Biochemical and Biophysical Research Communications 422 (2012) 333–338

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Semaphorin3A facilitates axonal transport through a local calcium signaling and tetrodotoxin-sensitive voltage-gated sodium channels

Masayuki Yamane [a], Naoya Yamashita [a], Hiroshi Yamamoto [a], Akira Iizuka [a,1], Masayuki Shouji [a], Hiroshi Usui [a], Yoshio Goshima [a,b,*]

[a] Department of Molecular Pharmacology and Neurobiology, Yokohama City University, Graduate School of Medicine, Yokohama 236-0004, Japan
[b] CREST, Japan Science and Technology Corporation, Kawaguchi 332-0012, Japan

ARTICLE INFO

Article history:
Received 21 April 2012
Available online 7 May 2012

Keywords:
Semaphorin3A
Axonal transport
Ryanodine receptor
L-type voltage-gated calcium channel
TTX-sensitive voltage-gated sodium channels

ABSTRACT

Semaphorin3A (Sema3A), a secreted factor that navigates axons and dendrites of developing neurons, facilitates axonal transport. However, little is known about the mechanism underlying Sema3A-induced facilitation and its functional implications. Here we show that Sema3A induces facilitation of axonal transport via local calcium signaling in growth cone. The facilitation of axonal transport was blocked by inhibitors of voltage-gated sodium channels (tetrodotoxin, TTX), L-type voltage-gated calcium channel, and ryanodine receptor (RyR). Sema3A evoked intracellular Ca^{2+} elevation in growth cone by local application of Sema3A to growth cone. Sema3A also activated RyR in growth cone as well as cell body. Notably, TTX suppressed Sema3A-induced RyR activation in cell body but not in growth cone. Our results identify a novel mechanism of Sema3A-induced axonal transport, and further suggest that Sema3A-induced local calcium signaling in growth cone is propagated to cell body in a TTX-sensitive manner.

1. Introduction

Intraneuronal transport is fundamental for neuronal survival, morphogenesis, and function. Proteins, mRNAs, and organelles are selectively transported to either axons or dendrites by kinesin superfamily motor proteins, and adaptor or scaffolding proteins [1]. Although the mechanism of selective transport of cargoes by motor/adaptor proteins has been clarified, regulation of this mechanism by extracellular environmental cues including axon guidance molecules remains unclear.

Semaphorins constitute a major family of axon guidance molecules in the central as well as the peripheral nervous system [2,3]. Semaphorin3A (Sema3A), the best-characterized class 3 semaphorin subfamily, repulses axons through the co-receptor protein neuropilin-1 and plexin-As [4,5]. Sema3A functions not only as a chemorepulsive cue but also in endocytosis, spine maturation, and as a chemoattractive cue [6–10] through the Fyn-cyclin dependent kinase 5 cascade [8,11–13]. Sema3A is thus thought to have multiple functions to regulate neuronal network formation. We have previously found that Sema3A facilitates axonal transport of dorsal root ganglion (DRG) neuron [14–16]. This action of Sema3A is mediated by neuropilin-1 at growth cone but not elsewhere [14], suggesting that the site of action is restricted at growth cone. However, little is known about the mechanism underlying Sema3A-induced facilitation and its functional implications.

Since Sema3A induces intracellular Ca^{2+} elevation and membranous depolarization in the growth cone [17,18], we speculated that ion-related signal is involved in Sema3A-induced facilitation of axonal transport. In this report, we found that L-type voltage-gated calcium channel (VGCC), ryanodine receptor (RyR), and tetrodotoxin (TTX)-sensitive voltage-gated sodium channels (VGSCs) are involved in Sema3A-induced axonal transport. We further provide evidence that Sema3A-induced local calcium signaling in growth cone is propagated to cell body by TTX-sensitive VGSCs in DRG neurons.

2. Material and methods

2.1. Cell culture and regents

The cultured DRG neurons were prepared from embryonic day 7 chick as previously described [15]. In a 37 °C, 5% CO_2 incubator, neurons were cultured for 1 day then subjected to the experiments unless otherwise noted. Sema3A was prepared as previously described [14]. The concentration of Sema3A (nM) was evaluated by the growth cone collapse assay using explanted DRG neurons [14]. Pharmacological reagents were purchased from Sigma (St. Louis, MO), Wako Pure Chemicals (Osaka, Japan), Peptide laboratory (Osaka, Japan), or Dojindo (Kumamoto, Japan).

* Corresponding author at: Department of Molecular Pharmacology and Neurobiology, Yokohama City University, Graduate School of Medicine, Fuku-ura 3-9, Kanazawa Ward, Yokohama 236-0004, Japan. Fax: +81 45 785 3645.
E-mail address: goshima@med.yokohama-cu.ac.jp (Y. Goshima).
[1] Present address: Department of Neurophysiology, Gunma University Graduate School of Medicine, Maebashi, Gunma 371–8511, Japan.

