1996). When administered *in vivo*, GA exhibits protective effects in a mouse model of allergic asthma (Kim et al., 2017), kidney injury (Abd El-Twab et al., 2016; Wu et al., 2015), auto-immune encephalomyelitis (Zhou et al., 2015), CCl₄-induced liver fibrosis (Chen et al., 2013), lipopolysaccharide-induced vascular permeability (Kim et al., 2013), lipopolysaccharide-induced hepatic failure (Yin et al., 2017), gastritis and gastric tumorigenesis (Cao et al., 2016), acetaminophen-induced liver toxicity (Yang et al., 2015) and obese animal models (Park et al., 2014), which is probably due to its anti-inflammatory action.

Carbenoxolone, a more water-soluble derivate of GA, has different cellular targets and also acts as an inhibitor of 11 β -hydroxysteroid dehydrogenase (Armanini et al., 1982). Specifically, carbenoxolone blocks voltage-gated Ca²⁺ currents in the retina (IC₅₀ 48 μ M) (Vessey et al., 2004), homomeric Panx1 and heteromeric Panx1/Panx2 channels in *X. laevis* oocytes (IC₅₀ 5 μ M) (Bruzzone et al., 2005), Panx1 channels in mouse (IC₅₀ 4 μ M) and human embryonic kidney (HEK)293 cells (IC₅₀ 2 μ M) (Ma et al., 2009; Pelegrin & Surprenant, 2006), P₂X₇ receptors (IC₅₀ 175 nM), HCs consisting of Cx26 (IC₅₀ 21 μ M) and Cx38 (IC₅₀ 34 μ M) in *X. laevis* oocytes and GJs (Ripps et al., 2002, 2004) (Table 2).

Recently, the mechanism of Panx1 channel inhibition of carbenoxolone has been elucidated. It seems that a mutation in the first EL reverses its action polarity and potentiates the voltage-gated channel activity of the Panx1 channel (Michalski & Kawate, 2016). Carbenoxolone displays different protective effects in a model of Parkinson's disease (Thakur & Nehru, 2015), ischemic brain injury (Tamura et al., 2011; Zhang et al., 2013), posttraumatic epilepsy (Chen et al., 2013), allergic airway inflammation (Ram et al., 2009) and fatty liver disease in obese mice (Rhee et al., 2012).

As for steroid hormones, such as testosterone, 17 β -estradiol, cortisone and their esters were found to impair GJIC independent of the shape of the molecules (25 μ M), but correlated with their size and lipophilicity (Hervé et al., 1996). Nevertheless, presence of the ester chain is necessary for inhibition of GJIC. This corresponds with the hypothesis that the mechanism of inhibition is an indirect effect of these structures. Indeed, the ester chains are incorporated in the lipid bilayer in the plasma membrane, thereby disturbing the organization of Cx channels (Goldberg et al., 1996).

2.2 Long-chain alcohols

Heptanol and octanol are often used as fragrances in perfumes and cosmetics because of their pleasant smell. Heptanol triggers Ca²⁺-activated and ATP-sensitive K⁺ channels, but inhibits voltage-gated Ca²⁺ channels (Matchkov et al., 2004). On its turn, octanol blocks Na⁺ currents and T-type of Ca²⁺ channels (122 μ M) and potentiates γ -amino butyric acid (GABA) responses in *X. laevis* oocytes (50 μ M) (Dildy-Mayfield et al., 1996; Hirche, 1985; Todorovic & Lingle, 1998). Both molecules inhibit P₂X₇ receptors and enhance glycine receptor function. Heptanol and octanol have been reported to inhibit GJs in the crayfish giant axon, rat glial cells and insect cells (Guan et al., 1997; Johnston et al., 1980; Weingart & Bukauskas, 1998). Furthermore, they have been shown to block GJIC in cardiac cells (Délèze & Hervé, 1983), stomach and pancreatic epithelial cells (Bernardini et al., 1984) or pancreatic acinar cells (Meda et al., 1986). Heptanol causes a stepwise decrease of ion current, mediated by Cx43 HCs, in a planar lipid bilayer (10 μ M) (Brokamp et al., 2012). Octanol also inhibits Cx50 currents (IC₅₀ 177 μ M) (Eskandari et al., 2002) (Table 2). The inhibitory actions of long-chain alcohols on GJs have been related to their deleterious effects on membrane fluidity (Bastiaanse et al., 1993; Takens-Kwak et al., 1992). Heptanol reduces GJ conductance by decreasing fluidity, in particular of cholesterol-rich membrane domains, in which GJs are embedded (Bastiaanse et al., 1993). The structural requirement for inhibition of GJs seems to be a certain length of the carbohydrate chain and therewith a given lipophilicity (Bodendiek & Raman, 2010). Heptanol has a marked protective effect on cell death during reoxygenation injury (Rodriguez-Sinovas et al., 2006) and ischemia (Chen et al., 2005; Miura et al., 2004) in rat heart.

2.3 Halothane and enflurane

Halothane and enflurane, both halogenated volatile anesthetics, have the ability to inhibit GJs in neonatal cardiac myocytes. Enflurane, isoflurane and halothane have been found to inhibit GJs in crayfish axons (Peracchia, 1991), cultured astrocytes (Mantz et al., 1993) and hippocampal slices (Wentlandt et al., 2006). They also affect several other cellular targets, such as tetrodotoxine (TTX)-resistant and TTX-sensitive Na⁺ channels, excitatory synaptic

transmission, G-protein-activated K⁺ channel currents, muscarinic receptors *via* protein kinase C, antagonization of glutamatergic neurotransmission at *N*-methyl-*D*-aspartate (NMDA) receptors, thromboxane A2 signaling and a number of glutamate receptor subtypes (Banks & Pearce, 1999; Burt & Spray, 1989; Dildy-Mayfield et al., 1996; Hönemann et al., 1998; Jones & Harrison, 1993; Mantz et al., 1993; Minami et al., 1997; Scholz et al., 1998; Sirois et al., 1998; Wentlandt et al., 2006) (Table 2). Halothane seems to have a certain Cx subtype specificity since at μM concentrations, heteromeric Cx40/43 channels are more sensitive than homomeric Cx40 or Cx43 channels (Bodendiek & Raman, 2010). The underlying mechanism is believed to be similar to that of long-chain alcohols (Bodendiek & Raman, 2010). However, it has been suggested that direct interaction between lipophilic compounds and susceptible membrane proteins occurs, which is supported by experiments showing that halothane binds to hydrophobic cavities in proteins (Johansson et al., 2000). Halothane is known to induce liver injury (Soleimanpour et al., 2015), but when applied *in vivo*, halothane can perform protective effects in acetylcholine-induced bronchoconstriction (Lele et al., 2006), retinal light damage (Keller et al., 2001) and myocardial reperfusion injury (Schlack et al., 1998).

