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Invited review

Synaptic rearrangement following axonal injury: Old and new players

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ABSTRACT

Following axotomy, the contact between motoneurons and muscle fibers is disrupted, triggering a retrograde reaction at the neuron cell body within the spinal cord. Together with chromatolysis, a hallmark of such response to injury is the elimination of presynaptic terminals apposing to the soma and proximal dendrites of the injured neuron. Excitatory inputs are preferentially eliminated, leaving the cells under an inhibitory influence during the repair process. This is particularly important to avoid glutamate excitotoxicity. Such shift from transmission to a regeneration state is also reflected by deep metabolic changes, seen by the regulation of several genes related to cell survival and axonal growth. It is unclear, however, how exactly synaptic stripping occurs, but there is substantial evidence that glial cells play an active role in this process. In one hand, immune molecules, such as the major histocompatibility complex (MHC) class I, members of the complement family and Toll-like receptors are actively involved in the elimination/reapposition of presynaptic boutons. On the other hand, plastic changes that involve sprouting might be negatively regulated by extracellular matrix proteins such as Nogo-A, MAG and scar-related chondroitin sulfate proteoglycans. Also, neurotrophins, stem cells, physical exercise and several drugs seem to improve synaptic stability, leading to functional recovery after lesion.

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1. General aspects

Synaptic plasticity is a process by which synapses are altered in structure and function in response to a number of stimuli and events. This may be the major mechanism by which learning and adaptation to environmental changes take place (Deller and Frotscher, 1997; Marrone and Petit, 2002). Changes in the molecular expression of synaptic molecules and structural changes of synapses can modulate the response produced in a target cell (Atwood and Karunanithi, 2002; Morris et al., 2013). Plasticity can occur over short timescales, utilizing a variety of molecular mechanisms to alter synaptic strength, remove and modify, and add new synaptic connections (Bear, 1999; Bliss and Collingridge, 1993; Holtmaat et al., 2005; Katz and Shatz, 1996; Luscher and Malenka, 2012; Morris et al., 2013).

In the developing nervous system, neurons produce excessive synapses and these connections are initially redundant (Chen and Regehr, 2000; Chung and Barres, 2012; Katz and Shatz, 1996; Mariani and Changeux, 1981; Walsh and Lichtman, 2003). During early postnatal life, such excessive connections are removed by a process called synapse elimination and subsequently, functional neural circuits are formed by strengthening the remaining synapses (Chung and Barres, 2012; Goda and Davis, 2003; Kano and Hashimoto, 2009; Katz and Shatz, 1996; Luo and O'Leary, 2005; Sanes and Lichtman, 1999).

The loss of synapses is also a hallmark of several neurodegenerative diseases, as well as normal aging (Coleman et al., 2004; Ferrer, 2009; Schafer and Stevens, 2010; Selkoe, 2002; Smith et al., 2005). Therefore, synapse elimination is crucial not only for the shaping of neural circuits during development but also in regulating synaptic plasticity in response to experience and memory (Chung and Barres, 2012). Thus, possibly a common mechanism may underlie elimination of synapses during development and disease. (Schafer and Stevens, 2010).

Synaptic terminals are affected, directly or indirectly, by virtually all kinds of nervous system disorders (Aldskogius et al., 1999). Central nervous system injuries are particularly traumatic due to limited capabilities of the CNS (Central Nervous System) for repair. Therefore, large motor and sensory deficits persist long after brain or spinal cord trauma, usually throughout life (Raineteau and Schwab, 2001). A prominent feature of retrograde degeneration

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in axotomized motoneurons is the extensive stripping of synapses from the membrane surface. This effect, which is more pronounced on the soma than on the dendrites (Brannstrom and Kellerth, 1998; Novikov et al., 2000), may become permanent if target reinnervation does not occur (Brannstrom and Kellerth, 1998; Novikov et al., 2000; Pastor et al., 1997).

In incomplete SCI (spinal cord injury), the reorganization of synaptic circuits might occur at two levels: in pre-existing circuits by modifications of synaptic strength (functional plasticity), or by the formation of new circuits through sprouting and anatomical reorganization, including growth of axonal branches and dendrites and synaptic elimination (structural or anatomical plasticity) (Raineteau and Schwab, 2001). Compensatory sprouting of intact fiber systems and formation of new circuits including indirect 'detour' pathways are currently emerging as important mechanisms underlying these functional recovery processes (Bareyre et al., 2004; Raineteau and Schwab, 2001; Schwab and Strittmatter, 2014; van den Brand et al., 2012).

2. Synaptic elimination following CNS/PNS injury

Neuronal connectivity and integration to a network can be affected/modified in a number of instances. During development, the exuberant neurogenesis triggers elimination of inappropriate connections and the stabilization of functional ones (Huh et al., 2000). Mechanical and chemical injuries also result in retraction of terminals, which in turn reduces the complexity and functionality of neural circuits. Such dynamic process seems to be a key element to be addressed in future therapies aiming at restoring injury/disease-related dysfunctions.

To date little is known about the molecular mechanisms behind synaptic stability/retraction processes. However, it is clear that glial cells are direct or indirectly involved (Aldskogius and Kozlova, 1998, 2002). Glial reaction is a hallmark of CNS or PNS (Peripheral nervous system) injury, which installs immediately after lesion and can be present in a long-term fashion (Nagamoto-Combs et al., 2010). The use of experimental models to address synaptic changes as well as to induce glial response are of great importance in this context.

