Abstract
"Role of BDNF and NGF in central nervous system myelination"

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Neurotrophins are a family of proteins essential for the development and regulation of Central Nervous System (CNS) and are widely implicated as potential modulator for important CNS functions such as neural stem cells differentiation, cell migration, myelination and synaptic plasticity. Neurotrophins comprises of four structurally related factors: brain derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5). In CNS myelination, oligodendrocytes form a stable and rigid layer of tightly packed lipid and protein layer known as myelin sheath which is wrapped around the axon of neurons. The oligodendrocytes undergo a specific lineage involving proliferation, migration and ultimately differentiating into the myelinating oligodendrocytes. In adult, oligodendrocytes also differentiate from Neural Stem Cells (NSCs). This lineage progression and differentiation is supported by a number of extracellular cues like growth factors. PDGF and neurotrophins are much known growth factors present in the surrounding milieu. NGF, a major neurotrophin is known to be involved in promoting growth, survival, and stabilization of primary afferents neurons and neurons axonal dendrites along with the differentiation of NSCs. BDNF, another vital neurotrophin, plays an important role in the initiation of the CNS myelination and stimulation of migration of cerebellar granule cells and Schwann cells. Neurotrophins also support for survival of myelinating cells and remyelination during inflammation and in chronic injury conditions where the myelin proteins' level goes down. However, the signalling mechanisms underlying the molecular action of these neurotrophins in regulation of CNS myelination through the differentiation of NSCs, oligodendrocyte migration and lineage progression along with their role in remyelination is still not well understood. Present study revealed the significant role of those two neurotrophins (BDNF & NGF) and their receptors (TrkA and TrkB) in NSCs differentiation into oligodendrocytes as well as enhanced Oligodendrocytes progenitor cells' (OPCs) migration and remyelination potential in cytokine affected myelination *in-vitro* study. In addition, 17β-estradiol (E2), a hormone, regulates NGF and BDNF expression in astrocytes which lead to neuroprotective effect of E2 for myelination regulation. Data from the present study reveals that both BDNF and NGF

regulate NSC differentiation into MBP positive oligodendrocytes cells through ERK pathway and via their respective receptors (TrkB and TrkA). In addition, OPC proliferation and migration was also regulated by TrkA and TrkB receptors in a time-dependent fashion. Myelin sheath and myelin protein concentration was affected in myelinating spinal cord cultures treated with inflammatory cytokine (TNF-α); both of these effects were, interestingly, up-regulated by both neurotrophins (BDNF & NGF) treatments in myelinating spinal cord culture. Additionally, E2 up-regulated NGF and BDNF expression in astrocytes through ERβ receptor activated ERK pathway which indicted hormone mediated regulation of CNS functions. In conclusion, both neurotrophins, NGF and BDNF, play a pivotal role in the regulation of CNS myelination which can be elaborated and extrapolated to look at NGF and BDNF as potential therapeutic targets for several demyelinating disorders such as Multiple Sclerosis.