

Pharmacology of Connexins-Still a Gap

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ABSTRACT

Between the cells are present the gap junctions which are made up of proteins named connexins. The connexin family in humans has cell-specific roles consisting of 21 members and the most studied one is connexin 43. Connexins have a ubiquitous distribution and their function is in cell-cell communication and also a site for protein-protein interactions in regulating the signaling pathways. Their half-life is very short for 5 hours with Cx46 present in lens fibres and Cx30 in keratinocytes being the exceptions. The normal physiology ensures the complete role of connexins and their dysfunction may result in genetic disorders (Eg: Mutations in Cx32 result in Charcot-Marie-Tooth neuropathy X type 1 characterised by progressive peripheral neuropathy), delayed wound healing, arrhythmia, etc. Its role in cancer is very complex making the connexins act as both suppressor and promoter for tumor progression. In therapeutics, connexins peptide mimetics are a good option since they mimic a particular sequence of connexins which enhances their specificity and inhibits the function of gap junction in animal models. By binding to the mRNA of connexins, antisense oligodeoxynucleotides downregulate connexins useful in skin wound healing and also in eye infections where treatment with AsODN was found to reduce scarring in animal studies. Repurposed drugs like modafinil and flecainide as low-dose glial connexin modulators and identification of the activity of clofazimine against connexins in trials show that targeting connexins shows promise in the future. Connexin modulators are now in trials for wound healing and to avoid off-targets, it is applied topically as a gel. This review will deal with the physiological role and highlight the pathological condition for which connexins can be a therapeutic target.

Keywords: Connexins, Connexin mimetics, Anti-sense oligodeoxynucleotides.

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INTRODUCTION

Cells communicate with each other with the help of protein complexes which include tight junctions, cell adhesion molecules, gap junctions and desmosomes. The compounds like ions and secondary messengers do exhibit this communication by passive diffusion using gap junctions. Gap junctions are characterized by the presence of an intercellular bridge with a gap of 2 nm to communicate between the cytoplasm of two cells. Gap junctions are made up of protein subunits called as connexins. Six connexins make up to form connexon which is also called a hemi-channel which gets connected to another hemi-channel leading to a complete gap junctional channel. In physiological conditions, new connexons are added to the periphery and remain dormant till connecting with adjacent cells whereas old connexons are removed from the center which is destroyed.¹ Connexins can also communicate with other proteins like cadherins, zona occludens to activate signaling pathways and dysfunction of connexins will

result in pathological states and hence, connexin has the potential as a promising therapeutic target.

Structure

The Connexin subunit has four hydrophobic transmembrane domains linked by two extracellular loops and a cytoplasmic loop. They also contain cytoplasmic terminus which are called amino and carboxyl termini. The function of transmembrane domains is that they act as the channel pore which is linked by two extracellular loops having a role in the recognition of cells and docking. In each extracellular loop, there is the presence of three cysteine residues forming disulfide bridges which stabilises the loops during the process of docking of the two hemichannels. The N-terminus helps in the oligomerization of connexins while the carboxyl terminus helps in the phosphorylation of connexins and can act as a binding site for other structural proteins which keeps the intercellular communication to be regulated. Recently identified is Src homology 3 binding domain which contributes to loop/tail interactions. Connexons can form homotypic or heterotypic channels. The difference is in homotypic, identical homomeric or heteromeric connexons are in connections whereas in heterotypic, different homomeric or heteromeric connexons are connected.²



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Nomenclature

The nomenclature of connexins is based on two systems as follows:

Number system

In this system, molecular weight from the complementary DNA sequence of the connexins indicates the connexin type. Eg: mCx26 and Cx32 are the connexins with the molecular weight of 26kDa and 32kDa respectively and "m" refers to species (mouse) from where it is derived.³

Sequence similarity

Based on the similar sequence of the cytoplasmic domain, subgroups have been made and named as α , β , γ . In this nomenclature, connexins are referred to as GJ referring to gap junction. Eg: mCx43 was the first connexin of α group (Gja1).⁴

Physiological functions

Connexins have a short half-life and so there is remodeling of gap junctions with a high turn-over rate. Connexins get degraded by proteasomes as they regulate the turnover of ZO-1 (Zona-Occludens-1) and another pathway for is via lysosomes. Connexin 43 has ubiquitous distribution and its interaction with other proteins makes this connexin the study of interest. Post-translational modification commonly occurring in connexins is phosphorylation which modulates the functions of gap junction channels. The physiological functions of connexins differ between the connexins and also between the tissues where it is present.

