August 9, 2013

Re: Manuscript #4396

Dear Editor, Jin-Lei Wang

Thank you very much for your letter on July 21 concerning our manuscript entitled "Neuritin: A therapeutic candidate for promoting axonal regeneration" together with referee's comments. We are glad to know that our revised manuscript will be considered for publication in *World Journal of Neurology.*

We have carefully examined the reviewer's comments raised in your letter, and addressed all of them point by point. We also followed "The revision policies of BPG for minireviews" that you attached on your letter. The following paragraphs describe our responses to the comments of reviewer and the changes in the revised version. Please find the enclosed manuscript in Word format (4396-Review.docx).

Title: Neuritin: A therapeutic candidate for promoting axonal regeneration

Author: Tadayuki Shimada, Hiroko Sugiura, and Kanato Yamagata.

Name of journal: *World Journal of Neurology.*

ESPS manuscript number: 4396

The manuscript has been changed according to the "Revision policies of BPG for minireviews".

1. According to the revision policies, manuscript now contains 51 references, and we updated the format of all the reference according to the format for reference in the "Revision policies of BPG for minireviews".
2. We asked copyediting service at NPG Language Editing. We changed in detail with following the editing service.

The manuscript has been improved according to the suggestions of reviewers:

Major point; *An "inhibitory mechanism for CNS axonal regeneration", introduced at the first few paragraphs, is never argued in later part of this review. It is advised to discuss how neuritin overcome "inhibitory mechanism of CNS regeneration" if you leave these introductory paragraphs. Or you can just omit these confusing sentences if you will not discuss neuritin in relate to inhibitory mechanism. When you leave the paragraphs on inhibitory mechanism, you are advised to discuss: 1) Is neuritin expresses differently between CNS and PNS? 2) Is expression related to the distinct capacity for neuro-regeneration between CNS and PNS?*

We removed the sentences concerning an inhibitory mechanism for CNS regeneration from INTRODUCTION. Also, we added several sentences to make more focuses on the aspects of the axonal regeneration itself on Page 5 line 9 and page 5 line 18.

Minor points:

1; Page 3 line 3: *"in adult mammals" Do you need to define only to adult? You are omitting adult in INTRODUCTION section.*

In accordance to the suggestion of the reviewer, we removed the word "adult".

2; Page 3 line 14: *The structure of this paragraph is unclear. What do you mean in "a model of diabetes mellitus? Do you indicate PNS in a model mouse of diabetes mellitus? Can you declare the causal relationship that decreased neuritin expression resulted in deficient axonal regeneration?*

We changed the latter part of the paragraph, as "Conversely, in a mouse model of diabetes mellitus, neuritin expression decreases in the PNS, and this reduced expression may result in deficient axonal regeneration." to indicate that neuritin expression is decreased in the PNS of the model mouse of diabetes mellitus, and to declare the relationship that decreased neuritin expression results in deficient axonal regeneration.

3; Page 3 bottom: *"axonal disorder" sounds strange. Temporal lobe epilepsy and brain ischemia are not axonal disorders. For example, you can replace the word, "disorder" with "pathology".*

According to the suggestion of the reviewer, we replaced the word "disorder" with "pathology".

4; Page 5 line4: *you describe the inhibition of CNS regeneration. In next paragraph, you mention regeneration. Is it appropriate that you mention about inhibition here? After reading this paragraph, we anticipate that you will discuss inhibitory mechanism, which will never be discussed.*

As we mentioned in Major point above, we removed the sentences about the inhibitory mechanism for axonal regeneration.

5; Page6 line 16: *the phrase, "activity-regulated genes", is inappropriate. You should explain which activity regulates this gene.*

We inserted word "neural" to explain that neuritin expression is increased by neural activity. Furthermore, we added the example of the situation where neuritin expression increases.

6; Page7 line1: *"Neuritin mRNA is predominantly expressed in the brain." Is it expressed in the PNS?*

We added the sentence indicating that neuritin is expressed in the PNS with the reference.

7; Page8 line2: *Is neuritin is directory controlled by NGF?*

We explained the relationships among the NGF, expression of neuritin, and axonal elongation.

8; Page9 line5: *downregulation >down regulation*

According to the suggestion, we changed “downregulation” to “down regulation”.

9; Page9 line11: *“signaling pathway”. It would be better if you discuss more about mechanism and cite reference.*

We added an example about the signaling pathway of neuritin with reference.

10; Page10 bottom: *you should mention whether androgen signaling is related to NGF signal or not.*

We explained androgen signaling may not be related to NGF signal.

Page 11 line 20*; “In addition, sequential seizures may lead to chronic epilepsy” Epilepsy itself is chronic disease.*
Page 11 bottom to page 12 line 1*; is “formation of closed circuits” related to (chronic state of) epilepsy?*

(Answering both suggestions) We have explained that mossy fiber sprouting may promote the formation of the recurrent circuit and consequently induce spontaneous bursting with the references. We have also discussed the possibility that axonal blanch may trigger epilepsy.

All changes for answering reviewer are highlighted with red color characters.

We wish to thank you again for your thorough review. We hope our revised manuscript will now be acceptable for publication in *World Journal of Neurology.*

Sincerely yours,

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