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Neuronal Fat and Dendrite Morphogenesis: The Goldilocks effect

Lakshmi Sundararajan¹ and David M. Miller III¹

¹Department of Cell and Developmental Biology, Vanderbilt University, Nashville

Abstract

Two recent studies by Meltzer et al. and Ziegler et al. use *Drosophila* larvae to demonstrate that cell autonomous regulation of lipid biosynthesis defines the complexity and function of highly branched nociceptive neurons. Their findings show that lipid biosynthesis in the neuron is fine-tuned for optimal dendrite morphology and sensitivity.

Keywords

dendrite morphogenesis; lipid biosynthesis; nociceptive sensory neuron; *Drosophila* da neuron

The extended and elaborately sculpted membranes of neurons likely account for the predominance of lipids in the nervous system, representing over 50% by dry weight of brain tissue[1]. Most of this lipid is synthesized in the brain, largely in non-neuronal glial cells, to support a wide range of neuronal functions including membrane formation, myelination and synaptogenesis[2]. Although recent studies point to the additional role of lipid biosynthesis in developing neurons, the necessity for this cell autonomous function has been largely unexplored[3,4].

This question has been addressed by two recent studies published in Cell Reports demonstrating that the maintenance of normal levels of lipid biosynthesis critically determines the size and complexity of sensory neuron dendritic arbors. Both studies exploit the utility of genetic analysis and live cell imaging in *Drosophila* to link lipid homeostasis to dendritic complexity[5,6]. *Drosophila* larvae are enveloped with ordered arrays of four different classes of sensory neurons that mediate responses to external cues. Of these, the class IV da neurons adopt the largest and most elaborate dendritic arbor and function as nociceptors[7] (Figure 1). An RNAi screen for defective class IV da neuron dendrite morphology detected a role for the *eas* (*easily shocked*) locus[5]. Originally identified as a “bang sensitive” paralytic mutant, *eas* encodes ethanolamine kinase, a key enzyme in the biosynthesis of phosphatidylethanolamine (PE)[8]. As the predominant phospholipid in the Dipteran nervous system, PE is a major constituent of the neuronal cell membrane[9]. The reduced overall length and number of class IV da neuron dendrites in *eas* mutants suggest

Correspondence to: David M. Miller, III.

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that PE is required for normal dendrite morphogenesis. Interestingly, time-lapse imaging revealed that dendrite outgrowth is largely unaffected but that retraction occurs more frequently in *eas* suggesting that normal PE levels are necessary for maintaining dendrite length. Importantly, these defects are rescued by transgenic expression of wild-type *eas* in class IV neurons thereby confirming a cell autonomous role for PE biosynthesis[5]. At this point, a parsimonious explanation of these defects would be that PE levels are too low in *eas* mutants to support dendrite outgrowth. An alternative explanation, however, is suggested by the finding that a conserved mechanism for limiting lipid biosynthesis is also required for normal dendrite morphogenesis. At low PE levels, the transcription factor SREBP (Sterol Response Element Binding Protein) is released from the ER for proteolytic cleavage and transport to the nucleus where it functions in a feedback loop that maintains fatty acid and phospholipid synthesis[9]. And, as expected, the activated form of SREBP is elevated in *eas* mutants. Surprisingly, however, a partial reduction in the level of SREBP expression (e.g., by RNAi or with a *srebp/+* heterozygote) restores apparently normal dendrite outgrowth to *eas* mutant class IV neurons[5]. That aberrant upregulation of fatty acid synthesis contributes to the *eas* dendritic defect is also consistent with additional findings: (1) Reduced levels of fatty acid biosynthetic enzymes, *fasn1* and *acc*, suppress the *eas* dendritic phenotype[5]; and (2) Forced expression of a constitutively active form of SREBP induces an *eas*-like dendritic defect[5,6].

