Differential Role of Pgp and BCRP in Drug Distribution into Brain, CSF and Nerve Tissues in Rats
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Purpose
P-glycoprotein (Pgp) (MDR1) and breast cancer resistance protein (BCRP) (ABCG2) play an important role in brain penetration. Dahlin et al (2012) reported that BCRP was expressed in human retinal nerve fiber through RNA expression profiling and immunohistochemistry. This study was designed to evaluate how the absence of Pgp, Bcrp or both affects distribution of probe substrates into sciatic nerve, brain and cerebrospinal fluid (CSF) in rats.

Methods
Drug concentrations (C) of five probe substrates were determined in sciatic nerve, plasma, brain, and CSF in wild-type (WT), Pgp, Bcrp or Pgp/Bcrp double knockout rats following intravenous infusion. In vitro permeability and efflux were measured in MDCK cells. Fraction unbound in rat plasma or brain homogenate was determined using the rapid equilibrium dialysis device.

Results
Pgp substrate (loperamide), BCRP substrates (dantrolene and proprietary compound X), and dual substrates (imatinib and proprietary compound Y) were well distributed into sciatic nerves with comparable $C_{\text{nerve}}/C_{\text{plasma}}$ between WT and knockout rats. In contrast, brain exposure of these probe substrates was low in WT rats. $C_{\text{brain}}/C_{\text{plasma}}$ increased ≥14.5-fold for loperamide in $Mdr1a(-/-)$, minimally to modestly for compound X and dantrolene in $Abcg2(-/-)$, and ≥10-fold for imatinib and compound Y in $Mdr1a(-/-)/Abcg2(-/-)$ rats. The deletion of Pgp or Bcrp alone had no effect on $C_{\text{brain}}/C_{\text{plasma}}$ of compound Y. $C_{\text{csf}}/C_{\text{u-brain}}$ in WT rats was ≥2.5 for dantrolene, compound X, imatinib and compound Y. While $C_{\text{csf}}/C_{\text{u-brain}}$ was reduced to 1 in $Mdr1a(-/-)/Abcg2(-/-)$ rats for imatinib, it was not affected in the knockout animals for the other three compounds.

Conclusion
Pgp and Bcrp do not play a significant role in drug distribution into peripheral nerve tissues in rats, while working in concert to regulate brain penetration. Our results further support that $C_{\text{csf}}$ is not a good surrogate for $C_{\text{u-brain}}$ of efflux substrates.