2.4 Fatty acids

Fatty acids are classified based upon the length of their aliphatic carbon chain and the number of double bonds. Oleic acid, arachidonic acid and docosahexaenoic acid were the first fatty acids to show strong inhibitory effects on GJs in heart, vascular smooth muscle and liver epithelial cell lines (Hii et al., 1995; Hirschi et al., 1993). Later on, arachidonic acid, linoleic acid and lauric acid were found to perform similar actions on GJs in cells derived from rat lacrimal glands. It is, however, still not clear whether these effects are caused by direct interaction of fatty acids with the Cx structure or if an indirect effect *via* protein kinases is involved (Upham et al., 2009). Linoleic acid was also shown to increase Cx HC activity in HeLa cells transfected with Cx26, Cx32, Cx43 or Cx45 within a few minutes of exposure (Figuerola et al., 2013). Furthermore, linoleic acid increases Cx43 HC activity in a human gastric epithelial cell line (Puebla et al., 2016). Linoleic acid has a biphasic effect on Cx46, by increasing HC currents at low concentrations (0.1 μM) and decreasing at high concentrations (100 μM) without affecting GJs (Retamal et al., 2011). Panx1 channel activity is increased in human and rat liver cell lines upon treatment with palmitic acid and stearic acid (Xiao et al., 2012), but this effect probably depends on the degree of saturation (Puebla et al., 2017) (Table 2). Certain fatty acids could have a beneficial outcome in diabetic nephropathy (Hills et al., 2015), lens cataract (Beyer & Berthoud, 2014), hypertension (Fischer et al., 2008) and cancer (Aasen et al., 2016).

2.5 Fenamates

Fenamates belong to the class of *N*-phenylanthranilic acids and are widely used as nonsteroidal anti-inflammatory drugs because of their ability to inhibit cyclo-oxygenases (Brogden, 1986). In addition, fenamates modulate a diversity of ion channels. They have been identified as inhibitors of voltage-gated and ATP-sensitive K⁺ channels (Grover et al., 1994; Lee & Wang, 1999), voltage-gated Ca²⁺ channels (Li et al., 1998), Ca²⁺-activated Cl⁻ channels (White & Aylwin, 1990) and non-selective cation channels (Gögelein, 1990). On the other hand, fenamates have been shown to activate Ca²⁺-activated and voltage-dependent

K⁺ channels (Farrugia et al., 1993; Ottolia & Toro, 1994). They were also found to block P₂X₇ receptors (IC₅₀ 655 nM). Flufenamic acid inhibits GJs composed of Cx26, Cx32, Cx40, Cx43, Cx46, and Cx50 in N2A mouse neuroblastoma cells (100 μM) and HCs consisting of Cx50, Cx46 and Cx38 in *X. laevis* oocytes (Table 2). They seem to function as chemical modifiers of channel gating, presumably by binding directly to a putative binding site within the membrane not accessible from the intracellular side (Bodendiek & Raman, 2010). Flufenamate provides protection against ischemic insult in isolated retina of chick embryos (Chen et al., 1998).

2.6 Quinine and analogs

Found in the bark of the cinchona tree, quinine has antipyretic, anti-inflammatory and analgesic properties, but is also widely used for its bitter taste in tonic water. Today, it is still used as a back-up drug for the treatment of infections related to the resistant *Plasmodium falciparum*. It is also used for treating benign nocturnal leg cramps (Young, 2002). Quinine affects many different cellular targets, including ion channels, receptors, transporters and enzymes. It blocks ATP-sensitive (IC₅₀ 3 μM) and voltage-gated K⁺ channels (IC₅₀ 8 μM) (Lin et al., 1998; Wang et al., 1994), inhibits Na⁺ currents (85 μM) (Lin et al., 1998) and prevents P-glycoprotein transport (IC₅₀ 6.8 μM). Furthermore, it is a blocker of nicotinic cholinergic receptors (IC₅₀ 1 μM) (Ballesterio et al., 2005) as well as inositol triphosphate (IP₃)-induced Ca²⁺ release (250 μM) (Palade et al., 1989) and is a well-known inhibitor of the cytochrome P450 isoenzyme 2D6 (IC₅₀ 4.9 μM) (Hutzler et al., 2003). In addition, quinine blocks HCs composed of Cx35 (100 μM), Cx46 (100 μM) and Cx38 in *X. laevis* oocytes and GJs built of Cx36 (IC₅₀ 32 μM) and Cx50 (IC₅₀ 73 μM) (Ripps et al., 2002; Srinivas et al., 2001) (Table 2).

A stereo-isomer of quinine, called quinidine, has also been found in the bark of the cinchona tree. It is used in the treatment of arrhythmias (Grace & Camm, 1998). Similar to quinine, quinidine has several cellular targets. It blocks different K⁺ channels (IC₅₀ 875 μM) (Grace & Camm, 1998; Yatani et al., 1993) and Na⁺ channels (IC₅₀ 20 μM) (Koumi et al., 1991), muscarinic (IC₅₀ 1.8 μM) (Hara & Kizaki, 2002) and nicotinic cholinergic receptors (IC₅₀ 1.4 μM) (Ballesterio et al., 2005), P-glycoprotein (IC₅₀ 0.9 μM) (Hsiao et al., 2008) and serotonin transporters in *Drosophila melanogaster* and human beings (Beckman et al., 2014). The quaternary quinine derivative *N*-benzylquininium inhibits Cx50 HCs and has been suggested to bind to its *N*-terminal tail (Rubinos et al., 2012) (Table 2). Quinidine protects the gut from platelet activating factor-induced vasoconstriction, edema and paralysis (Lautenschlager et al., 2015) and hypothermia-induced ventricular tachycardia and fibrillation (Gurabi et al., 2014).

Mefloquine, a synthetic analog of quinine, is useful in the prophylaxis of malaria and is applied as a therapeutic for chloroquine-sensitive or resistant *Plasmodium falciparum* malaria. It is deemed a reasonable alternative for uncomplicated chloroquine-resistant *Plasmodium vivax* malaria. It also inhibits voltage-gated L-type Ca²⁺ channels, ATP-sensitive K⁺ channels, delayed rectifier K⁺ channels, IP₃-induced Ca²⁺ release and serotonin transporters in *Drosophila melanogaster* and human beings (Beckman et al., 2014), P-glycoprotein, P₂X₇ adenosine receptors and GJs consisting of Cx36 (IC₅₀ 300 nM) and

Cx50 (IC₅₀ 1.1 μ M) in transfected N2A mouse neuroblastoma cells (Coker et al., 2000; Cruikshank et al., 2004; Kang et al., 2001; Lee & Go, 1996; Pham et al., 2000; Srinivas et al., 2005) and Cx40 and Cx43 GJs in vascular endothelial cells of guinea pig mesenteric arteries (Yamamoto & Suzuki, 2008). Moreover, mefloquine inhibits Cx26 (IC₅₀ 16 μ M) and Cx50 HC currents when expressed in *X. laevis* oocytes (Levit et al., 2015) (Table 2). Interestingly, mefloquine suppresses tremor in a mouse model of essential tremor and inhibits cortical spreading depression in a rat neocortical slice model (Margineanu & Klitgaard, 2006; Martin & Handforth, 2006).

2.7 2-aminoethoxydiphenyl borate

2-aminoethoxydiphenyl borate (2-APB), an IP₃ receptor modulator, inhibits capacitive current transients, reflecting GJ blockage, in normal rat kidney and HEK293 cells. 2-APB was also found to affect store-operated Ca²⁺ channels. In N2A neuroblastoma cells, 2-APB inhibits conductance of GJs composed of Cx36, Cx40 and Cx50 (IC₅₀ 3 μ M) as well as Cx26, Cx30 and Cx45 (IC₅₀ 18 μ M) (Bai et al., 2006). It also inhibits transient receptor potential (TRP) channels TRPC1, TRPC3, TRPC5, TRPC6, TRPC7, TRPM3, TRPM7, TRPM8 and TRPP2, yet its inhibition seems to be often incomplete (Bai, et al. 2006; Chung et al., 2004; Colton & Zhu, 2007; Harks et al., 2003; Hu et al., 2004; Ma et al., 2001; Maruyama et al., 1997). Its boro-axozolidine ring seems to be an essential part of the pharmacophore for blocking Ca²⁺ release (Table 2). Since diphenhydramine and phenytoin, both lacking the boroaxozolidine ring, block GJs, it has been suggested that the pharmacophore for the inhibition of GJs differs from the one responsible for suppressing Ca²⁺ release. Regarding the pharmacophore for GJ inhibition, it seems that a diphenyl moiety, linked by boron, a tetrahedral carbon or an oxygen is required and allows effective interaction with the channel or access to the channel by decent lipid solubility (Tao & Harris, 2007). 2-APB protects against acetaminophen hepatotoxicity when co-administered with acetaminophen. However follow-up study demonstrated the protection was only minor or completely lost when administered at later time points. In addition part of the effect could be attributed to solvent effect as well as by inhibiting cytochrome P450 enzymes and c-jun *N*-terminal kinase activation (Du et al., 2013).

