Brain Research Bulletin 129 (2017) 74–81

Contents lists available at ScienceDirect

Brain Research Bulletin

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

Review

Role of neuron-glia interactions in developmental synapse elimination

Beatrice Terni, Francisco José López-Murcia [1], Artur Llobet *

Laboratory of Neurobiology, Department of Pathology and Experimental Therapeutics, Institute of Neurosciences, University of Barcelona and Bellvitge Biomedical Research Institute (IDIBELL), 08907 L'Hospitalet de Llobregat, Barcelona, Spain

ARTICLE INFO

Article history:
Received 2 June 2016
Received in revised form 19 August 2016
Accepted 31 August 2016
Available online 4 September 2016

Keywords:
Synapse elimination
Synaptic pruning
Synapse disassembly
Neuron-glia interaction
Neurotransmitter release

ABSTRACT

During the embryonic development of the nervous system there is a massive formation of synapses. However, the exuberant connectivity present after birth must be pruned during postnatal growth to optimize the function of neuronal circuits. Whilst glial cells play a fundamental role in the formation of early synaptic contacts, their contribution to developmental modifications of established synapses is not well understood. The present review aims to highlight the various roles of glia in the developmental refinement of embryonic synaptic connectivity. We summarize recent evidences linking secretory abilities of glial cells to the disassembly of synaptic contacts that are complementary of a well-established phagocytic role. Considering a theoretical framework, it is discussed how release of glial molecules could be relevant to the developmental refinement of synaptic connectivity. Finally, we propose a three-stage model of synapse elimination in which neurons and glia are functionally associated to timely eliminate synapses.

Contents

1. Introduction

Interactions among neurons and glia play a fundamental role in the early stages of neuronal circuit assembly. The ability of astrocytes in the central nervous system, or Schwann cells in the peripheral nervous system to secrete molecules such as thrombospondin (Christopherson et al., 2005), glypicans (Allen et al., 2012) or TGF (Feng and Ko, 2008) is required for the massive formation of synaptic contacts during embryonic development. However, assembled neuronal circuits cannot properly process information until the excessive connectivity present after birth is refined. This is the reason why during post-embryonic development some synapses are strengthened while many others are pruned, following a process of selective elimination. Since synapse elimination takes place in a time window of several weeks (Lichtman and Colman, 2000), tracking changes over this period is technically

* Corresponding author at: Laboratory of Neurobiology, Faculty of Medicine, 08907 L'Hospitalet de Llobregat, Spain.
E-mail address: allobet@ub.edu (A. Llobet).
[1] Present address: Department of Molecular Neurobiology, Max Planck Institute of Experimental Medicine, 37075 Göttingen, Germany.

http://dx.doi.org/10.1016/j.brainresbull.2016.08.017
0361-9230/

challenging, requiring long, careful and detailed observations. As a result, developmental pruning of synaptic contacts is a process still poorly understood. Questions, such as how synapses are tagged for elimination, or, what molecules are involved, are not yet resolved.

Similarly to the formation of neuronal circuits, growing evidences support that glial actions are also required for the steps of refinement of connectivity, which at least involves two main stages: selection and subsequent removal (Fig. 1). The first stage is supposedly a neuron-autonomous process, mainly determined by activity. For example, the motor axon providing a more efficient activation of a muscle fiber has a greater likelihood of not being eliminated (Buffelli et al., 2003), homosynaptic long-term synaptic potentiation is required for selecting *winner* contacts established among climbing fibers and Purkinje cells in the cerebellum (Bosman et al., 2008), and, spontaneous activity of retinal ganglion cells defines the time-course of synaptic strengthening in the lateral geniculate nucleus (Hooks and Chen, 2006). In contrast, the second stage, when contacts are actively removed, requires the contribution of glia. The phagocytic activity of Schwann cells or microglia plays a fundamental role removing portions of synapses (Schafer et al., 2012; Smith et al., 2013) thus finalizing the process of synapse elimination.

However, current findings expand the role of glia during developmental rearrangement of synaptic contacts. The actions of glial cells are presumably not restricted to the last stages of synapse removal but rather playing a continuous involvement in all phases of remodelling of synaptic connectivity. We will next summarize results from recent works supporting this view, which was already proposed almost 30 years ago (Pomeroy and Purves, 1988) and highlight the active role of glial cells during the developmental pruning of excitatory synapses.

