available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainresrev

BRAIN RESEARCH REVIEWS

Review

Role of glial cells in the formation and maintenance of synapses

*Frank W. Pfrieger**

CNRS UPR 3212, University of Strasbourg, Institute of Cellular and Integrative Neurosciences (INCI), 5, rue Louis Pasteur, 67084 Strasbourg Cedex, France

ARTICLE INFO

Article history:
Accepted 11 November 2009
Available online 18 November 2009

Keywords:
Synaptogenesis
Neuromuscular junction
Neuroglia
Astrocyte
Schwann cell
Neurodegeneration
Regeneration

ABSTRACT

Synaptogenesis is a decisive process for the development of the brain, its plasticity during adulthood and its regeneration after injury and disease. Despite tremendous progress during the last decades, it remains unclear, whether neurons can form synapses autonomously. In this review, I will summarize recent evidence that this is probably not the case and that distinct phases of synapse development depend on help from glial cells. The results supporting this view come from studies on the central and peripheral nervous system and on different experimental models including cultured cells as well as living flies, worms and mice. Our understanding of synapse–glia interactions in the developing, adult and diseased brain is likely to advance more rapidly as new experimental approaches to identify, visualize and manipulate glial cells in vivo become available.

Contents

* Fax: +33388601664.
E-mail address: fw-pfrieger@gmx.de.
URL: http://pfrieger.gmxhome.de/work/intro.html.

Abbreviations: CEPsh, cephalic sheath; NMJs, neuromuscular junctions; PCs, Purkinje cells; PSCs, perisynaptic Schwann cells; RGCs, retinal ganglion cells; Tgfb1, transforming growth factor beta 1

0165-0173/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainresrev.2009.11.002

1. Introduction

Synapses are key elements for brain function, and their formation is a decisive process throughout life. Neurons establish synaptic connections not only during development but also in the adult brain to implement their natural turnover and plasticity-related changes in the neuronal circuitry (Chklovskii et al., 2004; De Roo et al., 2008). The assembly of a synaptic connection requires a cascade of precisely coordinated processes in two partner neurons. Once synaptic partners have found each other, they assemble complex pre- and postsynaptic structures that mediate transmitter-based communication. Subsequently, connections acquire their specific transmission properties. In a last break-up phase, superfluous connections are eliminated. Research within the last decade has greatly advanced our understanding of molecules and mechanisms that mediate synapse development (Waites et al., 2005; Akins and Biederer, 2006; Craig et al., 2006; Fox and Umemori, 2006; Gerrow and El Husseini, 2006; Paukert and Bergles, 2006; Prokop and Meinertzhagen, 2006; Chen et al., 2007b; Dalva et al., 2007; McAllister, 2007; Polleux et al., 2007; Arikkath and Reichardt, 2008; Bicker and Schratt, 2008; Biederer and Stagi, 2008; Greer and Greenberg, 2008; Hanus and Ehlers, 2008; Huang and Scheiffele, 2008; Margeta et al., 2008; Salinas and Zou, 2008; Chao et al., 2009). However, a key question remains unanswered: Can neurons form synaptic connections by themselves, or do they require help from neighboring glial cells? In this review, I will focus on recent experimental evidence for the latter. Complementary overviews on this subject can be found elsewhere (Slezak et al., 2006; Barker and Ullian, 2008; Feng and Ko, 2008b; Stevens, 2008; Bolton and Eroglu, 2010). Reviews of glial contributions to axon guidance and growth (Learte and Hidalgo, 2007; Pfrieger, 2009) and global views on astrocyte function (Wang and Bordey, 2008; Barres, 2008) have been published recently.

2. Glial cells in touch with synapses

The general term “glial cells” is used here for simplicity. In the mammalian nervous system, glial neighbors of synaptic connections are astrocytes and perisynaptic (or terminal) Schwann cells (PSCs). The glial coverage of synapses was first described more than 30 years ago in pioneering ultrastructural studies (Spacek, 1971) and has now been shown in 3D in the cerebellum (Grosche et al., 1999) and the hippocampus, where synapse size appears to correlate with the extent of astrocytic contacts (Witcher et al., 2007). A recent study of fly glia detected astrocyte-like cells near synapses of the antennal lobe indicating that synapse-surrounding glial cells are not limited to the mammalian CNS (Doherty et al., 2009). The intimate vicinity of synapses and astrocytes has led to speculations about the functional implications and inspired the concept of “tripartite synapses”, which regards glial cells as integral elements of synaptic connections (Araque et al., 1999). Information on the steady progress in this field is summarized elsewhere in this issue.

3. Timing of synaptogenesis and glial development

During brain development, most synapses are generated between the first and third postnatal weeks. This happens after the formation of astrocytes (Miller and Gauthier, 2007), which suggests that synaptogenesis requires glia (Pfrieger and Barres, 1996). Fluorescent labeling of individual astrocytes by dye injection followed by immunohistochemical staining revealed morphological changes in astrocytes during postnatal synapse development (Bushong et al., 2004). Notably, the temporal coincidence of synapse development and astrocyte differentiation applies only to glutamatergic connections. GABAergic neurons establish a functional network in the embryonic brain well before astrocytes are generated (Ben-Ari, 2002; Huang and Scheiffele, 2008). Therefore, the formation of GABAergic contacts is likely to proceed independently from the presence of astrocytes, but it may require help from other types of non-neuronal cells.

4. Formation of glutamatergic synapses in the absence of glia

Glia-free cultures allow to test directly whether neurons can form synapses without glia. Such cultures can be prepared from embryonic rodent brains before glial cells are generated or from postnatal brains after active separation from glial cells. This can be accomplished by immunopanning (Barres et al., 1988; Ullian et al., 2004; Steinmetz et al., 2006; Buard et al., 2010) or fluorescence-activated cell sorting (Calof and Reichardt, 1984; Tomomura et al., 2001; Pennartz et al., 2004). Finally, neurons can be generated from stem cells by manipulating their differentiation (Jungling et al., 2003; Berninger et al., 2007; Johnson et al., 2007). These methods reach purities of up to 99.5% and thereby establish virtually glia-free conditions. Studies on such neuronal preparations suggest that there is no absolute requirement for glia: in the absence of glia, some neurons form numerous synaptic connections (Fig. 1A) (Steinmetz et al., 2006), whereas others including retinal ganglion cells (RGCs; Nagler et al., 2001; Ullian et al., 2001), motoneurons (Ullian et al., 2004) and cerebellar Purkinje cells (PCs; Buard et al., 2010) form only very few connections (Fig. 1B). In some of these preparations, synapses may be regarded as artificial, as neurons lack their natural partners. However, few synapses were also observed in glia-free cultures of subplate neurons from embryonic rats or mice, which normally form synapses among each other (McKellar and Shatz, 2009). On the other hand, strong glutamatergic synaptic activity was found in glia- (and serum-) free cultures of neurons from superior cervical ganglia prepared from newborn rats (Perez-Gonzalez et al., 2008), from spinal cords of embryonic mice (Cuevas et al., 2005) and from hippocampi and cerebella of postnatal mice (Steinmetz et al., 2006). Together, these results suggest that the requirement for glia varies with the neuronal cell type and its state of differentiation.

Notably, the competence of neurons to form and to receive synapses may develop independently. RGCs immunoisolated from embryonic rats were shown to form, but not to receive, synapses and the latter required contact to astrocytes (Barker