2.8 Polyamines and cyclodextrins

Polyamines, like spermine and spermidine, are endogenous molecules present in nearly every cell and involved in processes, such as protein synthesis, cell division and growth (Pegg, 2009). Polyamines also modulate a number of ion channels, including Kir and NMDA channels (Williams, 1997). Spermine was found to inhibit Cx40 GJs in a transjunctional voltage-dependent manner (IC₅₀ 100 μ M) (Musa et al., 2004; Musa et al., 2001) (Table 2). Spermine protects against lipopolysaccharide-induced memory deficits (Fruhauf, et al., 2015) and pentylenetetrazol-induced kindling epilepsy in mice (Kumar & Kumar, 2017), and attenuates behavioral and biochemical alterations induced by quinolinic acid in the striatum of rats (Velloso et al., 2008).

The cyclodextrin ring structure with a hydrophobic inner cavity and a hydrophilic outer surface allows to capture lipophilic compounds in the cavity and to enhance their water solubility. Cyclodextrins enter into the Cx pore lumen *via* the cytoplasmic side followed by

direct occlusion of the pore. Spermidine protects against oxidative stress in inflammation models using macrophages (Jeong et al., 2017), is neuroprotective (Buttner et al., 2014; Wang et al., 2015; Yang et al., 2017), reduces blood pressure and decreases risk of cardiovascular disease (Eisenberg et al., 2017) and alleviates laurate-induced brain injury (Zhang et al., 2017).

2.9 Probenecid and Brilliant Blue FCF

Probenecid is a widely used drug for the treatment of gout and is a well-known blocker of organic anion transporters. Probenecid is used clinically to increase effective concentrations of antibiotics, chemotherapeutics and other drugs. It has been shown that probenecid inhibits Panx1 channel currents in a concentration-response manner (IC_{50} 150 μ M) (Silverman et al., 2008) in oocytes, but not HCs consisting of Cx46 and Cx32. The proposed mechanism of action is similar to CBX, namely by interactions with the first extracellular loop of Panx1 (Amacher, 2011).

Probenecid also blocks P_2X_7 -mediated dye uptake (IC_{50} 203 μ M) in HEK- P_2X_7 cells and human monocytes (Bhaskaracharya et al., 2014) (Table 2). Probenecid prevents acute tubular necrosis in mice (Baudoux et al., 2012), cerebral ischemia/reperfusion injury in rats (Wei et al., 2015) and oxygen/glucose deprivation injury in neocortical mouse astrocytes (Jian et al., 2016).

The food dye FD&C Blue No. 1 or Brilliant Blue FCF is structurally similar to Brilliant Blue, which is a well-known inhibitor of the ionotropic P_2X_7 receptor. It has been reported that Brilliant Blue FCF selectively inhibits Panx1 channels (IC_{50} 0.27 μ M) as evidenced by blockage of voltage-activated currents and inhibition of ATP release in *X. laevis* oocytes (Wang et al., 2013). It seems that the binding of Brilliant Blue FCF to Panx1 is similar to ATP, in the sense that positively charged amino acids are involved in forming the binding site (Wang et al., 2013) (Table 2). Brilliant Blue FCF acts in a neuroprotective way (Wang et al., 2017), has protective effects on graft *versus* host disease and improves liver function (Zhong et al., 2016).

3 RNA-based inhibitors

Following the discovery of RNA interference (RNAi) (Fire et al., 1998), it became clear that 20-30 nucleotide-long RNAs control the expression of genetic information (Carthew & Sontheimer, 2009). Dicer, a ribonuclease protein, cleaves double-stranded RNA (dsRNA) into dsRNA duplexes of a specific length, known as short interfering RNA (siRNA), consisting of 21-23 nucleotides. Each siRNA associates with the RNA-induced silencing complex (RISC). Subsequently, the endonuclease Argonaute component of the RISC cleaves the passenger strand of siRNA, while the guide strand can target a specific mRNA through base-pairing to influence its activity (Lam et al., 2015). Although microRNAs (miRNAs) and siRNAs are similarly associated with Dicer and RISC, they both have different effects. Specifically, miRNAs inhibit the expression of multiple mRNAs, while siRNAs regulate the expression of 1 specific target mRNA (Deng et al., 2014). Short hairpin RNAs (shRNAs) can also be used to influence the RNAi mechanism. shRNAs are stem-loop RNAs expressed in the nucleus usually *via* viral vectors. They are transported to the cytoplasm to load into

RISC for specific gene targeting similar to siRNAs (Rao et al., 2009). In this way, RNAi controls vital processes, such as cell growth, tissue differentiation and heterochromatin formation (Lu et al., 2008). RNAi is widely used for its application in experimental biology to study the function of specific genes, but is equally important as a potential therapeutic strategy for the treatment of a number of highly prevalent diseases, such as cancer, neurodegenerative disorders, cardiovascular diseases and viral infections (Crowe, 2003; Izquierdo, 2005; Jia et al., 2006; Kusov et al., 2006).

RNAi can be applied to target specific Cx and Panx species. In this respect, Cx43 expression and thus channel functionality, have been successfully suppressed (around 70 %) using RNAi-based approaches in human bone marrow stromal cells (Talbot, et al., 2017), human bronchial fibroblasts (Paw et al., 2017), rat renal tubular epithelial cells (Chi et al., 2016), human ovarian cancer cell lines (Qiu et al., 2016), human pulmonary endothelial cells (O'Donnell et al., 2014), mouse 3T3 fibroblasts and HL-1 cardiomyocytes (Osbourne et al., 2014), and murine bone marrow-derived dendritic cells (Yu et al., 2016). Likewise, in a number of preclinical models of tissue damage and wound repair, reducing protein translation of Cx43 mRNA using antisense oligodeoxynucleotides (5'-GTAATTGCGGCAGGAGGAATTGTTTCTGTC-3') has been demonstrated to decrease inflammation, edema and lesion spread, and to provide improved healing or functional outcomes. This has been observed in skin incision and excision wounds (Mori et al., 2006; C. Qiu et al., 2003), skin burns (Coutinho et al., 2005) and the cornea of the eye (Grupcheva et al., 2012). In human patients with severe chemical or thermal burns, Cx43 antisense oligodeoxynucleotides reduce inflammation within 1 to 2 days, and induce complete and stable corneal re-epithelialization (Ormonde et al., 2012).

