Review

Therapeutic potential of neuromodulation for demyelinating diseases

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Abstract

Neuromodulation represents a cutting edge class of both invasive and non-invasive therapeutic methods which alter the activity of neurons. Currently, several different techniques have been developed- or are currently being investigated – to treat a wide variety of neurological and neuropsychiatric disorders. Recently, *in vivo* and *in vitro* studies have revealed that neuromodulation can also induce myelination, meaning that it could hold potential as a therapy for various demyelinating diseases including multiple sclerosis and progressive multifocal leukencepalopathy. These findings come on the heels of a paradigm shift in the view of myelin's role within the nervous system from a static structure to an active co-regulator of central nervous system plasticity and participant in neuron-mediated modulation. In the present review, we highlight several of the recent findings regarding the role of neural activity in altering myelination including several soluble and contact-dependent factors that seem to mediate neural activity-dependent myelination. We also highlight several considerations for neuromodulatory techniques, including the need for further research into spatiotemporal precision, dosage, and the safety and efficacy of transcranial focused ultrasound stimulation, an emerging neuromodulation technology. As the field of neuromodulation continues to evolve, it could potentially bring forth methods for the treatment of demyelinating diseases, and as such, further investigation into the mechanisms of neuron-dependent myelination as well as neuro-imaging modalities that can monitor myelination activity is warranted.

Key Words: central nervous system; deep brain stimulation; myelination; neural activity; oligodendrocyte; optogenetic stimulation; transcranial electrical stimulation; transcranial focused ultrasound stimulation; transcranial magnetic stimulation

Introduction

Neuromodulation is an emerging class of therapy that excites or inhibits dysfunctional circuits to alter them back to a more physiological state. Since it became apparent that dysfunctional circuitry in the brain leads to neurological symptoms and aggravates ongoing pathogenic conditions, several techniques have been developed to re-establish the affected circuitry. With the promising outcomes, the clinical use of neuromodulation has changed the way that neurological diseases are managed and understood. Non-invasive stimulations such as transcranial electrical stimulation (TES) and transcranial magnetic stimulation (TMS) have shown therapeutic effects for treating a wide range of diseases. Transcranial focused ultrasound stimulation (TFUS) is another evolving technique for non-invasive neuromodulation (Kubanek, 2018). Interest in TFUS is sharply increasing because it provides a better spatial resolution and accessibility to deep brain areas than TES and TMS. This ability has been utilized to modulate activities of specific brain regions in the context of functional neurosurgery as well (Martin et al., 2009; Elias et al., 2013). Although deep brain stimulation has an invasive nature, it is an established treatment for Parkinson's disease. It has been shown that implanted devices could significantly improve mobility and reduce dyskinesia in patients with advanced stages of Parkinson's disease (Limousin et al., 1998; Obeso et al., 2001). Moreover, deep brain stimulation has been Food and Drug Administration approved for essential tremor, dystonia, refractory epilepsy and obsessive-compulsive disorder (Lee et al., 2019). In line with these findings, deep brain stimulation of the thalamus has shown to improve tremors in multiple sclerosis (MS) patients, and TMS of the motor cortex ameliorated lower urinary tract dysfunction and spasticity in MS patients (Berk et al., 2002; Centonze et al., 2007a, b; Oliveria et al., 2017). However, the effect that neuromodulation has on oligodendrocytes and myelination has not been examined in this context.

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Recently, *in vivo* and *in vitro* studies have provided compelling evidence that neuromodulation is an effective tool not only for restoring neural circuits, but also for inducing myelination (Gibson et al., 2014; Mitew et al., 2018; Ortiz et al., 2019). Such findings strongly suggested that neuromodulation could be a therapeutic approach for demyelinating diseases including MS and progressive multifocal leukoencephalopathy. We would like to take this opportunity to discuss the molecular mechanisms underlying myelination mediated by neuromodulation. These include specific soluble factors, contact-mediated factors and signaling pathways associated with neuromodulation. This article then discusses an overview of upcoming technologies and challenges in neuromodulation.

We used the PubMed to search the literature published from January 1990 to January 2020 or to April 2020 with the search terms including neural activity, neuronal regulation, myelination, remyelination, myelin plasticity, DBS, TES, TMS and TFUS.

Cellular and Molecular Mechanisms Associated with Myelination via Neural Activity

Myelin has been considered as a relatively passive structural component of neural circuits compared to axons which propagate action potentials. For decades, the presumption was held that change of neural circuits was as a result of structural and functional remodeling of neurons (Suminaite et al., 2019). Given that oligodendrocytes are the myelinating cells of the central nervous system (CNS), it is logical to speculate that they participate in the change of neural circuits. However, it has not been clear whether myelin contributes to the plasticity of the CNS. With the recent advances in molecular and genetic technologies, experimental evidence is accumulating that the plasticity of myelin in the CNS exists in several different contexts. These diverse examples include stimulation or blockage of neural activity in co-cultures, social isolation or environmental deprivation, genetic modulation of neural activity in the zebrafish and optogenetic or pharmacogenetic stimulation of the mouse brain (Liu et al., 2012; Gibson et al., 2014; Hines et al., 2015; Mensch et al., 2015; Wake et al., 2015; Lee et al., 2016; Mitew et al., 2018).

