May, 28, 2014

Dear Editor,
Please find enclosed the edited manuscript in Word format (file name: 10381-review.doc)

Title: Beneficial Effects of Adenosine Triphosphate-Sensitive K^+ Channel Opener on liver ischemia/reperfusion injury

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

1. **Although this study provides some interesting data, protective effects of diazoxide after hepatic warm I/R in rats and cold I/R (transplantation) in rats and mice have been reported previously. Protection against mitochondrial cytochrome c release after hepatic warm I/R in rats by diazoxide has also been reported. Therefore, it is important to discuss what new information is provided by this study.**
Although there are reports that demonstrate a beneficial effect on diazoxide in liver ischemic/reperfusion injury in our study we demonstrated that this protective effect is due to a reduction in mitochondria dysfunction and we also demonstrated a significant effect of diazoxide on inflammatory cytokines that could be related to a reduction of liver injury or even to a specific effect of diazoxide on the immunological system. We did demonstrate a protective effect on liver however no effect on distant organs could be demonstrated. In this study even after 4 h of reperfusion we found lung damage that was not reduced by diazoxide administration. Creatinine levels at 4 and 24 h after the reperfusion were also not affected by diazoxide administration.

2. It would be more convincing if liver histology is shown and necrosis and apoptosis are quantified.
Although we could not demonstrate an effect of diazoxide on liver histology (necrosis reduction was not statistically significant) we demonstrated a reduction in transaminases and TGFbeta that indicates a reduction in liver injury.

3. Damage to remote organs often occurs later than damage to the liver. Moreover, creatinine takes time to accumulate in serum. In this study, lung injury was evaluated at 4 h and the time point for creatinine measurement was not mentioned. Whether the lung and kidney injury at later time point was attenuated by diazoxide?

We agree that most of distant organ damage occurs later than liver damage however we did demonstrated in this study that even at 4 hour we found lung damage that was not attenuated by diazoxide administration. We did measured creatinine serum levels at 4 and 24 h after reperfusion (these data were included in the manuscript) and we also did not find any kidney protection by diazoxide administration. We may conclude that diazoxide protects liver but does not reduce distant organ damage.

4. Figs 1 and 2 can be combined into one figure.

We did modified the manuscript

5. Please clarify how the lung was rinsed before EBD (via trachea or blood vessel).

Lungs were perfused via tracheal with 30-50 mL of 0.9% NaCl at 10 mL/min, using a syringe pump (model 975) from Harvard Apparatus, and fragments were harvested and divided for analysis of microvascular permeability, mieloperoxidase (MPO) activity. This text was included in the manuscript.

6. On p11, line 2, "to" is missing after "compared".

It was corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

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