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Review

The electrical coupling and the hippocampal formation theta rhythm in rats

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ABSTRACT

Gap junctions (GJs) were discovered more than five decades ago, and since that time enormous strides have been made in understanding their structure and function. Despite the voluminous literature concerning the function of GJs, the involvement of these membrane structures in the central mechanisms underlying oscillations and synchrony in the neuronal network is still a matter of intensive debate. This review summarizes what is known concerning the involvement of GJs as electrical synapses in mechanisms underlying the generation of theta band oscillations. The first part of the chapter discusses the role of GJs in mechanisms of oscillations and synchrony. Following this, *in vitro*, *ex vivo*, and *in vivo* experiments concerning the involvement of GJs in the generation of hippocampal formation theta in rats are reviewed.

Contents

1. Introduction

In the second half of the nineteenth century a discussion took place between proponents of the cell theory, who considered neurons to be independent units, and those who believed that cells were interconnected by protoplasmic bridges. It remained for light microscopy to show that each neuronal cell was surrounded by its own plasma membrane. However, electron microscopy provided further evidence that continuity between certain cells occurs, but in the form of tenuous connections of molecular dimensions, which were further labeled as gap junctions. Gap junctions were discovered more than five decades ago, and since that time enormous strides have been made in understanding their structure and function. Despite the voluminous literature concerning the function of GJs, the involvement of these membrane structures in central mechanisms underlying oscillations and synchrony in the neuronal network is still a matter of intensive debate.

2. The morphology of neuronal gap junction

Neural tissue is not only the sum of neurons but also incorporates cell regulation circuits. Their physiological efficiency is largely

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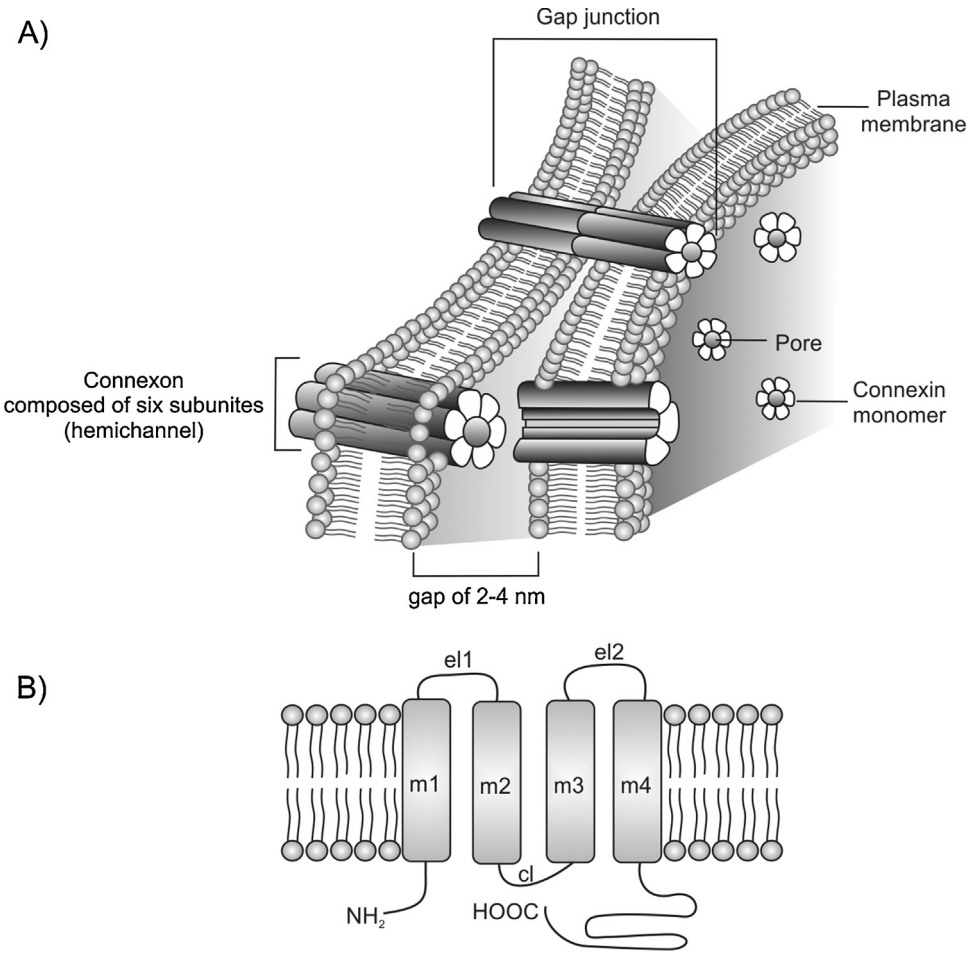