0006-291X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bbrc.2012.05.003

2.2. Quantitative analysis of axonal transport and growth cone collapse

Axonal transport of dissociated DRG neurons was analyzed using video-enhanced microscopy [14]. The number of organelles crossing the line drawn on the video monitor was repeatedly counted for 2 min at 1-min intervals. The average number of organelles crossing the line before the application of Sema3A (5 nM) was set to be the base and changes in both anterograde and retrograde transport rate was calculated. Sema3A, inhibitors, or agonists were applied by replacing the culture solution, and thereafter the reagents were present throughout the experiments. Inhibitors were applied 7 min before the application of Sema3A. The concentrations of inhibitors were determined as inhibitors per se had no effect on axonal transport (data not shown). Growth cone collapse of explanted DRG neurons was analyzed as previously described [14].

2.3. Calcium imaging

Dissociated DRG neurons were loaded with 4 μM Fluo4-AM (Invitrogen, Cergy Pontoise, France) diluted in culture medium for 1 h at 37 °C. After loading, cells were incubated for over 10 min at 37 °C for recovery. Calcium imaging was done by Yokogawa confocal microscopy (Yokogawa, Tokyo, Japan) controlled with MetaMorph (Molecular Devices, Sunnyvale, CA). The dye was excited at 488 nm and the emission signals were collected at 530 ± 15 nm. Fluorescence images were collected every 2 s for up to 6 min. Sema3A solution was applied to growth cone or soma by using micropipette. The tip of micropipette (0.5 μm) was positioned on the surface of the growth cone or soma and Sema3A (10 nM) or culture medium were applied. The amount of applied solution was 760 pL at 11 PSI for 4 s. Fluo4 fluorescence intensity was calculated by dividing ROI average values (intensity performs background subtraction) by MetaMorph.

2.4. Visualization of activated ryanodine receptor

Activated ryanodine receptor was visualized by staining with BODIPY FL-X ryanodine (Invitrogen). DRG neurons were loaded with 1 μM of 6-((4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-propionyl)amino)hexanoic acid (BODIPY FL-X ryanodine, Invitrogen) at 37 °C for 1 h, followed by the bath application of nimodipine (1 μM) or TTX (100 nM) 5 min before Sema3A. After the bath application of Sema3A for 3 min, cells were fixed with 4% paraformaldehyde, washed three times with phosphate buffered saline (PBS), permeabilized with 0.3% Triton X-100, washed with PBS again, and then imaged by LSM510 confocal microscopy (Carl Zeiss, Inc., Jena, Germany). Average fluorescence intensities within the growth cone or cell body were calculated and expressed as a percentage to the average intensity of control experiments.

3. Results

3.1. L-type VGCC, RyR, and TTX-sensitive VGSCs mediate Sema3A-induced facilitation of axonal transport

To investigate whether ion-related signal is involved in Sema3A-induced facilitation of axonal transport, we tested the effect of pharmacological inhibition of calcium and sodium channels in DRG neurons. The concentrations of inhibitors were determined as inhibitors per se had no effect on axonal transport (data not shown). Absence of extracellular Ca^{2+} markedly suppressed the facilitation of both anterograde and retrograde transport rate (Fig. 1A). Several classes of VGCCs inhibitors were tested to determine their effects on Sema3A-induced facilitation of axonal transport in DRG neurons. Cd^{2+} and Co^{2+} are pharmacological inhibitors of a broad range of calcium channels including N, P/Q, and L-type VGCCs. The bath application of Cd^{2+} (15 μM) and Co^{2+} (20 μM) suppressed the transport rate (Fig. 1A). Nimodipine (1 μM) and nifedipine (1 μM), both L-type VGCC inhibitors, significantly suppressed the facilitation, while Ni^{2+} (20 μM), a T/R type VGCC inhibitor; ω-conotoxin GVIA (1 μM), an N-type VGCC inhibitor; and ω-agatoxin IVA (0.3 μM), a P/Q type VGCC inhibitor, did not (Fig. 1A), indicating the involvement of L-type VGCC.

