Study sheds light on mechanism of neuronal activity

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Neurons communicate by passing electrical messages, known as action potentials, between each other. Each neuron has a highly specialized structural region, the axon initial segment (AIS), whose primary role is in the generation and sending of these messages. The AIS can undergo changes in size and location in response to alterations of a neuron's ongoing electrical activity. However, until now, all such 'AIS plasticity' has been exceptionally slow, occurring over a timescale of days. Work by researchers from the MRC Centre for Developmental Neurobiology (MRC CDN), has found that AIS plasticity can happen quickly, influencing the way cells fire action potentials. These results were published today in the online edition of the journal *Cell Reports*.

Located near the start of the axon, the neuron's major output structure, the AIS has a crucial role in kick-starting communication between brain cells. However, for AIS plasticity to play a more prominent role in the brain's responses to altered activity, the structure needs to be able to change far more quickly than was previously shown. For this reason, Evans, Dumitrescu and colleagues decided to investigate how rapidly an AIS could be altered. Using a technique called 'optogenetics', which allows precise control of neuronal activity with light, they discovered that 3 hours after elevating neuronal activity, the AIS of hippocampal neurons in culture was shortened by approximately 25%.

"We knew this part of a neuron could change, but we had no idea it could happen as rapidly as this. Something that takes a brain cell 3 hours might not sound especially fast, but for a big structure like the AIS, it really is surprisingly quick!", said senior author Matthew Grubb, Lecturer at the MRC CDN.

What does a shorter AIS mean for the function of a neuron? The researchers expected that these neurons would be less excitable and therefore would send fewer action potentials. However, to their surprise, after 3 hours of sustained neuronal activation, neurons with shorter AISs were functionally indistinguishable from their unstimulated counterparts. It turned out that a second form of plasticity was also in action at the same time as AIS shortening, involving molecular alterations to the proteins that drive action potential generation - voltage-gated sodium channels. This sodium channel modulation acted to balance out any neuronal excitability changes caused by AIS shortening.

"I was surprised to discover that AIS shortening did not immediately lead to a reduction neuronal excitability. The interplay between AIS shortening and sodium channel modulation was a fascinating lesson in the ability of a neuron to balance its levels of excitability.", said Mark Evans, co-first author of the study".

Once the researchers re-set this second form of plasticity using a cocktail of specific drugs, the functional effects of rapid AIS plasticity became clear. They found that changes in AIS length were now associated with alterations in neurons' action potential firing responses: a neuron with a shorter AIS was less excitable and sent less action potentials. Their discovery is the clearest demonstration to date that AIS structure determines neuronal function.

"These findings reveal another mechanism of plasticity a neuron can use to regulate its excitability within hours. How this form of plasticity integrates with other plasticity mechanisms will be an intriguing area of future study" added Evans.

The results suggest that brain cells can rapidly alter their structure to fine-tune their function. Since a shorter AIS is associated with decreased electrical excitability in neurons, it could represent a form of adaptation, or 'homeostasis': when neuronal activity is too high in a network, for instance during the early development of the brain, cells shorten their AIS, become less excitable, send fewer action potentials, and thereby return the network to normal levels of activity. This could prove to be an important factor in the brain's responses to perturbed activity, allowing ongoing maintenance of appropriate levels of electrical signalling, even when the inputs to a network have been significantly altered, which might happen in diseases such as epilepsy and bipolar disorder.

"This work adds a bit of data to confirm the 'biology is messy' dictum. We saw shorter AISs and automatically assumed that our experiments would prove that this results in an excitability reduction. It took some intellectual head scratching and extra experiments to figure out that sodium channels were modulated by a separate pathway and actively counteracted the AIS shortening phenotype. We showed what the plasticity potential is in an in vitro context; it would be interesting to study whether it can be replicated in vivo next." concluded Adna Dumitriescu, co-

author of the study.

These findings open the door to future studies on the intracellular molecular pathways controlling AIS plasticity and other forms of plasticity that interact with it. Uncovering these might lead to the discovery of novel targets for drugs that could allow precise control over neuronal excitability, with potential uses in psychiatric disorders.

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