4 Antibody-based inhibitors

Cx antibodies that are used as inhibitors usually target the extracellular sites of desired Cx subtypes. However, the mechanism that links targeting extracellular Cx epitopes with inhibition of Cx channels remains unknown (Riquelme et al., 2013). The injection of fragments of antibodies, named Gap13 and Gap15, raised against the CL regions of Cx43, allowed to interrupt GJIC in mouse embryos (Becker et al., 1995). Similar results have been obtained with fragments targeting the CL of Cx32 in rabbit tracheal airway epithelial cells (Boitano et al., 1998). Furthermore, re-aggregated Novikoff cells treated with antibodies directed against the second EL domains of Cx43 showed markedly reduced cell-cell dye transfer. Neither GJs nor formation plaques were observed between cells, indicating that the antibodies prevented the assembly of GJ structures in contrast to simple closure of GJs (Meyer et al., 1992) (Table 3). Antibodies directed against the extracellular domains of Cx proteins offer an interesting approach, because the ELs of unopposed Cx HCs are accessible, while this is not the case in GJs, where the loops are engaged in docking interactions. As a consequence, they are expected to specifically affect free Cx HCs, but not GJs. A possible drawback relates to the fact that the ELs are well-conserved between different Cxs, enabling the antibodies to affect HCs composed of other Cx isotypes (Hervé & Dhein, 2010).

5 Peptide-based inhibitors

5.1 Peptides targeting the connexin extracellular loop

Given its ubiquitous presence in a wide spectrum of cells, most efforts to produce Cx mimetic peptide have been focused on Cx43 (Table 1) (Willecke et al., 2002). Among the first peptides were ⁴³Gap26 and ⁴³Gap27, which reproduce the amino acid sequences VCYD and SRPTEK, respectively, in the first and second EL of Cx43 (Figure 2). These peptides are thought to interact with complementary sites within the EL regions of Cx43 of opposing HCs, and thereby to prevent their docking and hence the formation of GJs (Evans & Boitano, 2001). In course of time, it has been found that they also affect Cx32, Cx40 and Cx37 channels (De Vuyst et al., 2006; De Vuyst et al., 2009; Evans & Boitano, 2001). *In vitro*, both ⁴³Gap26 (0.25 mg/L) and ⁴³Gap27 (3-300 μM) inhibit Cx HC-mediated ATP release and dye uptake upon short exposure (Braet et al., 2003; Eltzschig et al., 2006), while longer exposures also result in the suppression of the corresponding GJ activity (Braet et al., 2003; Decrock et al., 2009). Additionally, exposure of cells to ⁴³Gap27 may have effects on Cx43 phosphorylation, especially occurring at serine368, and therefore could influence Cx43 channel activity (Solan & Lampe, 2005, 2009). Both peptides have been used extensively in studies of the immune system (Matsue et al., 2006; Neijssen et al., 2005; Neijssen et al., 2007; Oviedo-Orta et al., 2001), vascular system (Chaytor et al., 1997; Matchkov et al., 2006), heart (Davidson et al., 2012; Hawat et al., 2010), lung (Sariieddine et al., 2009), brain (De Bock et al., 2012), skin (Evans & Leybaert, 2007; Pollok et al., 2011; Wright et al., 2009) and liver (Vinken et al., 2012). In order to generate more specific inhibitors, a modified Gap27 peptide, namely ⁴⁰Gap27, was developed. This peptide incorporates a sequence in the second EL of Cx40 and has also proven useful in vascular tissues (Sorensen et al., 2008). The same was performed for a part of the second EL of Cx32, generating ³²Gap27 (Figure 2), which showed inhibition of ATP release in primary hepatocytes (0.25 mg/mL) and no effect on GJ activity (Vinken, et al., 2010).

⁴³Gap26M is a modified version of ⁴³Gap26 that has an acylated *N*-terminus and shows greater solubility and stability. ⁴³Gap26M significantly increased migration rates across scrapes in keratinocytes and fibroblasts by blocking GJ functionality (Wright et al., 2009).

Peptide5 (VDCFLSRPTEKT) is a peptide shifted 5 amino acids in *N*-terminal direction compared to Gap27 (Figure 2) (Danesh-Meyer et al., 2012). It inhibits Cx HCs at low (5-10 μM) concentration, while equally inhibiting GJs at higher concentration (100 μM) (O'Carroll et al., 2008). *In vitro*, peptide5 has been used to study a variety of cellular processes, such as dynamic Ca²⁺ signals (Braet et al., 2003), release of neurotransmitters (Romanov et al., 2007) as well as propagation of cell death (Decrock et al., 2009). *In vivo*, peptide5 reduces tissue damage secondary to spinal cord injury and attenuates a vascular permeability increase following retinal ischemia/reperfusion insult (Chen et al., 2015; Chen et al., 2013; Guo et al., 2016; Kim et al., 2017; O'Carroll et al., 2013).

5.2 Peptides targeting the connexin cytoplasmic loop

The L2 peptide, corresponding to a sequence in the CL moiety of Cx43, inhibits its HC opening without affecting GJs independent of the time of exposure (Seki et al., 2004). Based

on this observation, the hypothesis was raised that prevention of the interaction between the CT and the CL areas of Cx43 leads Cx HC closure, which means that this interaction is necessary for Cx HC opening. By contrast, CT-CL interaction results in the closure of GJs. Indeed, physical binding of the CT and the L2 region of Cx43 in the CL induces a residual state with very low conductance (Ponsaerts et al., 2010).

It has been shown that Gap19, a synthetic nonapeptide (KQIEIKKFK) derived from the CL region of Cx43, inhibits its HC activity without influencing the corresponding GJ activity over time. Cx HC inhibition is due to the binding of Gap19 to the CT area of Cx43, thereby preventing intramolecular CT-CL interactions (Wang et al., 2013). By doing so, Gap19 was found to inhibit Cx43 HCs in Cx43-overexpressing C6 rat glioma cells (Wang et al., 2013), cultured primary mouse astrocytes and murine hippocampal slices (Abudara et al., 2014). Treatment with Gap19 protects cardiomyocytes against volume overload and cell death following ischemia/reperfusion *in vitro* and modestly decreases the infarct size after myocardial ischemia/reperfusion in mice (Wang et al., 2013).

³²Gap24, which mimics a sequence in the CL region (GHGDPLHLEEVKC) of Cx32 (Figure 2), specifically inhibits Cx32 HCs and not their full channel counterparts. ³²Gap24 (0.25 mg/L) completely blocked Ca²⁺-triggered ATP responses in ECV304 bladder cancer epithelial cells (De Vuyst et al., 2006). However, it was found that ³²Gap24 also attenuated Panx currents in a dose-dependent manner (500 μM - 2 mM) (Wang et al., 2007). It is believed that ³²Gap24 acts in a mechanistically similar way as Gap19.

5.3 Peptides targeting the pannexin extracellular loop

¹⁰Panx1, a synthetic peptide that mimics a sequence (WRQAAFVDSY) in the second EL area of Panx1 (Figure 2), was introduced as a tool to elucidate the role of Panx1 in the caspase 1 cascade that leads to the induction of inflammatory responses (Brough et al., 2009; Chekeni et al., 2010). This peptide, which potently inhibits Panx1 currents, dye uptake and ATP release in primary astrocyte cultures (200 μM), was found to counteract purinergic receptor activation and hence the maturation and ATP-mediated release of interleukin-1β in mouse and human macrophages. However, ¹⁰Panx1 also inhibits Cx46 HCs in *X. laevis* oocytes (200 μM). ¹⁰Panx1 has been successfully used in several other studies that substantiate the importance of Panx1 in the inflammasome in various cell types (Karpuk et al., 2011; Lamkanfi et al., 2009), whereby it was shown that ¹⁰Panx1 suppresses the production of interleukin-1α, interleukin-1β and interleukin-18 (Pelegrin, 2008). Besides acting in an anti-inflammatory way, ¹⁰Panx1 also protects against cell death in a number of cell types (Orellana et al., 2011; Pelegrin, 2008) and acetaminophen-induced hepatotoxicity *in vivo* (Maes et al., 2016). Furthermore, ¹⁰Panx1 has been successfully used to inhibit ATP-induced ethidium bromide uptake coupled to P₂X₇ receptors activation in HEK293 cells (500 μM) (Reyes et al., 2009) and in rat carotid body cultures (100 μM) (Murali et al., 2017).

