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Physiological and pharmacological roles of ABCG2 (BCRP): Recent findings in Abcg2 knockout mice☆

Maria L.H. Vlaming [1], Jurjen S. Lagas [1], Alfred H. Schinkel *

Division of Experimental Therapy, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

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ABSTRACT

The multidrug transporter ABCG2 (BCRP/MXR/ABCP) can actively extrude a broad range of endogenous and exogenous substrates across biological membranes. ABCG2 limits oral availability and mediates hepatobiliary and renal excretion of its substrates, and thus influences the pharmacokinetics of many drugs. Recent work, relying mainly on the use of *Abcg2*$^{-/-}$ mice, has revealed important contributions of ABCG2 to the blood-brain, blood-testis and blood-fetal barriers. Together, these functions indicate a primary biological role of ABCG2 in protecting the organism from a range of xenobiotics. In addition, several other physiological functions of ABCG2 have been observed, including extrusion of porphyrins and/or porphyrin conjugates from hematopoietic cells, liver and harderian gland, as well as secretion of vitamin B_2 (riboflavin) and possibly other vitamins (biotin, vitamin K) into breast milk. However, the physiological significance of these processes has been difficult to establish, indicating that there is still a lot to learn about this intriguing protein.

Contents

1. Introduction

The ATP-binding cassette (ABC) transporter ABCG2 (BCRP) is expressed at the apical membrane of hepatocytes and epithelial cells of intestine and kidney where it pumps a wide variety of endogenous and exogenous compounds out of the cell. Due to its activity in these excretory organs, ABCG2 can have a profound effect on the pharmacokinetics of many drugs and their metabolites, by enhancing their

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* Corresponding author.
E-mail address: a.schinkel@nki.nl (A.H. Schinkel).

[1] These authors contributed equally to this work.

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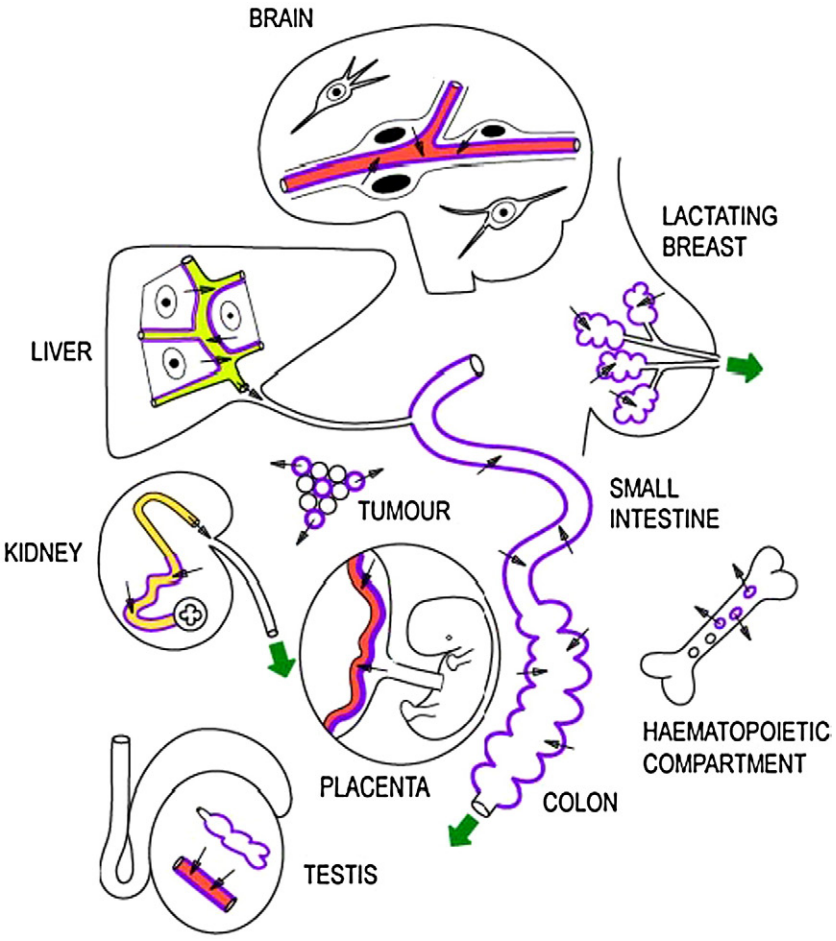

Fig. 1. Schematic overview of ABCG2 expression throughout the body. Purple (or grey) bold lines indicate the location of ABCG2. At all expression sites where small arrows indicate the direction of ABCG2-mediated transport, *in vivo* functionality of ABCG2/Abcg2 has been demonstrated. Wide arrows indicate net body excretion of ABCG2 substrates. For testis the situation in humans is depicted, where ABCG2 is found in both myoid cells of the seminiferous tubules and in blood capillary endothelial cells. However, only the Abcg2 barrier function of testis endothelial cells as demonstrated in mice is indicated with arrows. Expression of ABCG2 in endothelial cells of blood capillaries and veins, or in "side population" cells throughout many tissues in the body is not indicated. This figure was modified from reference [2].

excretion and limiting their uptake from the intestinal lumen after oral administration. In addition, ABCG2 can confer multidrug resistance to tumor cells [1–3]. ABCG2 might further be important for the pharmacological sanctuary properties of several tissues, due to its expression in the blood-brain, blood-placental and blood-testis barriers, where it could limit the penetration of its substrates into these critical tissues [1–5]. ABCG2 is also found in stem cell-enriched cell populations and progenitor cells of a number of tissues, where it might potentially protect these important cells from insult by a variety of toxic or carcinogenic xenobiotics [2]. A schematic overview of ABCG2 tissue distribution is shown in Fig. 1. In general, ABCG2 appears to have a xenobiotic protective function, reducing levels of noxious compounds in individual cells, in certain organs, and in the body as a whole. Nevertheless, recently also a high expression of ABCG2 in the lactating mammary gland was demonstrated, in the luminal membrane (Fig. 1). Here ABCG2 concentrates its (often toxic) substrates into the milk [6], leading to the question whether ABCG2 may have additional, yet unrecognized physiological functions. The physiological and pharmacological roles of ABCG2/Abcg2 elucidated thus far have been extensively described in earlier reviews [1–3]. Characterization of *Abcg2* knockout (*Abcg2*$^{-/-}$) mice has greatly contributed to the knowledge of *in vivo* ABCG2 functions [7,8]. This review will focus on some of the more recently gained insights into the physiological and pharmacological functions of Abcg2, obtained using these valuable mouse models.

2. Recently established pharmacological functions of ABCG2/Abcg2

2.1. Functional role of Abcg2 at the blood-brain barrier; value of compound transporter knockout mice

P-glycoprotein (P-gp, MDR1/ABCB1) was the first ABC multidrug transporter that was found to be highly expressed at the blood-brain barrier (BBB), where it efficiently restricts the entry of a wide variety of compounds into the brain (Fig. 1) [9,10]. More recently, ABCG2 was also identified at the BBB of humans, pigs and rodents, where it colocalizes with P-gp at the luminal side of endothelial cells of brain capillaries [11–15]. *Mdr1a* knockout mice have proven to be a valuable tool to unravel the dominant function of P-gp at the BBB [9]. In contrast, for ABCG2 it was not as straightforward to unequivocally establish a functional role at the BBB, despite the availability of mouse models deficient in either P-gp or Abcg2 [7–9]. This was illustrated by a number of studies, with sometimes contradicting outcomes. Shortly