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INTRINSIC ACTIVITY

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MEETING ABSTRACT

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Impact of a moderate decrease in the abundance of P-glycoprotein at the blood–brain barrier on the brain distribution of model P-glycoprotein substrates

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Background: P-glycoprotein (P-gp/ABCB1) is an efflux transporter which is abundantly expressed in the luminal (blood-facing) membrane of brain capillary endothelial cells forming the blood–brain barrier (BBB). Experiments in P-gp knockout mice (*Abcb1a/b*$^{-/-}$) revealed pronounced increases in the brain distribution of various P-gp substrates (*e.g.* ivermectin, vinblastine, digoxin, loperamide, verapamil) in absence of P-gp activity. However, a complete absence of P-gp activity is unlikely to occur under different pathophysiological conditions (*e.g.* in neurodegenerative diseases), in which the abundance of P-gp was shown to decline only moderately. The aim of this work was to compare the effect of a moderate decrease in P-gp abundance with a complete absence of P-gp on the brain distribution of radiolabelled model P-gp substrates by means of positron emission tomography (PET) imaging. To this end, we used wild-type, heterozygous (*Abcb1a/b*$^{+/-}$) and homozygous (*Abcb1a/b*$^{-/-}$) *Abcb1a/b* knockout mice as models with controlled levels of cerebral P-gp abundance.

Methods: Wild-type, *Abcb1a/b*$^{+/-}$ and *Abcb1a/b*$^{-/-}$ mice underwent PET scans after intravenous injection of (*R*)-[^{11}C]verapamil, [^{11}C]*N*-desmethyl-loperamide or [^{11}C]metoclopramide. After the PET scan, brains were collected to quantify cerebral P-gp abundance with immunohistochemistry. Brain uptake of all three P-gp substrates was expressed as the area under the brain concentration–time curve (AUC_{brain}).

Results: Wild-type, *Abcb1a/b*$^{+/-}$ and *Abcb1a/b*$^{-/-}$ mice had normal, intermediate and no cerebral P-gp abundance, respectively. All three radiotracers had markedly increased AUC_{brain} values in *Abcb1a/b*$^{-/-}$ mice *vs.* wild-type mice (2.5- to 5.7-fold, $p < 0.0001$). However, in *Abcb1a/b*$^{+/-}$ mice AUC_{brain} values were only significantly increased over wild-type mice for [^{11}C]metoclopramide (1.46-fold, $p < 0.001$), but not for (*R*)-[^{11}C]verapamil and [^{11}C]*N*-desmethyl-loperamide.

Discussion: The effect of a moderate decline (−50%) in cerebral P-gp abundance as it is expected to occur in neurodegenerative diseases was markedly less pronounced than complete absence of P-gp activity and appeared to be substrate-dependent. Brain distribution of the avid P-gp substrates (*R*)-[^{11}C]verapamil and [^{11}C]*N*-desmethyl-loperamide was unchanged in heterozygous *Abcb1a/b*$^{+/-}$ mice. This may be related to the high transport capacity of P-gp for these compounds, which can effectively restrict their brain distribution even under conditions of partially decreased P-gp abundance. On the other hand, the brain distribution of the weak P-gp substrate [^{11}C]metoclopramide was significantly increased which suggests a better sensitivity of this radiotracer to detect disease-related changes in P-gp abundance/activity.

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Keywords: P-glycoprotein – blood–brain barrier – brain distribution

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