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ORIGINAL ARTICLE

# Characterization of a novel brain barrier ex vivo insect-based P-glycoprotein screening model

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## Abstract

In earlier studies insects were proposed as suitable models for vertebrate blood–brain barrier (BBB) permeability prediction and useful in early drug discovery. Here we provide transcriptome and functional data demonstrating the presence of a P-glycoprotein (Pgp) efflux transporter in the brain barrier of the desert locust (*Schistocerca gregaria*). In an in vivo study on the locust, we found an increased uptake of the two well-known Pgp substrates, rhodamine 123 and loperamide after co-administration with the Pgp inhibitors cyclosporine A or verapamil. Furthermore, ex vivo studies on isolated locust brains demonstrated differences in permeation of high and low permeability compounds. The vertebrate Pgp inhibitor verapamil did not affect the uptake of passively diffusing compounds but significantly increased the brain uptake of Pgp substrates in the ex vivo model. In addition, studies at 2°C and 30°C showed differences in brain uptake between Pgp-effluxed and passively diffusing compounds. The transcriptome data show a high degree of sequence identity of the locust Pgp transporter protein sequences to the human Pgp sequence (37%), as well as the presence of conserved domains. As in vertebrates, the locust brain–barrier function is morphologically confined to one specific cell layer and by using a whole-brain ex vivo drug exposure technique our locust model may retain the major cues that maintain and modulate the physiological function of the brain barrier. We show that the locust model has the potential to act as a robust and convenient model for assessing BBB permeability in early drug discovery.

## Abbreviations

ABC, ATP-binding cassette; AUC, area under curve; B/P, brain:plasma ratio; BBB, blood–brain barrier; BCRP, breast cancer-resistant proteins; Cbz, carbamazepine; CNS, central nervous system; CsA, cyclosporin A; KO, knockout; LLOQ, lower limit of quantification; MDCK, Madin-Darby canine kidney; MDR1-MDCK, MDR1-transfected MDCK; MDR1, multidrug resistance protein-1; NCBI, National Center of Biotechnology Information; Pgp, P-glycoprotein; Rho123, rhodamine 123; SD, standard deviation; WT, wild type.

## Introduction

The mammalian blood–brain barrier (BBB) is composed of capillary endothelial cells that control the entry of nutrients and xenobiotics to the brain and thus preserve homeostasis of the neural microenvironment, a prerequisite for reliable neural transmission and function (Abbott et al. 2006, 2010). However, the protection of brain function by the BBB restricts the permeation of drugs and results in a low brain target exposure concentration being