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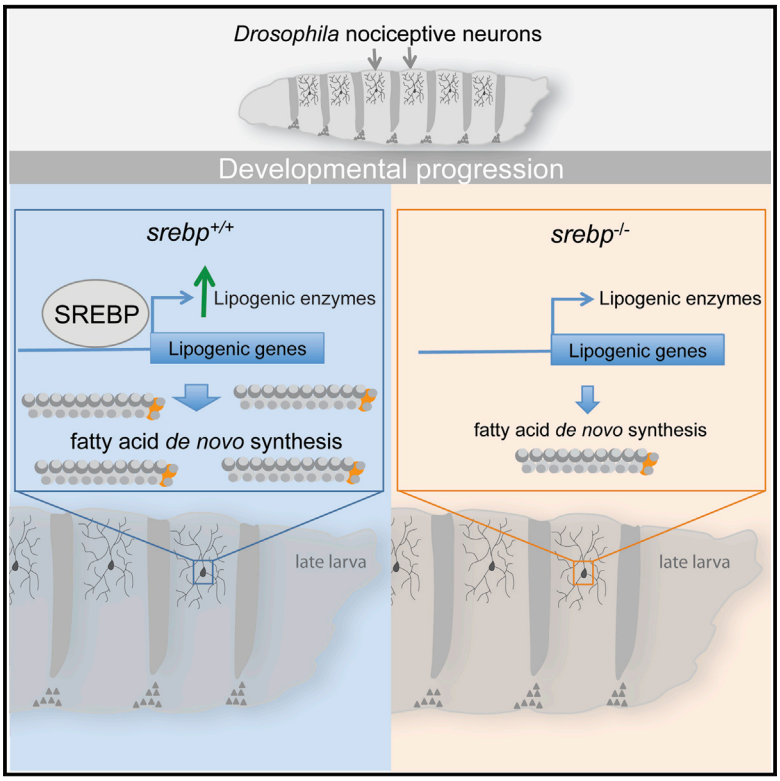
Cell-Autonomous Control of Neuronal Dendrite Expansion via the Fatty Acid Synthesis Regulator SREBP

Graphical Abstract



Highlights

- Cell-autonomous fatty acid synthesis promotes dendrite expansion
- In large CIVda neurons, SREBP is involved in dendritogenesis
- SREBP influences brain lipid composition and neuronal function

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In Brief

Ziegler et al. highlight the endogenous role of fatty acid synthesis for proper neuronal dendrite growth during development. Using *Drosophila* da neurons, they show that large CIVda neurons cell-autonomously rely on fatty acid synthesis through the lipid synthesis master regulator SREBP.

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Cell-Autonomous Control of Neuronal Dendrite Expansion via the Fatty Acid Synthesis Regulator SREBP

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SUMMARY

During differentiation, neurons require a high lipid supply for membrane formation as they elaborate complex dendritic morphologies. While glia-derived lipids support neuronal growth during development, the importance of cell-autonomous lipid production for dendrite formation has been unclear. Using *Drosophila* larva dendritic arborization (da) neurons, we show that dendrite expansion relies on cell-autonomous fatty acid production. The nociceptive class four (CIV) da neurons form particularly large space-filling dendrites. We show that dendrite formation in these CIVda neurons additionally requires functional sterol regulatory element binding protein (SREBP), a crucial regulator of fatty acid production. The dendrite simplification in *srebp* mutant CIVda neurons is accompanied by hypersensitivity of *srebp* mutant larvae to noxious stimuli. Taken together, our work reveals that cell-autonomous fatty acid production is required for proper dendritic development and establishes the role of SREBP in complex neurons for dendrite elaboration and function.

INTRODUCTION

Neuronal diversity is reflected in specific neuron-type dendrite morphologies. The larger the dendritic arbor, the more lipids are needed to support its growth. Major building blocks for most lipid classes are fatty acids. It was believed that glial fatty acid production provides key support for neuronal neurite growth (Camargo et al., 2009; Nieweg et al., 2009; Rodríguez-Rodríguez et al, 2004). However, recent studies revealed that lipids can also be cell-autonomously synthesized by cultured neurons or neuronal progenitor cells. For example, mouse adult neuronal stem and progenitor cells contain fatty acid synthase (FASN), which is involved in adult neurogenesis (Knobloch et al., 2013). However, whether fatty acid synthesis is also cell-autonomously required in neurons to ensure their proper morphological development and function remains unclear.

