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INVITED REVIEW

Adult myelination: wrapping up neuronal plasticity

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Abstract

In this review, we outline the major neural plasticity mechanisms that have been identified in the adult central nervous system (CNS), and offer a perspective on how they regulate CNS function. In particular we examine how myelin plasticity can operate alongside neurogenesis and synaptic plasticity to influence information processing and transfer in the mature CNS.

Key Words: *oligodendrocyte; OPC; adult; central nervous system; NG2; oligodendrogenesis; plasticity; remodelling; myelination; neural stem cells; synapse*

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Central nervous system plasticity in normal adulthood

The adult CNS is remarkably adaptable – it retains the ability to generate and integrate new cells, and remodel pre-existing circuits. Intense research over the last 25 years has provided critical insight into the cell generation and differentiation potential of endogenous neural stem and progenitor cells, and has described three core CNS plasticity mechanisms. While we are still a long way from fully understanding how neural plasticity is regulated from the level of the individual cell, to the level of the neural network, there is growing evidence to support the idea that neurogenesis, synaptogenesis and myelin remodelling dynamically and co-operatively alter the structure and function of neural circuits in the adult CNS.

Synaptic plasticity

Throughout the CNS, neurons are connected through specialised junctions called synapses, which comprise a pre- and post-synaptic site, often referred to as the bouton and spine respectively. The electrical signal of the pre-synaptic neuron is converted to a chemical signal in the form of neurotransmitter release, which in turn activates the postsynaptic cell. This process of neurotransmission underpins CNS function. Synapse formation requires an active and rapid rearrangement of the actin cytoskeleton at the point of the future pre- and post-synaptic site. This rearrangement is followed by the coordinated recruitment of presynaptic release machinery and organisation of postsynaptic protein scaffolds and receptors into a postsynaptic density (PSD) (Sheng and Hoogenraad, 2007). While synaptogenesis occurs during embryogenesis and unwanted synapses are pruned during a critical period in early postnatal life, CNS neurons retain the ability to remodel and adapt their connectivity in response to environmental influence, experience, and disease (Choquet and Triller, 2013). This process is broadly referred to as synaptic plasticity.

In associative or Hebbian synaptic plasticity, repetitive neurotransmitter release from the presynaptic terminals induces synchronised firing of the postsynaptic neurons and results in a process known as long-term potentiation (LTP). While the specific events involved in LTP can vary between neurons, it crucially involves the reorganisation of postsynaptic receptors such as AMPA-, NMDA-, GABA-, and glycine-receptors, and a variety of metabotropic receptors (Malenka and Bear, 2004). These receptors have been shown to diffuse in and out of the postsynaptic density membrane, be recycled at high rates between the membrane and the intracellular compartments, and be targeted to multiple synapses during their life-time (Hoerndli et al., 2013; Vitureira and Goda, 2013). By influencing the number of receptors found in the postsynaptic density membrane, neuronal activity alters the ability of the postsynaptic cell to respond to neurotransmitter release, changing the efficacy or strength of the synapse (Malenka and Bear, 2004).

Synaptic plasticity not only modifies synaptic function, but also induces changes to the morphology of the synapse - for example spine growth is closely associated with LTP and spine shrinkage with long-term depression (Matsuzaki et al., 2004; Nägerl et al., 2004; Zhou et al., 2004). Sensory enrichment (Knott et al., 2002) or deprivation (Zuo et al., 2005) induce changes in spine length and shape, the area and density of the PSD, as well as spine retraction and stabilisation rates in CNS regions responding to the stimulus. Some of the key elements involved in this coordinated structural plasticity have recently been characterised *in vivo*. In response to an LTP-inducing stimulus, actin-scaffold associated proteins (including cofilin) are rapidly activated and associate with actin, leading to an 'immediate' increase in spine size (Bosch et al., 2014). Such early structural changes likely correspond to the functional state described as early LTP. In persistently

enlarged spines, PSD-95 and Homer1b expression increase over 1–3 hours, followed by enlargement of the presynaptic bouton (Bosch et al., 2014; Meyer et al., 2014). These later structural changes are dependent on protein translation, and likely correspond to the functional state called late or stable LTP (Straub and Sabatini, 2014).

Due to the activity-dependent nature of synaptic plasticity, it has long been correlated with memory coding and cognition. However, it was not possible to directly test this theory until now. A recent study has demonstrated that memories formed during a fear conditioning paradigm, in which foot shock was paired with the optogenetic activation of auditory inputs, can be subsequently inactivated by optogenetic LTD conditioning of the auditory inputs. Furthermore, the memory can be reactivated by LTP conditioning (Nabavi et al., 2014). These data provide clear evidence that synaptic plasticity is a critical cellular mediator of learning and memory.

