Myelin and saltatory conduction

Maurizio De Pittà
The University of Chicago, USA
EPI BEAGLE, INRIA Rhône-Alpes, France
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Myelin allows fast and reliable conduction of nerve pulses

Myelin is a fatty substance that ensheathes the axon of some nerve cells, forming an electrically insulating layer. It is considered a defining characteristic of jawed vertebrates and is essential for the proper functioning of the nervous system of these latter. Myelin is made by different cell types, and varies in chemical composition and configuration, but performs the same insulating function. Myelinated axons look like strings of sausages under a microscope, and because of their white appearance they are integral components of the “white matter” of the brain. The myelin sausages ensue from wrapping of axons by myelin in multiple, concentric layers and are separated from each others by small unmyelinated axonal segments known as *nodes of Ranvier*. Typically the length of a node is very small (0.1%) compared to the length of the myelinated segment. Single myelinated fibers range in diameter from 0.2 to 20 µm on average, while unmyelinated fibers range between 0.1 and 1 µm [1]. Peripheral axons are myelinated only if their diameter is larger than about 1 µm, and the axonal caliber maintains a rather constant ratio to the myelin sheath thickness [2]. A normal myelin ensheathing of a mature peripheral nerve is usually 100 times as long as the diameter of the corresponding axon [3].

Like insulating tape around an electrical wire, myelin helps to insulate the axons from electrically charged atoms and molecules that are found in the fluid surrounding the entire nervous system. Yet, the main purpose of myelin likely is to increase the speed at which neural electrical impulses propagate along the nerve fiber. Along unmyelinated fibers, impulses move continuously as waves, but, in myelinated fibers, they “hop” or propagate by a process known as *saltatory conduction*. Myelin in fact decreases capacitance and increases electrical resistance across the cell membrane (the axolemma) thereby helping to prevent the electric current from leaving the axon. This is achieved by a heterogeneous distribution of voltage-gated sodium channels along myelinated fibers, whose density is low (~25 channels/µm²) along myelinated *internodes* (i.e. the myelin “sausages”) but high at the nodes of Ranvier (between 2000 and 12000 channels/µm²) [4]. In this fash-
ion, sodium leakage into the extracellular fluid (ECF) is reduced along the myelinated internodes, thereby maintaining a strong separation of electrical charge between the intracellular fluid and the ECF. This increases sodium’s ability to travel along the axon more freely. However, although sodium diffuses along the axolemma rapidly, this process is decremental by nature so that sodium cannot trigger the opening of the voltage-gated sodium channels as it becomes weaker. The nodes of Ranvier, on the contrary, contain large amounts of voltage-gated sodium channels and are easily excited as they are exposed to the ECF allowing enough sodium into the axon to regenerate the action potential [5]. An action potential is thus restored to the original depolarization at onset at the axon hillock each time it reaches a node of Ranvier and travels fast along the myelinated axon, hopping from one node of Ranvier to the following one, with a propagation speed that can exceed 10–50 m/s in humans [6, 7].

**Specialized glial cells are responsible of myelin production**

Production of myelin – a process known as *myelination or myelogenesis* – is by specialized glial cells: oligodendrocytes myelinate the axons of the central nervous system (CNS), whereas Schwann cells supply the myelin for the peripheral nervous system (PNS). Oligodendrocytes and Schwann cells are small cells with relatively few processes, yet with distinct structural differences. While oligodendrocytes can envelop from one to 30 axonal segments (i.e. internodes) depending on axon diameter, one Schwann cell only envelops a single segment of one peripheral axon. Moreover, Schwann cells, but not oligodendrocytes, are surrounded by a basal lamina that forms the demarcation to the mesenchymal environment with the nerve [8]. Both oligodendrocytes and Schwann cells not only influence axons by enhancing signal conduction by myelin sheaths but are also responsible of segregating voltage-sensitive ion channels into distinct axonal domains that form the nodes of Ranvier. In addition to formation, maturation and maintenance of nodes of Ranvier are further key functions of these cells [9].
The periodicity of nodes of Ranvier along axons is directly and positively related to axon caliber [10]. In the CNS, internodal lengths are relatively uniform, ranging from 50 to 500 µm depending on oligodendrocyte nature [11, 12], and nodal periodicity is established developmentally before myelin compaction [13, 14]. As axons grow in length, unmyelinated gaps are myelinated by late developing oligodendrocytes, and this continues well into adulthood, which could explain the extremely short internodes observed in oligodendrocytes of late myelinated areas such as the cortex [15]. In the PNS, on the contrary, the internodal distance can reach 1 to 1.5 mm [16]. This means that if we consider the human femoral nerve, whose primary axon is approximately 0.5 m, there are approximately 300 to 500 nodes of Ranvier occurring along a primary afferent fiber between the thigh muscle and the cell body in the dorsal root ganglion. Because each internodal segment is formed by a single Schwann cell, then as many as 500 Schwann cells could participate in the myelination of each peripheral sensory axon [9].

