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Review

Gap junctions and neurological disorders of the central nervous system

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Abstract

Gap junctions are intercellular channels which directly connect the cytoplasm between neighboring cells. In the central nervous system (CNS) various kinds of cells are coupled by gap junctions, which play an important role in maintaining normal function. Neuronal gap junctions are involved in electrical coupling and may also contribute to the recovery of function after cell injury. Astrocytes are involved in the pathology of most neuronal disorders, including brain ischemia, Alzheimer's disease and epilepsy. In the pathology of brain tumors, gap junctions may be related to the degree of malignancy and metastasis. However, the role of connexins, gap junctions and hemichannels in the pathology of the diseases in the CNS is still ambiguous. Of increasing importance is the unraveling of the function of gap junctions in the neural cell network, involving neurons, astrocytes, microglia and oligodendrocytes. A better understanding of the role of gap junctions may contribute to the development of new therapeutic approaches to treating diseases of the CNS.

Keywords: Gap junction; Neurological disease; Neuron; Glial cell; Connexin

1. Introduction

The gap junction is the site of the intercellular membrane channels which provide for direct cytoplasmic continuity between adjacent cells [1]. The structural unit of the gap junction is the *connexon*, a proteinaceous cylinder with a hydrophilic channel. They span the plasma membranes of closely apposed cells to align end-to-end, forming intercellular channels which provide for the exchange of small molecules (less than 1200 Da). The gap junction protein, *connexin* (Cx), is encoded by a multi-gene family consisting of at least 20 members in mammals [1]. Several connexins exhibit a characteristic tissue and cellular distribution in the adult animal, and many tissues and cells have been shown to express multiple connexins. Eleven subtypes are found in the central nervous system (CNS). The subset and the expression of connexins vary depending on the type of cell and the stage of development [2] (see Table 1 for details of cellular expression in the CNS).

The CNS is mainly composed of neurons and glial cells such as astrocytes, microglia and oligodendrocytes. Neurons are interconnected by axons and dendrites and play an important role in transmitting signals through synaptic interactions. Astrocytes have many processes and compose an astrocytic syncitium which provides physical and metabolic support of neurons. Microglia are CNS residential macrophages and play a role in the immune response of the CNS. Oligodendrocytes form myelin sheaths which surrounds neuronal axons, providing acceleration of the conduction process in the neuronal axons.

In the nervous system, intercellular coupling via gap junctions occurs between neurons, astrocytes, oligodendrocytes, microglia and ependymal cells [3–5] as well as between different cell types, such as neuron–astrocyte [6] and astrocyte–oligodendrocyte [3,4]. The non-neuronal junctions presumably play a role in ion transfer and metabolic cooperation. Expression of multiple connexins has been demonstrated in the CNS (Table 1) [7]. Given the heterogeneous composition of brain tissue, some of this expression is likely accounted for by endothelial cells which are known to express Cx37 [8] and Cx40 [9], as well as Cx43 [10], and meningeal cells which express Cx43 and Cx26 [11]. However, the expression of many of these connexins remains to be determined at the cellular level.

Neurological disorders can be classified into two groups: the peripheral nervous system (PNS) diseases and the CNS diseases. Several studies have noted the involvement of gap junctions in CNS disorders, including cerebrovascular dis-

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Table 1
Connexin subtype and cellular expression in the CNS

Connexin subtype	Cell type (expressed stage)	References
26	neuron	[29,30,35]
	astrocyte	[73]
29	oligodendrocyte	[101]
30	astrocyte (matured)	[3,72]
32	neuron (matured)	[32]
	oligodendrocyte	[95–100]
36	neuron	[34,36,37]
	oligodendrocyte	[5]
	microglia	[5]
37	neuron	[39]
40	neuron (developing)	[39]
	astrocyte	[73]
43	neuron (mainly developing)	[29,32]
	astrocyte	[70,71]
	microglia (activated)	[91,92]
45	neuron	[40,63]
	astrocyte	[73]
46	astrocyte	[73]
47	neuron	[38]
	astrocyte	[2]
	oligodendrocyte	[102]

eases such as brain ischemia and brain hemorrhage [12–14], neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [15,16], epilepsy [17,18] and brain tumors [19,20]. In this review, possible functions of gap junctions and hemichannels, which are composed of a single connexon opened to the extracellular space, will be described separately in each of the cell types of the CNS, and the role of the hemichannels and gap junctions in various neurological diseases will be discussed.