CNS

In the central nervous system, cell adhesion and migration play a vital role in the development of CNS in the embryonic neuroepithelium. Cell adhesion is required for stabilization of astrocytes in mature CNS. Preclinical studies have revealed the role of connexins in cell division, learning and memory and its imbalance results in neurological conditions like inflammation, epilepsy and behavioral alterations. Connexin 43 has a vital role in regulating the blood-brain barrier in modulating brain functions and this connexin is one of the most abundant connexins present in CNS. Overexpression of this connexin in neurodegenerative disorders by forming adhesion with astrocytes leads to detrimental effects. Cx32 plays a crucial role in the maintenance and homeostasis of myelinated axons by forming functional GJs. Cx36 which is the connexin in neurons in the retina, brain and spinal cord in abundance has a role in establishing synapse circuitry and for a synchronous activity of neurons in the adult brain.

Clinical Implication

Using non-selective inhibitor carbenoxolone and Gap19 (selective Cx43 inhibitor) has shown beneficial effects in providing neuroprotection in *in vivo* studies.⁵

Eye

Connexins have a role in the development of the eye and its normal physiology, the most commonly studied is Cx43. They are useful for processing of the visual image. Cx43 has a role in the repair of the cornea due to injury and connexins are downregulated in case of wounds affecting the cornea.⁶ The property of inhibiting the activity of connexins is shown in animal models of diabetes mellitus and wound closure is increased indicating that the cornea is a viable target for drugs that modulate connexins.

Heart

Connexins present in the heart include Cx43, Cx40, Cx45 and Cx30.2 and disruption of these connexins leads to disturbances in electrical impulses and also structural abnormalities.⁷ This is seen in preclinical studies showing the importance of the connexins where knockout of connexins leads to cardiac pathologies. Sodium and potassium currents are found to be dependent on the expression of Cx43 present in intercalated discs necessary for the synchronous beating of the heart. Alteration of the ion balance will affect the action potential leading to arrhythmias. There are multiple communication mechanisms, one among them is the interaction of connexin 43 with an apoptosis-inducing factor and the β -subunit of the electron-transfer protein regulating the mitochondrial respiration and generation of reactive oxygen species and this property is helpful in Ischemia-reperfusion injury which shows the connexins have a role in preconditioning. Preconditioning refers to a short time of ischemia before a longer interval of ischemia which protects the heart from reperfusion injury.⁸ Connexins have a role in normal cardiac conduction and abnormality in expression or lateralization do occur in case of arrhythmias.⁹ Lateralisation can also occur in hypoxia or ischemia by activating Src kinase and preventing the function of Cx43 from hooking ZO-1 by competing with Cx43.

Vascular system

Endothelial cells of blood vessels express Cx37, Cx40, Cx43 and Cx45.¹⁰ In the presence of disease, the expression of connexins will be altered. In atherosclerosis, endothelial Cx43 is upregulated by the cytokines like TGF-beta and it replaces the normally present connexins Cx37 and Cx40 in the healthy arteries of endothelium. Cx37 was the first connexin to be found in platelets and animal studies involving deletion of Cx37 showed reduced bleeding time. In restenosis after acute vascular injury, Cx43 expression is found to be increased and treatment with ACE inhibitors and statins decreases the levels of Cx43 and this in turn leads to a decrease in proliferation of smooth muscle cells and also a decrease in inflammation.¹¹

Respiratory system

Connexins have a role in modulating lung functions like ciliary movement and secretion of surfactant using propagation signals involving calcium. In animal studies, it has been found that deficiency of Cx43 is related to delayed development of lung alveoli.¹² The role of connexins in asthma and COPD is that mitochondria can be transferred via connexins as there will be mitochondrial dysfunction which occurs due to inflammatory mediators (interleukins). In preclinical studies, mitochondrial transfer was found to reduce alveolar destruction in rats.¹³

GIT

Connexins like Cx36 and Cx43 have their roles in gastrointestinal function and disease conditions like H. Pylori will alter the connexin function thereby suggesting a role in maintenance of normal GI function.¹⁴ Connexin 36 present in neuronal cell bodies containing Nitric Oxide Synthase (nNOS) throughout GIT is found to improve contractility and knockdown of Cx36 will result in an increase in contraction of the colon and also the amplitude of contraction. During acute injury, a toll-like receptor is induced which recognises the bacterial epitope and stimulates the gap junction intercellular communication correlating with connexins 43 and any dysfunction of connexins will lead to infection. Levels of TLR-2 and Cx43 have a direct correlation and the absence of them indicates poor prognosis. GI symptoms present in autism spectrum disorder can be linked to an abnormality in connexins since enteric glial cells have a close resemblance to astrocytes and there appears to be an alteration in the gut-brain axis.