In case of intracellular Ca^{2+} stores, dantrolene (1 μM), a ryanodine receptor (RyR) inhibitor, potently blocked the facilitation (Fig. 2A). Ryanodine locks RyR at open-gate state and exhausts the intracellular calcium store; thus it acts as a RyR agonist shortly after the application and thereafter it acts as a RyR antagonist. Pretreatment with 100 μM of ryanodine, which was used as a RyR antagonist, also potently blocked the Sema3A-induced facilitating (Fig. 1A). In contrast, the facilitating action of Sema3A was not inhibited by 50 μM of 2-Aminoethoxydiphenyl borane (2-APB), an inhibitor of inositol-1,4,5-trisphosphate receptor (IP_3R) (Fig. 2A). However, we could not exclude the involvement of IP_3R since we could not apply 2-APB at the concentration (70–80 μM), which is usually used to block IP_3R. At that concentration, not only 2-APB blocks IP_3R, but also it stops the axonal transport (data not shown), which makes it difficult to observe the effect of Sema3A.

Absence of extracellular Na^+ also suppressed Sema3A-induced facilitation of axonal transport (Fig. 1A). Tetrodotoxin (TTX, 100 nM), a highly selective VGSC blocker, almost completely suppressed the facilitation by Sema3A (Fig. 1A). We further investigated the effect of agonistic activation of Ca^{2+} and Na^+ channels on the facilitation. KCl, which induces membranous depolarization and elevation of intracellular Ca^{2+}, facilitated axonal transport at the concentration of 10 mM but not at 5 or 25 mM (Fig. 1B, left panel). Caffeine (100 μM), a RyR agonist (Fig. 1B, middle panel) and veratridine (0.5 μM), a VGSCs activator (Fig. 1B, right panel), also facilitated axonal transport in DRG neurons. These results indicate that axonal transport is tightly regulated by ion-related signal, and that Sema3A modulates axonal transport through L-type VGCC, RyR, and TTX-sensitive VGSCs.

The effects of calcium channel blockers on Sema3A-induced axonal transport (Fig. 1A) were roughly parallel to those in Sema3A-induced growth cone collapse in DRG neurons (Fig. 1C). Absence of extracellular Ca^{2+} also suppressed Sema3A-induced growth cone collapse (Fig. 1C). In contrast, the involvement of sodium channel differs among Sema3A-induced actions. Withdrawal of extracellular Na^+ did not modify Sema3A-induced growth cone collapse. TTX also did not suppress the growth cone response (Fig. 1C). These findings indicate that Sema3A activates distinct pathways for axonal transport and growth cone collapse, respectively. Thus, TTX can be used as a selective inhibitor, which inhibits the facilitation of axonal transport, but does not inhibit growth cone collapse.

3.2. Sema3A evokes Ca^{2+} elevation at growth cone

It has been demonstrated that guidance molecules could induce growth cone membrane potential changes [18,19]. Sema3A induces intracellular Ca^{2+} elevation and membranous depolarization in the growth cone [17,18]. To investigate whether Sema3A evokes intracellular Ca^{2+} elevation in the growth cone of DRG neurons, we monitored intracellular Ca^{2+} using fluorescent Ca^{2+}-sensitive dye, Fluo4. We found that local application of Sema3A to growth cone induced a significant increase in the average Ca^{2+} levels in the growth cones (Fig. 2). In contrast, local application of Sema3A to cell body could not evoke Ca^{2+} elevation in cell body (Fig. 2). Since we previously demonstrated that Sema3A facilitates axonal transport of DRG neuron through its receptor neuropilin-1 at the growth

