Role of connexins in neurodegenerative diseases (Review)

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Abstract. Neurodegenerative diseases are neurological disorders characterized by progressive neuronal degeneration, such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis and Huntington's disease. The neuronal damage caused by these diseases may be associated with abnormal alterations of connexins in glia. These changes may cause glia to lose their ability to support and protect neurons and induce abnormal increases in levels of ions and metabolites, such as calcium ions, glutamate and ATP, around neurons. These processes eventuallys lead to neuronal death. In the present review, the abnormal expression of connexin and its primary role in neurodegenerative diseases was investigated.

Contents

1. Introduction

Neurodegenerative diseases can cause pain-associated syndromes and conditions, including musculoskeletal pain, chronic body pain (central or visceral), fluctuation-related pain, oro-facial pain and radicular pain, and comprise a heavy medical burden worldwide. The prevalence and incidence of neurodegenerative diseases increases with age (1-3). Therefore, an effective treatment plan is required to aid patients with neurodegenerative disease and alleviate suffering. The central nervous system is composed of neurons and glial cells. Glial cells include astrocytes, microglia and oligodendrocytes (4). Glia have been regarded as support cells for neurons, and glial cells can be activated by pathological stimuli, such as neuronal injury or other insults, on the central nervous system. During these processes, ions and metabolites, such as Ca^{2+} and glutamate, are released, which adversely affect neuronal activity (5-7).

Connexin is expressed on glial cells and neurons, and different types of this protein, including connexin, pannexin and innexin, exist according to the nature of the phenotype of the nerve cells (5,8,9). Connexins can form gap junctions. These proteins differ between vertebrates and invertebrates. In vertebrates, the gap junction protein is termed connexin, whereas the gap junction protein of invertebrates is termed innexin (10). Connexin is a protein that is composed of hemichannels and gap junctions (9). It serves a key role in both physiological and pathological conditions of the human body. Moreover, connexin opens in response to pathological conditions, such as cell damage (mechanical stimulation), changes in pH and ion concentration and induction of ischemia (11,12). The opening of the hemichannel causes small molecules to be released from the cell interior to the extracellular space, where they participate in signal transduction of pro-inflammatory and pro-cell death members (13,14). Nerve cell damage and death are pathological features of neurodegenerative disease. Considering the potential connection between connexin and neuronal damage, the present review focused on the role of connexins in neurodegenerative disease.

2. Roles of gap junction and hemichannel-mediated communication

In the human genome, >20 connexin members are present in the multigene connexin family (15). Connexins are named according to their molecular weight in kDa, such as Cx43, Cx30, Cx36, Cx45 and Cx50. Connexin consists of four α-helical transmembrane domains and two extracellular loops (Fig. 1), which are highly conserved among family members (9). The N- and C-termini and the intracellular loop are located in the

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Abbreviations: PD, Parkinson's disease; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; GSH, glutathione; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SD, Sprague-Dawley

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cytoplasm (16). Connexins are oligomerized into connexons or hemichannels (a connexin hexamer). The hemichannels dock with each other to form gap junction channels (17-19).

The body requires cell communication for appropriate function. As a result, several communication mechanisms have been developed. Gap junctions are the most direct and fastest communication channel between cells (16,20). The opening and closing of gap junction channels are regulated by various mechanisms, such as changes in connexin, intracellular Ca^{2+} levels and pH, as well as phosphorylation and dephosphorylation reactions (10). Gap junctions mediate the diffusion of small molecules and ions between cells and serve a vital role in physiological processes, such as cell proliferation and development, signal transduction between nerve cells and hormonal secretion (9,21). Gap junctions facilitate electrical and metabolic coupling between adjacent cells and contribute to communication between adjacent cells (21). Electrical coupling is key in excitatory tissue, notably in the heart. The transfer of current between cells occurs via gap junction channels (22). Gap junctions do not need to recognize receptors and can transmit signals faster than chemical synapses. This allows multiple neurons to be activated simultaneously, so that gap junctions are abundant and can activate mechanisms that require rapid responses, such as escape mechanisms (20,23).