Clinical implication

Invasion of bacteria (Eg: Shigella) is due to cytoskeletal reorganisation and opening of gap junctions resulting in inflammatory response of the epithelium. Using gap junction inhibitors in cell culture studies like α -glycyrrhetic acid is found to reduce the invasion of the bacteria.

Skin

The isoform of connexin which is predominant in the skin is Cx43 and they have a role in regulating the activity of the cell which includes cell growth, differentiation, migration and proliferation. In case of wound injury, the connexins get upregulated leading to differentiation of keratinocytes and the inflammatory mediators which are present after an injury do pass via the gap junctions to exert their effects. Downregulating the activity of connexins will be a therapeutic strategy to accelerate the healing process by upregulating transforming growth factors- beta and collagen and downregulation of the inflammatory mediators. The effects of downregulating the connexins will be a decrease in inflammatory response, decreased fibrosis and improved angiogenesis which in the end increases vascularity to tissues and increases the contraction of the wound thereby facilitating the process of healing of the wound.¹⁵ Connexins also have a role in

keratoderma which occurs due to mutation in Cx43 and present in Oculodentodigital dysplasia.

Role in cancer

The role of connexins in cancer is complex since they can act as promoters and act as a tumor suppressor protein. Bystander effect means both antitumor agents and toxic metabolites cross neighboring cells using gap junction leading to the death of cancer cells.¹⁶

Tumor suppressors

In knock-out models, Cx32 knock-out mice were found to be more at risk of liver tumors. Overexpression of connexins will cause elongation of G1 phase of the cell cycle leading to a decrease in the proliferation of cells. S-phase kinase-associated protein-2 responsible for p27 degradation is decreased by connexins thereby resulting in the accumulation of p27 which is a cyclin-dependent kinase inhibitor.

Mechanisms of tumor suppressor action of connexins

The binding of Connexin 43 to tubulin will inhibit the binding of tubulin to Smad2/3 (proteins that are transducers of TGF-B family) leading to the release of Smad2/3. Connexins promote c-Src inhibition and interaction of connexin 43 with beta-catenin prevents the transcriptional activity of beta-catenin favoring the role of tumor suppressor activity of connexions.¹⁷

Promoters of malignancy

Connexin expression may be increased under certain conditions to facilitate tumor malignancy. Connexins can form heterologous gap junctions between tumor cells and endothelial cells for intravasation and recent research also shows that connexins do have a role in the biology of cancer stem cells. This will give nutrition to metastatic growth and cause resistance to chemotherapy.

Mechanism of tumor promoter function of connexins

Cx26 has a role in acting as tumour promoter by forming a complex with NANOG and FAK (focal adhesion kinase) and this promotes the self-renewal of cancer stem cells thereby favoring tumorigenesis in triple-negative breast cancer. NANOG, having its origin from Tir nan Òg, the mythical Celtic land of youth, is a transcription factor needed for pluripotency. This shows that connexins have both tumor favouring and suppressing activity.¹⁸

Endocrine

Connexins have a vital role in endocrine functions. They have a role in sensing the changes in intravascular pressure and this property is found in animal models of hypertension. The endothelial cells are joined to adjacent cells using Cx40 and Cx37 and Cx45 is expressed in smooth muscle cells.¹⁹

Connexins have a role in the pathogenesis of diabetes mellitus. Cx36 forms the gap junction between beta cells of the pancreas which are needed for insulin secretion. In preclinical studies, loss of Cx36 is shown to have a loss of pulsatile insulin release. High blood glucose levels will induce oxidative stress resulting in degradation of Cx43 present in retinal pericytes via the proteasome pathway. Long-term uncontrolled diabetes will result in a non-healing ulcer and in non-healing wounds, Cx43 has been found in the margins. Studies have shown that there exists a difference between animals-induced diabetes and control. Eg: Cx43 was found to be upregulated in streptozotocin-induced diabetes whereas downregulated in controls.²⁰ The target of therapy must be to close the wounds and accelerate the healing process by downregulating the action of connexins hence providing a therapeutic effect.

