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Review

GAP JUNCTIONS, HEMICHANNELS AND CONNEXINS AND THEIR ROLE IN THE NEUROVASCULAR UNIT

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ABSTRACT

Recent advances have come to suggest that connexins (Cxs), the core gap junction (GJs) and hemichannels (HCs) composing proteins, play a crucial role in neurodegenerative and neuroprotective conditions. GJs and HCs syncytia in the complex neuroglial network allows glial cells to support and even modulate neuronal function in both physiological and pathological conditions. In this review we aim at reviewing the current knowledge in the context of neuroglial crosstalk and neurovascular units (NVU) and at delivering up-to-date insights on cell populations interplay in physiological and pathological central nervous system (CNS) conditions.

1. Introduction

Central nervous system (CNS) is a privileged tissue in which resident cells are protected by physical barriers that select, balance and modulate blood stream mediators (1). The cellular substrates exerting these functions are both vascular cells (i.e. endothelial cells and pericytes of brain capillaries) and nervous cells (i.e. glial cells), collectively indicated as blood-brain barrier (BBB) (2). The cellular structure of BBB has been intensely studied and revealed that cells are organized in a complex tight junctions-mediated composition between endothelial cells in the non-fenestrated capillaries of the CNS. Over the last decades the knowledge on BBB composition and function have been improved by current imaging techniques, such as electron microscopy, finding that BBB is actually an interface in which endothelial cells, astrocyte, pericytes and neurons communicate and are organized in so called neurovascular unit (NVU) (3). In physiological conditions NVU cells are the guardian of the CNS, ensuring homeostatic nutrients and ions maintenance, efficient scavenging processes and selecting peripheral-derived messengers, thus contributing to the signalling and functional performance of CNS resident cells (4-6). During pathological affections of the CNS, such a role is threatened by autocrine and paracrine stimuli in the NVU microenvironment, which alters its functions and dramatically affect BBB function, concomitantly increasing peripheral derived detrimental stimulation.

CNS inflammatory disorders such as traumatic brain injury, neurodegenerative and autoimmune diseases together comprise a large group of human diseases (7).

Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Multiple Sclerosis and Amyotrophic Lateral Sclerosis despite showing heterogeneous clinical and pathophysiological characteristics, show as common hallmarks accumulation of detrimental proteins/mediators and an active role of glial cells in contributing to the pathological course of the disease (8-11).

Such a scenario represents an open challenge that require new knowledge on therapeutic approaches but, in particular, on underlying biological mechanisms that either sustain or counteract neuronal loss in the late stages of disease either using CNS confined or systemic regenerative approaches (11-16).

The multifactorial and pleiotropic microenvironment that is established during neurodegenerative process is a hurdle that still limits current therapeutic approaches.

Advances in neurodegenerative diseases knowledge have come to suggest that detrimental processes, such as calcium-mediated signalling, glutamate excitotoxicity and reactive oxygen species (ROS)-induced stress, are of central importance in mediating neurodegeneration and may represent promising targets for compensatory/regenerative approaches (17).

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In such a complex multi-mediators and multi-cellular environment, gap junctions (GJs) and hemichannels (HCs) are major players in mediating cell-to-cell communication and cell-to-extracellular environment communication either inducing or suppressing restorative processes. Herein, we aimed at reviewing the current concepts on NVU and intercellular signalling networking mediated by GJs and HCs in pathophysiological conditions and the molecular signalling inducing either neurodegenerative or neurotrophic effects in the context of neuroglial suffering conditions.

2. Gap junctions, hemichannels and connexin

GJs are involved in direct intercellular communications and are characterized by the juxtaposition of two HCs of adjacent cells, that allow the exchange of ions (K^+, Ca^{2+}), metabolites (glucose, lactate and small metabolites), second messengers (cAMP, IP3, ATP) and other mediators < 1 kDa between intracellular fluids (ICF) of adjacent cells (18). In addition, HCs connect ICF and extracellular fluids (ECF) also acting as regulated membrane pore. GJs channels are aggregates in defined plasma membrane regions of adjacent cells forming the so called GJs plaques, in which GJs are rapidly assembled, disassembled or remodelled (19). HCs are added to the periphery of existing plaques and are docked with HCs of adjacent cells, whereas old HCs are removed from the central portion of plaques to be destroyed (20, 21). Each HC is composed by 6 subunits called connexin (Cxs), that arranging in a circle, delimit the central aqueous pore of HCs (22). Cxs are a family of proteins encoded by 21 genes in human, each one named according to its theoretical molecular mass (18). Their molecular weight range from 26 to 56 kDa, however showing similar biophysical structures and features. Cxs are composed by 4 transmembrane domains, 2 extracellular loops, 1 intracellular loop, and 1 intracellular carbo-tail with specific structural and functional tasks (18). Cxs composition allow to discriminate among homomeric HCs (i.e. 6 units of same Cx) and heteromeric HCs (i.e. 6 units of different Cxs, Figure 1). Such HCs structural properties is reflected on GJs structures, classifying homomeric homotypic GJs, constituted by the same homomeric HCs, homomeric heterotypic GJs, constituted by different homomeric HCs, heteromeric homotypic GJs, constituted by the same heterotypic HCs, and finally heteromeric heterotypic GJs, which are composed by different heteromeric HCs (Figure 1).