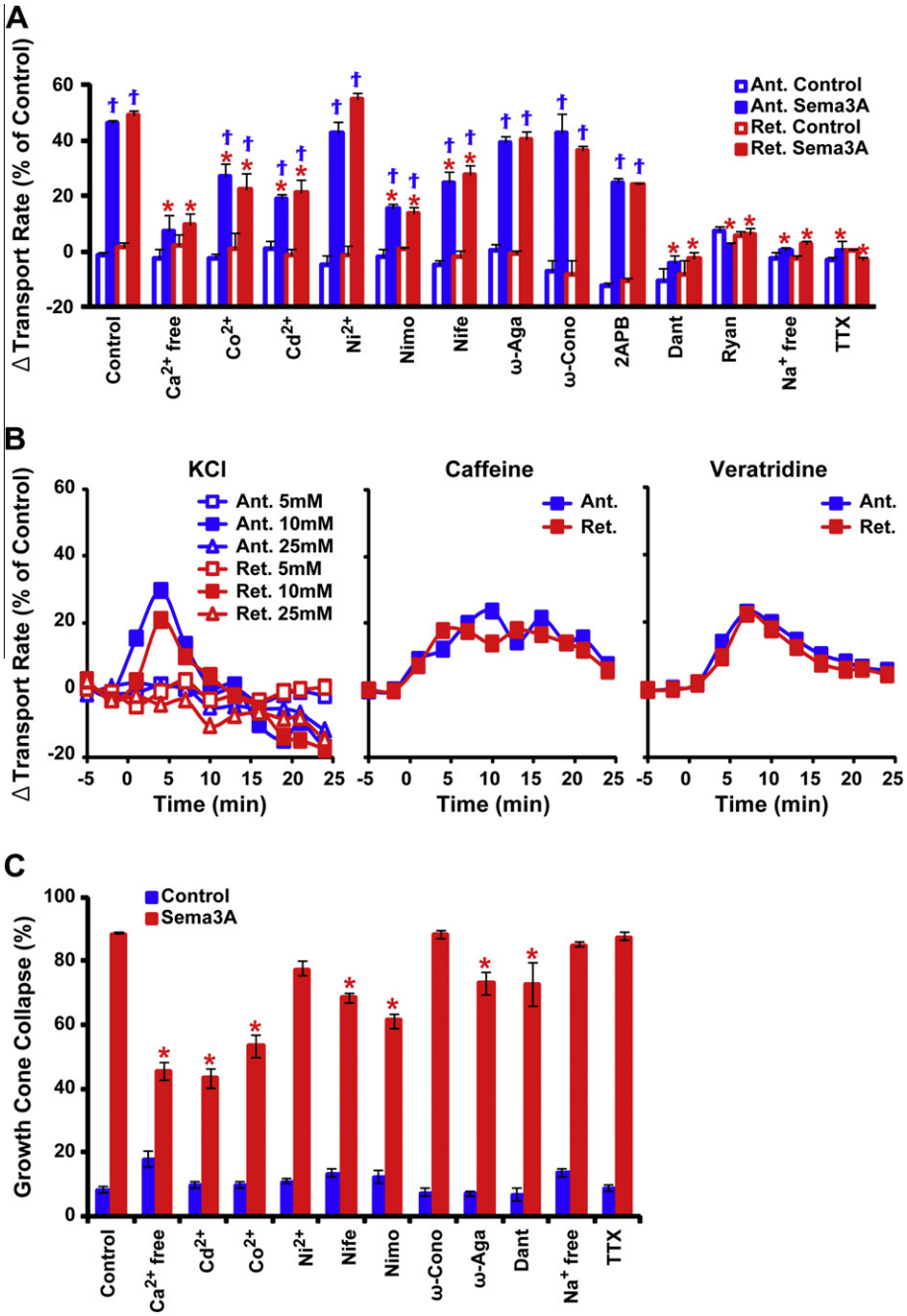

Fig. 1. L-type calcium channel, RyR, and TTX-sensitive VGSCs mediate Sema3A-induced axonal transport. (A) Effect of inhibition on calcium or sodium channels in Sema3A-induced facilitation of axonal transport in DRG neurons. The changes in both anterograde (Ant) and retrograde (Ret) transport rate (Δ transport rate) was measured 3–5 min before (Control) and 8–10 min after (Sema3A) bath application of Sema3A ($n = 5$ neurons). Nimo (nimodipine), Nife (nifedipine), ω-aga (ω-agatoxinIVA), ω-cono (ω-conotoxinGVIA), 2APB (2-Aminoethoxydiphenyl borane), Dant (dantrorene), Ryan (ryanodine), TTX (tetrodotoxin). These drugs tested did not modify the basal level of antero- and retrograde axonal transport (data not shown). (B) Ca^{2+}, RyR, or Na^{+} channels agonists facilitate axonal transport in DRG neurons. (C) Effect of inhibition of calcium or sodium channels on Sema3A-induced growth cone collapse in DRG neurons ($n = 5$ explants). Data are presented as mean ± s.e.m. $^{*}p < 0.001$ by t-test compared to corresponding control without inhibitors, $^{\dagger}p < 0.001$ by t-test compared to before (A) or without (C) Sema3A.

cone but not elsewhere [14], our data suggest that Sema3A evokes Ca^{2+} elevation in the growth cone to facilitate axonal transport.

3.3. Sema3A activates RyR through L-type VGCC and TTX-sensitive VGSCs

Because Sema3A-induced axonal transport was inhibited by dantrolene and RyR antagonist (Fig. 1A), we tried to detect Sema3A-induced activation of RyR by use of a conjugated compound of ryanodine with a fluorescence probe, BODIPY FL-X ryanodine. This compound preferentially binds to RyR at open-gate state, and is reported to be a useful tool to image RyR activation [20]. The increase in the staining of the active RyR was detected throughout the DRG neurons within 3 min after Sema3A stimulation (Fig. 3). Pretreatment of nimodipine attenuated Sema3A-induced increase in the staining of active RyR both at growth cone and cell body (Fig. 3). Although TTX had no effect on growth cone, it significantly suppressed Sema3A-induced