The expression of genes related to lipogenesis depends on a family of conserved transcription factors (TFs) named sterol regulatory element binding proteins (SREBPs) (Bennett et al., 1995; Osborne and Espenshade, 2009). SREBPs are translated as multidomain pre-proteins, which are anchored in the endoplasmic reticulum. Under lipid deprivation, SREBPs are translocated to the Golgi where their TF domain is liberated by a two-step proteolytic cleavage mechanism. The resulting activated TF domain travels into the nucleus and activates downstream target genes involved in lipid metabolism (Eberlé et al, 2004). Thus, SREBP activation couples *de novo* lipid synthesis to cellular metabolic needs. Mammalian genomes encode two *srebp* genes. Their downstream target genes are related to either sterol or *de novo* fatty acid synthesis, respectively. However, overlap between downstream targets complicates the investigation of SREBP function in specific lipogenic pathways (Amemiya-Kudo et al., 2002). By contrast, invertebrate genomes encode only one SREBP protein, which is related to fatty acid *de novo* synthesis (Dobrosotskaya et al., 2002; Osborne and Espenshade, 2009). In *Drosophila,* SREBP activation is regulated by levels of available membrane lipids, in particular by phosphatidylethanolamine (PE), which is the most abundant membrane lipid (Dobrosotskaya et al., 2002; Guan et al., 2013). Activated SREBP in turn enhances the expression of lipogenic genes such as acetyl-CoA synthase (*acs*), acetyl-CoA carboxylase (*acc*), and fatty acid synthase (*fas*) (Seegmiller et al., 2002). Thus, *Drosophila* is ideal for studying the downstream effects of SREBP on fatty acid synthesis.

The role of SREBPs has been extensively characterized in peripheral organs (Jeon and Osborne, 2012). Within the nervous system, recent studies mainly investigated the function of glial SREBPs (Camargo et al., 2009) including the role of astrocyte SREBP1 in synapse maturation (van Deijk et al., 2017). Although SREBP1 is expressed in neurons, little is known about its endogenous role in neuronal fatty acid metabolism (Chen et al., 2017; Ong et al., 2000).

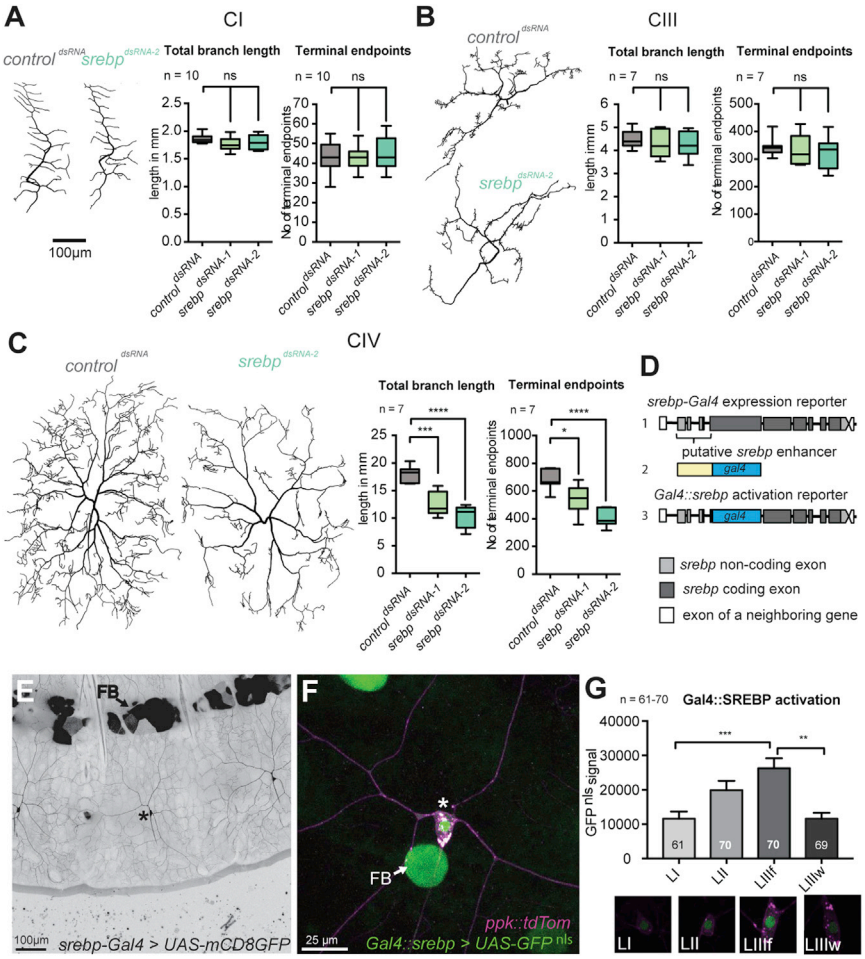


Figure 1. SREBP Regulates Dendrite Extension in CIVda Neurons

(A–C) Hand tracings of CIda (vpdA) (A), CIIIda (v′pdA) (B), and CIVda (ddaC) (C) neurons at the LIIIw stage of control larvae or after cell-specific *srebp* knockdown (*srebp*^{dsRNA}) (see Figures S1A–S1F). Total dendritic branch length and total number of dendritic terminal endpoints were quantified.

(D) 1, Schematic drawing of the *srebp* genomic locus. 2, A genomic fragment upstream of the *srebp* open reading frame (bracket) was cloned in front of *Gal4* to generate a *srebp-Gal4* expression reporter construct. 3, In the *Gal4::srebp* transgene, the TF domain-encoding sequence was replaced by a *Gal4*-encoding sequence to report SREBP activation.