Despite such a heterogenicity, GJs show common features including 2 nm diameter pore, low ionic selectivity and a preferential open-state configuration, even if the gating is related to a rotation of the subunits which allows the pore formation.

Notably, functional properties of GJs are related to their Cxs composition and depend on the microenvironment and tissue context in which they are operating. Cxs profile is also highly dynamic dramatically impacting on channels selectivity and gating. It is well known that GJs expert critical roles in a number of physiological processes including development and growth, control of cell fate and differentiation and hold great potential in spreading inflammatory and degenerative signalling. Besides their function as intercellular channels throughout GJs, Cxs are able to assemble and induce communication between ICF and ECF throughout HCs.

The increased number of HCs have been associated with intracellular calcium levels while HCs gating is dynamically modulated by factors including voltage, pH and ions concentrations.

From a pathological perspective, accumulating evidences suggest that HCs activity correlates with increased damage and ions dysregulations, with a peculiar role in spreading detrimental signalling molecules and degenerative stimuli.

Cx43, among Cxs that characterize GJs/HCs in specific tissue and/or cell populations, is the main glial cells Cx ubiquitously expressed in the CNS (22, 23). Complex Cx43-composed GJs syncytia allow glial cells to cooperate with neurons in both physiological condition and from acute to chronic pathological conditions. Astrocytes as guardians of the CNS are able to reduce excitotoxic damage on neurons exerting a constant scavenging role and reducing glutamate and ions accumulation, thus preventing secondary damages. They also support tissue trophism by releasing neurotrophic factors and spreading of damaging stimuli.

Reactive astrocytes expressing high levels of Cx43 and increase Cx43-induced coupling is a feature of a number of acute and chronic degenerative affections of CNS (24-26). Recent evidences support the hypothesis of a detrimental role of such a coupling that is believed to increase cell death signalling and inflammatory/degenerative insults in the CNS (27-29). In the CNS neuroglial axis also relies on GJs and HCs activity, which is of crucial importance to maintain tissue homeostasis and to promote repair. Understanding the molecular mechanisms by which GJs exert their modulatory functions in pathophysiological conditions is of key importance to develop new approaches for neurodegenerative diseases.

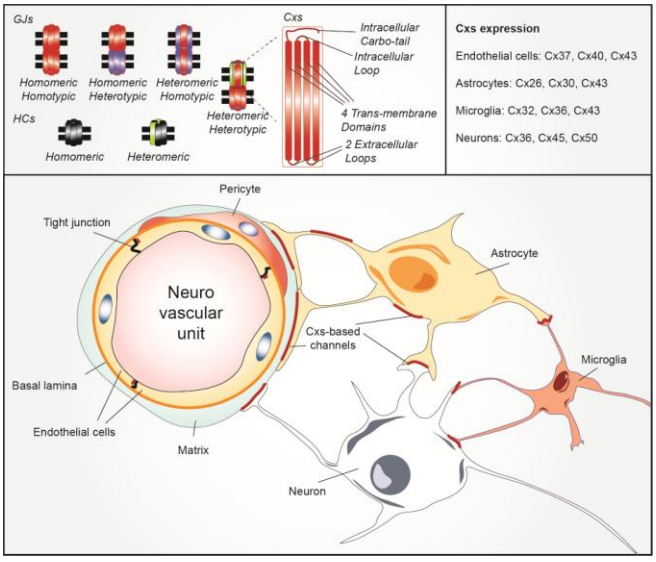

Figure 1. Schematic representation of gap junctions, hemichannels and connexins in the neurovascular unit. Representation of gap junctions (GJs) composition and structural properties, as hemichannels (HCs)-composed structures, in turn composed by 6 juxtaposed connexin (Cxs). The intracellular carbo-tail, intracellular loop, 4 transmembrane domains, 2 extracellular loops of Cxs are shown. Schematic representation of neurovascular units and of the complex cellular microenvironment including GJs and HCs in endothelial cells, pericytes, astrocytes, microglia and neurons.