2. Gap junctions in the cells of the nervous system

2.1. Neurons

Electrotonic coupling between mammalian neurons has been shown in many areas of the CNS and has been implicated in neuronal synchronization [21–24]. During development, there is a high degree of intercellular coupling between neurons. Studies in the rat indicate that neuroblasts are coupled with approximately 30–60 others in columns within the ventricular zone of the developing cerebral cortex [25–28]. The zone is comprised of mitotically active epithelial cells lining the ventricles. These cells have been shown to express Cx43 and Cx26 [29], and the coupling appears to involve both neural precursors and radial glia [30]. Thus gap junctional intercellular communication (GJIC) may establish cortical domains in the developing neocortex that underlie the adult pattern of functional architecture [27,28,31]. Although Cx43 has been reported in neurons of the cortical plate, the expression of Cx32 in mature neurons [32] is controversial [33,34]. The expression pattern of Cx26 [35] and Cx36 [36,37] in the developing brain is more consistent with the transient gap junctional coupling observed in the neocortex. In addition, Cx47 is also observed in the CNS [38], but its expression seems to be different from that of Cx36 in neurons of developing CNS, but there is some co-localization with Cx36 in cerebellum [38]. Cx37 is observed in motor neurons and Cx40 is expressed in developing neurons of spinal cord [39].

In the adult CNS, neurons are coupled via gap junctions mainly composed of Cx36 [34] and Cx45 [40] in the cortex and hippocampus. These neuronal gap junctions play an important role in forming electrical synapses [41,42]. Cx45 is expressed widely in the developing brain and in the adult brain localized in cerebral cortex, hippocampus and thalamus [40]. Cx45 is also observed in olfactory nerves [43]. In the retina, Cx26 is expressed in horizontal cells [44] and Cx36 in AII amacrine cells [45], although Cx26 is not shown in the neurons in the adult cortex and hippocampus [46]. Recently, it has been reported that hemichannels of horizontal cells in the retina are mainly composed of Cx26 and regulate the activity of the Ca^{2+} channels and subsequent glutamate release [44]. The availability of various antibodies has made it possible to detect connexins which compose gap junctions [34,47] as well as hemichannels [48,49], allowing characterization of the functional state, distribution and co-localization of connexins.

In order to understand the role of specific connexins in the CNS, a knockout strategy has been employed by several investigators (see Table 2 for summary). Initial examination suggested some subtle neural changes may be apparent in the Cx43 knockout mice at birth [50]. However, the neural

Table 2
The observed abnormalities in connexin knockout mice

Knockout mouse	Abnormalities	References
Cx26	embryonal lethal	[61]
($Cx26^{fl/fl}$, Otog-cre)	hearing impairment	[62]
Cx30	severe hearing impairment	[89]
Cx32	demyelination in PNS	[55,56]
	hyperexcitability in CNS	[57]
	enhanced neuronal injury in ischemia	[124]
Cx36	visual deficit	[59]
	synchronization defect in hippocampus	[60]
	disturbed synchronous inhibitory activity	[41]
	disrupted gamma frequency oscillations in cortex	[42]
Cx43	neonatal lethal	[51]
	subtle neural changes in embryo	[50]
	neural crest migration defect	[52,53]
	disturbance of neural migration in embryonic neocortex	[54]
(Cx43 +/−)	enhanced neuronal injury in ischemia	[87,117]
($Cx43^{fl/fl}$,GFAP-cre)	increased spreading depression in hippocampus	[88]
	enhanced neuronal injury in ischemia	
Cx45	embryonic lethal	[63]
Cx47	vacuolation in nerve fibers	[102]
(Cx47/32 double)	severe demyelination in CNS	[102,112]

