MOLECULAR AND SYNAPTIC MECHANISMS

COMMENTARY
Shedding light on mitochondrial movements in axons (Commentary on Obashi & Okabe)

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Neuronal communication depends on energetically demanding processes such as reversing the ion influxes involved in action potential generation and synaptic transmission, which require mitochondrial ATP production (Harris *et al.*, 2012). Owing to the length and compartmentalization of neuronal processes, the localization and trafficking of mitochondria is crucial to maintain function. In this interesting study, Obashi & Okabe (2013) shed new light upon the characteristics of mitochondrial behaviour in axons. Using live cell imaging over time scales ranging from seconds to days, the authors show how manipulations of neuronal activity as well as structural features, such as synapse size, influence the movements and positioning of mitochondria.

It has previously been shown that mitochondria in neurons are trafficked in an activity-dependent manner, whereby an increase in neuronal signalling reduces mitochondrial movements (MacAskill & Kittler, 2010; Zhang *et al.*, 2010). Here, the authors now demonstrate, using field stimulation to generate action potentials, that short pauses, a feature of mitochondrial movements, occur more frequently at synaptic sites than at inter-synaptic positions, whereas a block of action potentials with tetrodotoxin increases mitochondrial velocity.

Interestingly, the study also compares mitochondrial movements in 2 and 3-week-old cultures, and reveals an increase in mitochondrial stability as synapses mature. This is especially exciting, as it suggests that mitochondria are more mobile during developmental periods characterized by significant synaptic remodelling. It also raises the question of cause and effect: does the immaturity of young cultures contribute to mitochondrial motility, or does mitochondrial positioning reciprocally affect the stability of synapses?

The elegance of the present study also lies in the imaging of mitochondrial trafficking performed over intermediate (3 h) and long (4 days) time scales, which allowed the researchers to examine transitions of mitochondria from a stationary state, where the mitochondria were still for 30 min or more, to a mobile state and *vice versa*. Surprisingly, at synapses, the authors measured increases not only in the transition from the mobile to the stationary state but also in the transition from the stationary to the mobile state upon tetrodotoxin treatment, thus suggesting that these transitions may be coordinated – perhaps to avoid depletion of mitochondria from synapses or inter-synaptic positions. To allow for increases both in mitochondrial motility and in stability during a reduction in neuronal activity, it seems that two mechanisms could be required. It is shown here, in agreement with previous reports (MacAskill *et al.*, 2009; Wang & Schwarz, 2009), that activity-dependent stopping of mitochondria depends on calcium entry. A lack of a rise in calcium level during decreased activity might thus increase motility, and an additional activity-dependent mechanism (perhaps binding to a local tether) could increase stability simultaneously. This latter mechanism remains to be revealed, but could be physiologically relevant in burst firing patterns, where mitochondrial stabilization in between bursts might occur in this way.

Long-term imaging of mitochondrial dynamics also allowed the researchers to observe a positive correlation between synaptic bouton size and the stability of mitochondria therein. It would be interesting to establish which possible interaction partners in boutons, such as, perhaps, syntaphilin (Kang *et al.*, 2008), contribute to these differences in stability. In future, determining the underlying mechanisms and confirming the present findings *in vivo* will be highly rewarding. Thus, the appealing results presented here clearly raise as many interesting questions as they answer, and represent a promising addition to the fast-moving field of mitochondrial motility.

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