6 Conclusions

Gap junctions and Cx HCs play important roles in physiological and pathological processes in various organs, including brain, heart, blood vessels, liver, intestines, skin, lung and eye

(Glass et al., 2015; Kwak et al., 2002; Maes et al., 2015; Martin et al., 2014; Meens et al., 2015; Saredidine et al., 2009; Scheckenbach et al., 2011; Willebrords et al., 2016). The same holds true for Panx channels (Barbe et al., 2006; Chen et al., 2010; Crespo Yanguas et al., 2017; Eugenin, 2014; Glass et al., 2015; Kurtenbach & Zoidl, 2014; Maes et al., 2015; Penuela et al., 2014). Several agents are currently available to inhibit Cx and Panx channels both as experimental tools or potential clinical therapeutics. Regarding the latter, Cx43 antisense oligodeoxynucleotides have yet been successfully used in clinical trials to treat severe ocular surface burns, with reduction of inflammation within 1 to 2 days and complete and stable corneal re-epithelialization when delivered in a gel structure (Ormonde et al., 2012). Synthesized peptides, in contrast to the chemical-based inhibitors, have better selectivity for Cx and Panx channels. Over the past decade, several peptides have been demonstrated to block Cx HCs and Panx channels, including ⁴³Gap26 (Wang et al., 2013), ⁴³Gap27 (De Bock et al., 2011), Peptide5 (Danesh-Meyer et al., 2012), ⁴³Gap19 (Wang et al., 2013), ³²Gap24 (De Vuyst et al., 2006) and ¹⁰Panx1 (Pelegri & Surprenant, 2007). However, not all of these peptides specifically act on Cx HCs or Panx channels, and/or uniquely affect 1 Cx or Panx species (Bodendiek & Raman, 2010). Although a multitude of protective effects have been observed by inhibition of GJs and HCs, a number of studies also demonstrates the promotion of cell death, as is the case for GA (Ozog et al., 2002), carbenoxolone (Tamura et al., 2011) and Cx43-targeted siRNA (Kar et al., 2013).

While a plethora of information has been gathered regarding Cx and Panx channel inhibitors, less is known about activators of Cx and Panx channels. Retinoids and carotenoids have been found to exhibit chemopreventive effects through enhancement of GJIC and upregulation of Cx43 expression (Vine & Bertram, 2002). Other GJ enhancers are polyphenols and flavonoids (Chaumontet et al., 1994; Stoner & Mukhtar, 1995). Interestingly, several peptides that open these channels already entered clinical trials. Thus, ACT1 is a 25-amino acid synthetic peptide containing the CT of Cx43. Application of ACT1 in *in vivo* wound healing and ischemic cardiac injury studies revealed anti-inflammatory, anti-fibrotic and tissue regenerative properties through GJIC stabilization (Ghatnekar et al., 2015; Gourdie et al., 2006; O'Quinn et al., 2011; Rhett, et al., 2008). Topical administration of this peptide augments healing of chronic neuropathic foot ulcers (Grek et al., 2015) and venous leg ulcers (Ghatnekar et al., 2015) in diabetic patients. Other GJ activators currently in clinical trials include rotigaptide and its dipeptide analogue GAP-134 as a drug for treating atrial fibrillation and endothelial dysfunction (Butera et al., 2009; Lang et al., 2008). In general, peptides have evolved as highly potent signal transduction molecules, exerting powerful physiological effects. However, they are mostly characterized by a relatively short circulating plasma half-life as well as suboptimal physical and chemical properties, which are required for their use as therapeutics (Fosgerau & Hoffmann, 2015). For this reason, it remains to be investigated whether Cx and Panx mimetic peptides as such can be used in clinical settings. Given the considerable therapeutic potential and translational relevance, future efforts should be focused in parallel on the generation of stable, potent and highly specific non-peptide modifiers of Cx and Panx channels.

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List of abbreviations

2-APB	2-aminoethoxydiphenyl borate
ATP	adenosine triphosphate
CT	C-terminal tail
Cx(s)	connexin(s)
dsRNA	double-stranded RNA
EL(s)	extracellular loop(s)
GA	glycyrrhetic acid
GABA	γ -amino butyric acid
GJ(s)	gap junction(s)
GJIC	gap junctional intercellular communication
HC(s)	hemichannels(s)
HEK	human embryonic kidney
IC₅₀	half maximal inhibitory concentration
IL	intracellular loop
IP₃	inositol triphosphate
miRNA	microRNA
NMDA	<i>N</i> -methyl- <i>D</i> -aspartate
Panx(s)	pannexin(s)
RISC	RNA-induced silencing complex
RNAi	RNA interference
shRNA	short hairpin RNA
siRNA	short interfering RNA
TRP	transient receptor potential cation channel
TTX	tetrodotoxin

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Figure 1.
Connexin and pannexin structure.

Figure 2.
Mimetic peptides targeting connexin and pannexin channels.

Table 1
Connexin and pannexin expression in different cell types.

(Cx, connexin; Panx, pannexin).

Organ	Cell type	Cx/Panx species	References
Brain	Astrocytes	Cx30, Cx43, Panx1, Panx2	(Boassa et al., 2014; Dermietzel et al., 1991; Nagy & Rash, 2000)
	Microglial cells	Cx26, Cx32, Panx1	(Eugenín et al., 2001; Garg et al., 2005; Kielian, 2008; Parenti et al., 2002; Penuela et al., 2013; Takeuchi et al., 2006)
	Oligodendrocytes	Cx32, Cx47, Cx29	(Altevogt, Kleopa, Postma, Scherer, & Paul, 2002; Dermietzel, et al., 1989; Odermatt, et al., 2003)
	Neurons	Cx36, Cx45, Panx1, Panx2	(Boassa et al., 2014; Penuela et al., 2013; Takeuchi & Suzumura, 2014)
	Blood-brain barrier endothelial cells	Cx37, Cx40, Cx43	(De Bock et al., 2014; Little et al., 1995; Nagasawa et al., 2006; Traub, et al., 1998)
	Blood-brain barrier pericytes	Cx37, Cx40, Cx43	(De Bock et al., 2014; Little et al., 1995; Nagasawa et al., 2006; Traub et al., 1998)
Heart	Smooth muscle cells	Cx40, Cx43, Cx45	(Gros & Jongsma, 1996; Severs et al., 2004)
	Cardiomyocytes	Cx40, Cx43, Cx45, Panx1	(Gros & Jongsma, 1996; Petric et al., 2016; Severs et al., 2004)
Blood vessels	Endothelial cells	Cx43, Cx37, Cx40, Panx1	(Chadjichristos et al., 2010; Lohman et al., 2012; Lohman et al., 2015; Scheckenbach et al., 2011)
	Smooth muscle cells	Cx43, Cx45, Cx40, Cx37, Panx1	(Chadjichristos et al., 2010; Scheckenbach et al., 2011)
Liver	Sinusoidal endothelial cells	Cx26, Cx43	(Hernández-Guerra et al., 2014)
	Hepatic arteries and portal vein endothelial cells	Cx37, Cx40	(Fischer et al., 2005; Shiojiri et al., 2006)
	Hepatocytes	Cx26, Cx32, Panx1, Panx2	(Crespo Yanguas et al., 2017; Iwata et al., 1998; Kyoj et al., 1992; Maes et al., 2015; Ohkusa et al., 1995; Radebold et al., 2001)
	Kupffer cells	Cx26, Cx43, Panx1	(Crespo Yanguas et al., 2017; Eugenín et al., 2007; González et al., 2002)
	Stellate cells	Cx26, Cx43	(Fischer et al., 2005; Maes et al., 2015)
Stomach and intestines	Stomach	Cx26, Cx32, Cx40, Cx43, Cx45	(Cousins et al., 2003; Liu et al., 2010; Wang et al., 2014; Wang & Daniel, 2001)
	Foveolar cells	Cx32	(Fink et al., 2006)
	Small intestine	Cx26, Cx31, Cx57	(Filippov et al., 2003)
	Myenteric plexus cells	Cx36, Cx40, Cx43, Cx45	(Frinchi et al., 2013; Liu et al., 2008; Wang & Daniel, 2001)
	Small intestine epithelial cells	Cx32, Cx37, Cx43	(Hakim et al., 2008; Husøy et al., 2004; Traoré et al., 2003)
	Interstitial cells of cajal	Cx43	(Seki & Komuro, 2002)
	Colon	Cx31, Cx31.9, Cx43	(Ismail et al., 2014; Li et al., 2015)
	Musculus externa cells	Cx26, Cx40, Cx43, Panx1	(Maes et al., 2015; Mattii et al., 2013; Wang & Daniel, 2001)
	Myenteric plexus cells	Cx36, Cx40, Cx43, Cx45	(Frinchi et al., 2013; McClain et al., 2014; Wang & Daniel, 2001)

