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Review

Gap junctions in inherited human disorders of the central nervous system ☆

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ABSTRACT

CNS glia and neurons express connexins, the proteins that form gap junctions in vertebrates. We review the connexins expressed by oligodendrocytes and astrocytes, and discuss their proposed physiologic roles. Of the 21 members of the human connexin family, mutations in three are associated with significant central nervous system manifestations. For each, we review the phenotype and discuss possible mechanisms of disease. Mutations in *GJB1*, the gene for connexin 32 (Cx32) cause the second most common form of Charcot–Marie–Tooth disease (CMT1X). Though the only consistent phenotype in CMT1X patients is a peripheral demyelinating neuropathy, CNS signs and symptoms have been found in some patients. Recessive mutations in *GJC2*, the gene for Cx47, are one cause of Pelizaeus–Merzbacher-like disease (PMLD), which is characterized by nystagmus within the first 6 months of life, cerebellar ataxia by 4 years, and spasticity by 6 years of age. MRI imaging shows abnormal myelination. A different recessive *GJC2* mutation causes a form of hereditary spastic paraparesis, which is a milder phenotype than PMLD. Dominant mutations in *GJA1*, the gene for Cx43, cause oculodentodigital dysplasia (ODDD), a pleitropic disorder characterized by oculo-facial abnormalities including micropthalmia, microcornia and hypoplastic nares, syndactyly of the fourth to fifth fingers and dental abnormalities. Neurologic manifestations, including spasticity and gait difficulties, are often but not universally seen. Recessive *GJA1* mutations cause Hallermann–Streiff syndrome, a disorder showing substantial overlap with ODDD. This article is part of a Special Issue entitled: The Communicating junctions, composition, structure and functions.

Contents

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1. Introduction

CNS glia and neurons express connexins, the proteins that form gap junctions (GJs) in vertebrates. (See Fig. 1 for nomenclature of gap junction channels and hemichannels.) To date 20 members of the connexin family have been identified in mice and 21 have been demonstrated in humans. (Reviewed by Rackauskas et al. [1].) Mutations in at least 10 of these connexin genes cause human disease [2], including three connexins with significant CNS manifestations; these are the focus of this review. Here we emphasize the clinical phenotypes and current understanding of the pathogenesis of these genetic diseases, which will require a brief overview of connexin expression within CNS glial cells, reviewed in more detail elsewhere [3,4].

2. Connexins expressed by astrocytes and oligodendrocytes

2.1. Distribution and coupling

Astrocytes (As)[2] express Cx30 and Cx43, which can form homotypic (Cx43/Cx43 and Cx30/Cx30) but not heterotypic (Cx43/Cx30) GJs in a model system of transfected cells [5]. Anatomical approaches also provide evidence that A/A GJs are composed of Cx43/Cx43 and Cx30/Cx30 homotypic channels [6–9]. Cx43-positive GJ plaques are found in both gray and white matter, whereas Cx30-positive GJ plaques are more prominent in gray matter. Although there are contradictory data [10], some astrocytes may also express Cx26 [7,9,11,12], which can also form homotypic as well as Cx26/Cx30 heterotypic channels. In mice, the deletion of the genes encoding Cx43 (*Gja1*) and Cx30 (*Gjb6*) results in the complete loss of A/A coupling [13]. Mutations in *GJB2* (encoding Cx26) and *GJB6* (encoding Cx30) are not associated with CNS abnormalities in humans or mice.

Oligodendrocytes (Os) express Cx29, Cx32, and Cx47 [9,14–17]. Cx29 is localized to the adaxonal membrane (apposing the axonal membrane) of CNS myelin sheaths, but does not form GJs [11,17–19]. In transfected cells, Cx29 does not form functional channels [20], but its human ortholog, Cx31.3, may form hemi-channels [21]. In rodents, Cx47 and Cx32 are found in GJ plaques that are localized on the cell bodies of oligodendrocytes [17], and Cx32 is also localized within the myelin sheaths themselves [15], although not as distinctly localized as in Schwann cell myelin sheaths [22]. Though O/O coupling was not seen in a number of brain regions by conventional electron microscopy (EM) or freeze replica immune labeling (FRIL) [8,23], two groups have recently reported the functional O/O coupling in the mouse corpus callosum [24,25]. The O/O coupling is mediated by Cx32/Cx32 and Cx47/Cx47 homotypic channels, as it is present in mice lacking Cx32 or Cx47, but is lost in mice that lack both Cx32 and CxCx47. Furthermore, EM demonstrated that oligodendrocytes are directly joined by GJs [24].