phenotype of the Cx43 knockout mice is confounded by cardiac malformation and neonatal death [51]. In these mice, the abnormal migration of neural crest was observed [52,53]. More recently, we have reported a disturbance in the migration of neurons in the neocortex of the Cx43 null mice [54]. Cx32 knockout mice are viable and fertile, and display demylenation in the PNS [55,56]. Moreover, neuronal hyperexcitability and myelin defects in the neocortex were observed [57], and the accumulation of oligodendrocyte progenitor cells and amplified apoptosis has been reported in the CNS of Cx32 knockout mice [58]. Cx36 knockout mice are viable and display no obvious anatomical abnormalities [59], however detailed neurodevelopmental and anatomical studies have not been reported. Studies using Cx36 knockout mice in vitro suggest that the neuronal gap junctions are critical in the formation of gamma frequency oscillations in the hippocampus [42] and in generating synchronous activity in the cortex [41]. These mice show selective impairment of hippocampal gamma oscillations [60]. Knockout of the other neuronal candidate, Cx26, is lethal at E9–10 [61], and thus additional strategies must be followed to investigate its function in neuronal development [62]. Cx45 knockout mice die at E8–9 due to abnormal vascular development. Therefore, it is impossible to study the gap junctional function using adult Cx45 knockout mice. The expression of Cx45 has also been reported in the embryonic cortex and hippocampus [63], but its role in the development of the CNS remains to be determined.

In vitro studies have suggested a role for gap junctional coupling in neuronal differentiation. When NT2 human embryonal carcinoma cells differentiate into neurons in response to retinoic acid (RA), the expression of Cx43, and the level of gap junctional coupling, progressively disappear [64]. Blocking of gap junctions disrupts RA-induced neuronal differentiation of both human NT2 [65] and mouse P19 cells [66]. Moreover, the differentiation of NT2/D1 progenitor cells are reduced by blocking of gap junctions and hemichannels, suggesting hemichannels also play a role in the neuronal differentiation [67]. It therefore appears that the temporal pattern of connexin expression and gap junctional coupling during neuronal differentiation is critical.

2.2. Astrocytes

The main cell type in the brain coupled by gap junctions is the astrocyte. Astrocytes have traditionally been viewed to have a role in the metabolic and trophic support of neurons [68]. Intimate interactions have been shown to be involved in the role of radial glia in directing migration of neurons in the cortex [69]. Indeed, gap junctional coupling between radial glia and neural precursors may be critical for this process [30]. Gap junctions in astrocytes are primarily composed of Cx43 [70,71], in addition to other connexins, including Cx30 [3,72], Cx47 [2], Cx40, Cx45, Cx46 and Cx26 [73]. Moreover, gap junctions provide a substrate for formation of a functional astrocytic syncytium [70,71,74,75], implicated in the spatial buffering capacity of astrocytes, particularly in dealing with extracellular K^+ arising from neuronal activity [76,77]. The propagation of intercellular Ca^{2+} waves is an important feature of astrocytes in response to activation [78]. Studies from several laboratories have shown that gap junctions are involved in mediating intercellular Ca^{2+} signaling throughout the glial syncytium [79–81]. Astrocytic hemichannels also play a role in the release of adenosine triphosphate (ATP) associated with Ca^{2+} signaling [82,83]. Moreover, the inhibition of glycolytic and oxidative metabolism resulted in an increase of astrocytic hemichannels [84], suggesting involvement of hemichannels in this pathological condition.

Astrocytes cultured from Cx43 knockout mice exhibit reduced gap junctional coupling and Ca^{2+} wave propagation [85,86]. Meanwhile, Cx43 knockout astrocytes express other connexin subtypes (Cx30, 40, 45, 26, 46) [73], suggesting that connexins other than Cx43 could not compensate for the reduction of GJIC in astrocytes. Even astrocytes derived from heterozygote Cx43 knockout mice showed a significant reduction in gap junctional coupling [85,87]. These heterozygote mice have been used for in vivo studies (see below). Recently, mice lacking Cx43 specifically in astrocytes have been generated by using the cre-recombinase system [88]. These mice can survive to adulthood, unlike Cx43 knockout mice, and exhibit amplified motor activity with increased hippocampal spreading depression, providing a valuable model for in vivo studies. Although Cx30 has been shown only in astrocytic gap junctions in the CNS, no major abnormality was observed in the brains of Cx30-deficient mice, although they exhibit severe hearing loss [89].