3. Neurovascular units and blood-brain barrier modulation

Endothelial cells by means of Cxs and tight junctions are the core cell populations in the NVU (Figure 1). In particular endothelial cells highly express Cx43, Cx37 and Cx40 encoded respectively by Gja1, Gja4 and Gja5 (22, 30). Such Cxs profile is of particular importance given the effects on GJs compositions. On one hand, it has been observed that vascular endothelial growth factor (VEGF) influences Cx43 levels, thus contributing to modify the intercellular communication finally resulting in an increased BBB permeability (31, 32). On the other hand, increased Cx43 expression levels have been associated with induction of shield function mediated by endothelial cells, thus suggesting a significant Cx43-mediated role in maintaining BBB function (33). Despite such evidences, Cx43 role is still controversial given accumulating evidences on the reactive Cx43 expression in pathological CNS conditions. Indeed, De Bock and collaborators demonstrated that reactive Cx43 over-expression upon acute inflammatory injury in the BBB is related to Cx43-based HCs activities, instead of GJs per se (34). Primary effects are indeed associated with reactive Cx43-HCs induced Ca^{2+} signalling that modify ions composition of the intracellular fluids and it has been associated with BBB dysfunctions (31, 35, 36). Such a change in intracellular milieu mediated by HCs in endothelial cells is propagated throughout GJs intercellular communications and may not be confined to endothelial cells, but also affects periphery blood-derived cells and immune cells (37-40).

In NVU composition a crucial role is played by astroglial cells (Figure 1). Nutrients and small metabolites are selected and transferred to neurons by astrocytes a cell population that intensely express Cxs such as Cx26, encoded by Gjb2, Cx30, encoded by Gjb6, and in particular Cx43 (17, 22, 27, 41). The latter is the most abundant Cxs in astrocytes and have been associated with adhesion, energy metabolism (42) and astroglial signalling (43, 44) and injury sprouting (45, 46).

The role of astrocytes in controlling extracellular milieu compositing is of crucial importance at the level of synapses. Astrocytes are highly active in shaping NVU and in exerting vascular regulatory activity; in particular they are wrapped around capillaries throughout their endfeed blood stream and playing crucial role in NVU maintenance and permeability (47-49). It has been reported that astrocytes shaping endothelial functions by releasing both soluble factors such as angiopoietin I and II, sonic hedgehog able to exerts dramatic effects also on other CNS cell populations (2, 50). The physiological role of astroglial cells in NVU microenvironment is of crucial importance when it turns into pathological conditions. Indeed, astrocytes-derived detrimental stimuli such as ROS and inflammatory cytokines are released in close proximity to NVU and may induces endothelial suffering and BBB disruptions (51). In this context, HCs play a primary role in conditioning NVU microenvironment leading to BBB disfunctions, instead of a direct coupling between astrocyte and endothelial cell or between endothelial cells (52). As such, it is widely accepted that a chief role in pathological NVU dysfunctions are played by Cx43-formed HCs (36, 53). While double knockout Cx30 and Cx43 severely impact BBB function just upon alteration of artery pressure (54), genetic ablation of Cx30 showed that BBB alteration are not present (53). It is worth to notice that ablation of Cx43 in astrocytes prompts at the level of NVU antigen presentation, infiltration and autoimmune responses by recruiting periphery blood-derived infiltration of macrophages, neutrophils and T-cell (12, 55).

4. Concluding remarks

During the last decade a great effort has been placed in understanding the cellular and molecular players in modulating NVU microenvironment and BBB functions. In this review we have focussed a brief up-date on NVU related to GJs/HCs/Cxs mediating cross-talk interplay, pointing out astroglial Cxs apparatus and, in particular, astroglial Cx43-based HCs, as a major influencer of NVU microenvironment. Neuroglial-endothelial axis holds a critical role in a number of CNS degenerative injuries, throughout both intercellular direct- and microenvironmental-mediated communication. Future investigations aiming at highlighting new molecular players in this scenario, likely related to GJs/HCs acting on NVU cell populations, are promising to reveal the still unmet biological processes underlying such a strictly controlled and complex intercellular NVU crosstalk.

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