Notably, *in vivo* optogenetic stimulation of neurons in the pre-motor cortex increased neural activity accompanied by oligodendrocyte progenitor cells (OPC) proliferation, differentiation and thicker myelin formation (Gibson et al., 2014). Consistent with these findings, a recent study employed a pharmacogenetic approach to demonstrate that neural stimulation in the mouse brain enhances OPC proliferation, differentiation and myelination within the underlying white matter (Mitew et al., 2018). Likewise, *in vivo* optogenetic stimulation of neurons could induce OPC proliferation, differentiation and remyelination in demyelinated lesions (Ortiz et al., 2019). Interestingly, non-invasive neural stimulation by TMS did not alter the rate of OPC proliferation but enhanced myelination via promoting newborn oligodendrocyte survival (Cullen et al., 2019). While these studies have investigated broad aspects of neural-activity dependent myelination such as OPC proliferation, differentiation and oligodendrocyte survival, other studies have elucidated local signaling mechanisms between axons and oligodendrocytes that promote myelination through modulation of axonal conduction rates.

Several soluble factors including glutamate, brain-derived neurotrophic factor, leukemia inhibitory factor and ATP released from neurons in an activity-dependent manner could promote myelination (Choi et al., 2019). These factors modulate the activity of transcription factors, which ultimately alter the transcription of mRNAs required for differentiation of OPCs into myelinating oligodendrocytes. Also, the signaling pathways activated by the soluble factors can affect chromatin remodeling, transcription regulatory elements and even regulatory RNAs. Interestingly, different classes of glutamate receptors such as N-methyl-D-aspartate (NMDA), aminomethylphosphonic acid, mGluR and kainate have been identified in OPCs and oligodendrocytes (Gallo et al., 1996; Karadottir et al., 2005; Salter and Fern, 2005; Kukley and Dietrich, 2009; De Biase et al., 2010). Among these glutamate receptors, NMDA receptors are preferentially localized at myelin sheaths of post-mitotic oligodendrocytes (Salter and Fern, 2005; Saab et al., 2016). Recent studies have shown that NMDA receptors in oligodendrocytes can trigger the translocation of GLUT1 to the myelin and lead to subsequent glucose uptake (Saab et al., 2016). This is followed by the release of lactates from the myelin to fuel axons. Also, activation of NMDA receptors induces the movement of mitochondria within the myelin sheath. Therefore, the release of glutamate from axons upon neural stimulation has the potential to induce myelination and promote metabolic coupling between axons and oligodendrocytes. These findings demonstrate that axons and myelinating oligodendrocytes could be considered as an integrated functional unit and that neural activity can regulate the plasticity of this unit.

Besides the soluble factors released from axons, contact-mediated factors play a role in neural activity-dependent myelination. Both *in vitro* and *in vivo* studies have revealed that modulation of neural activity induces myelination through N-cadherin, a calcium-dependent cell adhesion molecule. *In vivo* imaging of the developing zebrafish has demonstrated that neural stimulation could increase the transport of N-cadherin to axons and subsequently facilitate myelination (Chen et al., 2017). It was further supported by evidence, that blocking of N-cadherin function with oligopeptide reduced neural activity-dependent myelination. In addition to N-cadherin, neuregulin-1 (NRG1) has been identified as another player involved in myelination upon stimulation of neural circuits (Makinodan et al., 2012). Alteration in prefrontal cortex activity through social isolation decreased NRG1 expression as well as the degree of myelination. Conditional knockout of the NRG1 receptor, referred to as epidermal growth factor receptor 3, demonstrated that the blockage of NRG1-epidermal growth factor receptor 3 signaling led to the formation of thinner myelin (Makinodan et al., 2012). Together, these studies represent an important aspect of neural activity-dependent myelination through contact-mediated factors.

Over the past decade, evidence from various studies has changed the traditional view of myelin being passive and static. It has been apparent that myelin participates in the plasticity of CNS, and the activity of neurons can regulate myelin. However, only a handful of studies have investigated the consequences of neural activity on myelination at the cellular and molecular level. Clearly, many critical questions remained to be answered. In particular, lipid metabolism in oligodendrocytes with modulation of neural activity could be an important area of investigation because oligodendrocytes generate an enormous amount of lipids in a relatively short time during the active phase of myelination. Change in

mitochondria trafficking in both neurons and oligodendrocytes could be another area of investigation because few studies scratched the surface of the metabolic coupling between axons and oligodendrocytes upon neural stimulation. It has been reported that synapses can form on oligodendrocytes, but the function of these synapses is still unknown. It is conceivable that firing patterns of neurons could affect the synapses between axons and oligodendrocytes. Although glutamate has been identified as a neurotransmitter playing a role in neural activity-dependent myelination, different neurotransmitters could be released depending on the types of neurons. Therefore, it is essential to study whether only certain types of neurons or brain regions could induce myelination with modulation of neural activity.