(E) *srebp-Gal4*-driven expression of mCD8GFP in the fat body (FB) and CIVda neurons (asterisk) of LIII larvae.

(F) CIVda neurons were labeled by *ppk*::tdCD4Tomato expression (magenta, asterisk). SREBP activation in the FB and CIVda neurons marked by Gal4-driven expression of nuclear GFP (GFP^{nls}, green) of LIII larvae using *Gal4::srebp*.

(G) Quantified levels of GFP^{nls} driven by activated *Gal4::srebp* in LI, LII, LIIIf, and LIIIw larvae and related pictures (bottom panel). Full genotypes and statistics are indicated in Supplemental Experimental Procedures.

ns represents not significant, *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001 for all figures. N, neurons per genotype. Error bars in (G) represent SEM. See also Figure S1.

The *Drosophila* larval sensory dendritic arborization (da) neurons are ideal for examining genetic factors that mediate dendritic arborization (Jan and Jan, 2010). The four subtypes of da neurons are morphologically and functionally distinct. The smallest and least complex are the class I (CI) da neurons with a total dendritic length of about 2 mm (Iyer et al., 2013). In contrast, CIVda neurons exhibit the largest and most complex dendritic tree with a total dendritic length of over 20 mm (Grueber et al., 2002).

Here, we show that the proper development of da neurons relies on endogenous fatty acid synthesis. In addition, SREBP and the SREBP-controlled enzyme FASN1 are expressed at high levels in CIV neurons, where SREBP, FASN1, and ACC are cell-autonomously required for large dendrite formation.

RESULTS

Control of Dendritic Branching by SREBP

To investigate a potential role for regulated neuronal fatty acid synthesis in neurite growth, we cell-autonomously knocked down *srebp* expression using RNAi in da neurons. Knockdown of *srebp* in CIda or CIIIda neurons left dendritic length and branching almost unaffected (Figures 1A and 1B; Figures S1A, S1B, S1D, and S1E). However, *srebp* knockdown in the larger CIVda neurons led to a decrease in overall dendritic branch length and to a reduction in the number of terminal endpoints (Figure 1C; Figures S1C and S1F). By contrast, CIVda neuron dendritic branching appeared unmodified when *srebp* was knocked down in adjacent glia or epidermal cells (Figures S1G and S1H). These data point to a cell-autonomous role for SREBP in regulating dendrite extension of CIVda neurons.

SREBP Is Expressed and Activated in CIVda Neurons

Given this indication of cell-autonomous function of SREBP in CIVda neurons, we investigated its expression pattern. We first used a *srebp-Gal4* driver line (*srebp-Gal4*; Figure 1D). Expression of *UAS-mCD8GFP* under the control of the *srebp* enhancer was observed in previously described SREBP-expressing tissues, including the fat body (Kunte et al., 2006). We additionally found robust expression in CIVda neurons (Figure 1E), correlating with the observed phenotype.

To investigate the time course of SREBP activation, we made use of a *Gal4::srebp* transgene (Kunte et al., 2006). Transcription of this construct depends on the native SREBP promoter and the resulting chimeric protein (GAL4::SREBP) is proteolytically processed as wild-type SREBP, yielding detectable reporter