Organ	Cell type	Cx/Panx species	References
	Epithelial cells	Cx26, Cx32, Cx37, Cx43, Panx2	(Kanady et al., 2015; Kanczuga-Koda et al., 2004; Maes et al., 2015)
	Muscularis mucosa cells	Cx43, Panx1	(Ismail et al., 2014; Maes et al., 2015)
Skin	Keratinocytes	Cx26, Cx30.3, Cx30, Cx31.1, Cx31, Cx40, Cx43, Cx45, Panx1, Panx3	(Brandner et al., 2004; Churko & Laird, 2013; Cowan et al., 2012; Di et al., 2001; Martin et al., 2014; Wang et al., 2007)
	Fibroblasts	Cx43, Cx45, Cx40	(Cogliati et al., 2015; Meyer et al., 2014; Tarzemany et al., 2015; Wright et al., 2009)
	Melanocytes	Cx43	(Haass et al., 2004; Penuela et al., 2012; Rezze et al., 2011)
Kidney	Smooth muscle cells	Cx37, Cx45	(Arensbak et al., 2001; Hanner et al., 2010; Li et al., 2015)
	Podocytes	Cx43, Cx45	(Hanner et al., 2010; Morioka et al., 2013; Yang et al., 2014)
	Pericytes	Cx37	(Hanner et al., 2010; Q. Zhang et al., 2006)
	Mesangial cells	Cx40, Cx45	(Arensbak et al., 2001; Hanner et al., 2010; Kurtz et al., 2007; Morioka et al., 2013)
Lung	Alveolar epithelium	Cx26, Cx32, Cx43, Cx46, Panx1, Panx2	(Koval, 2002; Lohman et al., 2012; Lohman et al., 2015)
Eye	Lens epithelial cells	Cx43, Cx46, Cx50, Panx1	(Berthoud et al., 2014; Slavi et al., 2014)
Immune cells	T-cells	Cx40, Cx43, Panx1	(Oviedo-Orta et al., 2000; Velasquez et al., 2016)
	B-cells	Cx40, Cx43, Panx1	(Oviedo-Orta et al., 2000)
	Monocytes	Cx43	(Navab et al., 1991)
	Macrophages	Cx37, Cx43, Panx1	(Alves et al., 1996; Beyer & Steinberg, 1991; Kwak et al., 2002)
	Neutrophils	Cx43, Panx1	(Glass et al., 2015)
	Dendritic cells	Cx43, Panx1	(Glass et al., 2015)
Pancreas	β -cells	Cx36, Cx43, Cx45	(Charollais et al., 1999)
	Exocrine pancreas	Cx32, Panx1	(Frossard et al., 2003; Kowal et al., 2015)
Skeletal muscle	Myoblasts	Cx39, Cx40, Cx43, Cx45, Panx1, Panx3	(Langlois & Cowan, 2016; Merrifield & Laird, 2015)
Bone	Osteocytes	Cx37, Cx43	(Krüger et al., 2000; Pacheco-Costa et al., 2014; Paic et al., 2009)
	Osteoblasts	Cx37, Cx43, Cx45, Cx46, Panx3	(Chaible et al., 2011; Civitelli et al., 1993; Donahue et al., 1995; Krüger et al., 2000; Penuela et al., 2013; Plotkin & Bellido 2013)
	Osteoclasts	Cx37, Cx43	(Pacheco-Costa et al., 2014; Paic et al., 2009)
	Chondrocytes	Cx32, Cx43, Cx45, Cx46, Panx3	(Mayan et al., 2013; Penuela et al., 2013)

Table 2
Chemical-based inhibitors of gap junctions, connexin hemichannels and pannexin channels.

(2-APB, 2-aminoethoxydiphenyl borate; Cx, connexin; GA, glycyrrhetinic acid; GABA, γ -amino butyric acid; GJs, gap junctions; HCs, hemichannels; IP₃, inositol triphosphate; NMDA, *N*-methyl-*D*-aspartate; Panx, pannexin TRP, transient receptor potential cation channel; TTX, tetrodotoxin).