Myelinating glial cells and axons are entirely interdependent and should be regarded as functional units rather than separate functional entities per se [15]. Neuronal signaling molecules and electrical activity trigger the proliferation of axon-associated glial cells and control the synthesis of myelin [17–19]. Likewise, myelin proteins are essential for axon radial growth and protection from extracellular insults. Additionally, in the presence of injury or pathology, axonal signals are allegedly required for survival of myelinating glial cells, and reciprocally, demyelinated axons do not survive indefinitely when they lose their myelin. Severed myelinated fibers may only regenerate in the PNS but not in the CNS [9].

**Myelination is fundamental for normal brain function**

In humans, myelination begins as early as in the third trimester after birth, although little myelin already exists in the brain at the time of birth – and quickly occurs during infancy leading to a child’s fast development, including crawling and walking in the first
Myelination continues through adolescence up to the fifth decade of life. Normal aging, on the other hand, correlates with degenerative changes in myelin, such as shorter internodes or thinner myelin sheaths or splitting, blebbing, ballooning of these latter. Magnetic resonance imaging has revealed many examples of differences in white matter structure that correlate with specific cognitive abilities such as learning to read, juggling or complex skills like playing the piano. In this latter case, for example, the level of white matter structure seems to increase proportionately to the number of hours each subject practice piano, indicating that white matter changes in acquiring the skill, rather than performance being pre-determined by a limitation on white matter development. On the other hand, lack of myelination, active demyelination, loss of myelinating glial cells or a combination thereof, associate with age-related cognitive decline as well as neurological disorders like major depressive disorder and schizophrenia.

When a peripheral fiber is severed, the myelin sheath provides a track along which regrowth can occur. However, the myelin layer does not ensure a perfect regeneration of the nerve fiber. Some regenerated nerve fibers do not find the correct muscle fibers, and some damaged motor neurons of the peripheral nervous system die without regrowth. Damage to the myelin sheath and nerve fiber is often associated with increased functional insufficiency.

In general, many diseases of the nervous system involve myelin. Multiple sclerosis (MS) is one of the most common neurological diseases affecting the CNS. It involves demyelination, likely due to an autoimmune attack on myelin and oligodendrocytes. Although, in most cases of relapsing and remitting MS, it appears that there is initial remyelination due to the generation of new oligodendrocytes and new myelin, at some point in the disease this repair process fails leading to unrecoverable motor and cognitive deficits. In the PNS, autoimmune reactions to proteins P₀ and PMP22 that are main components of peripheral myelin produce instead a demyelinating peripheral neuropathy.
the Guillain-Barré syndrome. Mutations in myelin protein genes also cause a variety of demyelinating diseases in both peripheral and central axons. In the CNS, one example is the Pelizaeus-Merzbacher disease, a leukodystrophy in humans resulting from a recessive mutation of the gene on the long arm of the X-chromosome (Xq21-22) that codes for a myelin protein called proteolipid protein 1 (or PLP1). In the PNS, a duplication of the PMP22 gene on chromosome 17 causes instead one form of Charcot-Marie-Tooth disease, which is the most common inherited peripheral neuropathy, and is characterized by progressive muscle weakness, greatly decreased conduction in peripheral nerves, and cycles of demyelination and remyelination.

