Neuropharmacology 75 (2013) 567–582

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Gap junction channels and hemichannels in the CNS: Regulation by signaling molecules

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ARTICLE INFO

Article history:
Received 18 September 2012
Received in revised form
8 February 2013
Accepted 26 February 2013

Keywords:
Connexins
Pannexins
Paracrine factors
Brain
Astrocytes
Microglia
Neurons

ABSTRACT

Coordinated interaction among cells is critical to develop the extremely complex and dynamic tasks performed by the central nervous system (CNS). Cell synchronization is in part mediated by connexins and pannexins; two different protein families that form gap junction channels and hemichannels. Whereas gap junction channels connect the cytoplasm of contacting cells and coordinate electric and metabolic activities, hemichannels communicate intra- and extra-cellular compartments and serve as diffusional pathways for ions and small molecules. Cells in the CNS depend on paracrine/autocrine communication via several extracellular signaling molecules, such as, cytokines, growth factors, transmitters and free radical species to sense changes in microenvironment as well as to adapt to them. These signaling molecules modulate crucial processes of the CNS, including, cellular migration and differentiation, synaptic transmission and plasticity, glial activation, cell viability and microvascular blood flow. Gap junction channels and hemichannels are affected by different signaling transduction pathways triggered by these paracrine/autocrine signaling molecules. Most of the modulatory effects induced by these signaling molecules are specific to the cell type and the connexin and pannexin subtype expressed in different brain areas. In this review, we summarized and discussed most of the relevant and recently published information on the effects of signaling molecules on connexin or pannexin based channels and their possible relevance in CNS physiology and pathology.

This article is part of the Special Issue Section entitled 'Current Pharmacology of Gap Junction Channels and Hemichannels'.

1. Introduction

Coordinated interaction among cells is critical to perform the extremely complex and dynamic tasks performed by the brain. Cell ability to sense local and neighboring microenvironments has evolved in different ways in more complex organisms. In vertebrates, cell interaction and synchronization is in part mediated by intercellular communication via connexin- and pannexin-based channels. Connexins and pannexins comprise two different gap junction protein families, which in mammals are composed of about 20 and 3 members, respectively (Abascal and Zardoya, 2012). Eumetazoans, with the only exception of echinoderms, express pannexins (called innexins in non-chordates), whereas the connexin family is exclusive to chordates (Abascal and Zardoya, 2012; Phelan and Starich, 2001; Shestopalov and Panchin, 2008). Despite the fact that connexins and pannexins do not share a relevantly homologous primary structure, they have similar secondary and tertiary structures with four α-helical transmembrane domains, connected by one cytoplasmic and two extracellular loops, where both N- and C-termini are intracellular (Fig. 1). Pannexins and connexins oligomerize into hexamers to constitute single hemichannels, except for pannexin2 (Panx2), which seems to form octamers (Ambrosi et al., 2010).

After assembly, connexin hemichannels are transported to the non-junctional plasma membrane and diffuse laterally to dock with connexin hemichannels from a neighboring cell to form gap junction channels (Sáez et al., 2003a) (Fig. 1). Gap junctions are aggregates of these intercellular channels and mediate an important form of direct intercellular communication in the animal kingdom. Gap junction channels favor the intercellular exchange of metabolites (e.g., ADP, glucose, glutamate and glutathione), second messengers (e.g., cAMP and IP_3) and ions, allowing the intercellular spread of electrotonic potentials in excitable and non-excitable tissues (Evans et al., 2006; Sáez et al., 2003a; Sohl et al., 2005). For a long time, the main function attributed to connexin

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http://dx.doi.org/10.1016/j.neuropharm.2013.02.020