Connexins have a very important role in male and female reproductive health. In disorders involving the female reproductive system like endometriosis, expression of connexins is decreased and the therapeutic aim is to restore the balance of gap junction and maintain homeostasis. In male reproductive system, connexins have a role in spermatogenesis and any abnormal expression of connexins will lead to testicular dysfunction and infertility.²¹

Genetic

Connexins are encoded by genes and any mutation in genes will result in a development disorder. Connexins have a role in the maintenance of blood-nerve barrier. Mutations of connexins Cx32 are related to peripheral neuropathy present in X-linked Charcot Marie tooth disease. Mutations in Cx43 lead to oculodentodigital dysplasia which is characterised by facial abnormalities and syndactyly. Epithelial cells in the lens and fibers are joined via Cx50 which is essential to maintain the ionic conditions to avoid cataract formation. Mutation in Cx50 leads to opacity of the lens resulting in cataracts. Multisystem development disorder which occurs due to mutation in *GJA1* gene encoding Cx43 is oculodentodigital dysplasia.²² As the name indicates, it is characterized by small eyes, loss of tooth enamel and soft tissue fusion of fingers and toes. Mutation of connexin 40 leads to atrial fibrillation and the important point about heart is that the disease will be manifested until there is massive loss of connexins. These congenital defects are referred to as connexinopathies.

Role of connexins in epilepsy

Drug-resistant epilepsy presents significant challenges and affects individual health and the quality of life, with a heavy burden on society. An important characteristic of drug-resistant epilepsy is that many patients are resistant to several, if not all anti-epileptic drugs (AEDs).²³ It is well documented that genetic factors play a significant role in the modulation of anti-seizures medications efficacy, adverse effects, and dose changes such as phenytoin, carbamazepine, sodium valproate.^{24,25}

Enhanced gap junctional communication (GJC) between neurons is considered a major factor underlying the neuronal synchrony driving seizure activity. In drug-resistant epilepsy, connexins, as integral components of gap junctions, are implicated in several key processes contributing to the resistance to antiepileptic drugs (AEDs). Firstly, connexins facilitate the synchronization of neuronal activity within epileptic networks, promoting the generation and spread of seizures. This synchronization may create a substrate that is less responsive to the mechanisms of action of AEDs. Additionally, altered expression or function of connexins can disrupt intercellular communication and homeostasis within neuronal networks, potentially leading to reduced effectiveness of AEDs. Moreover, connexins may play a role in the formation and maintenance of drug-resistant phenotypes by modulating cellular mechanisms involved in drug metabolism, efflux, or target site alterations. While the connection with connexins is evident, the intricacies of their involvement and the precise mechanisms for therapeutic intervention are still being investigated. This underscores the complexity of neurological conditions and the ongoing efforts to advance our comprehension and treatment approaches.²⁶ Understanding the specific contributions of connexins to drug-resistant epilepsy could provide insights into novel therapeutic strategies targeting connexin-mediated signalling pathways or gap junction function to overcome drug resistance and improve seizure control.

Role of connexins in therapeutics

Connexins act as a therapeutic target for many conditions because of their ubiquitous distribution. It includes drugs that are specifically designed to block the activity of connexins and also the repurposed drugs. First class of gap junction channel inhibitors named glycyrrhetic acid which was found to act via stereospecific interactions was described in the 1980s.

The derivatives of GA like carbenoxolone which was shown to have neuroprotective activity in preclinical studies had limitations in being non-specific (affects connexin and pannexin channels). Carbenoxolone and arsenic trioxide were found to decrease calcium signalling in bone metastasis in mice giving us that they act by inhibiting the gap junction.

Boldine which is found to block connexin Cx43 channels in animal models of Alzheimer's disease is found to have neuroprotective activity.

Tonabersat was found to have an effect in a model of age-related macular degeneration and this property is due to blockage of connexin hemichannels.²⁷ Initially, it was in trials for migraine where it showed effect when given orally.²⁸

Connexin mimetic peptides are the peptides which contain similar sequences of connexin protein for more specific targeting of connexins. The main idea for the synthesis of these peptides is to prevent the communication between gap junction channels.