Inhibitor	Cx/Panx targets	Other targets	References
18α-, 18β-GA	GJs in human fibroblasts (IC ₅₀ 1.5 μ M), Cx50, Cx46 HCs in <i>X. laevis</i> oocytes (IC ₅₀ 2 μ M), Panx1 channels and P ₂ X ₇ receptors in <i>X. laevis</i> oocytes (IC ₅₀ 50 μ M)	Activation of mineralo- and glucocorticoid receptors, inhibition of 11 β -hydroxysteroid dehydrogenase (IC ₅₀ 0.26-4.3 μ M), voltage-sensitive Ca ²⁺ currents (10 μ M), Cl ⁻ conductance (40 μ M)	(Amagaya et al., 1984; Armanini et al., 1983; Armanini et al., 1982; Böhmer et al., 2001; Bruzzone et al., 2005; Davidson & Baumgarten, 1988; Davidson et al., 1986; Eskandari et al., 2002; Locovei et al., 2007; Matchkov et al., 2004; Su et al., 2007; Walker & Edwards, 1991)
Carbenoxolone	GJs in human fibroblasts (IC ₅₀ 3 μ M), HCs: Cx26 (IC ₅₀ 21 μ M) and Cx38 (IC ₅₀ 34 μ M) in <i>X. laevis</i> oocytes, Panx1 channels (IC ₅₀ 2-5 μ M)	Inhibition of 11 β -hydroxysteroid dehydrogenase (IC ₅₀ 5 μ M), voltage-gated Ca ²⁺ currents (IC ₅₀ 48 μ M), P ₂ X ₇ receptors (IC ₅₀ 175 nM), NMDA-evoked currents (IC ₅₀ 104 μ M)	(Bruzzone et al., 2005; Bühler et al., 1991; Bujalska et al., 1997; Davidson & Baumgarten, 1988; Davidson et al., 1986; John et al., 1999; Ma et al., 2009; Pelegrin & Surprenant, 2006; Ripps et al., 2002, 2004; Suadicani et al., 2006)
Heptanol	GJs in rat glial cells, insect cells, cardiac cells, stomach and pancreas epithelial cells, pancreatic acinar cells	Activation of Ca ²⁺ -activated and ATP-sensitive K ⁺ channels (150 μ M), glycine receptor function, inhibition of voltage-gated Ca ²⁺ channels, kainate receptor-mediated responses, P ₂ X ₇ receptors	(Bernardini et al., 1984; Déléze & Hervé, 1983; Dildy-Mayfield et al., 1996; Guan et al., 1997; Johnston et al., 1980; Matchkov et al., 2004; Meda et al., 1986; Suadicani et al., 2006; Weingart & Bukauskas, 1998)
Octanol	GJs in rat glial cells, insect cells, cardiac cells, stomach and pancreas epithelial cells, pancreatic acinar cells, HCs: Cx50 in <i>X. laevis</i> oocytes (IC ₅₀ 177 μ M)	Activation of GABA responses in oocytes (50 μ M), inhibition of NMDA receptors (100 μ M), Na ⁺ currents, T-type Ca ²⁺ channels (IC ₅₀ 122 μ M)	(Bernardini et al., 1984; Déléze & Hervé, 1983; Dildy-Mayfield et al., 1996; Eskandari et al., 2002; Guan et al., 1997; Hirche, 1985; Johnston et al., 1980; Meda et al., 1986; Todorovic & Lingle, 1998; Weingart & Bukauskas, 1998)
Halothane	GJs in cardiac cells, neonatal rat cardiac myocytes (2 mM), crayfish axons (IC ₅₀ 28.5 mM), cultured astrocytes (0.1-1 mM), hippocampal slices (2.8 mM)	Inhibition of TTX-resistant and TTX-sensitive Na ⁺ channels, excitatory synaptic transmission, G-protein-activated K ⁺ channel currents, muscarinic receptors, NMDA receptors, thromboxane A ₂ signaling; glutamate receptors	(Banks & Pearce, 1999; Beirne et al., 1998; Burt & Spray, 1989; Dildy-Mayfield et al., et al., 1996; Hauswirth, 1969; Hönemann et al., 1998; Jones & Harrison, 1993; Krnjević, 1992; Mantz et al., 1993; Milovic et al., 2004; Minami et al., 1997; Peracchia, 1991; Scholz et al., 1998; Sirois et al., 1998; Wentlandt et al., 2006)
Oleic acid	GJs in vascular smooth muscle cells (0.1-1 μ M), rat liver epithelial cell line (20 μ M) and cultured rat astrocytes (50 μ M)	TRPV1 in HEK293 cells (5 μ M), ATP-sensitive K ⁺ channels (100 μ M), Cl ⁻ channels (6.5 μ M)	(Bai et al., 2013; Hii et al., 1995; Hirschi et al., 1993; Lavado, Sanchez-Abarca et al., 1997; Linsdell, 2000; Morales-Lázaro et al., 2016)
Linoleic acid	GJs in rat liver epithelial cell line (0.01-3 mg/dl), HCs: Cx46 activation (0.1 μ M) and inhibition (100 μ M) in <i>X. laevis</i> oocytes, inhibition of Cx26, Cx32, Cx43, Cx45 in HeLa cells (100 μ M), Cx43 in human gastric epithelial cells	Cl ⁻ channels in hamster kidney cell lines (6.5 μ M), Na ⁺ currents in rat ventricular myocytes (IC ₅₀ 26 μ M)	(Figueroa et al., 2013; Hayashi et al., 1997; Kang & Leaf, 1996; Leifert et al., 1999; Linsdell, 2000; Puebla et al., 2016; Retamal et al., 2011)
Arachidonic acid	GJs in cells derived from rat lacrimal glands (50-100 μ M), neonatal rat heart cells (4 μ M), Cx36-HeLa cells (10 μ M),	Cl ⁻ channels in hamster kidney cell lines (6.5 μ M), K ⁺ channels in CHO cells (IC ₅₀ 6.1 μ M), L-type Ca ²⁺ -channel activity in rat arteriolar myocytes (10 μ M)	(Bai et al., 2015; Fluri et al., 1990; Giaume et al., 1989; Heler, Bell, & Boland, 2013; Kur et al., 2014; Linsdell, 2000; Safrany-Fark, et al., 2015; Samuels, Lipitz, Wang, Dahl,

Inhibitor	Cx/Panx targets	Other targets	References
	Panx1 channel inhibition in <i>X. laevis</i> oocytes (100 μ M)		& Muller, 2013; Schmilinsky-Fluri, Valiunas, Willi, & Weingart, 1997; Xiao, et al., 2012)
Palmitic acid	Panx1 channel activation in human and rat liver cell lines (100-500 μ M)	Cl ⁻ channels (6.5 μ M)	(Linsdell, 2000; Xiao et al., 2012)
Flufenamic acid	GJs: Cx26, Cx32, Cx40, Cx43, Cx46, Cx50 in N2A cells (20-60 μ M), HCs: Cx50, Cx46, Cx38 in <i>X. laevis</i> oocytes (IC ₅₀ 3 μ M)	Activation of large-conductance Ca ²⁺ -activated K ⁺ channel currents, GABA-activated currents, inhibition of voltage-gated Ca ²⁺ channels, ATP-sensitive and voltage-gated K ⁺ channels, cardiac Na ⁺ channels, nonselective cation channels, Ca ²⁺ -activated Cl ⁻ channel, P ₂ X ₇ receptors (655 nM)	(Coyne et al., 2007; de Roos et al., 1997; Doughty et al., 1998; Eskandari et al., 2002; Farrugia et al., 1993; Gögelein et al., 1990; Greenwood & Large, 1995; Grover et al., 1994; Harks et al., 2001; Lee & Wang, 1999; Li et al., 1998; McCarty et al., 1993; Ottolia & Toro, 1994; Srinivas & Spray, 2003; Suadicani et al., 2006; Wang et al., 1997; Wang et al., 1997; White & Aylwin, 1990; Zhang et al., 1998; S. S. Zhou et al., 2002)
Quinine	GJs: Cx36 (IC ₅₀ 32 μ M), Cx50 (IC ₅₀ 73 μ M), Cx45 (300 μ M), HCs: Cx35, Cx46, Cx38 in <i>X. laevis</i> oocytes (100 μ M)	Inhibition of ATP-sensitive and voltage-gated K ⁺ channels (IC ₅₀ 3 μ M and 8 μ M), Na ⁺ currents (20 μ M), nicotinic cholinergic receptors (IC ₅₀ 1 μ M), IP ₃ binding (100 μ M) as well as IP ₃ -induced Ca ²⁺ release (250 μ M), cytochrome P450 2D6 (IC ₅₀ 4.9 μ M), P-glycoprotein (IC ₅₀ 1.2 μ M)	(Ballesterio et al., 2005; Gribble et al., 2000; Hayeshi et al., 2006; Hsiao et al., 2008; Hutzler et al., 2003; Lin et al., 1998; Misra et al., 1997; Palade et al., 1989; Ripps et al., 2002; Srinivas et al., 2001; Wang et al., 1994)
Mefloquine	GJs: Cx36 (IC ₅₀ 300 nM) and Cx50 (IC ₅₀ 1.1 μ M) in N2A cells and Cx40 and Cx43 in vascular endothelial cells of guinea-pig mesenteric arteries	Inhibition of voltage-gated L-type Ca ²⁺ channels, ATP-sensitive K ⁺ channels (IC ₅₀ 3 μ M), delayed rectifier K ⁺ channels (IC ₅₀ 1 μ M), IP ₃ -induced Ca ²⁺ release (IC ₅₀ 42 μ M), P-glycoprotein (1-20 μ M), P ₂ X ₇ (IC ₅₀ 2.5 nM)	(Coker et al., 2000; Cruikshank et al., 2004; Kang et al., 2001; Lee & Go, 1996; Pham et al., 2000; Srinivas et al., 2005; Yamamoto & Suzuki, 2008)
2-APB	GJs in monolayers of normal rat kidney cells and HEK293 cells: (IC ₅₀ 5.7 μ M), Cx36, Cx40 and Cx50 (IC ₅₀ 3 μ M), Cx26, Cx30 and Cx45 (IC ₅₀ 18 μ M), Cx32, Cx43, Cx46 (IC ₅₀ 30-50 μ M)	Activation of TRPV1 (IC ₅₀ 114 μ M), TRPV2 (IC ₅₀ 129 μ M) and TRPV3 (IC ₅₀ 34 μ M), inhibition of IP ₃ receptors (IC ₅₀ 42 μ M), TRPC1, TRPC3, TRPC5, TRPC6 and TRPC7, TRPM3, TRPM7, TRPM8 and TRPP2 (30-100 μ M)	(Bai et al., 2006; Chung et al., 2004; Colton & Zhu, 2007; Harks et al., 2003; Hu et al., 2004; Ma et al., 2001; Maruyama et al., 1997)
Polyamines	GJs: Cx40 (IC ₅₀ 100 μ M)	NMDA channels	(Musa et al., 2004; Musa et al., 2001; Williams, 1997)
Cyclodextrins	HCs: Cx32, Cx26 in HeLa cells (6 mM)	Complexation of cholesterol	(Kline et al., 2010; Locke et al., 2004)
Probenecid	Panx1 channel currents (IC ₅₀ 150 μ M)	P2X7-mediated dye uptake in HEK-P ₂ X ₇ cells and human monocytes (IC ₅₀ 203 μ M)	(Bhaskaracharya et al., 2014; Silverman et al., 2008)
Brilliant Blue FCF	Panx1 channels (IC ₅₀ 0.27 μ M)	/	(Wang et al., 2013)

