Measurement of P-glycoprotein activity at the lung epithelial barrier using positron emission tomography

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Introduction

There is an increasing evidence of drug transporters belonging to the solute carrier (SLC) and ATP-binding cassette (ABC) families being functionally expressed at the apical and basolateral membranes of the lung-epithelial barrier (Fig. 1). These transporters may play pivotal roles in the pharmacokinetics, safety and efficacy of orally inhaled medicines. Variability in pulmonary transporter activity may lead to changes in the lung disposition of inhaled drugs and thereby affect their therapeutic activity. So far, the study of pulmonary membrane transporters has been mainly limited to *in vitro* and *ex vivo* approaches. In this study, we used positron emission tomography (PET) to assess the influence of P-glycoprotein (ABCB1) on the lung disposition of the model ABCB1 substrates *(R)*-[^{11}C]verapamil and [^{11}C]-*N*-desmethyl-loperamide administered *via* intratracheal aerosolization in rats (Fig. 3). To this end, we examined wild-type rats without and with co-administration of the ABCB1 inhibitor tariquidar and transgenic rats lacking the gene which encodes ABCB1 (*Abcb1a/b*$^{(-/-)}$) (Fig. 2, Table 1).

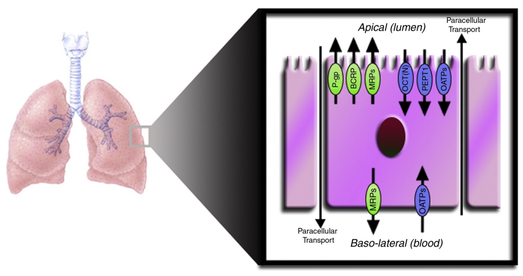


Figure 1: Transporter protein expression at the lung epithelial barrier [1].

Methods

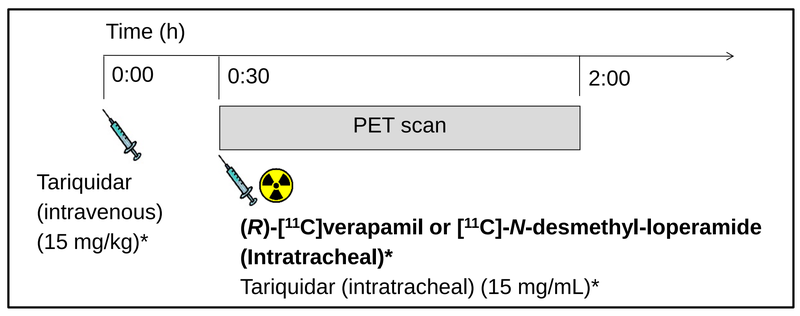


Figure 2: Schematic representation of the study design. *Vehicle: 2.5% aqueous glucose solution.

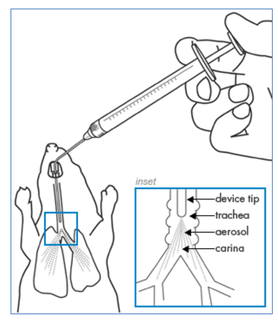


Figure 3: Intratracheal aerosolization of radiotracers in rats using the Microsprayer™ device (Penn-Century, Inc.).

	(*R*)-[^{11}C]verapamil	[^{11}C]-*N*-desmethyl-loperamide
Wild-type	5	6
Wild-type + tariquidar	7	5
Abcb1a/b$^{(-/-)}$	3	7

Table 1 Number of animals included in each study group.