Overall, demyelination slows down, or even stops, conduction of the action potential in an affected axon, because it allows electrical current to leak out of the axonal membrane. Thus, demyelinating diseases have devastating effects on neuronal circuits in the brain, spinal cord, and peripheral nervous system.

Iron balance is critical to myelination

Iron is an essential metal in biological systems where it is necessary for the consumption of oxygen and production of adenosine trisphosphate (ATP) which is a key molecule for intracellular energy transfer. It is also involved in cholesterol and neurotransmitter synthesis and protein degradation. Because of the ability of iron to interact with oxygen, it can also be a potent generator of free radicals. Thus cells have developed an elegant system to keep iron bound to proteins during delivery to cells and storage therein.

Iron and glia have both distinctive regional and cellular distribution. At the regional level, iron is most prominent in areas associated with motor functions such as basal ganglia, substantia nigra (pars reticulata) and deep cerebellar nuclei and is also present in high concentration in white matter. At the cellular level, the cells that most prominently need iron for normal function appear to be oligodendrocytes. These cells may acquire iron either in earlier stages of development or uptake it as H-ferritin,
both from the blood-brain barrier (mainly, but not exclusively, by astrocyte-mediated pathways) and from microglia. Ferritin is then used by oligodendrocytes for maturation and myelin production [38].

Oligodendrocytes are also the most sensitive to low iron insofar as hypomyelination is a consistent finding of decreased iron availability both in development and adults [39]. There is also emerging evidence that iron changes in white matter tracts may mark demyelination, which could be clinically meaningful information to guide timing of treatment intervention [40]. A further area of active investigation is on the role of genetic variations that impact brain iron status, and hence myelination, leading to alterations in rates of cognitive decline with age or degree of damage with disease.

Iron balance is critical to glial function given that proinflammatory cytokines, hypoxia and other means of damage to the brain use the ability of iron to generate oxidative stress to promote cell death in all of glial subtypes, but the most sensitive are oligodendrocytes followed by astrocytes and then microglia [41]. Remarkably, the ability of iron chelation to protect oligodendrocytes not only from direct exposure to proinflammatory cytokines but also from the toxic effects of activated microglia, suggest that attempts to use this method to treat hypoxic or ischemic injury and demyelinating diseases are well founded [42, 43]. There is indeed clear evidence that iron chelation will decrease inflammatory reaction, although the challenge remains in the delivery of the iron chelator and the timing of delivery. The chelating compound or the mechanism of delivery must be able to traverse the blood-brain barrier in adequate amounts. Moreover, the chelating compound has to discern between “good” and “bad” iron not to limit energy production that may be needed for remyelination.

Preliminary experiments in cell culture models suggest that commercially available chelators like deferoxamine (DFOA) could be viable clinical options to limit damage of glial cells by hypoxia, ischemia and traumatic brain injury, although more research is needed to identify the physiological mechanisms that could regulate the chelating compound both in terms of amount of iron being chelated and the distribution of the chelator
with the brain. Lowering dietary iron may be one way to limit iron available to exacerbate damage associated with neurological trauma, but again, iron must be reintroduced for remyelination and return to normal function.

Oxidative stress could be a key mechanism in demyelinating disorders. Substantial histological evidence exist indeed for ongoing oxidative stress in demyelination by multiple sclerosis. Moreover, in support of a role of iron and oxidative stress in promotion of demyelination is the finding that iron deposit in the white matter in multiple sclerosis and that treatment with an iron chelator or an antioxidant can limit the amount of demyelination and behavioral abnormalities that are associated with experimental allergic encephalomyelitis.

A further area that involves oxidative stress damage is radiation used to treat brain tumors. Oligodendrocytes are the most radiosensitive of glial cells and human white matter specimens obtained post-radiation confirm a delayed onset of demyelination which correlates with loss of oligodendrocyte function. Although there is not direct evidence that iron could contribute to radiosensitivity of oligodendrocytes, it is worth noting that exposing oligodendrocytes in cell cultures to radiation increases oxidative stress sixfold in these cells, suggesting that such increase in oxidative stress could be prevented by iron chelation.
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