Author's response to reviews

Title: I(f) Current Channel Inhibitor (Ivabradine) Deserves Cardioprotective Effect via Down-Regulating the Expression of Matrix Metalloproteinase (MMP)-2 and attenuating apoptosis in Diabetic mice

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Dear Editor-In-Chief

Our manuscript entitled by “I(f) Current Channel Inhibitor (Ivabradine) Deserves Cardioprotective Effect via Down-Regulating the Expression of Matrix Metalloproteinase (MMP)-2 and attenuating apoptosis in Diabetic mice” is submitted to your outstanding journal.

Ivabradine, a specific heart rate-lowering drug, has been extensively used for treatment of angina and congestive heart failure, without any alternation of blood pressure. Its main molecular mechanism was reported to anti-oxidation via NADPH pathway. However, effect of Ivabradine on cardiac function and the underlying mechanisms in diabetic animals were not fully studied.

Twenty diabetic mice were randomly assigned as IVBD (ivabradine was added in the diet at a dosage of 10 mg/kg/day, for 3-month) and Control (ivabradine was replaced by saline, for 3-month) groups. After 3-month treatment, microarray was performed to identify the differentially expressed genes, and cardiac function was measured by echocardiography. Immunohistochemistry analysis of ventricular myocardium was used to compare the difference in staining up-regulated gene(s) between two groups.
At 3-month, cardiac functional indexes in IVBD group were improved significantly, as shown by increment of left ventricular (LV) eject fraction, fraction of shortness, wall thickness at the end-systole, and by reduction of LV cavity. Ivabradine treatment attenuated the expression and staining score of matrix metalloproteinase (MMP)-2. Expression of several genes participated in the modulation of inflammation and apoptosis was up-regulated, as such demonstrated by the increased expression and activity of 6Ckine, ACE/CD143, ALK-1, CT-1, CD27, Endoglin, IL-17E/F, IL-1ra/IL-1F3, and IL-2 Rα, macrophage inflammation protein-3 β (MIP-3β ), Epigen. Ivabradine induced the dephosphorylation of Caspase 3, BAX and MMP-2, but enhanced the phosphorylation of NF-kB.

We thus feel that your readers would benefit from our findings and respectfully submit the revised manuscript for publication in your prestigious journal.

We certify that 1) the paper is not under consideration elsewhere; 2) none of the paper or contents have been previously published; 3) all authors have read and approved the manuscript; and 4) the full disclosure of any potential relationship with industry.

Again, the authors are indebted to the Editorial Board and Reviewers for their expert input and
Sincerely yours,

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