Brain Research 1648 (2016) 214–223

Contents lists available at ScienceDirect

Brain Research

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

Research report

Spatial patterns and cell surface clusters in perineuronal nets

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ARTICLE INFO

Article history:
Received 15 December 2015
Received in revised form
29 June 2016
Accepted 13 July 2016
Available online 15 July 2016

Keywords:
Perineuronal nets
Extracellular matrix
Chondroitinsulfate proteoglycans
Somatosensory cortex
Synaptic plasticity
Cell surface compartments

ABSTRACT

Perineuronal nets (PNN) ensheath GABAergic and glutamatergic synapses on neuronal cell surface in the central nervous system (CNS), have neuroprotective effect in animal models of Alzheimer disease and regulate synaptic plasticity during development and regeneration. Crucial insights were obtained recently concerning molecular composition and physiological importance of PNN but the microstructure of the network remains largely unstudied. Here we used histochemistry, fluorescent microscopy and quantitative image analysis to study the PNN structure in adult mouse and rat neurons from layers IV and VI of the somatosensory cortex. Vast majority of meshes have quadrangle, pentagon or hexagon shape with mean mesh area of 1.29 μm^2 in mouse and 1.44 μm^2 in rat neurons. We demonstrate two distinct patterns of chondroitin sulfate distribution within a single mesh – with uniform (nonpolar) and node-enriched (polar) distribution of the *Wisteria floribunda* agglutinin-positive signal. Vertices of the node-enriched pattern match better with local maxima of chondroitin sulfate density as compared to the uniform pattern. PNN is organized into clusters of meshes with distinct morphologies on the neuronal cell surface. Our findings suggest the role for the PNN microstructure in the synaptic transduction and plasticity.

1. Introduction

Perineuronal nets (PNN) are formed on neuronal surface during early postnatal development as an important functional element of mature synaptic circuits (Medini and Pizzorusso, 2008; Dityatev et al., 2010; Kwok et al., 2012; Fawcett, 2015; Miyata and Kitagawa, 2015). PNN are expressed in the brain cortex, hippocampus, cerebellum, spinal cord and other parts of the CNS. The role of PNN in maturation of the synaptic circuitry of parvalbumin-positive interneurons in somatosensory and visual cortex has been studied in particular detail (Pizzorusso et al., 2002; McRae et al., 2007; Miyata et al., 2012). PNN ensheath synaptic boutons on neuronal soma and proximal dendrites (Brückner et al., 2006; Carulli et al., 2013; Geissler et al., 2013). PNN consist of chondroitin sulfate proteoglycans (CSPG) assembled on the hyaluronan scaffold (Kwok et al., 2012). The PNN molecular complex involves tenascin R, link proteins and other CSPG binding molecules such as Sema3A and Otx2 (Carulli et al., 2006, 2013; Beurdeley et al., 2012, Vo et al., 2013). PNN development is controlled by synaptic activity (Lander et al., 1998; Brückner et al., 2004; McRae et al., 2007; Carulli et al., 2010) and the formation of PNN terminates the critical period of synaptic plasticity (Pizzorusso et al., 2002; Miyata and Kitagawa, 2015). Enzymatic digestion of PNN with chondroitinase ABC results in the relief of synaptic plasticity in adult animals (Pizzorusso et al., 2002). Genetic ablation of PNN components leads to retained synaptic plasticity in the adulthood (Carulli et al., 2010) and to abnormal synaptic transduction (Weber et al., 1999; Saghatelyan et al., 2001). It has been suggested that PNN may serve as a molecular substrate for the storage of long-lasting memories (Tsien, 2013).

At the level of molecular mechanisms it was shown that PNN

Abbreviations: PNN, perineuronal nets; CNS, central nervous system; CSPG, chondroitin sulfate proteoglycans; AMPA receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; WFA, *Wisteria floribunda* agglutinin; GalNAc, N-acetyl-galactosamine; CS, chondroitin sulfate; PSD95, postsynaptic density protein 95; ECM, extracellular matrix; 2D, two-dimensional; 3D, 3-dimensional; RMSD, root mean square deviation; BDNF, brain-derived neurotrophic factor; NT-3, neurotrophin-3; FGF, fibroblast growth factors; VEGF, vascular endothelial growth factor; GDNF, glial cell-derived neurotrophic factor; PTPsigma, receptor-type tyrosine-protein phosphatase S; Sema3A, Semaphorin-3A

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http://dx.doi.org/10.1016/j.brainres.2016.07.020
0006-8993/