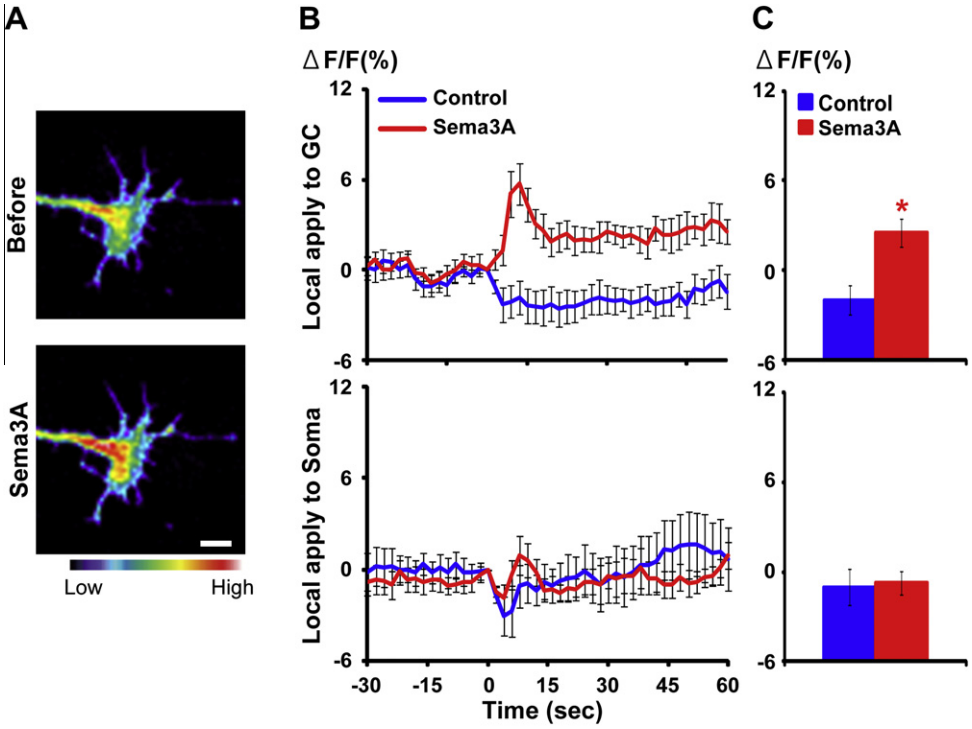

Fig. 2. Local stimulation by Sema3A to growth cone induces Ca^{2+} elevation in the growth. (A) Representative images of a growth cone of DRG neuron before and after local application of Sema3A to growth cone (scale bar, 5 μm). The neuron was loaded with calcium indicators, Fluo4-AM. Changes in intracellular Ca^{2+} were assessed by fluorescent intensity of Fluo4. The magnitude of the fluorescent intensity is expressed by pseudo-color in a linear scale (left; red and purple representing the highest and lowest, respectively). (B) Time course of percentage changes in Fluo4 fluorescence (ΔF/F). Sema3A was locally applied to either growth cone (upper panel) or cell body (lower panel) and images are collected at growth cone or cell body, respectively. (C) Mean ΔF/F (%) at 0–30 s after the stimulation. Data are presented as mean ± s.e.m. from 6 to 12 neurons. $^{*}p < 0.01$ by *t*-test compared to vehicle control. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

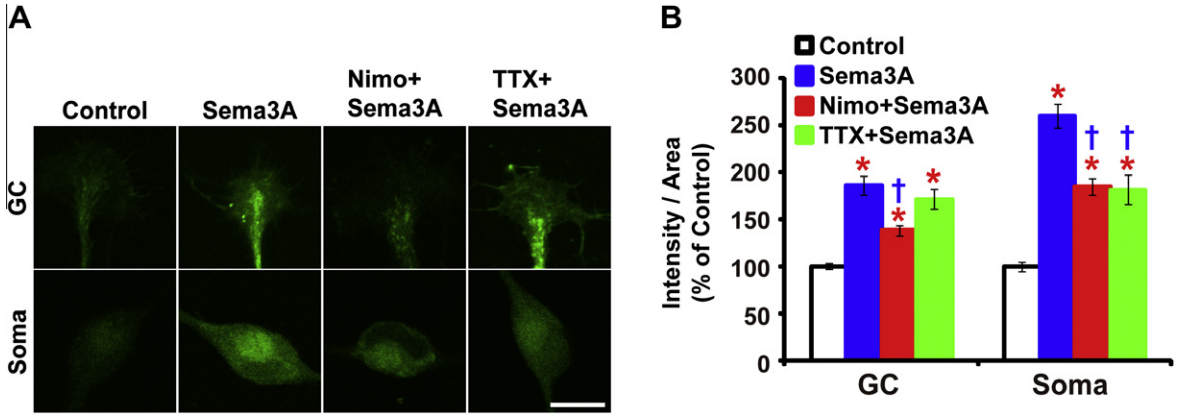

Fig. 3. Sema3A activates RyR through L-type VGCC and TTX-sensitive VGSCs. (A) Representative images of a growth cone (GC) or soma of DRG neurons with or without Sema3A and inhibitors staining with BODIPY FL-X ryanodine to image RyR activation (scale bar, 10 μm). (B) Percentage changes in mean fluorescence BODIPY FL-X ryanodine. Data are presented as mean ± s.e.m. from 16 to 29 neurons. $^{*}p < 0.01$ by ANOVA compared to control, $^{\dagger}p < 0.01$ by ANOVA compared to Sema3A without inhibitors.