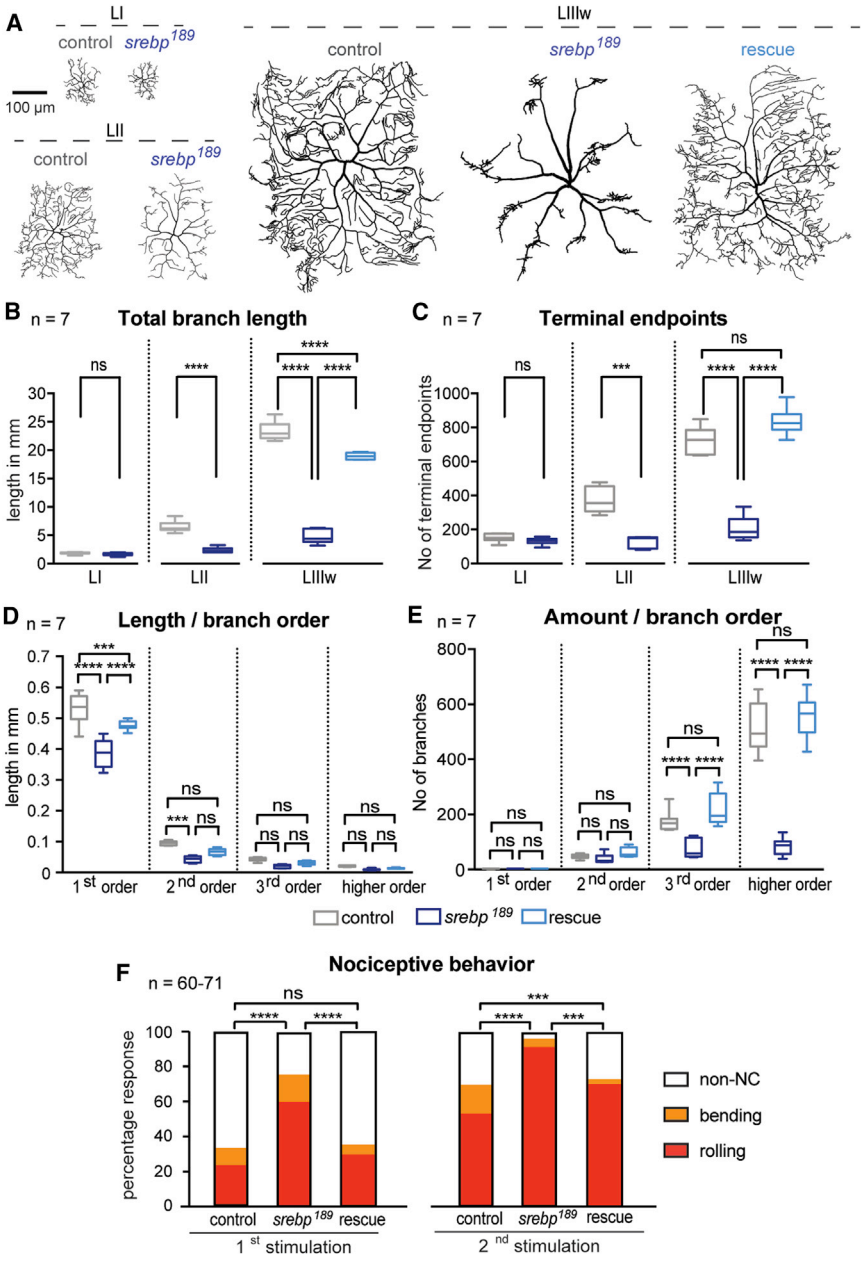


Figure 2. SREBP Is Cell-Autonomously Required for Dendritic Growth and Function of CIVda Neurons

(A) Representative tracings of CIVda neurons (ddaC) in control or *srebp*-null mutant larvae (*srebp*^{189}) at the LI, LII, and LIIIw stage in which lethality was rescued by re-expression of *srebp* in the gut and the fat body. (rescue): *srebp* expression was rescued by additionally re-expressing *srebp* in CIVda neurons.

(B–E) Quantified dendritic morphological parameters at LI, LII, LIIIw (B and C) or at LIIIw (D and E). N, neurons per genotype.

(F) Nociceptive (NC) behavior of feeding LIII larvae was elicited two times with a calibrated 45 nm von Frey filament.

non-NC, no reaction, stopping. N, animals per genotype; n = 60 for control, n = 63 for *srebp*^{189}, and n = 71 for rescue. Full genotypes and statistics are indicated in Supplemental Experimental Procedures. See also Figure S2.

SREBP Controls CIVda Dendritic Growth Cell-Autonomously

To investigate SREBP function in CIVda neurons with independent tools, we analyzed CIVda neurons in the lethal *srebp*^{189}-null mutants. As previously reported, re-expressing wild-type *srebp* in gut and fat body via the *OK376-Gal4* driver rescued *srebp*^{189} lethality and allowed study loss of *srebp* function in null mutant CIVda neurons (Kunte et al., 2006). No aberrations in dendritic growth could be observed in CIVda neurons of mutant LI larvae. However, dendritic length and complexity were decreased in LII and LIIIw mutants (Figures 2A–2C; Figure S2A). In particular, the average length of the main branches (first and second order) and the number of higher-order branches (third and higher) were reduced in *srebp*^{189} (Figures 2D and 2E). Re-expression of *srebp* in genetic null mutant CIVda neurons largely rescued dendritic growth, confirming the cell autonomy of this phenotype (Figures 2A–2E; Figure S2A). Simple overexpression of full-length SREBP did not significantly alter da neuron morphology, possibly due to a lack of SREBP proteolytic activation (Figure S2B). We thus expressed a constitutively active form of SREBP in CI or CIVda neurons and observed a dramatic downscaling of da neuronal dendritic morphology, suggesting a neurotoxic effect (Figures S2C–S2C″). Growth-inhibiting and lipotoxic effects of constitutive active SREBP were observed in the *Drosophila* wing and heart (Lim et al., 2011; Porstmann et al., 2008). In addition, SREBP activation is linked to the cell response to early excitotoxic damage in flies and rodents (Liu et al., 2015; Taghibiglou et al., 2009).

expression (Figure 1D) (Kunte et al., 2006). SREBP was specifically activated in CIVda neurons (Figure 1F). Average activation levels increased from LI to the feeding LIII (LIIIf), correlating with the time course of CIVda neuron growth. However, SREBP activation levels declined at the wandering larval stage (LIIIw) when the animals stop growing and CIVda neuron dendrite growth rate is reduced (Figure 1G) (Parrish et al., 2009). *srebp-Gal4* sporadically showed additional expression in cells adjacent to the CIVda neuron (Figures S1I–S1K). Therefore, it remains possible that SREBP is also expressed at low levels in other classes of da neurons. Taken together, the two reporter tools indicate that SREBP is expressed and activated to high levels in the large CIVda neurons, coinciding with the phenotypic defect.