2. Contribution of glial cells to synapse elimination in the peripheral and central nervous system

Considering the excellent reviews on synapse elimination in the peripheral and central nervous system (Boulanger and Shatz, 2004; Eroglu and Barres, 2010; Lichtman and Colman, 2000; Schafer and Stevens, 2013; Stephan et al., 2012) our goal is not providing an extensive description of the process. The aim of this review is illustrating synapse elimination as a process that occurs throughout the nervous system, requiring continuous communication among neurons and glia. The next sections summarize the stages of postnatal refinement of synaptic connectivity in the peripheral and central nervous system, highlighting the contribution of glial cells.

2.1. Synaptic competition and elimination refine the connectivity of the peripheral nervous system

The accessibility, as well as a relatively simple connectivity, are the main reasons why some pioneer studies investigating post-embryonic changes in the innervation of the nervous system were carried out in autonomic ganglia. Works from Purves, Licthman and collaborators described in great detail the extensive rearrangements that cholinergic synapses established by preganglionic terminals undergo during postnatal development. Changes in ganglionic connectivity occur as a result of a net reduction in the number of axons projecting on postganglionic neurons. Synaptic contacts from retracting axons are removed but the contribution of remaining ones is strengthened (Lichtman, 1977). Consequently, the required balance between convergence and divergence is set by rearranging the position of ganglionic synapses, which allows the correct flow of information. An example comes from mouse submandibular ganglion neurons. Multispectral labelling shows that preganglionic axons apparently target random neurons within the ganglion. However, those neurons with a common input display closer projections in the submandibular gland when compared to those receiving information from different preganglionic axons (Tsuriel et al., 2015).

It should be noticed that there are differences in the postnatal refinement of synaptic connectivity between parasympathetic ganglia, such as the submandibular ganglion, and sympathetic ganglia, as the superior cervical ganglion. For example, developmental elimination of synaptic contacts in the submandibular ganglion is restricted to the neuronal cell body, because postganglionic neurons generally lack dendrites. In contrast, superior cervical ganglion neurons, which display a postnatal increase in the complexity of their dendritic trees (Hume and Purves, 1981; Voyvodic, 1987), show that larger and more elaborated dendrites are the preferred targets to establish stable synapses in comparison to cell bodies (Forehand, 1985). Therefore, the elimination of embryonic redundant connectivity does not only precede the strengthening of synaptic contacts but also determines the formation of dendritic domains.

The ability of different preganglionic neurons to establish synapses on specific dendritic regions (Forehand and Purves, 1984) illustrates another hallmark of postnatal refinement of connectivity: the competition of axons for defined postsynaptic regions. Synaptic competition has been particularly well addressed in another cholinergic synapse of the peripheral nervous system: the neuromuscular junction. Muscle fibers receiving multiple motor inputs after birth gradually shift from being innervated by several axons to a single one. The vacant territory generated by the elimination of synaptic inputs is occupied by the *winner* axon, experimenting an increase in synaptic strength (Colman et al., 1997). The trimming of axonal branches occurs asynchronously, thus showing each neuromuscular junction is a local arena of synaptic competition (Keller-Peck et al., 2001). Retraction of presynaptic terminals is associated to an increase of lysosomal activity (Song et al., 2008) and axosome shedding (Bishop et al., 2004). By these means axon remnants are digested within neurons and/or phagocytosed by perisynaptic Schwann cells

2.2. Role of glia in synaptic competition and elimination in the peripheral nervous system

Is phagocytosis of synaptic remnants the unique cellular response of glia related to synapse elimination? The involvement of a wider range of neuron-glia interactions actively deciding *winner* contacts is still a matter of debate. The constitutive phagocytic activity of perisynaptic Schwann cells can apparently not decide the fate of neuromuscular junctions, because it operates randomly, without discriminating contacts (Smith et al., 2013). Vacant spaces are occupied by competing motor axons until single innervation of a neuromuscular junction is achieved. Phagocytosis mediated by perisynaptic Schawnn cells is thus independent of the gradual changes in synaptic strength during developmental elimination of synaptic contacts.

This view, however, contrasts to observations showing that perisynaptic Schwann cells take advantage of their privileged location to sense synaptic activity by experimenting transient increases of their intracellular free calcium concentration (Jahromi et al., 1992). As a result, this type of Schwann cells constantly monitor the strength of competing terminals and may actually discriminate among weak and strong inputs during developmental synapse elimination (Darabid et al., 2014). Although decoding of synaptic activity is apparently unable to modify the phagocytic activity of Schawnn cells, the consequent increases in intracellular calcium concentration might favour the release of given neurotrophins, for example NGF (Huang et al., 2010) or BDNF (Luo et al., 2014). Similarly, other secreted molecules promoting the consolidation of contacts can also be secreted, such as TGF-β1 (Feng and Ko, 2008) or