Results

(*R*)-[^{11}C]verapamil

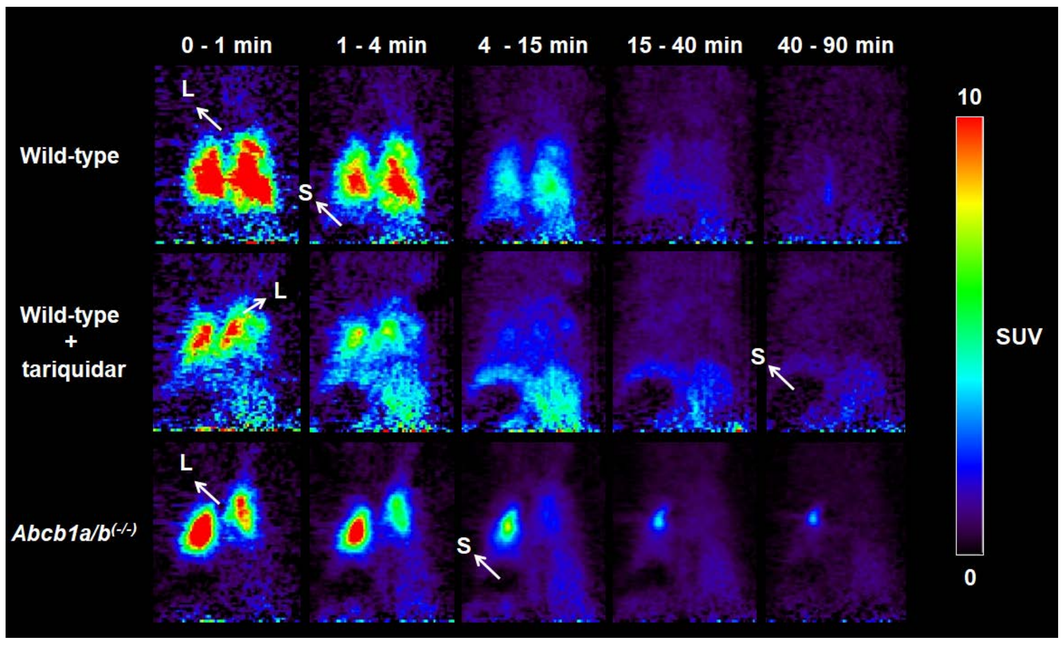
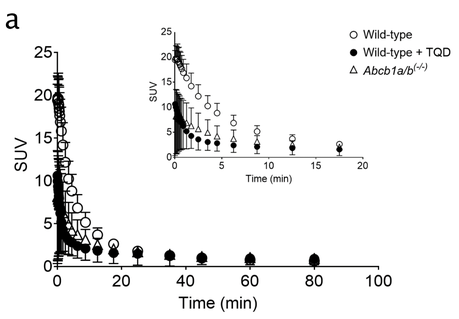
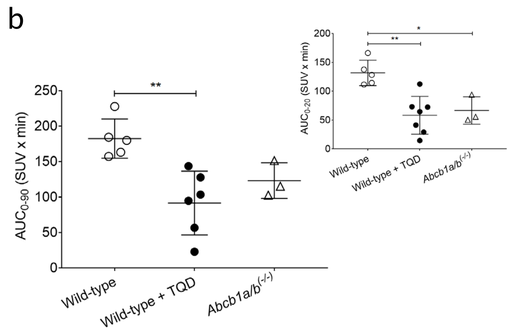


Figure 4: Representative serial PET images of the lung distribution of *(R)*-[^{11}C]verapamil in representative wild-type rats without and with co-administration of tariquidar and in one *Abcb1a/b*$^{(-/-)}$ rat. Anatomical structures are labeled with arrows (L: lungs, S: stomach).





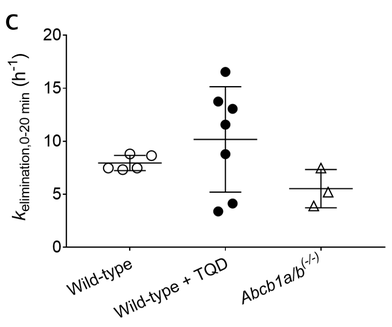


Figure 5: (a) *(R)*-[^{11}C]verapamil time-activity curves expressed as standardized uptake value (mean SUV ± SD) for the whole duration of the PET scan and for the first 20 minutes (insert). (b) Lung exposure (AUC_{lung}) for the different groups over 90 and 20 minutes. (c) Pulmonary elimination rate ($k_{elimination}$) calculated for the first 20 minutes of the PET scan for the different study groups . $*p < 0.05$, $**p < 0.005$, one-way ANOVA followed by a Dunnett's multiple comparison tests against a reference group (wild-type).