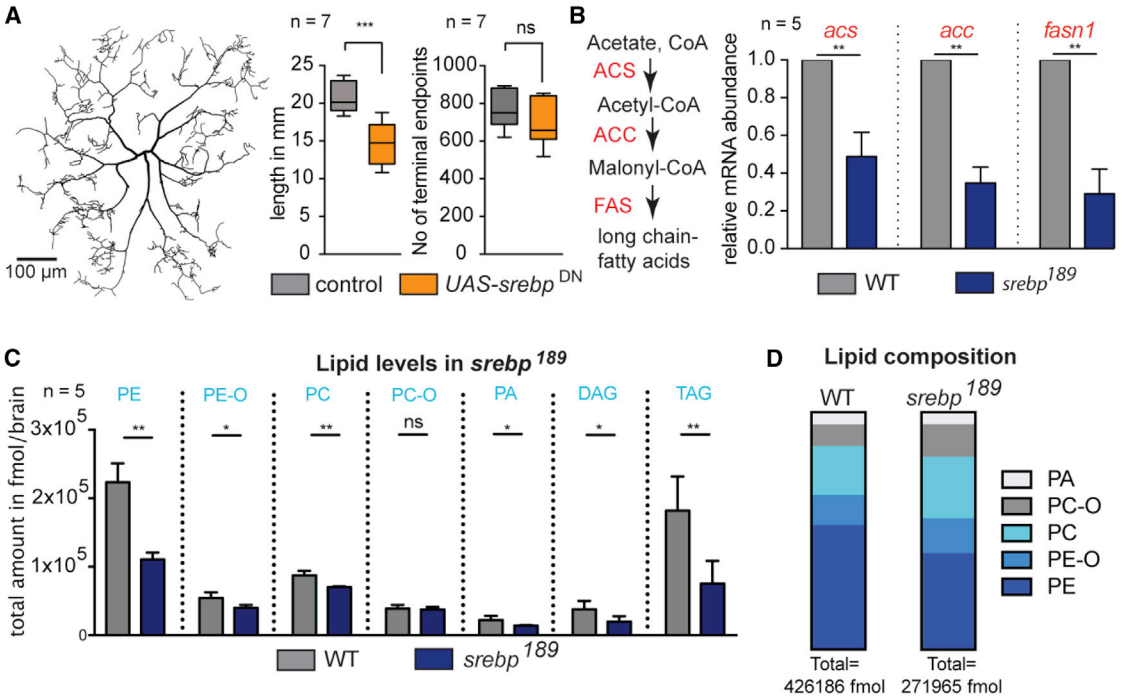


Figure 3. SREBP Controls Fatty-Acid-Synthetizing Enzymes and Lipid Levels in the Nervous System

(A) Representative tracing of a CIVda neuron expressing $SREBP^{DN}$ and quantification of dendritic parameters. N, neurons per genotype.

(B) *acs*, *acc*, and *fasn1* are directly involved in *de novo* fatty acid synthesis. Their mean relative expression level quantified by qRT-PCR is reduced in larval brains of $srebp^{189}$ mutant escapers. N, samples of ten brains.

(C) Absolute levels of the main brain lipid classes in brains of control larvae and $srebp^{189}$ mutant escapers: phosphatidylethanolamine (PE), PE-ether (PE-O), phosphatidylcholine (PC), PC-ether (PC-O), phosphatidic acid (PA), diacylglycerol (DAG), and triacylglycerol (TAG). N, samples of ten brains.

(D) Brain membrane lipid composition in control and $srebp^{189}$ mutant larvae. Full genotypes and statistics are indicated in Supplemental Experimental Procedures. Error bars represent SEM.

See also Figure S3.

Larvae with *srebp* Mutant CIVda Neurons Exhibit Hypersensitive Mechanonociceptive Behavioral Responses

We next tested whether the profound simplification of their dendrites affects the function of mutant CIVda neurons. Those neurons are nociceptive and respond to harsh mechanical touch (Zhong et al., 2010). Pinching larvae at segment A3–A5 with a 45-nm filament induced nociceptive behavior, characterized by larval bending or rolling (Hu et al., 2017). Larvae with *srebp* mutant CIVda neurons exhibit increased nociceptive reaction toward the stimulus (Figure 2F). When stimulated twice, they almost always responded with rolling, the most extreme nociceptive behavior. This phenotype was reverted by expression of *srebp* in CIV neurons revealing its specificity and cell autonomy (Figure 2F).

Mutant CIVda neurons display progressive axon loss developing between the end of the LII and the LIIIf stage and affecting the longest, most posterior axons of segments A5–A7 (Figures S2D and S2D″). Since axonal loss of CIVda neurons likely suppresses mechanonociceptive responses, we suggest that it might be uncoupled from the hyperexcitability of *srebp* mutants.