Neurogenesis

Correct development of the CNS relies on the generation of a large number of neuroblasts from neural stem cells located within the neuroepithelium of the brain and spinal cord. These stem cells later switch from generating neurons to generating glia (Kohwi and Doe, 2013). However, it is now accepted that the end of developmental neurogenesis is not the end of neurogenesis, which instead continues throughout life in two brain regions. Neural stem cells remain within the dentate gyrus of the hippocampus and subventricular zone of the lateral ventricles of the brain, and produce new dentate granule neurons and olfactory bulb interneurons respectively (reviewed by Gage and Temple, 2013; Bacigaluppi et al., 2014).

In the mature nervous system, the proliferation of neural stem cells and the integration of new neurons is highly activity dependent, and both increase in response to physical and mental exercise (Tong et al., 2014). Adult-born immature neurons have enhanced synaptic plasticity and are hyperexcitable relative to mature neurons, allowing them to fire preferentially (reviewed by Ming and Song, 2011). The neuroblasts that migrate to the olfactory bulb differentiate into a diverse range of inhibitory interneuron types, broadly categorized as olfactory bulb granule neurons and periglomerular neurons. As they develop they rapidly receive synaptic input from surrounding excitatory and inhibitory neurons, and form inhibitory synapses onto mitral and tufted cells, the projection neurons of the olfactory bulb (Nissant and Pallotto, 2011). The new glutamatergic dentate granule neurons added to the hippocampus project their axons to make mossy fibre connection with target CA3 pyramidal neurons, and additionally innervate GABAergic neurons, some of which in turn inhibit dentate granule neurons (Szabadics and Soltesz, 2009). Recent studies have shown that the unique properties and inhibitory influence of adult-born immature neurons allow them act as individual processing units and contribute to a number of distinct forms of learning and memory (Abraham et al., 2010; Gu et al., 2012; Marin-Burgin et al., 2012).

Myelin plasticity

During embryonic development neurogenesis is followed by the generation of a glial cell type known as oligodendrocyte progenitor cells (OPCs) which proliferate and populate the CNS, before differentiating into myelinating oligodendrocytes in the postnatal period (Kessaris et al., 2008; Zhu et al., 2011). An individual oligodendrocyte myelinates many axon segments, each of which is termed an internode. Myelin internodes have a high electrical resistance, and effectively lower the capacitance of the ensheathed axon segment, facilitating rapid saltatory conduction of the action potential from one node of Ranvier to the next (Buttermore et al., 2013; Arancibia-Carcamo and Attwell, 2014). The mechanisms underlying the assembly of these multi-layered myelin sheathes was only recently discovered (Snaidero et al., 2014).

During postnatal development not all OPCs undergo terminal differentiation. A substantial population of progenitors remain in the mature nervous system, and are referred to as OPCs, oligodendrocyte precursors (OLPs) and NG2 glia (reviewed by Richardson et al., 2011). While adult neural stem cells can generate new OPCs, their contribution in normal adulthood is small (Young et al., 2010). The OPC population is proliferative and largely self-sustaining (Rivers et al., 2008), with symmetric division producing two new OPCs which have the ability to subsequently divide or differentiate into mature myelinating oligodendrocytes as the environment dictates (Hughes et al., 2013). A number of soluble and contact mediated signalling systems have been implicated in regulating OPC division and differentiation (reviewed by Emery, 2010). However there is growing evidence to support a role for electrical signalling in regulating these processes.

OPCs are the only glial cell type to receive direct synaptic input from neurons (reviewed by Bergles et al., 2010; Dietrich and Sun, 2013), and glutamatergic synaptic signalling can direct the local translation of a myelin protein (myelin basic protein) to the site of axon-OPC contact *in vitro* (Wake et al., 2011). While the effect of axon-OPC synaptic communication on OPC behaviour has not been examined directly *in vivo*, cortical neuron activation has been shown to increase OPC proliferation (Li et al., 2010), oligodendrocyte generation, and myelin thickness in mice (Gibson et al., 2014). Electrical activity also influences the mature progeny, as the depolarisation of mature oligodendrocytes has been shown to regulate action potential synchronicity (Yamazaki et al., 2014). These data suggest that neuronal activity is a key *in vivo* regulator of oligodendrogenesis, myelination and ultimately action potential conduction within the CNS. The magnitude of the change induced in the conduction velocity of individual neurons, as a result of adult myelination, is likely to be vary by neuron type and CNS location. However even the small change in conduction velocity of mouse retinal ganglion neuron axons, estimated to occur during normal adulthood (Young et al., 2013), would have a significant impact on neural function (Pajevic et al., 2013).