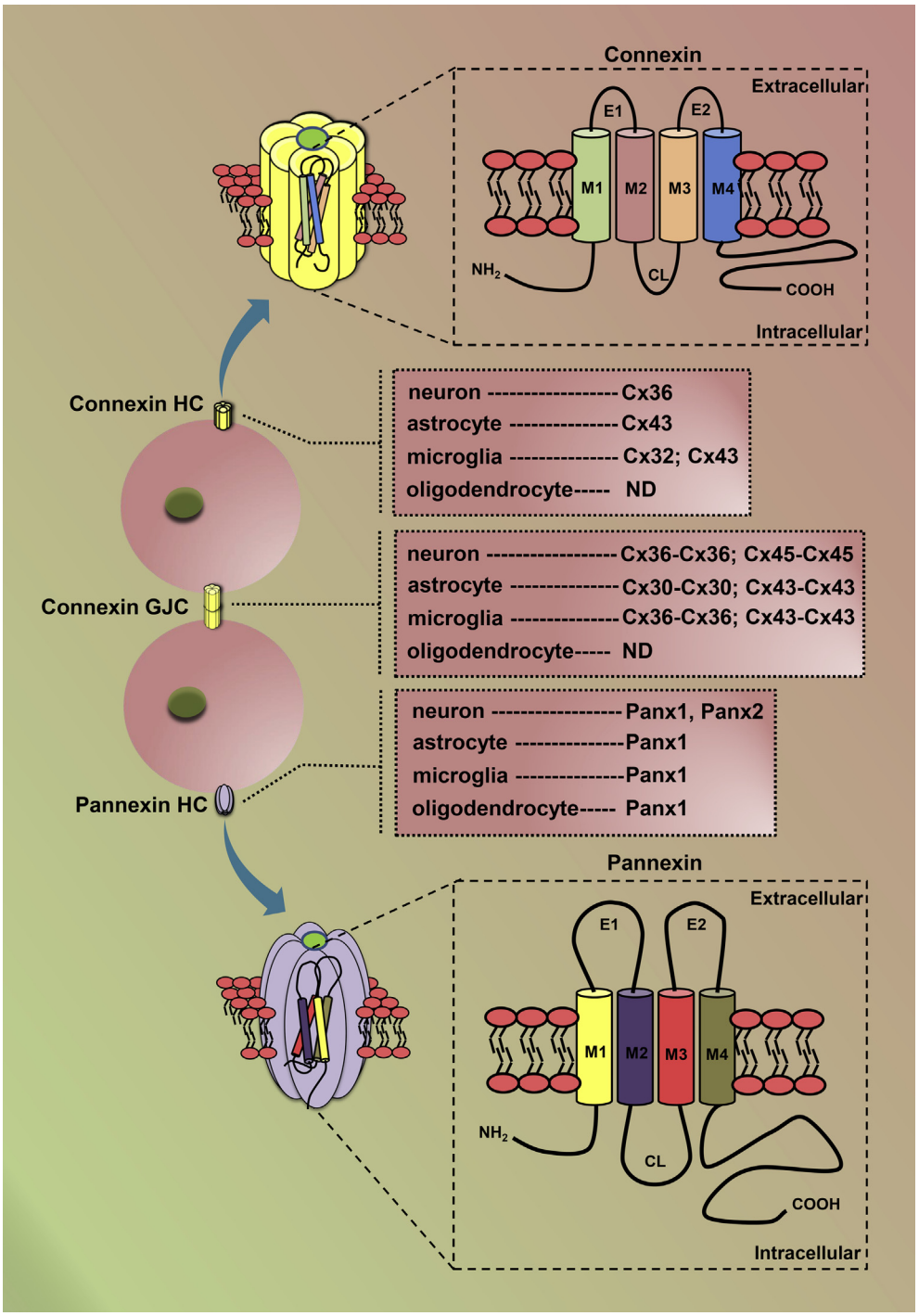

Fig. 1. Diagram illustrating basic structures of connexin- and pannexin-based channels and their patterns of expression in brain cells. Connexins and pannexins share similar membrane topology, with four α-helical transmembrane domains (M_1–M_4) connected by two extracellular loops (E_1 and E_2) and one cytoplasmic loop (CL), where both amino (NH_2)- and carboxy (COOH)-termini are intracellular. The top and bottom of the center show hemichannels formed by six connexin or pannexin subunits each, respectively. Recently, a banding pattern more consistent with an octamer than hexamer in pannexin hemichannels was observed by cross-linking and native gels of purified homomeric full-length and C-terminal Panx2 truncation mutants (Ambrosi et al., 2010). The middle center shows a connexin gap junction channel at close contact between two cells. A hemichannel is formed by connexins or pannexins that oligomerize laterally leaving a central pore in the activated state. Under resting conditions, hemichannels remain preferentially closed, but they can be activated by diverse physiological and pathological conditions, offering a diffusional transmembrane route between the intra and extracellular milieu. Note: Cellular distribution of hemichannels and gap junction channels is depicted in the respective brain cells as well. This description includes only the available information obtained under *in vivo* and/or *in vitro* studies using more than one experimental approach. Although there is no evidence that glial cells and neurons actually form heteromeric hemichannels or heterotypic gap junction channels, the evidence obtained from connexin and pannexin exogenously expressed in mammalian cell lines, support this possibility. Further studies will clarify this matter. ND: not determined.