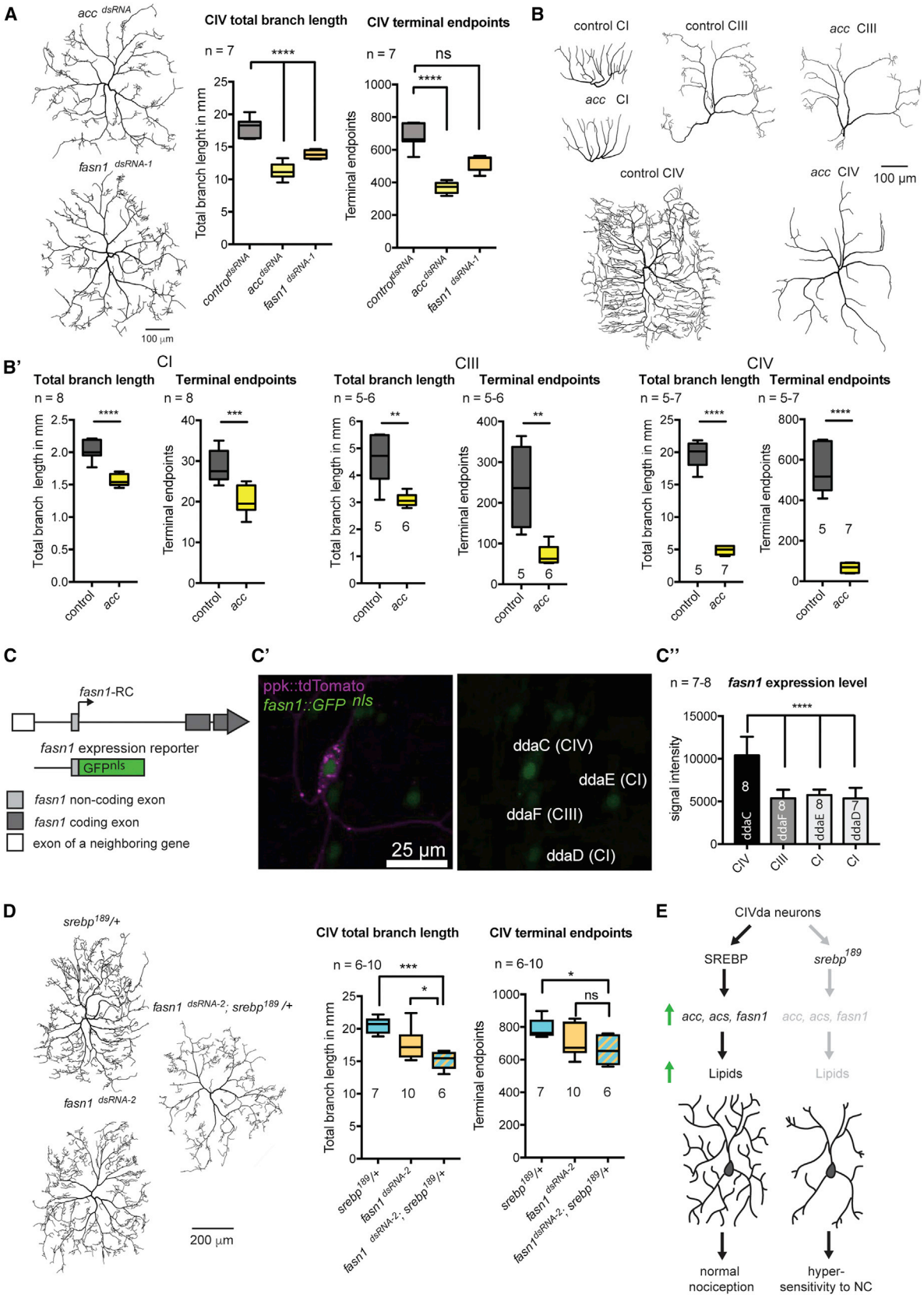
Taken together, impairment of SREBP function in CIV neurons changes their functional properties.

SREBP Regulates Lipid Levels in the Nervous System

SREBP transcriptionally regulates lipid synthesis enzyme expression in LI larvae (Kunte et al., 2006; Sieber and Spradling, 2015). To test whether transcriptional regulation is involved in SREBP-dependent control of CIVda neurons dendritic arbor complexity, we expressed a dominant-negative form of SREBP ($SREBP^{DN}$). This protein is able to block transcriptional activity of endogenous SREBP (Sato et al., 1994). The expression of $SREBP^{DN}$ led to a reduction of total dendritic length in CIVda neurons (Figure 3A; Figure S3A). By contrast, expressing $SREBP^{DN}$ in either CIda or CIIIda neurons did not decrease dendritic branch length (Figures S3B and S3C).

The known transcriptional targets of *Drosophila* SREBP promote fatty acid production in LI larvae (Kunte et al., 2006). SREBP expression was detectable in the CNS (Figures S3D and S3D′). We thus addressed whether SREBP promotes lipid synthesis in the brain. In brain extracts of $srebp^{189}$ LIIIf larvae, the relative mRNA abundance of the known SREBP downstream target genes including *acs*, *acc*, and *fasn1* was reduced (Figure 3B).

