The Myelin cannot change the basic mechanisms of axonal conduction.

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Keywords: myelin, nervous conduction, ATP, gap juctions, neuroscience.

Abstract

Starting from recent literature data, we propose a novel interpretation of nerve conduction mechanism in myelinated nerves. A new hypothesis is proposed, tending to bridge the theoretical gap existing to date between the basic physical-chemical mechanism of nerve conduction and its adaptation to myelination. The considerations exposed imply a unification of the nerve conduction mechanism, also identifying a precise role for myelin: an ATP-supplying energetic role. The latter would allow to overcome the theories that as yet have not found a solid physical-chemical confirmation. A radical simplification of is envisaged: it can be supposed that the physical-chemical mechanism of nerve conduction remains unaltered in the passage from the unmyelinated to the myelinated conditions.

Introduction.

The universally accepted hypothesis that myelin is a mere electrical insulator is old, and apparently worn-out (Fields, 2008). Today, new roles are emerging. Evidence from modern analytical methodologies and theoretical considerations concur, suggesting a simplified hypothesis on the effect of myelination on the nerve conduction velocity, more adherent to basic physical-chemical properties. White matter has been repeatedly hypothesized to play a main trophic role for the axon (Stevens & Fields, 2000)(Fields & Stevens, 2000) (Fields, 2008) (Fields, 2014) (Fünfschilling et al., 2012) (Nave, 2010b) (Nave, 2010a). In a recent review (Saab & Nave, 2017) Authors emphasize a myelin-modeling action on neuronal functions. Another very recent review (Kaller et al., 2017) highlights the link between neural activity and myelin plasticity, but the ultimate mechanism underlying the neural activity is not analyzed in-depth.

In the November 2016 issue of *Journal of Neurophysiology*, in their paper "*White matter and cognition: making the connection*", Filley and Fields (Filley & Fields, 2016) highlight the primary role of white matter in cognition, showing that white matter dysfunction is relevant to neurodegenerative disorders. Myelin would essentially mediate connectivity. However, the molecular bases still need substantiation.

Here, we propose a new hypothesis about the physical-chemical mechanisms of nerve conduction in myelinated nerves, tending to bridge the theoretical gap existing to date between the basic neuronal activity and its adaptation to myelination.

Plausible link: speed ATP supply- speed nerve conduction.

The degeneration of myelinated axons in neurodegenerative diseases is compatible with energy shortage. Recently, this energetic role was experimentally confirmed by nice measurements of the axonal ATP concentration in a myelinated nerve, by a fluorescent endocellular sensor (FRET technology). It was found that firing resulted in a 35% drop in axonal ATP concentration, while blockade of aerobic ATP synthesis by sodium-azide resulted in a drop of the action potential (Trevisiol et al., 2017). Authors stated that "*glycolysis is not sufficient to robustly sustain CAPs and physiological ATP levels, but mitochondrial function is needed to provide ATP*". Notably, the experiments by Trevisiol et al. (Trevisiol et al., 2017) can be interpreted as demonstrative of myelin able to support in some way the aerobic metabolism of nutrients. Nerve cells apparently need the support of other cells, the oligodendrocytes, already implied in the support of the axons (Lee et al., 2012), for the generation of chemical energy. This is quite surprising in that the axon ensheathing has been long supposed to sensibly lower its ATP need, being myelin essentially an energy-saving device (Harris & Attwell, 2012).

The complex of data highlights a central role of ATP supply in nervous conduction. Let us focus firstly the role of ATP supply in the unmyelinatd nerve. Almost a quarter of a century ago, a direct action of exogenous ATP on the nerve polarization has been demonstrated (Trezise, Kennedy & Humphrey, 1993). Such action was effective at high ATP concentrations (10 mM), so ex post such action appears to be mass-based rather than in a cell-signaling mode. The total mitochondrial volume in the unmyelinated nerves is scarce (Perge et al., 2009) therefore there is a limit in their ability to supply ATP required for the sodium-potassium pump to restore the ionic distribution to the sides of the plasmalemma. In conclusion, conduction speed in unmyelinated nerves is low because low is the rate at which ATP is regenerated. Establishing such close interdependence we can override the terms of the question and wonder whether the sharp rise in the conduction rate in myelinated nerves is due to an efficient ATP supply to the axon. The higher the rate of ATP supply, the faster the speed of the nerve impulse. But where may this ATP come from?

A set of experimental and theoretical reports converges to identify myelin as able to supply ATP aerobically synthesized to the axon (Ravera et al., 2009) (Morelli, Ravera & Panfoli, 2011) (Ravera et al., 2016). So, the recent data from Trevisiol et al. no-doubt represents a milestone, as they demonstrate for the first time that firing causes a net decrease in the myelinated axon ATP content, i.e. nerve conduction would not proceed in an inexpensive way, as it was presumed. Also the myelinated axon needs ATP, but the mitochondrial numbers does not appear to rise as dramatically as the conduction speed. The complex of data appears to support the hypothesis of myelin acting in the energy support for the axon (Morelli, Ravera & Panfoli, 2011) (Morelli et al.,

2013). Moreover, the existence of a passage of metabolites between myelin and axon is depicted, which conflicts with the classical vision of myelin as an insulator. Is myelin an insulator or has it got a metabolite-delivery function? The two functions appear mutually exclusive. If myelin is not a mere insulator, the traditional "electrical insulator" hypothesis for myelin, proposed about 70 years ago (Huxley & Stämpfli, 1949) would need a revision.

Radical simplification of nerve conduction in the myelinated nerves.