A number of possible scenarios have been proposed to explain internode addition in the mature CNS, the simplest being *de novo* myelination (Wang and Young, 2013). In this scenario activity-dependent neuronal firing initiates the myelination of previously unmyelinated axons. This idea largely stems from human studies in which motor task acquisition was shown to induce a significant increase in fractional anisotropy in CNS regions activated by the task

– a change which is suggestive of increased myelination (reviewed by Zatorre et al., 2012; Wang and Young, 2013). We previously proposed that *de novo* myelination would involve the coordinated myelination of an entire axon (Young et al., 2013). However, a recent study in mice revealed that even in adulthood cortical neurons are only intermittently myelinated along their length (Tomassy et al., 2014), indicating that adult myelination is just as likely to add further internodes to partially myelinated axons. Furthermore, our previous observation that myelinating oligodendrocytes are continually added to regions of the mouse CNS that lack a pool of unmyelinated or partially myelinated axons, such as the optic nerve (Young et al., 2013), supports a further role for adult myelination in processes such as myelin remodelling or internode replacement (reviewed Wang and Young, 2013).

An integrated view of CNS plasticity

In adulthood synaptic plasticity, neurogenesis and myelination occur simultaneously. Despite the fact that each plasticity mechanism is activated in response to increased neuronal activity, and maybe essential for learning and memory, their combined influence on nervous system regulation and function has not been considered. One area of potential overlap is in the support of life-long neurogenesis. Adult-born neurons make and receive synaptic connections as they 'plug-in' and respond to the neuronal network (Mizrahi and Katz, 2003; Toni et al., 2008; Panzanelli et al., 2009; Chancey et al., 2014). As adult-born olfactory bulb interneurons and dentate granule neurons remain unmyelinated, myelin plasticity does not appear to directly influence the fate or function of adult-born neurons. Despite this, OPCs in the hilus of the hippocampus receive synaptic input from granule cells (Mangin et al., 2008). The purpose of synaptic communication between OPCs and axons that are not destined for myelination is unclear, but implies that OPCs sense the activity of local neurons (including adult-born neurons), and can potentially influence their function independent of myelination (see Maldonado and Angulo, 2014).

Adult CNS plasticity mechanisms would not have to influence the same cell to cooperatively modify neuronal activity across connected brain regions. This may be where myelin plasticity plays its most important role – adding new internodes to developmentally-generated neurons in adulthood. Memory formation and contextualisation involves significant communication between cortical regions and other brain regions including the hippocampus (Lee and Lee, 2013). In mice, axons in each of these regions are subject to ongoing myelination in adulthood (reviewed in Wang and Young, 2013). This also appears to be the case in humans, where cortical myelination has been shown to continue past adolescence (Miller et al., 2012), and learning an activity such as juggling, at any stage of adulthood can produce a change in fractional anisotropy in the brain, consistent with elevated myelination (reviewed Wang and Young, 2013)– in this case, the white matter of the intraparietal sulcus (Boyke et al., 2008; Scholz et al., 2009), a region implicated in perceptual motor co-ordination and visuospatial working memory.

In adult mice, changing the activity of a subset of neurons is sufficient to drive their myelination (Gibson et al., 2014), and is also sufficient to induce synaptic plasticity (Nabavi et al., 2014). As neurons not only form synaptic connections with other neurons, but also synapse onto OPCs, it is possible that synaptic plasticity is an early event regulating myelination. Axon-OPC synapses are plastic and respond to altered neural activity in a process that has been termed 'glial LTP' (Ge, 2006; Zonouzi et al., 2011). At present the physiological importance of glial-LTP for OPC differentiation is unknown and it would be intriguing to determine whether this process occurs *in vivo* and precedes adult myelination. However this may not be the only functional overlap between myelination and synaptic plasticity. The activity-dependent myelination of excitatory cortical projection neurons would be expected to increase the speed and reliability of information transfer to neurons in other brain regions such as the entorhinal cortex. Such modifications could in turn influence synaptic plasticity and potentially the myelination of the post-synaptic neuron. This is a particularly intriguing example as a subset of neurons in the entorhinal cortex synapse onto mature and immature dentate granule neurons in the hippocampus.

Herein we highlight the potential for interaction between key CNS plasticity mechanisms. While new genetic and imaging tools have led to major advances in our understanding of each plasticity mechanism separately, much work remains to be done to determine whether synaptic plasticity, neurogenesis and myelin plasticity operate in a coordinated and synergistic manner, as we have proposed, to regulate neural networks and support functions such as learning and memory, which span multiple CNS regions.

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