Since SREBP positively regulates lipogenesis through fatty acid production, we analyzed by mass spectrometry to what extent it may regulate lipid levels in nervous tissue. We found



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that the amount of membrane lipid and storage lipid was lower in mutant larval brains (Figure 3C). The biggest reduction was found for PE, the most abundant membrane lipid in *Drosophila* (Guan et al., 2013). Furthermore, lack of SREBP function led to a change in the overall membrane lipid composition (Figure 3D). Taken together, these data indicate that SREBP contributes to the lipid synthesis and composition in the larval brain.

SREBP Downstream Targets Are Involved in Developmental Dendrite Expansion

We next asked whether SREBP downstream target genes, which are linked to fatty acid *de novo* synthesis, are involved in dendrite expansion. We first knocked down *fasn1* or *acc* via RNAi and observed that total dendritic branch length and the amount of terminal endpoints were negatively affected in both cases (Figure 4A; Figures S4A and S4A′). We then used the "mosaic analysis with a repressible cell marker" (MARCM) technique to generate *acc* mutant single-cell clones in an otherwise wild-type background. *acc* mutant CIda and CIIIda clones showed a mild but significant dendritic phenotype in which total dendritic branch length was reduced by approximately 25%. By contrast, CIVda neurons had severely shorter (75%) dendrites (Figures 4B and 4B′; Figures S4B–S4B′′′′). We thus asked whether, although SREBP was primarily detected in CIVda neurons, downstream target genes of SREBP might also be expressed in other classes of da neurons. To this end, we generated fly lines bearing constructs that allowed the direct visualization of *fasn1* expression, including epidermis and fat body. A genomic region fragment upstream of the *fasn1-RC* isoform promoted expression in da neurons (Figures 4C and 4C′; Figures S4C and S4C′). The *fasn1-RC*-driven GFP^{nls} signal intensity in CIVda neurons was significantly higher than in CIda or CIIIda neurons (Figure 4C″).

Given the similar CIVda neuron dendrite phenotype caused by loss of *srebp* function or of its reported downstream effectors *acc* and *fasn1*, we finally tested whether removal of one *srebp* copy in a mild knockdown of *fasn1* expression would impact on dendritic branch length. Indeed, compared to *fasn1* knockdown or to $srebp^{189}$ heterozygote animals, larvae carrying the combination of these conditions displayed decreased dendritic branch length in CIVda neurons (Figures 4D and 4E).

Taken together, we conclude that cell-autonomous lipid synthesis is important for dendrite elaboration during development. Additional, SREBP-promoted activity supports the expansion of large CIVda neuron dendrites.

DISCUSSION

Dendrites of neurons covering large receptive fields can become very extended and complex. This feat is accompanied by a high demand of lipids for membrane expansion, especially during the developmental growth phase. As with many metabolic functions within the nervous system, lipid synthesis was thought to happen mostly in glia to support neuronal growth and function (Camargo et al., 2009). For example, oleic acid secreted by cultured glia cells stimulates neurite outgrowth of co-cultured neurons (Tabernero et al., 2001). However, it remained largely unexplored whether cell-autonomous synthesis of lipids is also required for establishing proper neuronal morphology. Here, we show that fatty acid synthesis is cell-autonomously needed for dendrite growth in *Drosophila* larval da neurons. In addition, neurons with large dendrite trees, such as the CIVda neurons, depend on supplementary fatty acid synthesis promoted by SREBP.

Our data indicate that neuronal dendrite extension relies on distinct cell-autonomous lipid regulation, depending on the level of dendrite complexity. Indeed, we provide evidence that the lipogenic enzyme FASN1 is expressed in all da neurons. Moreover, reduction or loss of *acc* or *fasn1* function limited dendrite complexity in CIda, CIIIda, and CIVda neurons, albeit most dramatically in CIVda neurons. In addition to this basal requirement in all analyzed neurons, we report that neurons with complex dendrites display an intrinsic regulatory control mediated by SREBP and linking fatty acid requirement with cell-autonomous lipid synthesis. First, two independent reporters indicated that SREBP expression and activation, respectively, are boosted in complex CIVda neurons. Second, RNAi induction and $SREBP^{DN}$ expression did not impair branching in CIda or CIIIda, but they phenocopied the dendrite reduction observed in *srebp* mutants in CIVda neurons.

The results presented here strongly support the view that SREBP promotes sustained dendrite growth in complex dendrites by controlling lipid synthesis through the transcriptional regulation of lipogenic enzymes. First, the expression in CIVda neurons of a dominant-negative form of SREBP that suppresses transcriptional activity of the endogenous protein decreased the total dendritic branch length. Second, the expression of SREBP transcriptional target genes related to *de novo* lipid synthesis such as *acc*, *acs*, and *fasn1*, was reduced in the brain of *srebp*-null mutant escapers, which in turn showed lowered overall lipid levels. Third, cell-autonomous knockdown or loss of *acc*

Figure 4. SREBP Downstream Target Genes Control Dendritic Growth

(A) Representative tracings of *acc* and *fasn1* knockdown CIVda neurons and quantification of total dendritic branch length and number of dendritic terminal endpoints.