increase in the staining of active RyR at cell body (Fig. 3). These findings suggest that Sema3A initiates the calcium cascades at the growth cone then the signal propagates to the cell body in a TTX-sensitive manner.

4. Discussion

Signals received in distal subcellular compartments often travel long distances to reach the cell body through many processes in neurons [21]. In the present study, we found that Sema3A mobilizes intracellular Ca^{2+} in growth cones and that the local Ca^{2+} rise in growth cones can trigger calcium signaling in the other cellular regions, axon and cell body through activation of RyR in a TTX-sensitive manner. We here propose that such signal propagation by release of internal Ca^{2+}, and by the axonal transport elicited by this calcium signaling, may play a role in efficiently conveying information received at the growth cone to cell body.

Although the involvement of Sema3A-induced calcium signaling has been controversial [22–24], the Ca^{2+} concentration in the growth cone has been implicated in local signaling elicited by attractive and repulsive axon guidance molecules [19]. For instance, local membranous depolarization has shown to be induced by Netrin-1, another axonal guidance cue [25], or brain-derived

neurotrophic factor [26]. Sema3A when applied locally to growth cone but not to elsewhere, induces axonal transport [14], suggesting that local signaling in growth cone is also involved in Sema3A-induced signaling. Consistent with this idea, previous reports demonstrated that the exposure of Sema3A at the axonal growth cone induces membrane potential shifts [18], and that Ca^{2+} entry through cyclic-nucleotide-gated channels is required to mediate the Sema3A-induced signal [27]. Similar to this observation, we found that L-type VGCC, RyR, and TTX-sensitive VGSCs mediate Sema3A-induced facilitation of axonal transport (Fig. 1A). We also found that intracellular Ca^{2+} elevation in the growth cone is induced by the local application of Sema3A to growth cone (Fig. 2). Furthermore, the activation of RyR was partially suppressed by nimodipine (Fig. 3). This result indicate that Sema3A induced activation of RyR in growth cone, which was accompanied with L-type VGCC opening and Ca^{2+} entry from outside. This suggests that Sema3A-induced activation of RyR in the growth cones coupled with extracellular Ca^{2+} entering through L-type VGCC, a similar process of excitation–contraction coupling in cardiac muscles, regulates axonal transport.

Given that activation of RyR was also observed at cell body (Fig. 3), Sema3A-induced calcium signaling is probably transmitted toward the cell body. Neurons utilize multiple mechanisms for signaling from distal subcellular regions to cell body [21]. Particularly local neuronal calcium signaling is propagated to cell body through regenerative calcium waves or membranous electric signaling [28]. Since pretreatment of TTX suppressed RyR activation in cell body but not in growth cone (Fig. 3), the electric signaling by TTX-sensitive VGSCs might at least in part be involved in propagation of Sema3A-induced signal from growth cone to cell body. However, at present, we could not detect the propagation of membranous depolarization as well as calcium wave from growth cone to cell body. This is probably due to undetectable changes in membrane potential and/or intracellular Ca^{2+} concentrations in neurons. We also found that TTX can be used as a selective inhibitor of Sema3A-induced axonal transport but not growth cone collapse (Fig. 1). The axonal transport of endosomes plays a role in transmitting the local signal in growth cone back to cell body [29]. Additionally, calcium signaling arisen from endosomes could activate RyR through calcium-induced calcium release [30]. These findings support the idea that activation of RyR at the cell body is caused by Sema3A-induced axonal transport. We should also notice that Sema3A-induced RyR activation is partially suppressed by either nimodipine or TTX (Fig. 3). This finding suggests that other unknown signaling(s) might also be involved in Sema3A-induced signal propagation. RyR could be activated by redox signaling [31], which plays a crucial role in Sema3A signaling [32].

In conclusion, our results identify a novel mechanism of Sema3A-induced axonal transport through local calcium signaling and this signaling propagates to other cellular region. Since Ca^{2+} plays an important role in regulating a great variety of neuronal processes, this finding provides evidence for a novel link between growth cone and cell body: local calcium signaling involving RyR and TTX-sensitive VGSCs is probably essential to keep the signal propagation from the growing tip of the axons to the cell body active.