Typically, retrograde transsynaptic alterations are obtained following axotomy that may be performed at a certain distance from the CNS, e.g. peripheral nerve crushing or transection. Such lesion leads to retrograde reaction reaching motoneuron cell bodies at the spinal cord, inducing loss of pre-synaptic terminals from their surface and proximal dendrites. The retraction of boutons seems stereotyped, but slightly smaller when the lesion is far from the neuron cell body (e.g. mid-thigh). In this way, about 40% of the motoneuron inputs are withdrawn after peripheral injury (Sabha et al., 2008), while about 52% (Spejo et al., 2013) to 57% (Barbizan et al., 2014) of synapses are lost 4 weeks after proximal lesion (interface of CNS/PNS). This adaptive remodeling mechanism may switch off functioning neurons into the circuitry (Raineteau and Schwab, 2001; Raisman, 1969; Tyzack et al., 2014) enhancing neuronal viability (Hardingham, 2009; Tyzack et al., 2014).

Of notice is the preferential loss of excitatory inputs to the motoneurons, enhancing the inhibitory input influence during the repair process (Carlstedt, 2009; Linda et al., 1985) and protect neurons from excitotoxicity (Eroglu and Barres, 2010). Activated microglia is involved in the retraction of glutamate-containing presynaptic boutons (Cullheim and Thams, 2007; Eroglu and Barres, 2010).

Circuitry rewiring contributes to changing the neuron to a state where the primary goal is to survive and produce new axons (Carlstedt, 2009). One mechanism underlying this mainly excitatory stripping response involves the signaling between neurons and glia through MHC class I. The inhibition of this molecule leads to an aberrant stripping response by microglia, that also removes inhibitory synapses (Eroglu and Barres, 2010; Oliveira et al., 2004).

Astrogliosis and microglial reaction also occur in this scenario and are thought to influence the elimination of synapses (Emirandetti et al., 2010; Victorio et al., 2012). Already 24 h after facial motoneuron axotomy, GFAP is upregulated in astrocytes (Tetzlaff et al., 1988). The astroglial reaction to axotomy is characterized by increased levels of GFAP in active resident protoplasmic astrocytes, which become reactive and transform into fibrous astrocytes (Graeber and Kreutzberg, 1986; Tetzlaff et al., 1988). The increase of fibrous astrocytes is well documented in various neuropathologies (Graeber and Kreutzberg, 1986). Also, the time course and extent of GFAP synthesis are strongly influenced by successful or unsuccessful regeneration (Tetzlaff et al., 1988).

Interestingly, reactive microglia and astrocytes processes may remove synapses from injured motoneurons during the first stages of synaptic rearrangements (Stephan et al., 2012; Tyzack et al., 2014; Wake et al., 2013). However, the later structural recovery of synaptic inputs to motoneurons is mostly carried out by reactive astrocytes (Tyzack et al., 2014). The astrocytic processes frequently enwrap individual synaptic boutons and interpose between the pre- and post-synaptic membranes (Brannstrom and Kellerth, 1998). Ramified microglial processes contribute to structural plasticity through the elimination of synapses via phagocytic mechanisms (Morris et al., 2013).

Nevertheless, recent evidence that equal levels of astrogliosis and microglial reaction (seen by immunohistochemistry) occur in mutant mice that display either decreased or increased synaptic elimination post injury, reinforce the complexity of neuron/glial interactions (Berg et al., 2013). This corroborates previous work showing that absence of interferon gamma expression influences synaptic elimination without changing glial response general pattern. However, it is important to emphasize that such interpretation does not take into account local morphological changes such as hypertrophy versus hyperplasia, which may have microenvironmental effects on synapses (Victorio et al., 2012).

Reactive astrocytes express increased levels of different molecules related to cell-to-cell communication, such as connexin-43 and clusterins, growth factors and neurotransmitter receptors. More recently, expression of immune-related proteins, such as MHC-I, complement system components and toll-like receptors broaden the astroglial response to injury (Downes and Crack, 2010; Freria et al., 2012; Hanke and Kielian, 2011; Lehnardt et al., 2002; Okun et al., 2009; Pascual et al., 2011; Pineau et al., 2010; Stevens et al., 2007; Stridh et al., 2011).

Following peripheral nerve injury, such as sciatic nerve transection, a substantial loss of about 50% of pre-synaptic terminals develop during the first week post axotomy (Oliveira et al., 2004). Such input loss affects a great percentage of inhibitory inputs, seen at the ultrastructural level as containing flat vesicules (F-terminals) (Conradi, 1969a, b, c; Conradi and Ronnevi, 1977; Ronnevi and Conradi, 1974) (Fig. 1). Nevertheless, even after input elimination, most of the remaining terminals are GABA/Glycine positive, contributing to the inhibited state that the axotomized neuron acquires. Excitatory synapses (S-terminals), derived from primary afferents, also detach from lesioned motoneurons contributing to less that 5% of the remaining terminals apposed to the postsynaptic membrane (Oliveira et al., 2004).

Reduction of gliosis correlates with improved synaptic stability and functional recovery, as demonstrated in different instances (Freria et al., 2012; Scorisa et al., 2011; Simoes and de Oliveira, 2012; Zanon and Oliveira, 2006). In this sense, pharmacological approach seems to be an important measure following injury, which can improve the clinical outcome. So far, we have shown evidence that G-CSF, glatiramer acetate and ganglioside GM1 are able to decrease