Neuromodulation Devices and Spatiotemporal Precision

Neuromodulation devices have become a class of tools considered for alternative or adjunct to conventional therapies. While the fundamental mechanisms of actions are different across the neuromodulation devices, they offer the ability to excite, inhibit or regulate neural circuits depending on the parameters. Along with the mechanism of actions, precision in dosing of neuromodulation should be investigated for true progress in these technologies. The parameters of the devices mediate the biological effects of neuromodulation. Also, the physiologic response to the neuromodulation will be affected by various factors of an individual including anatomy, age, sex and concomitant pharmacological interventions. While the factors of an individual are not modifiable, the parameters involved in the dose of neuromodulation can be further investigated and optimized. Indeed, the understanding of the dose will bring the fullest clinical efficacy from neuromodulation devices. For TES and TMS, the dose can be defined by the parameters determining the spatial distribution of the electromagnetic field and other parameters affecting the temporal characteristics of the electromagnetic field (Peterchev et al., 2012). The shape, size, position and electrical properties of electrodes or coil determine the spatial distribution while the pulse shape, amplitude, polarity and repetition frequency affect the temporal characteristics (Peterchev et al., 2012). In future basic and clinical studies, it will be critical to accurately document and report the parameters. The documented parameters and doses will contribute to an enhancement of safety and reproducibility.

While TES and TMS are known as the two established modalities, the interest in ultrasound neuromodulation, such as TFUS, is rapidly growing (Kubanek, 2018; di Biase et al., 2019). Compared to TES and TMS, TFUS has a higher spatial resolution and reaches deep brain structures. Also, TFUS can be readily combined with neuroimaging modalities such as MRI and electroencephalography without interfering with the recordings (McDannold et al., 2010; Jeanmonod et al., 2012; Fasano et al., 2018). However, the current knowledge about the safety profile of TFUS limits its application in humans. A recent systematic review reported that the adverse effect of TFUS was minimal in human but the systematic review also included two cases where TFUS lead to microhemorrhages in a subset of tested animals (Pasquinelli et al., 2019). Although the doses of TFUS used in these cases were higher than the safety limits of the Food and Drug Administration guidelines for diagnostic, it is still possible that the therapeutic window of TFUS for neuromodulation could be higher than the safety limits for diagnostic. Therefore, further investigations are urgent to validate its safety for clinical translation.

Concluding Remarks

Neuromodulation has become a powerful tool for the treatment of neurological disorders. Upcoming advances in basic science and engineering will allow us to evaluate neuromodulation as a therapeutic tool for demyelinating diseases and bring this technique closer to clinical translation. To develop a safe and effective tool, it is crucial to assess the safety of neuromodulation in every aspect and identify physiological effects when the CNS is perturbed with the interventions. One of the unknown questions is the effect of TES, TMS or TFUS on the vasculature, blood-brain barrier and non-neuronal cells residing in the CNS. Various studies demonstrated neural activity-dependent myelination with specific stimulation of neurons. For example, *in vivo* studies utilized optogenetic or pharmacogenetic stimulation to induce the excitation of neurons (Gibson et al., 2014; Mitew et al., 2018; Ortiz et al., 2019). Several *in vitro* studies employed compartmentalized chambers to stimulate neurons but not oligodendrocytes or OPCs (Choi et al., 2019). The consequences of the simultaneous stimulation of neurons and oligodendrocytes have not been rigorously investigated. Moreover, astrocytes and microglial could react directly to TES, TMS or TFUS and subsequently release inflammatory factors. Indeed, several lines of evidence have revealed gliosis following electrical stimulation (Salatino et al., 2017). Therefore, non-neuronal response to the stimulation and hardware-related complications should be investigated as well (Oh et al., 2002).

Although many studies demonstrated that neural activity can enhance myelination, most of them have been conducted under normal conditions. Therefore, it is difficult to determine the therapeutic benefits of neuromodulation for demyelinating diseases. To assess whether neuromodulation can promote myelination in demyelinated lesions, further investigations need to be performed with *in vitro* and *in vivo* models recapitulating the pathogenic conditions.

Lastly, the development of imaging modalities to monitor myelin loss and formation is essential. Human myelin structure is generally inferred or modeled from non-specific properties because the spatial resolution of human MRI is not sufficient to provide specific information about myelin structure. Also, emerging tools including artificial intelligence and machine learning can assist the imaging analysis and precise application of neuromodulation to target regions with proper parameters. Improving these tools will invariably lead to a more consistent measurement of therapeutic efficacy as well as a reliable application. In many ways, the field of neuromodulation is rapidly evolving. Interdisciplinary collaboration between neuroscientists, engineers, physicists and clinicians will be critical to improving further the quality of life for individuals with demyelinating diseases.

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