Acknowledgments

We thank Drs. M. Iino, K. Hong, M. Nishiyama, Y. Hiromi, T. Takahashi, Y. Kubo, Y. Yamada, T. Andoh, and Y. Kamiya for helpful discussion and constructive inputs. We also thank Y. Usui and S. Chen for carefully editing the manuscript. This work was supported by Grants-in-aid from the CREST (Core Research for Evolutional Science and Technology) of JST (Japan Science and Technology Agency) Uehara Memorial Foundation (Y.G.) and Grant-in-Aid for Young Scientists (N.Y.).

References

[1] N. Hirokawa, R. Takemura, Molecular motors and mechanisms of directional transport in neurons, Nat. Rev. Neurosci. 6 (2005) 201–214.
[2] F. Polleux, R.J. Giger, D.D. Ginty, A.L. Kolodkin, A. Ghosh, Patterning of cortical efferent projections by semaphorin–neuropilin interactions, Science 282 (1998) 1904–1906.
[3] J.A. Raper, Semaphorins and their receptors in vertebrates and invertebrates, Curr. Opin. Neurobiol. 10 (2000) 88–94.
[4] T. Takahashi, A. Fournier, F. Nakamura, L.H. Wang, Y. Murakami, R.G. Kalb, H. Fujisawa, S.M. Strittmatter, Plexin–neuropilin-1 complexes form functional semaphorin-3A receptors, Cell 99 (1999) 59–69.
[5] L. Tamagnone, S. Artigiani, H. Chen, Z. He, G.I. Ming, H. Song, A. Chedotal, M.L. Winberg, C.S. Goodman, M. Poo, M. Tessier-Lavigne, P.M. Comoglio, Plexins are a large family of receptors for transmembrane, secreted, and GPI-anchored semaphorins in vertebrates, Cell 99 (1999) 71–80.
[6] Y. Goshima, T. Ito, Y. Sasaki, F. Nakamura, Semaphorins as signals for cell repulsion and invasion, J. Clin. Invest. 109 (2002) 993–998.
[7] A.B. Huber, A.L. Kolodkin, D.D. Ginty, J.F. Cloutier, Signaling at the growth cone: ligand–receptor complexes and the control of axon growth and guidance, Annu. Rev. Neurosci. 26 (2003) 509–563.
[8] A. Morita, N. Yamashita, Y. Sasaki, Y. Uchida, O. Nakajima, F. Nakamura, T. Yagi, M. Taniguchi, H. Usui, R. Katoh-Semba, K. Takei, Y. Goshima, Regulation of dendritic branching and spine maturation by semaphorin3A-Fyn signaling, J. Neurosci. 26 (2006) 2971–2980.
[9] F. Nakamura, R.G. Kalb, S.M. Strittmatter, Molecular basis of semaphorin-mediated axon guidance, J. Neurobiol. 44 (2000) 219–229.
[10] F. Polleux, T. Morrow, A. Ghosh, Semaphorin 3A is a chemoattractant for cortical apical dendrites, Nature 404 (2000) 567–573.
[11] Y. Sasaki, C. Cheng, Y. Uchida, O. Nakajima, T. Ohshima, T. Yagi, M. Taniguchi, T. Nakayama, R. Kishida, Y. Kudo, S. Ohno, F. Nakamura, Y. Goshima, Fyn and Cdk5 mediate semaphorin-3A signaling, which is involved in regulation of dendrite orientation in cerebral cortex, Neuron 35 (2002) 907–920.
[12] Y. Uchida, T. Ohshima, Y. Sasaki, H. Suzuki, S. Yanai, N. Yamashita, F. Nakamura, K. Takei, Y. Ihara, K. Mikoshiba, P. Kolattukudy, J. Honnorat, Y. Goshima, Semaphorin3A signalling is mediated via sequential Cdk5 and GSK3beta phosphorylation of CRMP2: implication of common phosphorylating mechanism underlying axon guidance and Alzheimer's disease, Genes Cells 10 (2005) 165–179.
[13] N. Yamashita, A. Morita, Y. Uchida, F. Nakamura, H. Usui, T. Ohshima, M. Taniguchi, J. Honnorat, N. Thomasset, K. Takei, T. Takahashi, P. Kolattukudy, Y. Goshima, Regulation of spine development by semaphorin3A through cyclin-dependent kinase 5 phosphorylation of collapsin response mediator protein 1, J. Neurosci. 27 (2007) 12546–12554.
[14] Y. Goshima, H. Hori, Y. Sasaki, T. Yang, M. Kagoshima-Maezono, C. Li, T. Takenaka, F. Nakamura, T. Takahashi, S.M. Strittmatter, Y. Misu, T. Kawakami, Growth cone neuropilin-1 mediates collapsin-1/Sema III facilitation of antero- and retrograde axoplasmic transport, J. Neurobiol. 39 (1999) 579–589.
[15] Y. Goshima, T. Kawakami, H. Hori, Y. Sugiyama, S. Takasawa, Y. Hashimoto, M. Kagoshima-Maezono, T. Takenaka, Y. Misu, S.M. Strittmatter, A novel action of collapsin: collapsin-1 increases antero- and retrograde axoplasmic transport independently of growth cone collapse, J. Neurobiol. 33 (1997) 316–328.
[16] C. Li, Y. Sasaki, K. Takei, H. Yamamoto, M. Shouji, Y. Sugiyama, T. Kawakami, F. Nakamura, T. Yagi, T. Ohshima, Y. Goshima, Correlation between semaphorin3A-induced facilitation of axonal transport and local activation of a translation initiation factor eukaryotic translation initiation factor 4E, J. Neurosci. 24 (2004) 6161–6170.
[17] M. Nishiyama, K. Togashi, M.J. von Schimmelmann, C.S. Lim, S. Maeda, N. Yamashita, Y. Goshima, S. Ishii, K. Hong, Semaphorin 3A induces CaV2.3 channel-dependent conversion of axons to dendrites, Nat. Cell Biol. 13 (2011) 676–685.
[18] M. Nishiyama, M.J. von Schimmelmann, K. Togashi, W.M. Findley, K. Hong, Membrane potential shifts caused by diffusible guidance signals direct growth-cone turning, Nat. Neurosci. 11 (2008) 762–771.
[19] J. Henley, M.M. Poo, Guiding neuronal growth cones using Ca^{2+} signals, Trends Cell Biol. 14 (2004) 320–330.
[20] M. Sukhareva, S.V. Smith, D. Maric, J.L. Barker, Functional properties of ryanodine receptors in hippocampal neurons change during early differentiation in culture, J. Neurophysiol. 88 (2002) 1077–1087.
[21] T.H. Ch'ng, K.C. Martin, Synapse-to-nucleus signaling, Curr. Opin. Neurobiol. 21 (2011) 345–352.
[22] O. Behar, K. Mizuno, M. Badminton, C.J. Woolf, Semaphorin 3A growth cone collapse requires a sequence homologous to tarantula hanatoxin, Proc. Natl. Acad. Sci. USA 96 (1999) 13501–13505.
[23] G. Ming, J. Henley, M. Tessier-Lavigne, H. Song, M. Poo, Electrical activity modulates growth cone guidance by diffusible factors, Neuron 29 (2001) 441–452.
[24] H. Song, G. Ming, Z. He, M. Lehmann, L. McKerracher, M. Tessier-Lavigne, M. Poo, Conversion of neuronal growth cone responses from repulsion to attraction by cyclic nucleotides, Science 281 (1998) 1515–1518.
[25] G.X. Wang, M.M. Poo, Requirement of TRPC channels in netrin-1-induced chemotropic turning of nerve growth cones, Nature 434 (2005) 898–904.

