Author’s response to reviews

Title: Cardiotonic pill attenuates white matter and hippocampal damage via inhibiting microglial activation and downregulating ERK and p38 MAPK signaling in chronic cerebral hypoperfused rat

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Author’s response to reviews:

Reviewer’s report

Title: Cardiotonic pill attenuates white matter and hippocampal damage via decreasing inflammation and microglial activation in chronic cerebral hypoperfused rats

Version: 3 Date: 6 October 2013
Reviewer: zhong-xiang Yao
Reviewer's report:

Minor Essential Revisions

1. In the title: “via decreasing inflammation and microglial activation”, these two mean the same mechanism? And not mentioned the signal mechanism.

; As your advice, we change the title as follows “Cardiotonic pill attenuates white matter and hippocampal damage via inhibiting microglial activation and downregulating ERK and p38 MAPK signaling in chronic cerebral hypoperfused rat”.

2. In the Abstract, line 1 of Background: “The cardiotonic pill (CP) is an herbal medicine”, the “an” should be “a”?

; This portion is corrected as follows “The cardiotonic pill (CP) is a herbal medicine”.

3. In the Abstract, the Conclusion is not wholly fitting for the results, for example, not mention the propective signal mechanism, the damaged targets (white matter and hippocampus), but expansion to vascular dementia (the proof is not satisfied).

; This portion is changed as follows “These results suggest that CP may have protective effects against chronic BCCAo-induced white matter and hippocampal
damage by inhibiting inflammatory processes including microglial activation and proinflammatory mediator expression, and downregulating the hyperphosphorylation of ERK and p38 MAPK signaling.”

4. In the results, the part of “CP inhibited microglial activation in the white matter and hippocampus induced by chronic BCCAo”, line 1 to 4, “Inflammation plays a key role in white matter lesions induced by chronic cerebral hypoperfusion [17,18]. Long-term changes in regional cerebral blood flow and glucose utilization have been reported in white matter regions of chronic BCCAo rats, including the corpus callosum, internal capsule, and optic tract [19].” It is best to transfer to the part of discussion.

; As your advice, this portion “Inflammation plays a key role in white matter lesions induced by chronic cerebral hypoperfusion [17,18]” has been transferred to the part of discussion, paragraph 2 line 1-2, and this portion “Long-term changes in regional cerebral blood flow and glucose utilization have been reported in white matter regions of chronic BCCAo rats, including the corpus callosum, internal capsule, and optic tract [19]” has been transferred to the part of discussion, paragraph 1 line 6-8 from bottom.

5. In the results, the part of “CP blocked the hyperphosphorylation of MAPKs in the hippocampus of rats with chronic BCCAo”, line 1 to 3, “MAPK signaling plays a major role in synaptic plasticity and hippocampus-dependent memory [23] and is involved in microglial activation and the production of proinflammatory mediators [24].” It is best to transfer to the part of discussion.

; As your advice, this portion “MAPK signaling plays a major role in synaptic plasticity and hippocampus-dependent memory [23] and is involved in microglial activation and the production of proinflammatory mediators [24]” has been transferred to the part of discussion, paragraph 2 line 8-10 from bottom.

6. In discussion, the last part of the first paragraph, “These findings suggest that CP may exert protective effects against white matter and hippocampal damage induced by chronic cerebral hypoperfusion via an inhibitory action of myelin degradation.” It should also mention the neuronal death.

; As your advice, this portion is changed as follows “These findings suggest that CP may exert protective effects against white matter and hippocampal damage induced by chronic cerebral hypoperfusion via inhibition of myelin degradation and the neuronal death.”, in discussion, last line of paragraph 1.

Reviewer’s report

Title: Cardiotonic pill attenuates white matter and hippocampal damage via decreasing inflammation and microglial activation in chronic cerebral hypoperfused rats

Version: 3 Date: 14 October 2013

Reviewer: Seong Yun Kim

Reviewer’s report:

Minor essential revisions
In this revised article, authors well responded to reviewers’ comments except for two items.

1. As you see, authors insufficiently respond to the first question, 'Are there some references in which the damage of the grey matter including the hippocampus was evaluated by immunostaining for MBP?'. Authors need to validate the evaluation of the hippocampal damage using immunostainign for MBP.

; As your advice, the damage of the grey matter including the hippocampus was evaluated by immunostaining for MBP under the lowest magnification of our microscope. This portion is mentioned in the results, the part of “CP restored the reduced expression of MBP in the white matter and hippocampus induced by chronic BCCAo”, line 12-14, and in discussion, paragraph 1 line 6-9 from bottom.

2. In lines 4-5 from bottom in the first page in Method section, 'seven rats that lost 80 or more of their pre-surgical weight during drug or vehicle administration were excluded from the present study' might be corrected to "seven rats that lost 20 or more of their pre-surgical weight ~~".

; As your advice, this portion is changed as follows “seven rats that lost 20% or more of their pre-surgical weight during drug or vehicle administration were excluded from the present study.”, in Animal surgery and drug administration part of Methods, paragraph 1, line 8.