(B and B′) Representative tracings of control or single-cell *acc* MARCM clones CI (ddaE), CIII (ddaF), and CIVda (ddaC) neurons (B) and quantifications of their total dendritic branch length and number of dendritic terminal endpoints (B′).

(C) Schematic drawing of the initial part of the *fasn1* gene. A genomic fragment upstream of the *fasn1-RC* splice form was cloned in front of GFP^{nls} to make a *fasn1-RC* expression reporter.

(C′) *fasn1*-GFP^{nls} was detected in da neurons (green). The class IV neuron is highlighted in magenta.

(C″) Quantified mean GFP^{nls} signal intensity is highest in CIVda neurons.

(D) Representative tracings, quantified dendritic branch length, and number of terminal endpoints of CIV (ddaC) neurons of $srebp^{189}$ heterozygote mutants, after *fasn1* knockdown, or in a combination of both elements ($fasn1^{dsRNA\text{-}2}$, $srebp^{189}$/+).

(E) SREBP might upregulate the expression of genes related to fatty acid synthesis and in turn lipogenesis in CIVda neurons to support developmental dendrite growth and normal functioning. Full genotypes and statistics are indicated in Supplemental Experimental Procedures.

(A–E) N, neurons per genotype. Error bars in (C) represent SEM. See also Figure S4.

or *fasn1* function phenocopied the *srepb* phenotype in CIVda neurons. We also interpret the high expression level of Fasn1 in CIVda neurons as potentially driven by SREBP specifically in these neurons.

We also highlight the importance of proper lipid synthesis for neuronal function. Previous studies reported conditions that caused reduced CIVda neuron dendrite complexity and deteriorated nociceptive responses (Sears and Broihier, 2016). In contrast, we show that *srebp* mutant animals that also display CIVda neurons with less complex dendritic arbors hyper-react to noxious stimuli. The cell-autonomous rescue in CIVda neurons of the *srebp* mutant phenotype points to a cell-autonomous rather than a circuit defect. We thus suggest two mutually non-exclusive scenarios to explain this phenotype. First, the stunting of dendrite extension, combined with increased density of the mechanical nociceptor Ppk26 (Figure S2E), might underlie increased excitability (Guo et al., 2014). Second, changes in membrane lipid composition, which we report also for *srebp* mutants, could lead to hyper-excitability, for instance by modulating the biochemistry or mechanics of nociceptors (Pavlidis et al., 1994; Vásquez et al, 2014). A complementary analysis of *srebp* function in CIVda dendrite elaboration was recently published in the accompanying paper (Meltzer et al., 2017). Further investigations will be needed to pinpoint the cause of hyper-excitation in *srebp* mutant CIVda neurons.

EXPERIMENTAL PROCEDURES

Genetics and Fly Husbandry

Flies were maintained on standard medium at 25°C, unless otherwise stated. Genotypes are indicated in Supplemental Experimental Procedures.

Live Imaging and Image Processing

The dendritic morphology of da neurons was observed by immobilizing living larvae between a glass slide and a coverslip in a mixture of halocarbon oil and ether (4:1). One da neuron per animal was imaged by confocal microscopy (Zeiss LSM700 or LSM780). Images were hand traced and analyzed using the TREES toolbox plug-in for MATLAB (R2014b) (Cuntz et al., 2010).

Quantitative Analysis of Transcripts

Ten brains of feeding LIII larvae were used per analysis. RNA extraction, cDNA synthesis, and real-time qRT-PCR were done using standard methods.

Lipidomics

Isolated larval brains were spiked with an internal lipid standard mix and extracted using chloroform/methanol/water. The chloroform phase was diluted with an alcohol mixture containing ammonium acetate and subjected to shotgun analysis in a Thermo Q Exactive Plus spectrometer in positive and negative mode.

Behavior

Behavioral experiments were conducted as previously described (Hu et al., 2017).

Detailed description of the experimental procedures can be found in Supplemental Experimental Procedures.

Statistical Analysis

Data were analyzed using Prism 5.0d (GraphPad). Normality was tested using the Kolmogorov-Smirnov test. Samples were compared using the unpaired t test (sets of two) or one-way ANOVA test followed by Bonferroni's post hoc test (sets of three or more). Data that did not pass the normality test were compared using the Mann-Whitney test (sets of two) or the Kruskal-Wallis test followed by Dunn's post hoc test (sets of three or more). Data with two variables were analyzed by two-way ANOVA followed by Dunnett post hoc test. Parts of whole were analyzed using the χ^2 test (ns, not significant; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$).

Detailed description of the experimental procedures can be found in Supplemental Experimental Procedures.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures and four figures and can be found with this article online at https://doi.org/10.1016/j.celrep.2017.11.069.

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AUTHOR CONTRIBUTIONS

A.B.Z. and G.T. designed the project and wrote the manuscript with contributions of all other authors. A.B.Z. performed in vivo imaging, genetic and morphological analysis, and immunohistochemistry. C.T. and P.L. carried out the lipidomics. M.R. performed qRT-PCR. F.T. and P.S. contributed behavioral analysis. A.H. cloned the *fasn1*::GFP^{nls} construct.

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