Additional genetic results helped disentangle the parallel effects of too little or too much lipid biosynthesis on dendrite morphogenesis. Both groups showed that genetic ablation of *srebp* attenuates class IV da dendrite arborization. This effect is likely cell autonomous because restoration of SREBP function to class IV da neurons rescues the *srebp* dendritic phenotype[5,6]. As expected, transcripts for *fasn1* and *acc* are reduced in *srebp* mutant neurons. In addition, mosaic analysis confirmed that *fasn1* and *acc* are required for normal class IV da neuron dendrite morphogenesis. Finally, mass spectrometry detected significant changes in the lipid composition of *srebp* mutant neural tissue, notably, a 50% reduction in PE[6]. Thus, taken together, these studies demonstrate that dendrite architecture is directly linked to homeostatic regulation of lipid biosynthesis in the affected sensory neurons.

Lipid homeostasis is also linked to function. Notably, despite their stunted dendritic arbors, *srebp* mutant class IV da neurons are hypersensitive to mechanical stimuli[6]. The physiological basis for this effect is unclear but could signify an intimate role for lipid bilayer composition in mechanosensory channel function[10]. Another indication of a potential effect of lipid homeostasis on ion channel activity derives from the additional finding that elevated calcium influx contributes to the dendritic defect in *eas* mutants[5]. Finally, it is interesting to consider the question of whether these observations in *Drosophila* are indicative of similar roles for lipid homeostasis in mammalian neurons. Although it is clear that the majority of mammalian neurons are myelinated due to lipid biosynthesis in Schwann cells[2], nociceptive sensory neurons in the skin are typically unmyelinated as are class IV da neurons and therefore may be especially susceptible to disrupted lipid biosynthesis.

References

1. O'Brien JS, Sampson EL. Lipid composition of the normal human brain: gray matter, white matter, and myelin. *The Journal of Lipid Research*. 1965; 6:537–544. [PubMed: 5865382]
2. Camargo N, et al. SREBPs: SREBP function in glia-neuron interactions. *FEBS J*. 2009; 276:628–636. [PubMed: 19143832]
3. Knobloch M, et al. Metabolic control of adult neural stem cell activity by Fasn-dependent lipogenesis. *Nature*. 2013; 493:226–230. [PubMed: 23201681]
4. Fünfschilling U, et al. Critical time window of neuronal cholesterol synthesis during neurite outgrowth. *J Neurosci*. 2012; 32:7632–7645. [PubMed: 22649242]
5. Meltzer S, et al. Phospholipid Homeostasis Regulates Dendrite Morphogenesis in *Drosophila* Sensory Neurons. *Cell Rep*. 2017; 21:859–866. [PubMed: 29069593]
6. Ziegler AB, et al. Cell-Autonomous Control of Neuronal Dendrite Expansion via the Fatty Acid Synthesis Regulator SREBP. *Cell Rep*. 2017; 21:3346–3353. [PubMed: 29262315]
7. Jan YN, Jan LY. Branching out: mechanisms of dendritic arborization. *Nat Rev Neurosci*. 2010; 11:316–328. [PubMed: 20404840]
8. Pavlidis P, et al. The *Drosophila* easily shocked gene: a mutation in a phospholipid synthetic pathway causes seizure, neuronal failure, and paralysis. *Cell*. 1994; 79:23–33. [PubMed: 7923374]
9. Dobrosotskaya IY, et al. Regulation of SREBP processing and membrane lipid production by phospholipids in *Drosophila*. *Science*. 2002; 296:879–883. [PubMed: 11988566]
10. Vásquez V, et al. Phospholipids that contain polyunsaturated fatty acids enhance neuronal cell mechanics and touch sensation. *Cell Rep*. 2014; 6:70–80. [PubMed: 24388754]

Figure 1. Lipid biosynthesis promotes nociceptor dendrite morphogenesis in *Drosophila* larvae

Top: schematic illustration of a *Drosophila* larvae and its nociceptive class IV da sensory neurons. Bottom, middle: The enzyme ‘easily shocked kinase’ (*eas*) initiates synthesis of the major plasma membrane phospholipid, phosphatidylethanolamine (PE). Normal levels of PE antagonize the lipogenic transcription factor, SREBP. Bottom, right: When PE levels are low (e.g., in *eas* loss-of-function mutant), SREBP is translocated from the ER to Golgi where the active monomer is cleaved and enters the nucleus to drive expression of lipogenic genes (*fasn1*, *acc*). Mutations that disable either *eas* or *srebp*, disrupt dendrite morphogenesis.