Table 3
Antibodies targeting connexin channels.

(CL, cytoplasmic loop; CT, C-terminal tail; Cx, connexin; EL, extracellular loop; GJs, gap junctions; HCs, hemichannels; Panx, pannexin).

Antibody	Sequence used to obtain antibodies	Location	Cx/Panx target	Inhibits	Cell type	Reference
EL186	TCKRDPCPHQVDCFLSRP	EL2	Cx43	GJs	Novikoff cells	(Meyer et al., 1992)
Gap13	VEMHLKQIEIKKFK	CL	Cx43	GJs	8 to 16-cell mouse embryo	(Becker et al., 1995)
Gap15	EIKKFKYGIEEH	CL	Cx43	GJs	8 to 16-cell mouse embryo	(Becker et al., 1995)
Des1	EKKMLRLEGHGHLEEVKRHK	CL	Cx32	GJs	Rabbit tracheal airway epithelial cells	(Boitano et al., 1998)
Des5	LEGHGDPHLEE	CL	Cx32	GJs	Rabbit tracheal airway epithelial cells	(Boitano et al., 1998)
Gap9	RRSPGTGAGLAEKSDRCSAC	CT	Cx32	GJs	Rabbit tracheal airway epithelial cells	(Boitano et al., 1998)
EL2-186	TCKRDPCPHQVDCFLSRPTEK	EL2	Cx43	GJs, HCs	Newborn rat astrocytes	(Hofer & Dermietzel, 1998)

Table 4
Mimetic peptides targeting connexin and pannexin channels.

(CL, cytoplasmic loop; Cx, connexin; EL, extracellular loop; HCs, hemichannels; HEK, human embryonic kidney cells; Panx, pannexin).

Peptide	Sequence	Cx/panx target	Inhibits	Cell type	References
⁴³ Gap26	VCYDKSFPISHVR	EL1 Cx43, Cx32, Cx40, Cx37	HCs GJs	Rabbit tracheal airway endothelial cells, Cx43-HeLa cells, rat brain endothelial cells, bovine corneal endothelial cells, embryonic chick neural retina, mouse astrocytes, rat ventricular myocytes, mouse taste cells, human aortic endothelial cells	(Berman et al., 2002; Boitano & Evans, 2000; Braet et al., 2003; Clarke & Jump, 1996; D'hondt et al., 2007; Gomes et al., 2005; Pearson et al., 2005; Retamal et al., 2007; Romanov et al., 2007; Shintani-Ishida et al., 2007; Vandamme et al., 2004; Wang et al., 2008)
^{37,40} Gap26	VCYDQAFPISHIR	EL1 Cx37	HCs	Mouse macrophages	(Martin et al., 1998)
⁴³ Gap27	SRPTEKTIFII	EL2 Cx32, Cx43	HCs GJs	Rabbit tracheal airway endothelial cells, human T and B lymphocytes, human gingival fibroblasts, rat alveolar epithelial cells, Cx43-HeLa cells, Cx32-HeLa cells, rat brain endothelial cells, human leukocytes, bladder cancer epithelial cells, mouse microglia neurons, bovine corneal endothelial cells, mouse astrocytes, human aortic endothelial cells, primary mouse keratinocytes, hippocampal slices, human keratinocytes and fibroblasts, <i>X. laevis</i> oocytes, embryonic chick heart myocytes	(Berman et al., 2002; Boitano et al., 1998; Boitano & Evans, 2000; Braet et al., 2003; Chaytor et al., 1999; De Vuyst et al., 2006; Dora et al., 1999; Eltzschig et al., 2006; Gomes et al., 2006; Isakson et al., 2001; Kandyba et al., 2008; Ko et al., 2000; Oviedo-Orta et al., 2002; Oviedo-Orta et al., 2000; Retamal et al., 2007; Samoilova et al., 2008; Wang et al., 2008; Warner et al., 1995; Wright et al., 2009)
⁴⁰ Gap27	SRPTEKNVFIV	EL2 Cx40	GJs	Rat aorta endothelial cells	(Sorensen et al., 2008)
³² Gap27	SRPTEKTVFT	EL2 Cx32	HCs	ECV304, Cx32-C6 cells, HEK293 cells, mouse microglia neurons, J774 murine macrophages, mouse taste cells	(De Vuyst et al., 2006; Pelegrin & Surprenant, 2007; Takeuchi et al., 2006; Wright et al., 2009)
Peptide5	VDCFLSRPTEKT	EL2 Cx43	HCs GJs	<i>Ex vivo</i> rat spinal cord culture, human cerebral microvascular endothelial cells	(Kim et al., 2017; O'Carroll et al., 2013; Qiu et al., 2003)
⁴³ Gap19	KQIEIKKFK	CL Cx43	HCs	Cx43-HeLa cells	(Wang et al., 2013)
³² Gap24	GHGDPLHLEEVKC	CL Cx32	HCs	ECV304 cells, Cx32-C6 cells, HEK293 cells	(De Vuyst et al., 2006)
¹⁰ Panx1	WRQAAFVDSY	EL1 Panx1	Panx1 channels	HEK293 cells, murine macrophages, oocytes, rat hippocampal brain slices	(Pelegrin & Surprenant, 2006, 2007; Reyes et al., 2009; Thompson et al., 2008; Wang et al., 2007)