In their basic work, Huxley and Stämpfli (Huxley & Stämpfli, 1949) proposed their hypothesis in a very cautious form. Strikingly, while those experiments have never been reproduced since, the chemical-physical mechanism hypothesized to allow the passage of CAP into the myelinated nerve has been assumed as a basic model. A main objection can be forwarded to the "electrical insulator" hypothesis: the existence of the mesaxon, realizing an aqueous layer between myelin and axon. Notably, any "insulating" material should be in a continuous close contact with the object to be isolated, otherwise it cannot exert its function.

However, supposing that the "insulator" function of myelin is not the primary one, then the critical task to sustain the rapid CAP progression along the myelinated axons would critically depend from the speed at which ATP is readily re-synthesized to empower the Na^+-K^+ ATPase pump. In Figure, myelin is depicted as crucial for its ability to supply ATP to the axon, likely through gap-junctions (Ravera et al., 2015). Such vision would also explain why increasing the number of the wraps results in an increase in CAP speed: the thicker the sheath the more ATP is produced. A study of myelin distribution along single axons showed that neocortical pyramidal in the murine brain neurons comprise unmyelinated tracts, longer than previously thought (Tomassy et al., 2014). Since the CAP can cross thousands of nodes, and it is supposed to be decremental, is it at risk of being extinguished? We propose that the chemical-physical nature of the nervous signal does not change in the passage from the non-myelinated to the myelinated nerve and in Figure is depicted a tentative and exemplified scheme of this overall process.

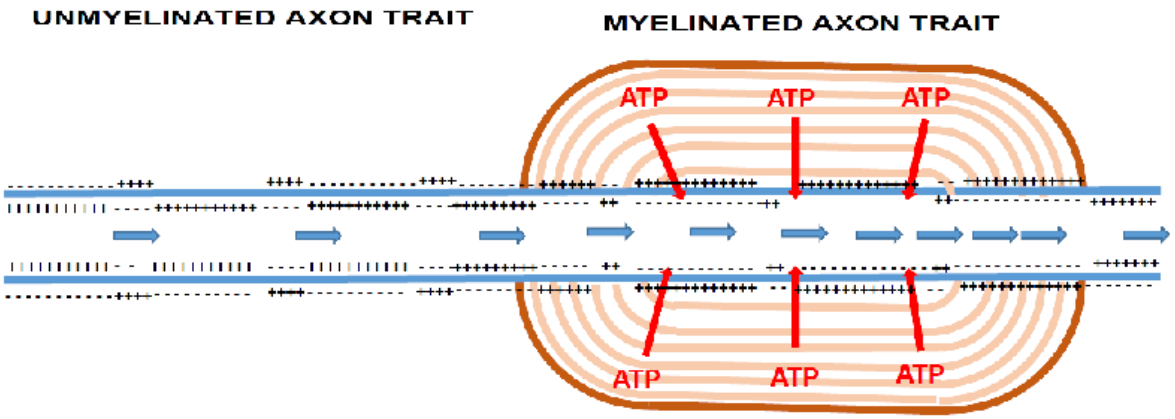

Figure – Simplified picture: in an unmyelinated axonal trait the speed of the Compound Axon Potential (CAP) is low because the supply of ATP is relatively slow. In a myelinated axonal trait the speed of CAP progressively increase thanks to the ATP supply by myelin, so that the correct polarization is quickly restored.

The working of the Na^+ and K^+ voltage-gated channels (Hodgkin & Huxley, 1952), would also be unmodified. The classical theory assuming that the voltage gated channels are "set aside" when the nerve is being wrapped from the sheath, gathering into the Ranvier Nodes, is put into serious doubt in light of recent findings (Tomassy et al., 2014). The prompt identification of the Na^+ and K^+ voltage-gated channels in the nodes by immunofluorescence techniques is likely due to easier access of the antibodies in the node, than in the myelinated tracts (Bhat et al., 2001). Notably, the Na^+ and K^+ voltage-gated channels were shown to be also present in the internode (Chiu & Ritchie, 1982) (Chiu & Schwarz, 1987) and recently a ion movement in the internode (Trigo & Smith, 2015) is proved and this is still incompatible with the hypothesis of the "electrical insulator".

Conclusions

All the above considerations imply a unification of the underlying theories, identifying a precise new role for myelin. The ATP-supplying energetic role for myelin allows to overcome the theories that as yet have not found a solid physical-chemical confirmation. A radical simplification of nerve conduction mechanism is envisaged: it is supposed that it remains unaltered in the passage from the unmyelinated to the myelinated conditions. Moreover, the increase in nerve impulse velocity due to myelination finds a convincing explanation in this acting as energy input. In fact, nerve conduction is energetically expensive for the remarkable ionic transport that it requires both in unmyelinated nerves and, as proposed herein, and suggested by the data from Trevisiol et al. (Trevisiol et al., 2017) also in unmyelinated nerves. New scenarios open in neuropharmacology: provided myelin is rich in gap junctions, acting on these it would be possible to modulate myelin activity. Notably, for example oleamide is a potent hypnotic, and also a gap junction blocker (Adriano et al., 2011) (Ravera et al., 2016). The importance of gap junctions is demonstrated by the severe pathology of the peripheral nervous system, Charcot-Marie-Tooth, consequent to connexin 32 gene alteration (Altevogt et al., 2002) (Kleopa, 2011). However, this topic needs further insights to clarify the reason why some authors find myelin gap junctions only in the Schmidh-Lantermann incisures, while others by both immunogold as well as immunofluorescence techniques (Adriano et al., 2011) detect them throughout myelin. Finally, it appears that the Fields's comment " *It is certainly time to set aside the frayed metaphor of myelin as insulation and appreciate the more fascinating reality*" (Fields, 2014) is quite timely.

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