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Homeostatic regulation of neuronal activity involves a wide range of both network-adaptive and cell-autonomous mechanisms. Among the latter, structural plasticity at the axon initial segment (AIS) has been recently described to regulate axonal excitability through the modulation of its position and length (Grubb & Burrone, 2010). Thus, altering neuronal activity correlates with structural changes in the AIS, such as its length or distance from the soma. These structural modifications, accompanied by modulation of the ion channel repertoire (Grubb & Burrone, 2010; Evans *et al.*, 2015; Kuba *et al.*, 2015), modify the biophysical properties of the AIS. These modifications can decouple the output of a hyper-excited circuit in a negative feedback loop or conversely, enhance the output of a silent network. These observations have extended the role of the AIS beyond the maintenance of neural polarity and the propagation of nervous impulse through its protein sorting action and facilitation of action potential initiation. However the core mechanisms involved in AIS structural plasticity have remained unclear.

In this issue of European Journal of Neuroscience, Evans *et al.* identify myosin II as a critical component of the complex involved in the activity-dependent control of the position and length of the AIS. This study reveals that the main structural changes occurring at the AIS during plasticity induced by the elevation of neuronal firing can be abrogated by pharmacological manipulation of myosin II. This observation identifies this single molecule as a common mediator of both plastic changes. Myosin II is well-known for its action on the contractibility of the actin cytoskeleton, making it an ideal candidate to be the final effector controlling the shape and position of the AIS (Figure 1). Modulation of calcineurin by L-type voltage-gated calcium channels has previously been described to control AIS position and length, linking overall activity levels to structural and biochemical changes of the AIS (Evans *et al.*, 2013). Evans *et al.* demonstrate that myosin II does

not control the activity of calcineurin, suggesting that it might act downstream of this calcium-regulated protein involved in AIS plasticity.

Such a mechanism has been investigated within the framework of structural plasticity that leads to distal displacement and elongation of the AIS and reducing neuronal excitability, a scenario regulated by calcineurin. The machinery leading to plastic changes in the AIS in the context of reduced activity level in excitatory neurons or after increased firing in inhibitory neurons might be distinct. Instead of calcineurin, AIS plasticity involves the neurotrophins BDNF and NT3 in hippocampal neurons with reduced activity (Guo *et al.*, 2017) or the kinase Cdk5 in olfactory inhibitory neurons (Chand *et al.*, 2015). Whether or not myosin II plays a role in these forms of structural plasticity is yet to be investigated, but its function deems it suitable for this process. This will shed light on the potential central role of myosin II in regulating plasticity-driven structural changes of the AIS and neuronal network homeostasis (Figure 1).

In a pathway involving both myosin II and calcineurin, the latter might be ideally placed to integrate activity level over time and initiate the modulation of AIS structure required for homeostasis. Temporal integration is a critical component of homeostasis that has not been investigated in the context of structural plasticity. A thorough understanding of AIS plasticity will require the elucidation of how neurons discriminate a brief increase in neuronal activity from a more sustained elevation that would trigger homeostatic mechanisms. Transient changes in neuronal activity are relevant for meaningful electrical signal propagation and should not be affected by plasticity. In other words, the mechanisms explaining how neurons are capable of reading their excitatory state are unknown. Tackling this question is critical to better describe how homeostatic mechanisms in general, and AIS structural plasticity in particular, does not lead to a loss of meaningful electrical signal propagation within a neuronal network.

Overall, the study of Evans *et al.* places myosin II as the central actor responsible for the structural modifications of the AIS induced during homeostatic changes of neuronal excitability. This actin cytoskeleton modulator has the potential to be a final effector shared by several forms of structural plasticity. Focusing further investigations on the relationship between myosin II and the activity-dependent regulators modulating AIS position and length will decipher the molecular pathways involved in AIS remodeling. This will identify how signaling pathways converge to integrate several inputs acting in the same or opposite directions on AIS structure, thus providing novel insights in the homeostasis of neuronal networks.