This is based on the work that giving exogenous peptides similar to domains on extracellular loops will prevent the docking of hemichannels. The crucial motifs that inhibited the function of gap junctions are used as synthetic peptides. Extracellular loop peptides include Gap26, Gap27 and Peptide 5. They mimic amino acid sequences of extracellular loops. The extracellular loops of connexins are accessible and because of this reason, it appears to be a promising target. Peptide 5 is in development as reducing vessel leak and inflammation and improve the survival of retinal ganglion cells after retinal ischemic injury. It also has a neuroprotective effect.²⁹

Alpha CT1 (alpha connexin carboxy-terminal) is a peptide with amino acids of 25 in number and it is found to restore gap junctional communication by having an anti-inflammatory effect. It acts by inhibiting the communication between Cx43 and zonula occludens-1 by binding to the PDZ2 domain and the result is the stability of gap junctional channel by phosphorylation of serine amino acid present in Cx43. The role of alpha CT1 in phase 2 trials was found to be efficacious in acute and chronic wounds. In phase 2 trial, 91 patients were randomized to a topical gel containing α CT1 and the other group to a Hydroheal Am gel. Both groups received standard of care and the group with α CT1 noticed a significant change in mean percentage ulcer area from baseline till 12 weeks and also participants who attained 100% ulcer re-epithelisation essential for wound closure.³⁰ Alpha connexin carboxyl terminal increases gap junction activity thereby maintaining Cx43 at cell-cell borders impairs the proliferation of cells in breast cancer cells and this property is found by adding α CT1 to tamoxifen to treat ER+ breast cancer cell lines which results in increased effects.

Rotigaptide (ZP123) is a hexapeptide that acts by activating the gap junctions for treating arrhythmias. It is found to decrease the size of infarct and ischemic reperfusion injury in animal models. Based on rotigaptide, dipeptide is discovered and it is called danegaptide and this was studied in dogs and pigs related to infarct size.³¹ Danegaptide was not able to reach the endpoint in phase 2 trials.³²

Another approach is through antisense oligonucleotides. The short-chain antisense oligodeoxynucleotide is designed in such a way to target RNA encoded by connexins to block protein expression. It is more specific for the particular connexin and their transient block of gap junction results in fast recovery and function mainly in CNS. Cx43 antisense oligodeoxynucleotide (Nexagon) in trials was used for ocular surface burns. It is applied topically placed beneath the lens to make sure it is in contact with the corneal surface for active drugs to enter the cell. It got orphan drug designation from the FDA. Antisense oligonucleotide is useful for the healing of ulcers in preclinical studies. It was found to reduce neutrophil count and macrophage invasion into wound sites.³³ Patients with glaucoma not controlled by 5-FU or

mitomycin with repeat needling were given anti-Cx-43 injection as compassionate use. The result in a decrease in scarring in the eye and resulted in normal intraocular pressure.³⁴ In other patients having non-healing corneal wounds, anti-Cx-43 is delivered as a gel beneath the contact lens and this has an anti-inflammatory effect and also causes limbus reperfusion.³⁵

A combination of modafinil and low-dose flecainide for narcolepsy is in development. The reason is that flecainide increases wake-promoting and cognitive effects of modafinil in orexin-deficient mice. This is being translated to humans and currently, it has been tested in 20 male subjects and the group with modafinil and low-dose flecainide was found to improve working memory and vigilance compared to the modafinil-only group.³⁶

Small molecules are screened and clofazimine, an antileprotic drug, was found to inhibit Cx46 function by inhibiting the tumour growth. Cx46 is found in glioblastoma cancer stem cells which are responsible for the growth of the tumour. Clofazimine was not found to cross the blood-brain barrier and combining with standard-of-care therapies will be useful for glioblastoma cancer stem cells.³⁷

The role of connexins in metastasis has made drugs to be used against them. Metastasis inhibitor was able to act against metastasis of melanoma cells. Monoclonal antibody against the EL2 of connexin 43 (MAbE2Cx43) resulted in a reduction in the burden of tumor. Fusion polypeptide is also in preclinical studies and Cx43₂₆₆₋₂₈₃ was found to inhibit FAK and Src activation resulting in decreased invasion of glioma cells.

Efforts have been for targeted delivery against tumour cells to avoid harmful effects on normal cells. In the rat glioma model, cisplatin is loaded by nano gels and conjugated by monoclonal antibodies towards connexins and they were found to reduce the growth of the tumours.³⁸ The reason for their specific action is because of the antibodies that help cisplatin to bind to the target site.

CONCLUSION

The connexins because of their ubiquitous distribution has various roles and it is exploited as a target in therapeutics. This will be an answer for many diseases but the limitations of the connexins have to be borne in mind. It is targeted by antisense oligonucleotides and peptide mimetics and the half-life of its action and specificity towards specific connexins without off-target effects should be considered. By overcoming these challenges, modulating the role of connexins will provide an answer to many pathological conditions.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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