By contrast to gap junctions, information on the structure and function of hemichannels is relatively limited. The hemichannel on the plasma membrane is generally closed and can be opened under pathological conditions, such as low extracellular Ca^{2+}, membrane depolarization, mechanical membrane stress and metabolic inhibition (24-26). In addition, previous studies have shown that intracellular ATP is released via hemichannels (27-29). The release of intracellular ATP is associated with a wide range of physiological processes that include a major source of energy, modulation of synaptic transmission, post-translational modifications and cofactor metabolism (30,31). In certain neurodegenerative diseases, the death and damage of the neurons may be directly associated with the opening of connexin in hemichannels. For example, in Parkinson's disease (PD), α-synuclein induces the opening of connexin hemichannels (32). The high level of hemichannel activity causes neurons to be more sensitive to damage caused by reactive oxygen generation (33). The harmful effects of hemichannel activation are associated with long-term Ca^{2+} influx, leading to the activation of Ca^{2+}-dependent hydrolase and the depletion of ATP (34).

3. Role of connexins in PD

PD is a common neurological degenerative disease, which was first described in detail by British doctor James Parkinson in 1817 (35). The overall incidence rate of PD in women who are ≥40 years old was 37.55 per 100,000 individuals/year, and 61.21 in men who are ≥40 years old between 2001 and 2014, in Europe, North America, Australia and South America (36). The lesions of PD are primarily located in the substantia nigra and develop due to degeneration of dopaminergic neurons (37,38). Dopamine acts on the striatum and directly on the subthalamic nucleus, globus pallidus and cortex. PD is associated with loss of dopamine input in these areas, which can cause abnormal firing of these nuclei (39). Dopamine differentially regulates the excitability of direct and indirect pathway spiny projection neurons. The activation of the dopamine 1 (D1) receptor in the direct pathway promotes the potentiation of excitatory synapses, whereas the activation of the D2 receptor in the indirect pathway promotes the depression of excitatory synapses (40). Therefore, degeneration of dopaminergic neurons in the substantia nigra causes excessive excitation of internal globus pallidus and substantia nigra reticulata, which subsequently inhibits the activity of the thalamus and decreases the excitatory projection of the thalamus to the cerebral cortex, resulting in PD (41,42).

α-synuclein misfolding and aggregation appears to have a close association with the majority of PD cases (43); α-synuclein can induce astrocyte reactivity and increase the synaptic capacity of astrocytes (44). Gap junctions mediate the synchronization of neuron activity in several brain regions, including the amygdala, hippocampus and cerebellum (45,46). Abundant gap junctions are present between astrocytes, which are regarded as support cells for neurons and have the ability to regulate neuronal activity as well as synaptic transmission and plasticity. These biological processes have received considerable attention in brain physiology research (47). Neuronal-astrocytic signal dysfunction is associated with the development of various neurological and neurodegenerative diseases, including neuropathic pain and PD (48-50). Alteration or uncoupling of gap junctions between astrocytes and neurons leads to excessive release of potassium ions or glutamate (51). As aforementioned, α-synuclein increases the synaptic capacity of astrocytes (44). Since the recognition of receptor signals is not required, the electrical synapse between astrocytes or neuron-astrocytes conducts faster than chemical synapses (52). When levels of α-synuclein increase, the conduction of electrical synapses and the synchronous activity of neurons increase, resulting in the development of PD (53,54).

The death of neurons is an important pathological mechanism of PD (55). It is reported that in a rat PD model induced by rotenone, the expression levels of the astrocyte marker Cx43 are significantly increased in the basal ganglia region, which contains dopamine neurons or their terminal regions (32). α-synuclein contributes to induction of the opening of astrocyte Cx43 hemichannels in the cerebral cortex of PD mice, which activates the release of ATP and glutamate in astrocytes (56,57). The Cx32 hemichannel is another source of glutamate released from microglia (58). The release of large amounts of glutamate induces neural excitotoxicity and leads to neuronal death (38,59). In addition, α-synuclein binds to Cx32 and enhances its post-translational modification. This indicates that α-synuclein regulates the gap junction of dopaminergic neurons by binding to Cx32 (60). Therefore, the involvement of Cx43 and Cx32 in the release of glutamate suggests that they may serve an important role in PD. In addition, previous studies have found that binding of α-synuclein oligomers to Cx32 promotes protein uptake and transfer in neurons and oligodendrocytes (61). Therefore, Cx43 and Cx32 may be considered a novel target for therapeutic intervention of PD.

Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is an effective neurotoxin that destroys dopaminergic neurons in the substantia nigra and induces PD (62). A previous study demonstrated that expression levels of Cx30 in mice

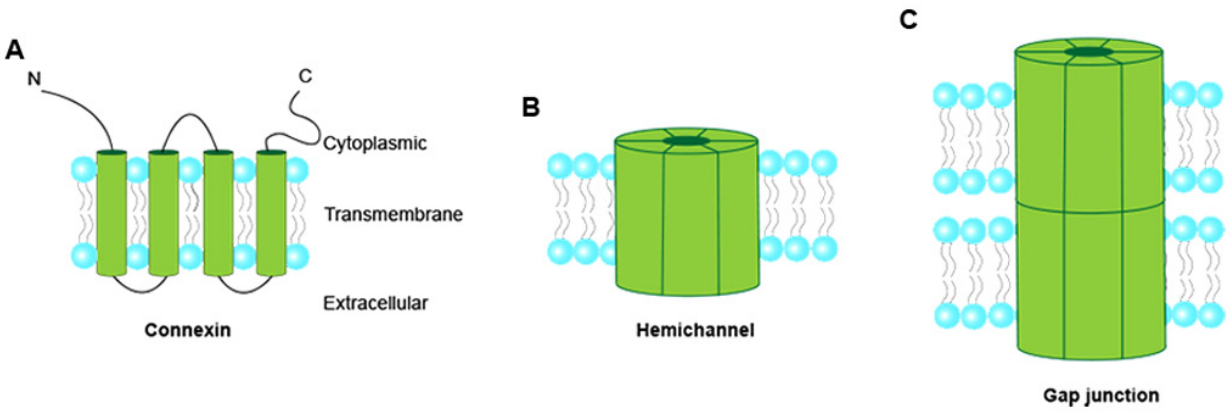

Figure 1. Connexin, hemichannel and gap junction. (A) Connexin consists of four α-helical transmembrane domains and two extracellular loops. The N- and C-termini and the intracellular loop are located in the cytoplasm. (B) Hemichannels are formed from six connexins. (C) Hemichannels can be docked with another hemichannel to assemble a complete gap junctional channel. N, -NH_2; C, -COOH.

treated with MPTP are upregulated, whereas knockout of Cx30 expression accelerates MPTP-induced loss of dopaminergic neurons (63). In total, two different types of reactive astrocytes have been identified, which are termed harmful A1 and protective A2 (64). Previous studies have shown that deficiency of Cx30 decreases protective A2 levels in an MPTP mouse model (63,65). Therefore, based on the fact that Cx30 is required for protective A2, Cx30 may protect astrocytes from the development of PD.

4. Role of connexins in Alzheimer's disease (AD)

Neurotic plaques formed by the deposition of amyloid β (Aβ) protein and the loss of brain neurons are considered signs of AD pathology. Neurotic plaques are the most unique pathological features of AD (66). The amyloid hypothesis suggests that Aβ is formed in the brain, triggering pathological effects, such as the increase in the concentration of intracellular calcium, to directly or indirectly lead to neuronal death (67). Since Aβ is the result of brain aging, rather than the cause, the mitochondrial cascade hypothesis suggests that Aβ is a sign of brain aging. It is proposed that during the development of AD, the expression and processing of amyloid precursor protein and the accumulation of Aβ protein are affected by mitochondrial function (68).

Connexins serve an important role in normal memory, learning and cognitive function (69,70). The role of connexins in AD has received extensive attention. Earlier studies have shown that in samples from an APP/PS1 mouse model, the expression levels of Cx43 and Cx30 in astrocytes are increased in the vicinity of Aβ plaques (71,72). The involvement of connexins in the development of AD is associated with mitochondrial dysfunction and the production of reactive oxygen species. Although the human brain only accounts for 2% of body weight, it is more susceptible to oxidative stress than other organs (73,74). Oxidative stress is an important mechanism involved in the pathogenesis of AD. Redox imbalance in the brain increases the susceptibility of neurons, which contain high levels of polyunsaturated fatty acids and small amounts of glutathione (GSH), to oxidative stress (75,76). GSH is involved in processing of peroxides by brain cells and protection from reactive oxygen species-induced cell damage (77). The content of GSH in the brain area containing reactive astrocyte proliferation is higher compared with that in the brain area containing neurons (78). The release of GSH in astrocytes has specific consequences for the synthesis of neuronal GSH and oxidative status in the brain. The specific consequences include the decrease of neuroprotective GSH, and the energy and redox imbalance of neurons, amongst other effects (79). In cases of insufficient GSH synthesis by neurons, oxidative stress and age-dependent neuronal degeneration develop (80). Although the content of neuronal GSH synthesis is lower than that in astrocytes, oxidative stress significantly increases the amount of GSH (81). It has been reported that GSH is released from the connexin hemichannel (82). A previous study also found that Aβ increases hemichannel activity in glia and neurons (83). Therefore, Aβ not only stimulates the release of GSH but also increase its release together with glutamate by increasing the activity of the connexin hemichannel. As aforementioned, accumulation of large amounts of glutamate causes excitotoxicity.

