Reply to: Hepatic microvascular dysfunction and endotoxemia in sepsis

To the Editor:

We thank Dr. Fujita [1] for the constructive and insightful comments about our recent report [2] and appreciate the opportunity to respond to the questions raised regarding: (1) the units used to express endotoxin concentrations detected in blood; and (2) the interpretation of our findings about the potential role of endotoxin in the hepatic microvascular responses to experimental sepsis.

We regret the confusion that resulted from expressing endotoxin concentrations in terms of both EU/ml and pg/ml. Although we did not measure endotoxin activity per se, the concentrations of endotoxin in plasma were analyzed using a chromogenic limulus test and were estimated based on standards constructed with endotoxin serotype 055:B5. This serotype has an approximate activity of 1 EU = 100 pg/ml, based on the manufacturer’s suggestions. Thus, our data can easily be converted by simply multiplying the EU/ml values provided in Table 2 by a factor of 100. However, since endotoxin was undetectable following cecal ligation and puncture (CLP), this conversion would not affect the overall outcome of the study.

Finally, we agree that rapid clearance of endotoxin may account for lowered endotoxin levels in the circulation of mice following CLP. Unlike the experiments wherein only one dose of endotoxin was injected, CLP likely induces the sustained release of endotoxin. As a result, large amounts of endotoxin should have been detected at any time point throughout the 6-h exposure, especially in the portal blood draining the gut. The absence of detectable endotoxin in blood does not, on its own, justify the conclusion that “our findings do not support a major role for LPS in the hepatic microvascular disturbances associated with polymicrobial sepsis”. This conclusion was based on a collective body of evidence that included the absence of enhanced mRNA expression for TLR-4 or the adaptor molecule MD-2 in the livers of septic mice, as well as our observation that the hepatic microcirculation of endotoxin-sensitive and -insensitive (TLR-4 deficient) mice responded in a nearly identical fashion to CLP, while the TLR-4 mutants were protected against exogenous endotoxin. We believe that these observations following CLP, coupled with the absence of detectable endotoxin in blood, warrant the conclusion drawn in our report. Additional work is needed to further address the importance of endotoxin and products from Gram-positive bacteria in liver pathology.

References


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