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Review

Perineuronal nets in the auditory system

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ABSTRACT

Perineuronal nets (PNs) are a unique and complex meshwork of specific extracellular matrix molecules that ensheath a subset of neurons in many regions of the central nervous system (CNS). PNs appear late in development and are supposed to restrict synaptic plasticity and to stabilize functional neuronal connections. PNs were further hypothesized to create a charged milieu around the neurons and thus, might directly modulate synaptic activity. Although PNs were first described more than 120 years ago, their exact functions still remain elusive. The purpose of the present review is to propose the nuclei of the auditory system, which are highly enriched in PN-wearing neurons, as particularly suitable structures to study the functional significance of PNs. We provide a detailed description of the distribution of PNs from the cochlear nucleus to the auditory cortex considering distinct markers for detection of PNs. We further point to the suitability of specific auditory neurons to serve as promising model systems to study in detail the contribution of PNs to synaptic physiology and also more generally to the functionality of the brain.

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1. Introduction

Perineuronal nets (PNs) are a complex composition of extracellular matrix (ECM) molecules which surround the somata and proximal dendrites of neurons forming lattice-like structures.

The scaffold of PNs is based on hyaluronan polymer chains which are anchored via hyaluronan synthase in the membrane of neuron somata and proximal dendrites. Chondroitin sulfate proteoglycans (CSPGs) bind to hyaluronan, and link proteins stabilize the interaction between hyaluronan and CSPGs (Asher et al., 1995; Köppe et al., 1997). Finally, tenascin-R binds to CSPGs forming a quaternary complex surrounding the neurons (Fig. 1). The CSPGs are characterized by glycosaminoglycan side chains (GAG), which are thought to determine the physiological function of the PNs (Pizzorusso et al., 2002; Yamaguchi, 2000). Because of these GAG components, PNs form strong negatively charged structures in the direct vicinity of neurons (Brückner et al., 1998a; Morawski et al., 2004). Different CSPGs were found to be expressed in the central auditory system, including aggrecan, brevican and neurocan (Blosa et al., 2013).

PNs were first described by Camillo Golgi in 1882 and thereafter more closely specified by influential scholars of the 19–20th century like Lugaro, Donnagio, Martinotti, Cajal, Bethe, Held, Besta, Alzheimer, and others (for review see Celio et al., 1998). In the early 20th century, Ramón y Cajal considered PNs to be artifacts caused by various histological procedures (Ramón y Cajal, 1909–1911). As a consequence, researchers lost interest in PNs which finally completely faded from the spotlight by the end of the Second World War. Only in the early 1980th different research groups around Brauer, Delpech, Lafarga, and Hockfield (Brauer et al., 1982, 1984; Delpech, 1982; Hendry et al., 1984; Lafarga et al., 1984)

Abbreviations: AVCN, anteroventral cochlear nucleus; CN, cochlear nucleus; CNS, central nervous system; CS-GAG, chondroitin sulfate glycosaminoglycan; CSPG, chondroitin sulfate proteoglycan; DCN, dorsal cochlear nucleus; DNLL, dorsal nucleus of the lateral lemniscus; ECM, extracellular matrix; GAG, glycosaminoglycan; IC, inferior colliculus; INLL, intermediate nucleus of the lateral lemniscus; LNTB, lateral nucleus of the trapezoid body; LSO, lateral superior olive; MGN, medial geniculate nucleus; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; NLL, nuclei of the lateral lemniscus; PN, perineuronal net; PVCN, posterior ventral cochlear nucleus; SOC, superior olivary complex; SPN, superior paraolivary nucleus; VNLL, ventral nucleus of the lateral lemniscus; VNTB, ventral nucleus of the trapezoid body; WFA, *Wisteria floribunda* agglutinin

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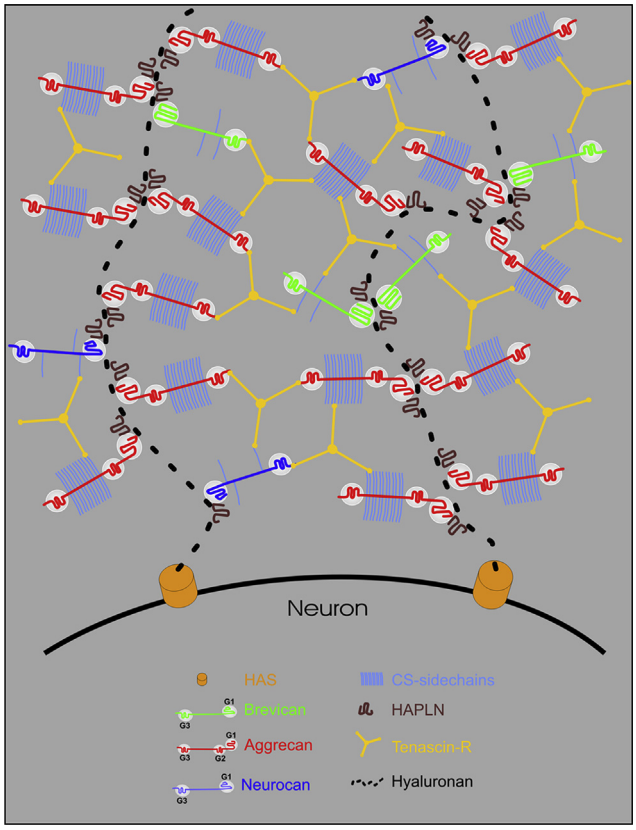