[26] R. Blum, K.W. Kafitz, A. Konnerth, Neurotrophin-evoked depolarization requires the sodium channel Na(V)1.9, Nature 419 (2002) 687–693.
[27] K. Togashi, M.J. von Schimmelmann, M. Nishiyama, C.S. Lim, N. Yoshida, B. Yun, R.S. Molday, Y. Goshima, K. Hong, Cyclic GMP-gated CNG channels function in Sema3A-induced growth cone repulsion, Neuron 58 (2008) 694–707.
[28] M.J. Berridge, Neuronal calcium signaling, Neuron 21 (1998) 13–26.
[29] L.S. Zweifel, R. Kuruvilla, D.D. Ginty, Functions and mechanisms of retrograde neurotrophin signalling, Nat. Rev. Neurosci. 6 (2005) 615–625.
[30] M.X. Zhu, A.M. Evans, J. Ma, J. Parrington, A. Galione, Two-pore channels for integrative Ca signaling, Commun. Integr. Biol. 3 (2010) 12–17.
[31] C. Hidalgo, Cross talk between Ca^{2+} and redox signalling cascades in muscle and neurons through the combined activation of ryanodine receptors/Ca^{2+} release channels, Philos. Trans. R. Soc. Lond. B Biol. Sci. 360 (2005) 2237–2246.
[32] J.R. Terman, T. Mao, R.J. Pasterkamp, H.H. Yu, A.L. Kolodkin, MICALs, a family of conserved flavoprotein oxidoreductases, function in plexin-mediated axonal repulsion, Cell 109 (2002) 887–900.