2.3. Microglia

Microglia are important cells in the CNS, participating in the reactive gliosis. Although resting microglia do not show phagocytosis, activated microglia behave like phagocytes [90]. Under normal conditions, microglia show little expression of Cx43, however, this increases following stimulation by inflammatory cytokines [91] or Ca^{2+} ionophores [92], allowing for enhancement of gap junctional coupling. Cx36 has been also found to form gap junctions in microglia [5], suggesting the direct communication between microglia. Moreover, brain macrophages/microglia decrease Cx43 expression and gap junctional coupling in co-cultured astrocytes [93,94]. It is important not only to understand the phagocytic function of microglia but also to understand the role of microglial gap junctions in the inflammatory response of the CNS.

2.4. Oligodendrocytes

Several reports have indicated that oligodendrocyte gap junctions are composed of Cx32 [95–100], Cx36 [5], Cx29 [101] and Cx47 [102]. We have shown that expression of Cx32 coincides with maturation of oligodendrocytes tem-

porally and spatially [97,103]. The function of gap junctions in oligodendrocytes is thought to be primarily metabolic to allow ions and nutrients to pass from the somata to all the layers of the myelin [104,105]. The importance of this channel has recently been realized by the reported mutations of Cx32 associated with X-linked Charcot–Marie–Tooth disease, a peripheral demyelinating disorder [106–110]. It was initially thought that human and rodent Schwann cells are susceptible to pathology, leading to peripheral nerve demyelination, while oligodendrocytes appeared not to be affected. Cx32 knockout mice showed a reduced myelin volume and an enhanced excitability in the CNS [57], and a progressive peripheral neuropathy has been observed after 3 months of age [55,56]. Cx29 has also been specifically observed in oligodendrocytes and Schwann cells [101]. The expression of Cx29 exists mainly at the paranodes and juxtaparanodes [101], whereas Cx32 is not observed in the paranodes [111], indicating a difference in the distribution of these two connexins. In the pathogenesis of demyelination associated with the Cx32 deficiency, the compensatory role of Cx29 may have to be explored.

Recently, Cx47 was observed to be expressed mainly in oligodendrocytes [102]. Cx47 null mice exhibit degeneration of nerve fibers, particularly in the optic tract [102]. Moreover, Cx47 and Cx32 double knockout mice exhibited a more severe demyelination in the CNS [102,112], indicating that both connexins play a critical role in myelination.

3. The role of gap junctions in neuropathological conditions

3.1. Brain ischemia

Cerebrovascular diseases rank as the third leading cause of death in the USA and fourth in Canada, most commonly manifesting as ischemic brain stroke [113,114]. In the context of experimental brain ischemia models, the neuroprotective role of astrocytic gap junctions is still controversial. Blocking astrocytic gap junctions enhances neuronal vulnerability to glutamate cytotoxicity in culture [115]. Moreover, blocking gap junctions in a hippocampal slice culture enhanced neuronal damage under experimental ischemia using oxygen and glucose depletion [116]. In vivo, heterozygote Cx43 knockout mice showed a significantly increased stroke volume compared to wild-type mice following middle cerebral artery occlusion (MCAO) [87] and exhibited enhanced apoptosis in the penumbra [117]. These results suggest that astrocytic gap junctions play a neuroprotective role in oxidative and metabolic stress. On the other hand, neuronal death caused by oxygen and glucose depletion was decreased when Cx43 was blocked by specific antisense oligodeoxynucleotide in the hippocampal slice culture [118]. Similarly, the stroke volume following MCAO in the rat model was reduced by blocking gap junctions using octanol [119]. Therefore, it has been suggested that the spreading depression caused by ischemic insult goes through astrocytic gap junctions which remain open during the ischemic condition, resulting in the expansion of the stroke volume [120]. However, there are problems in interpreting the results obtained with gap junction blockers such as octanol because of the lack of specificity, particularly when administered systemically. In addition, there is no selectivity with regard to astrocytic gap junctions since all gap junctions in the tissue are affected. The use of more specific approaches to target gap junctions is desirable, for example using Cx43 antisense and interfering RNA. More recent use of targeted deletion of connexins, specifically in astrocytes, is providing evidence that astrocytic gap junctions play a neuroprotective role in ischemic insults through reduction of apoptosis and inflammation [121].

