Reply to “The Brain, Amphotericin B, and P-Glycoprotein”

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We thank David A. Stevens et al. (1) for the letter suggesting different results regarding the effect of P-glycoprotein on the brain concentration of amphotericin B (AMB) by P-glycoprotein knockout mice. In contrast to our finding that blockage of P-glycoprotein with inhibitors enhances the brain uptake of AMB (2), they found that brain AMB concentrations were significantly lower in Mdr1a/-/- mice (3).

In our study we used verapamil, which is a classic P-glycoprotein inhibitor and has been widely used to evaluate P-glycoprotein-mediated drug transportation, to find that the brain uptakes of AMB were significantly influenced both in vitro and in vivo. Our results, together with the significant changes of AMB concentrations in P-glycoprotein knockout mice by Martinez et al. (3), strongly suggest a role of P-glycoprotein for AMB transportation.

The letter (1) mentioned the possibility that the effects on brain concentrations reported in our study were due to blockage of other drug transporters. We agree that other drug transporters, such as breast cancer resistance protein (BCRP), are likely to partially contribute to the effect, because verapamil also exhibits some inhibitory effects on other transporters (4). In addition, the decrease in brain AMB concentrations observed in P-glycoprotein knockout mice could also be due to a compensatory pump-out effect of other transporters.

Moreover, consistent with our observation in verapamil-treated mice, the blood AMB concentrations were also interestingly found to be lower in P-glycoprotein knockout mice by Martinez et al. (3), the reason for which remains unclear to us and warrants further study.

REFERENCES


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