Electron microscopic studies in the 1980s provided anatomical evidence that oligodendrocytes were GJ coupled to astrocytes, but not to themselves [26,27]. Our work in a model system of transfected cells shows that Cx43/Cx47 and Cx30/Cx32 (but not Cx43/Cx32 or Cx30/Cx47) form morphologic and functional GJs that have distinct electrophysiological properties [5], but using a different approach, another group [28] showed that Cx30 and Cx47 can form functional channels. Anatomical studies in the CNS [7,9,13,15] make a strong case that A/O GJs consist predominantly of Cx43/Cx47 and Cx30/Cx32 heterotypic channels (a role for Cx26/Cx32 channels remains to be excluded or proved). In the cerebral cortex, A/O coupling is lost in Cx47- (*Gjc2*), but not in Cx32- (*Gjb1*) null mice, indicating that Cx43/Cx47 channels (and not Cx30/Cx32 channels) are required for A/O coupling, at least in this region [24].

2.2. Roles of glial connexins in CNS glia

2.2.1. Lessons from mice with targeted ablation of one or more connexins

The roles of connexins in CNS glia are now beginning to be explicated. Mice with targeted deletion of oligodendrocyte connexins Cx29, Cx32, and/or Cx47 and mice with targeted deletion of astrocyte connexins Cx30 and/or Cx43 have been examined. A thorough understanding of the phenotypes of these mice is critical to understanding of the pathogenesis of disorders associated with mutations in these connexins. Cx32- (*Gjb1*-) null mice develop a

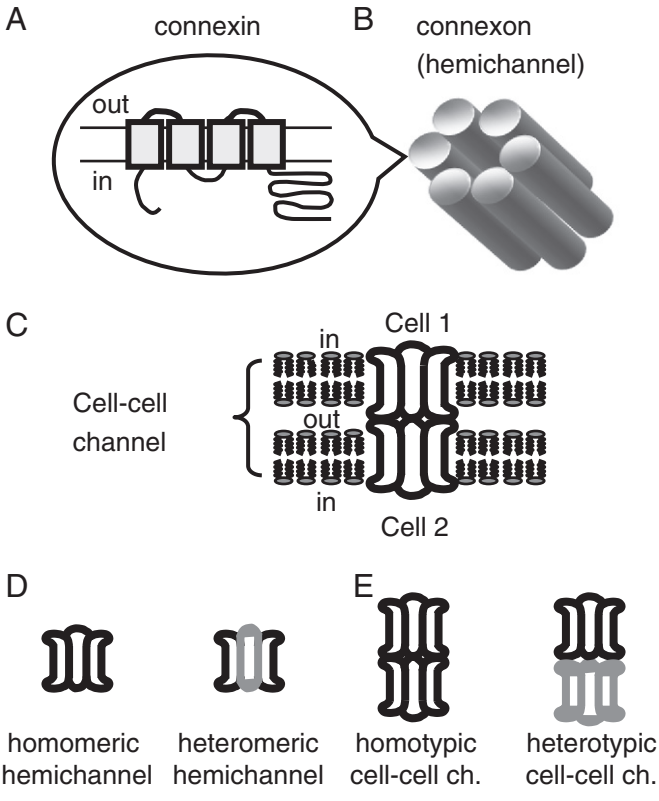

Fig. 1. Gap junction nomenclature A. Connexins are integral membrane proteins with four transmembrane domains and intracellular N and C termini. B. Each connexon or hemichannel is composed of six subunits called connexins. C. Cell–cell channels are formed by docking of two apposed connexons from apposed cells. D. If all six subunits are identical the connexon is termed homomeric. In cells expressing more than one type of connexin, different connexins may aggregate to form heteromeric connexons. E. Many members of the connexin family can form functional GJs by associating with a like connexon (a homotypic junction) or a different one (a heterotypic junction).

[2] Non-standard abbreviations. A—astrocyte O—oligodendrocyte GJ—gap junction KO—knockout(null) dKO—double knockout WMC: white matter changes.