The role of astrocytic hemichannels in ischemic insult is still unknown. Recently, it has been reported that astrocytic hemichannels, which are closed under normal conditions, remained open under experimental ischemia induced by glucose and oxygen depletion [84]. It is possible that open hemichannels allow for the release of glutamate causing loss of membrane potential [122], or hemichannels may contribute to the distribution of anti-apoptotic factors in the lesion area [123].

Cx32 knockout mice have been reported to exhibit an enhanced vulnerability of hippocampal neurons against brief global brain ischemia compared to wild-type mice [124], suggesting that gap junctions of hippocampal interneurons play a neuroprotective role in ischemic insults. Moreover, expression of astrocytic gap junctions can be affected by macrophages [93,94] and microglia express Cx43 following activation [91]. In this context, the regulation of connexin expression can be mediated by various types of cells other than neurons and astrocytes following ischemic stress.

3.2. Epilepsy

There are two major clinical symptoms of epilepsy: the partial seizure where excessive electrical discharge is restricted to a given area in the brain, and the general seizure involving the entire brain [125]. The pathogenesis of seizures may be associated with abnormal stimulation occurring in a certain region of the brain causing depolarization of the membrane, expanding to the surrounding cells. Gliosis at the lesion is usually observed in epileptic brain tissue. However, the participation of Cx43 which composes mainly astrocytic gap junctions is controversial (reviewed in Ref. [17]).

In models of experimental epilepsy, strong recurrent excitatory activity, such as that produced by GABA receptor blocking, K^+ pump blocking, and repetitive stimulation is used as the epileptic trigger [126]. Electrical coupling through neuronal gap junctions is reported to play an important role in the expansion of the epileptic wave [127]. Blocking of astrocytic gap junctions decreases Ca^{2+} oscillations in co-cultured neurons [128]. An increase of

Cx32 expression was observed in the hippocampus in a model of bicuculline-induced epileptiform activity [129], although a decrease in the level of Cx36 mRNA has been reported in the hippocampus of the kainate-treated rat [130]. Meanwhile, neuronal gap junctions are required for the appearance of very fast oscillations associated with seizure activity [18]. Cx43 mRNA levels were increased in the temporal cortex of epilepsy patients [131]. Therefore, the role of gap junctions in epilepsy is still controversial. In the future, the gap junctional coupling between various types of cells in vivo should be evaluated under epileptic stimulation.

3.3. Neurodegenerative disease

One of the major neurodegenerative diseases is Alzheimer's disease (AD). Clinically, cerebral atrophy is observed mainly in the frontal cortex of AD patients and pathologically, neurofibrillary degeneration and senile plaques are shown in the lesions [132]. The senile plaque is a round deposit composed of β-amyloid protein surrounded by astrocytic processes. An increase in the expression of Cx43 was observed at the site of these amyloid plaques [15]. Pathological evaluations have revealed the importance of astrocytic participation in the lesion using presenilin mutant knockin mice [133,134] and apoE null mice [135–137]. However, there is no report clarifying the relation between gap junctions and AD. AD is a progressive disease and the lesion exhibits a successive expansion, suggesting that the glial network may play a critical role in the pathogenesis of AD.