[^{11}C]-*N*-desmethyl-loperamide

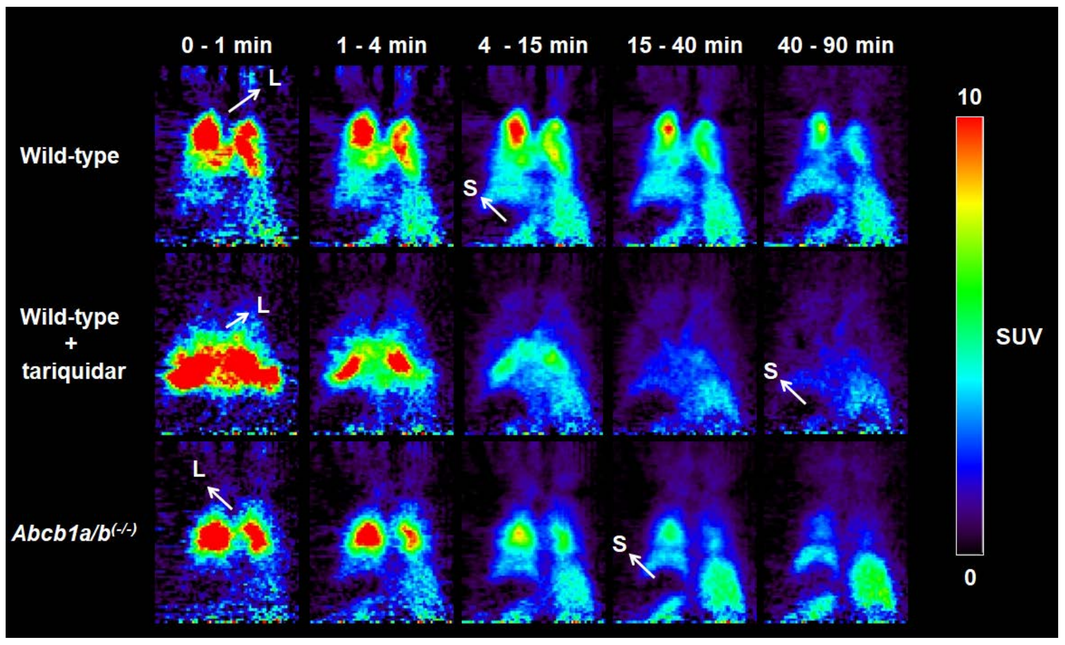
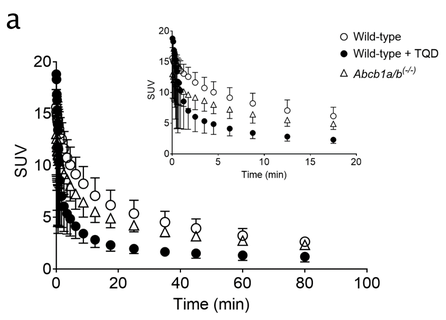
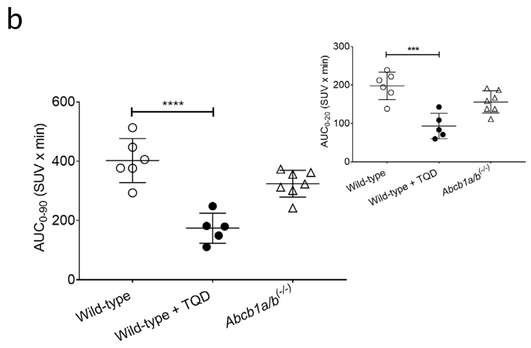


Figure 6: Representative serial PET images of the lung distribution of [^{11}C]-*N*-desmethyl-loperamide in representative wild-type rats without and with co-administration of tariquidar and in one *Abcb1a/b*$^{(-/-)}$ rat. Anatomical structures are labeled with arrows (L: lungs, S: stomach).





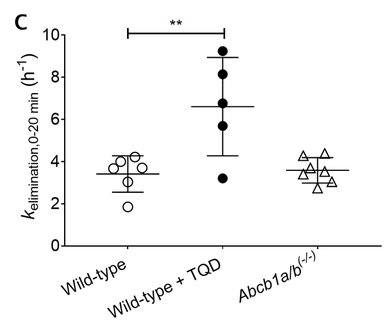


Figure 7: (a) [^{11}C]-*N*-desmethyl-loperamide time-activity curves expressed as standardized uptake value (mean SUV ± SD) for the whole duration of the PET scan and for the first 20 minutes (insert). (b) Lung exposure (AUC_{lung}) for the different groups over 90 and 20 minutes. (c) Pulmonary elimination rate ($k_{elimination}$) calculated for the first 20 minutes of the PET scan for the different study groups . $**p < 0.005$, $****p < 0.0005$, one-way ANOVA followed by a Dunnett's multiple comparison tests against a reference group (wild-type).

Conclusion

Our results suggest that PET with intratracheally aerosolized *(R)*-[^{11}C]verapamil and [^{11}C]-*N*-desmethyl-loperamide can be used to measure the activity of ABCB1 at the lung epithelial barrier in rats. Decreased ABCB1 activity at the pulmonary epithelium may lead to a lower lung exposure to inhaled ABCB1 substrates, which could lower their therapeutic efficacy.

References

[1] M. Gumbleton et al. Spatial expression and functionality of drug transporters in the intact lung: objectives for further research. *Adv Drug Deliv Rev*, 2011; 63(1-2)

Acknowledgements

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