Fig. 1. Molecular organization of gap junction channels. (A) Gap junction channels are formed by head-to-head docking of hexameric assemblies (connexons). Each connexon is composed of six membrane protein subunits (connexins). (B) Each connexin has four membrane-spanning domains (m1–m4), two extracellular loops (el1–el2), one amino- and one carboxy-terminal region, and one cytoplasmic loop (cl).

determined by the capability to communicate in the neuronal network. The notion that neurons forming a neuronal network can communicate electrically is almost as old as the idea of bioelectricity *per se* (Eccles, 1982). Electrical synapses are specialized sites where gap junction channels bridge the plasma membranes of two adjacent neurons. By providing low-resistance pathways for ions and small molecules, gap junctions serve as sites of rapid intracellular communication between neurons (Galarreta and Hestrin, 2001; Wolburg and Rohlmann, 1995).

Evidence for a direct electrical coupling was first found in invertebrate preparations (Furshpan and Potter, 1959; Watanabe, 1958), and later in vertebrate tissue by Bennett (1963). In 1971 Baker and Lilnas demonstrated electrical transmission in the mammalian brain for the first time. MacVicar and Dudek (1981) were the first to demonstrate direct intracellular passage of current between two simultaneously intracellularly recorded neighboring hippocampal CA3 neurons.

Gap junctions are clusters of intracellular channels formed by head-to-head docking of hexameric hemichannels (connexons) of membrane proteins, the connexins (Goodenough et al., 1996; Fig. 1A). The connexins have four membrane-spanning domains, two extracellular loops, three cytoplasmic components, one amino- and carboxy-terminal region and a cytoplasmic loop (Bennett et al., 1991; Söhl et al., 2005; Stauffer and Unwin, 1992; Fig. 1B). In vertebrates connexins arose by convergent evolution (Alexopoulos et al., 2004), to expand by gene duplication into a 21-member gene family (Cruciani and Mikalsen, 2007). In the most commonly used nomenclature, connexins (abbreviated as "Cx") are named for their molecular weight, calculated in kDa (e.g. Cx36 has a mass of 36 kDa).

Little is known of the pharmacological properties of pannexin (Panx) expression in mammalian cells. Panx1 and 2 are a widely expressed proteins that shares structural, but not amino acid, homology with gap junction proteins, the connexins. Pannexin does not form gap junctions in mammalian cells, but it may function as a plasma membrane hemichannel (Ma et al., 2008).

The distribution of connexin and pannexin isoforms in hippocampal formation is shown in Table 1. This table demonstrates that at least eight different connexins and two pannexins are present in this limbic region. Glial cells and interneurons are found to be rich in GJs. However, GJs were also noted in the principal cells of hippocampal formation.

It seems obvious today that electrical transmission mediates two different basic functions: (i) transmitting excitation from an active (depolarized) neuron to postsynaptic cell, and (ii) synchronizing the activity of neurons, in which coupling is excitatory to the less depolarized cell, and inhibitory to the more depolarized cell, since current flowing to one depolarized cell is making the other cell less depolarized (Bennett, 1997). As described by Bennett (1997) "*electrical synapses allow multiple cells to act with nearly the precision of a single cell*". This is probably the most spectacular expression which defines in a simple words the GJs function.