Reviewer’s report

Title: Pharmacological reversal of endothelin-1 mediated vasospasm of the spiral modiolar artery: a potential new treatment for sudden sensorineural hearing loss

Version: 4 Date: 3 August 2005

Reviewer: Hiroaki Shimokawa

Reviewer’s report:

General

Role of Rho/Rho-kinase pathway in the molecular mechanism of cerebral and coronary vasospasm and the potential usefulness of Rho-kinase inhibitors for the treatment of the disorders have recently attracted much attention. In this study, the authors examined whether Rho-kinase inhibitors also are effective for the treatment of endothelin (ET)-1-induced contraction of isolated gerbil spiral modiolar artery (SMA). They also examined the inhibitory effect of a cAMP analogue, db-cAMP. The results showed that all three Rho-kinase inhibitors and db-cAMP effectively suppressed ET-1-induced contraction. Thus, the authors concluded that Rho-kinase inhibitors and cAMP modulators may be useful for the treatment of sudden sensorineuronal hearing loss that may be caused by SMA vasospasm.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Although the authors addressed the potential therapeutic usefulness of Rho-kinase inhibitors and db-cAMP for the treatment of SMA vasospasm, they only examined the inhibitory effect of those inhibitors on the ET-1-induced contraction of normal SMA. It is now known that the extent of the involvement of Rho/Rho-kinase pathway in vascular contraction is quite different between normal and diseased blood vessels. Thus, the authors also should use diseased SMA taken from an ischemic stroke model. Otherwise, clinical importance of this study is unclear.

2. In connection to the comment 1, the authors should change the term “vasospasm” to “vasocontraction” throughout the text including the title as they only examined ET-1-induced vasocontraction of normal arteries.

3. It is unclear why the authors used ET-1 in this study. The authors should discuss the potential importance of ET-1 in the pathogenesis of SMA vasospasm in humans.

4. The authors should provide evidence that Rho-kinase activity in SMA is actually inhibited by the Rho-kinase inhibitors (e.g. the extent of phosphorylation of myosin binding subunit by Western blotting).

5. The addition of the data with db-cAMP has diluted the importance of the study. The authors should either delete this portion or add more supporting data showing the effect of db-cAMP on abnormal contraction of diseased SMA as well as intracellular cAMP data.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Throughout the text: Rho-kinase is more appropriate than Rho kinase as first described by Kaibuchi et al. (Ref. 3).

Page 4: How did the authors obtain hydroxyfasudil?

Page 9, Lines 7-8: Fasudil and hydroxyfasudil are reasonably selective inhibitors for Rho-kinase. Do not rely on only one paper (Ref. 17).

Discretionary Revisions (which the author can choose to ignore)

None

**Which journal?**: Not appropriate for BMC Medicine: an article of only archival interest, but might be suited to BMC Ear, Nose and Throat Disorders

**What next?**: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Quality of written English**: Needs some language corrections before being published

**Statistical review**: No