Parkinson's disease (PD) is a common neurodegenerative disease. Clinical symptoms are progressive tremor, muscle rigidity and gait disturbance [132]. In the brain of PD patients, the loss of dopaminergic neurons is observed in the substantia nigra-striatum [132]. The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-model of PD exhibited an increase of Cx43 expression in the striatum, although the coupling of astrocytes was not increased [16]. The alteration of gap junctions in the brains of PD patients has not yet been reported. Therefore, the pathological role of gap junctions in PD is still ambiguous. Although most of the mechanisms of tremors and dyskinesias which are commonly observed in PD patients are still obscure, the inferior olive has been focused on as the pathological generator of tremors [138,139]. Neurons of the inferior olive are electrically coupled through gap junctions which plays a role in creating oscillatory activity [140]. Some studies have reported that the GJIC of inferior olive neurons is responsible for tremors [139,140], however, no difference of the severity of tremor induced by harmaline was observed between Cx36 knockout mice and wild-type mice [141]. More experiments will be required to clarify the mechanism of tremors.

In neurodegenerative diseases, it is also important to evaluate the inflammatory response because both AD and PD exhibit inflammation in the lesion [142]. Indeed, anti-inflammatory drugs may reduce the incidence of AD and delay the progression of the disease [143,144]. As mentioned previously, activated microglia express gap junctions composed of Cx43 [91]. Moreover, activated macrophages decreased the expression of astrocytic gap junctions [93,94]. Therefore, further investigation of the possible gap junctional neuroprotective role of glial cells and inflammatory cells in neurodegenerative diseases is warranted.

3.4. Tumor

Glioma is the most common brain tumor [145]. The severity of gliomas is divided into four categories, from most malignant tumor to benign tumor. In general, glioma is a space-occupying mass in the brain and causes a high intracranial pressure, vessel occlusion and brain edema [145]. Investigating the tumor tissue has revealed that higher grade gliomas express lower levels of Cx43 [146,147]. However, the relation between gap junctions in tumor cells and metastasis is still ambiguous.

Up-regulated gap junctions reduce the in vitro proliferation of C6 glioma cells [148]. On the other hand, glioma cells aggregate and invade into the astrocytic syncitia using gap junctions [19]. Astrocytes co-cultured with C6 glioma cells overexpressing Cx43 underwent phenotypic transformation [149], suggesting that tumor cells may affect phenotypical alteration of surrounding tissue through gap junctions. The results obtained from in vitro studies are remained controversial.

Gene transduction is a potential strategy for glioma treatment [150]. Gap junctions of glioma cells may play a critical role in the mechanism of this therapy. Glioma cells infected with the herpes simplex virus thymidine kinase gene can be killed upon exposure to ganciclovir. Neighboring glioma cells that are intercellularly linked to the targeted cell subsequently die due to a "bystander effect" [151]. The lethal "bystander effect" can be enhanced when the glioma cells are forced to express Cx43 [152]. So far, the gap junctional role in the "bystander effect" remains ambiguous, and further investigations should be performed to discover the precise mechanism of gap junctions involved in glioma therapy.

Recently, several reports have described that Cx43 plays a role in suppressing tumor growth independent of gap junction formation [153–155]. In this case, Cx43 transfected into glioblastoma cells reduced cell proliferation without enhancing gap junctional coupling, suggesting that Cx43 acts as a tumor suppressor gene in human glioblastoma [156]. The C-terminal domain of Cx43 seems to be important in this tumor-inhibiting effect [154]. Cx43 may also regulate the cell cycle by acting on the S-phase kinase-associated protein [155]. Additional research may still need to explore the tumor suppressing role of Cx43.

4. Conclusions

The function of gap junctions and the difference of the connexins have been well studied in the CNS. Neuronal gap

junctions may play an important role in the regulation of the periodic synchronized activity between neurons. Astrocytes exchange ions and metabolic substrates, such as inositol 1,4,5-triphosphate and ATP, through gap junctions. Gap junctions of oligodendrocytes play a critical role in maintaining normal myelination. Moreover, the ischemic brain models or epilepsy models using various connexin knockout mice have revealed the possibility of neuronal protection of gap junctions against ischemic or metabolic stress, although opposite results have also been reported. Recent studies have described that macrophages may influence the expression of astrocytic gap junctions and that activated microglia may communicate with each other through gap junctions. It is important to be able to understand the gap junctional network in the entire neuronal system in the pathological condition. Then, the regulation of gap junctions in the nervous system may contribute to the development of new therapies for neurological diseases.

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