5. Role of connexins in amyotrophic lateral sclerosis (ALS)

ALS is a neurodegenerative disease that causes degeneration of upper and lower neurons. Its onset is characterized by minor symptoms, such as muscle weakness or muscle twitching, and eventually results in paralysis and death (84). The predisposing factors of ALS are still uncertain. Several pathological causes, including genetic mutations, excitotoxicity and oxidative stress, have been identified based on existing research (85-87). The majority of these processes are accompanied by an imbalance of Ca^{2+} homeostasis (88). In addition, the accumulation of misfolded proteins and neuroinflammation are common features of ALS (89). Neuroinflammation can develop in the brainstem and spinal cord of patients with ALS and ALS mouse models. It is also accompanied by the accumulation of a large number of activated astrocytes and microglia (90). Astrocytes and microglia contribute to the degeneration of neurons and exert this effect via gap junctions and hemichannels between glial cells (91). It has previously been shown that expression levels of Cx43 are increased in patients with ALS and mouse models, which contributes to degeneration of motor neurons (92). Large amounts of ATP are released from

astrocytes via Cx43. Subsequently, ATP binds to P2X receptors, which increases calcium signaling (93). Prior to stimulation with ATP, calcium signal decreases when astrocytes are incubated with the Cx43 mimic peptide Gap26 (92). This indicates that Cx43 gap junctions and hemichannels contribute to the transmission of calcium signals. Abnormal expression of Cx43 leads to abnormal transmission of calcium signals. Changes in intracellular Ca^{2+} levels serve a prominent role in regulating fundamental cellular functions, such as neuronal migration and differentiation, synapse formation and synaptic plasticity in various cell types, including neurons (94). In neurons, Ca^{2+} also participates in the transmission of depolarization signals. Changes in Ca^{2+} levels serve an important role in neuronal degeneration (95). Therefore, Cx43 gap junctions and hemichannel-mediated calcium signaling exert an important role in ALS. In addition, a delayed decrease in Cx36 expression on spinal cord neurons in ALS has been found. Cx36 expression is downregulated in late ALS (when neuronal degeneration has already occurred) (96). The reason for this delayed downregulation may be the primary and secondary death of Cx36-expressing neurons (96,97). This part of neurons is a component of overall neuronal damage. Administration of Cx36 gap junction channel blocker prevents the ALS-related death of neurons (96). Therefore, Cx36 is also an important target for the future treatment of ALS.

6. Role of connexins in Huntington's disease (HD)

In 1872, George Huntington wrote a report on hereditary chorea, which is now known as HD (98). However, chorea is not the only dyskinesia characteristic found in this disease. HD can cause a series of dyskinesia characteristics, such as chorea and rapid involuntary movements of the face, torso and limbs (99,100). A previous study demonstrated that neuronal cell death is most pronounced in the caudate nucleus and pallidum of the basal ganglia in the brains of patients with HD (101). In recent years, a growing awareness has been noted with regard to the important role of glial cells in the nervous system (102). Glial cells and gap junctions are involved in buffering of potassium ions around active neurons and protection of nerves from glutamate toxicity (59). Under normal conditions, persistent increases in glutamate act on N-methyl-D-aspartate receptor-type glutamate receptors on neurons, resulting in neuronal excitotoxicity (103). Therefore, abnormalities in gap junctions between astrocytes may lead to neuronal cell death in HD. Few studies have investigated the role of connexins in HD. However, one study demonstrated that Cx43 expression is abnormally increased in the caudate nucleus, whereas the density of Cx43 increases with development of HD (101). Altered connexin gap junctions result in the inability of astrocytes to maintain normal neuronal activity, which may be a factor in neuronal death in HD (101). Therefore, based on the key role of connexin gap junctions in HD, connexins may be considered an important addition in the investigation of the pathogenesis and etiology of HD.

7. Conclusion

Neurodegenerative diseases are associated with motor neuron damage and degeneration. It has been shown that the inhibition of connexin gap junctions and hemichannels can protect neurons from adverse effects of ion and metabolite homeostasis. Understanding the role of connexin gap junctions and hemichannels in neurodegenerative diseases may provide a novel research direction for the development of potential therapeutic strategies for neurodegenerative disease.

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Authors' contributions

JX conducted the literature search, wrote and revised the manuscript. CX designed the review. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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