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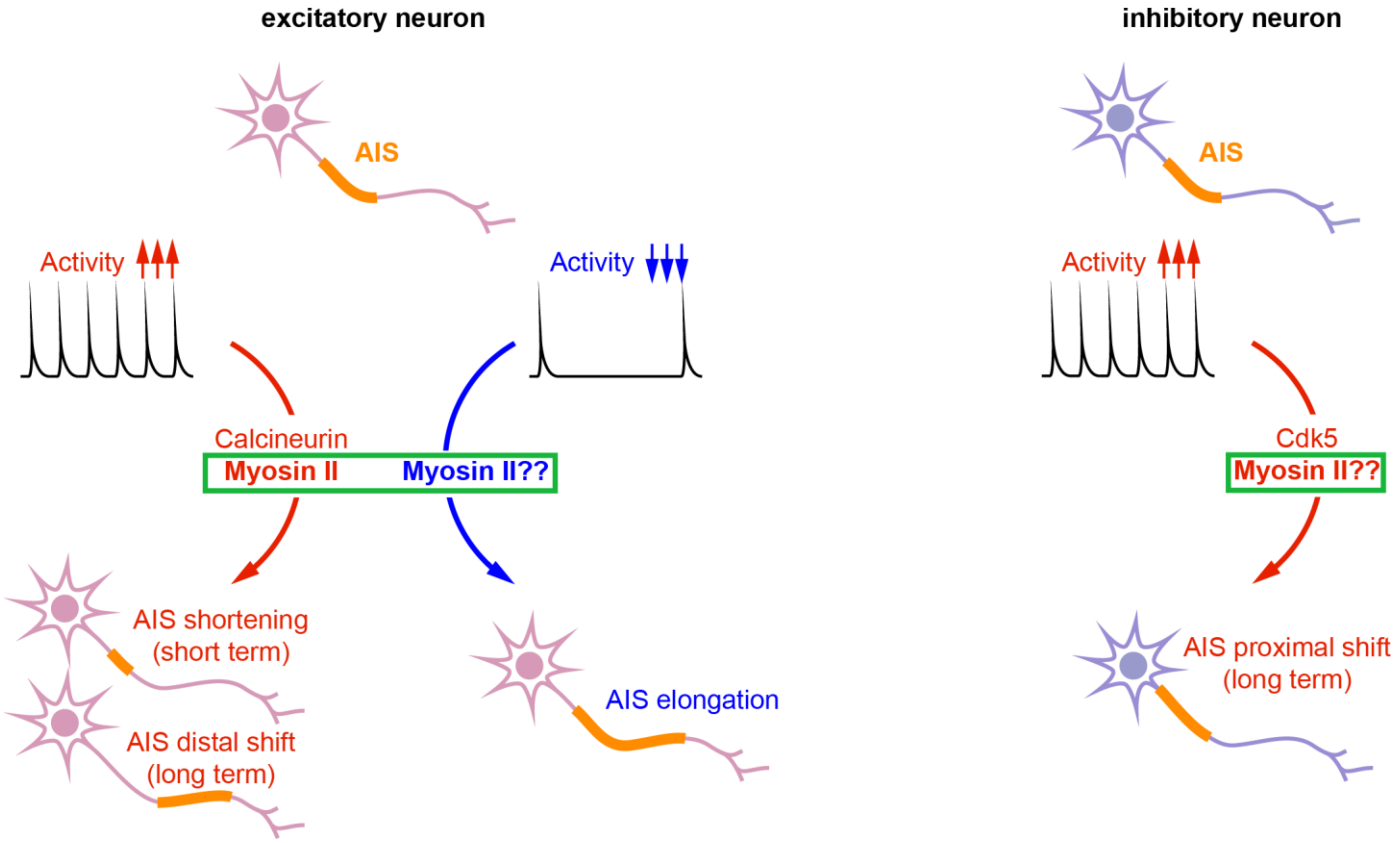
FIGURE LEGEND

Figure 1: Myosin II as a potential central regulator of AIS structural plasticity. Evans *et al.* identified myosin II as a required modulator of AIS plasticity occurring in excitatory neurons with elevated electrical activity. The ability of myosin II to modify the structure of the actin cytoskeleton makes this protein an ideal candidate to control other forms of AIS plasticity. This might include the plastic changes occurring after the reduction of overall activity or the modulation of AIS position and length in inhibitory neurons. Thus myosin II would be a key player in neuronal network homeostasis.


excitatory neuron
AIS
Activity
Activity
Calcineurin
Myosin II
Myosin II??
AIS shortening
(short term)
AIS distal shift
(long term)
AIS elongation
inhibitory neuron
AIS
Activity
Cdk5
Myosin II??
AIS proximal shift
(long term)