Fig. 1. Potential molecular identity and structure of hyaluronan-based perineuronal and perisynaptic extracellular matrix components. Schematic drawing of the composition of the perineuronal net. The main components and their potential composition and dimension around a neuron. A hyaluronan backbone is continuously secreted by hyaluronan synthase (HAS) from the cell membrane and a number of proteoglycans, mainly aggrecan and to lesser extend brevican and neurocan are attached. The connections are stabilized via a link protein (HAPLN). The proteoglycans are additionally stabilized by the small glycoprotein tenascin-R forming a quaternary macromolecular complex in the direct microenvironment of the PN-ensheathed neurons.

rediscovered the PNs. Research gathered pace in the early 1990th, when G. Brückner and others started to systematically investigate the structure, composition, and distribution of the PNs as well as related extracellular matrix components in brains of different species under physiological and pathological conditions and also speculated about their possible functions in brain development, homeostasis, and neuronal signal processing (Brückner et al., 1993, 1996, 1998a; 1999, 2000; 2008; Matthews et al., 2002; Morawski et al., 2004, 2012, 2014; for reviews see Celio and Blümcke, 1994; Wang and Fawcett, 2012; Zimmermann and Dours-Zimmermann, 2008). Recently, it was even hypothesized that PNs are part of the cortical memory storage system (Sejnowski, 2005; Tsien, 2013).

PNs are not uniformly distributed in the central nervous system (CNS) and only subsets of neuron types are associated with PNs. Many of these neurons seem to share a few common features, including high-frequency action potential activity (i.e. 'fast spiking' neurons) and the expression of the high-voltage gated potassium channel subunit $K_v3.1$ (Härtig et al., 1999). In the neocortex, PN-positive neurons were frequently identified as interneurons that release the neurotransmitter GABA (Härtig et al., 1992; Kosaka and Heizmann, 1989). However, there are also studies which link PNs with other neurotransmitter systems, such as acetylcholine-releasing neurons in the motor nerve nuclei (Armstrong et al., 1983; Morawski et al., 2010), glutamate-releasing pyramidal neurons in the neocortex (Alpár et al., 2006; Ojima et al., 1995), and aspartate-releasing neurons in the deep cerebellar nuclei (Kumoi et al., 1988).

PNs were associated with highly diverse functions. Among those are (1) stabilization of high-rate synaptic transmission via the specific hydrodynamic properties of strongly hydrated polyanionic matrix components in the microenvironment of neurons and synaptic terminals (Brückner et al., 1993; Härtig et al., 1999; Morawski et al., 2004, 2010a, 2012), (2) mechanical stabilization of synaptic contacts (Hockfield et al., 1990) restricting structural and functional plasticity in nervous system (Frischknecht et al., 2009; McRae et al., 2007; Pizzorusso et al., 2002; for review see Wlodarczyk et al., 2011), and (3) neuroprotection by reducing oxidative stress through scavenging redox-active cations (Morawski et al., 2004, 2005, 2010a, 2012; Suttkus et al., 2012; Suttkus et al., 2014). Still, to date the significance of the suggested functions and the mechanisms by which the PNs and the subcomponents convey a specific function remain elusive.

Much of our current ideas about the PN's role in synaptic plasticity comes from studies of the visual system (Pizzorusso et al., 2002; reviews: Wang and Fawcett, 2012; Wlodarczyk et al., 2011) and the hippocampus (Bukalo et al., 2001; Saghatelyan et al., 2001; reviews: Wang and Fawcett, 2012; Wlodarczyk et al., 2011). However, in those structures, same as in most of the other cortical and subcortical areas, only a small proportion of neurons are surrounded by PNs (Brückner et al., 2000; Morawski et al., 2010b; Seeger et al., 1994; Suttkus et al., 2014). It goes without saying that the functional role of PNs might best be studied in brain areas rich in these extracellular matrix components. This especially applies to nuclei of the central auditory system which are reported to have high proportions of net-bearing neurons (summarized in Table 1; Brückner et al., 2000; Friauf, 2000; Lurie et al., 1997; Morawski et al., 2010b; Myers et al., 2012; Seeger et al., 1994; Blosa et al., 2013) typically releasing three of the major neurotransmitters, e.g. GABAergic neurons in the inferior colliculus (Foster et al., 2014), glycinergic neurons in the medial nucleus of the trapezoid body (Cant and Benson, 2006; Friauf, 2000; Lurie et al., 1997; Myers et al., 2012; Blosa et al., 2013), and glutamatergic neurons in the cochlear nucleus (Cant and Benson, 2006; Friauf, 2000; Lurie et al., 1997). Given the fact that we have solid hypotheses about the functional role of the respective nuclei and their well-defined neuron types, the distribution of PNs in the auditory system received increasing attention.

In this review, we provide a comprehensive description of the distribution of PNs in the ascending central auditory system, from cochlear nucleus up to the auditory cortex. We focus on cell-specific heterogeneity of PN structures, consider species-specific differences, and discuss discrepancies in published data which might be due to distinct markers used for visualization of PNs. We will conclude our synopsis by (i) highlighting the potential roles of PNs in the auditory system considering the prevalent current hypotheses and (ii) emphasizing the suitability of auditory brainstem neurons as adequate model systems to study the contribution of PNs to brain functionality in future studies.

2. Visualization of PNs

Several markers, recognizing different molecules, are available for the identification of PNs in neural tissues. Antibodies against specific CSPGs can be used, e.g. aggrecan as a major constituent of PNs in the CNS. However, it is necessary to consider that the detection of aggrecan by distinct anti-aggrecan antibodies (e.g. Cat-301, Cat-315) depends on the state of glycosylation of this proteoglycan (Matthews et al., 2002). Thus, the respective antibodies do not reliably detect all PNs in the CNS. The most commonly used PN