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Does a toxic gas regulate hepatic sinusoidal blood flow?

R S McCuskey

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Editorial

The paper appearing in this issue by Suematsu et al. entitled, "Carbon monoxide: an endogenous modulator of sinusoidal tone in the perfused rat liver," (1) is an extremely interesting one and of high potential significance. The report presents data suggesting that carbon monoxide (CO) is a constitutively produced modulator of the tone of the perisinusoidal fat storing (Ito) cell and, thus, of hepatic sinusoidal diameter in the normal, unstimulated liver. Since nitric oxide synthase inhibitors (NOS) did not influence sinusoidal tone in these experiments, the authors also suggest that CO, rather than nitric oxide (NO), plays a major role in maintaining low hepatic vascular resistance.

While the experiments and data very convincingly support this conclusion for the isolated, perfused rat liver, it remains to be determined whether or not CO plays a predominate role, in contrast to NO, in the intact, innervated liver perfused with whole blood. This is a critical issue since hepatic microvascular responses in vivo may be totally different from those in the isolated liver perfused with a blood-free solution. In contrast to the current study, a recent in vivo microscopic study of the liver in situ suggests that NO does play a role in the regulation of sinusoidal blood flow in the intact mouse liver (2). Inhibition of NO synthesis with 30 mg/kg b.w. L-NMMA (N^G-monomethyl-L-arginine) elicited a significant reduction in the diameters of sinusoids that appeared to be caused by the contraction of sinusoidal lining cells since the size of hepatocytes (intersinusoidal distance) did not change. Which of the sinusoidal lining cells were responsible for narrowing the lumen was not clear since Kupffer cells, endothelial cells and perisinusoidal fat storing (Ito) cells all are responsive to a wide variety of pharmacodynamic substances (3–6). By contracting individually or collectively, these cells may selectively reduce the patency of the sinusoid lumen, thereby altering the rate and distribution of blood flow in all or portions of the sinusoidal network (3). However, since they all are cellular components of the sinusoidal wall, contraction of one cell type affects the configuration of the others. As a result, the relative roles of Kupffer and endothelial cells verus fat-storing (Ito) cells in this process has yet to be resolved, especially since all three cell types contain filaments, tubules, and contractile proteins suggestive of contractile activity (6). That NO plays a role in regulation of sinusoidal blood flow also has been suggested in studies of ethanol-induced hepatic vasoconstriction where NO and endothelin-1 were demonstrated to have opposing roles in modulating sinusoidal diameter (7). Finally, it must be remembered that portal perfusion pressures in isolated, perfused preparations are usually higher than normal which may affect sinusoidal tone and thus the diameters as well as the responsiveness of these vessels.

In summary, the results of this study together with the authors' initial report (8) are extremely interesting and potentially are of very high significance since they implicate a role for CO, derived from the ongoing metabolic process of heme degradation and bilirubin production, in the regulation of sinusoidal blood. However, the results need to be interpreted with a bit of caution until they can be verified in the intact liver perfused in vivo with whole blood. In addition, the potential clinical relevance remains unknown until confirmation of this mechanism is obtained in the human liver. It is hoped that the authors now have these experiments in progress and the results will be forthcoming in the near future.

Robert S. McCuskey
Department of Cell Biology and Anatomy
College of Medicine
University of Arizona

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