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Human ABC Transporters at blood-CNS Interfaces as Determinants of CNS Drug Penetration

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Abstract: Since the discovery of P-glycoprotein (P-gp) in brain microvessels composing the human blood-brain barrier (BBB), ATP-binding cassette (ABC) transporters have been recognized as bottlenecks in the development and delivery of neuropharmaceuticals. ABC transporters are expressed predominately at the plasma luminal membrane of brain capillary endothelial cells. These ABC transporters are responsible for the efflux of their substrates from the endothelial cells to the bloodstream against the concentration gradient and thus limit the entry of some drugs within the central nervous system (CNS). Advanced quantitative molecular biology tools allowed gene and protein quantification of the components of microvessels isolated from different species including human. Recently, positron emission tomography using radiolabelled probes that are substrates of ABC transporters allowed the determination of their functional activity at the human BBB. Here, we summarized new information regarding the relative expression, substrate recognition pattern for CNS drugs and functional activity of ABC transporters that are quantitatively expressed at the human BBB.

Keywords: ATP-binding cassette transporters, blood-brain barrier, blood-cerebrospinal fluid barrier, P-glycoprotein, breast cancer resistance protein, multidrug resistance protein.

1. INTRODUCTION

Differential expression of transporters and metabolizing enzymes is one of the main factors that significantly contribute to the inter-individual variation in the bioavailability and vulnerability to drugs and xenobiotics. ATP-binding cassette (ABC) transporters, solute carrier (SLC) transporters and phase I and phase II metabolizing enzymes play a prominent role in modulating the pharmacokinetics (i.e. absorption, distribution, metabolism and excretion) of a broad range of endogenous and exogenous compounds. ABC and SLC transporters are selectively expressed at interfaces in brain, intestine, kidney, liver, placenta and testis where they have an impact on drug absorption, disposition and elimination [1, 2].

SLC transporter superfamily comprises more than 370 *SLC* genes in the human genome. These transporters play a vital role in maintaining the homeostasis of the human body *via* selective and regulated transport of nutrients, hormones, electrolytes, metal ions, and metabolites [3, 4]. While SLC transporters essentially allow the entry of substrates into the cell down their gradient concentration, transporters of the ABC superfamily efflux substrates outside the cell and thus act as a key element in the pharmacokinetics of several molecules. In the intestine, ABC transporters extrude substrates back into the lumen and hamper their absorption into the blood or lymph circulation [5, 6]. These transporters are determinants of the renal and biliary clearance since they are also responsible for excretion of xenobiotics and metabolites *via* bile and urine [7, 8]. In protected tissues like brain, placenta and testis, ABC transporters are expressed at barriers where they limit substrate uptake and distribution by effluxing their substrates from the tissue into the bloodstream [9].

The primary interfaces between the peripheral circulation and the central nervous system are the blood-brain barrier (BBB) and the blood–cerebrospinal fluid barrier (BCSFB). Since the early concept of the BBB proposed by Ehrlich and Goldmann at the beginning of the last century, the development of molecular biology and biochemistry tools including quantitative transcriptomic and proteomic approaches considerably brought new insights into the phenotype of the human BBB. The BBB is a dynamic neurovascular unit with delicate cellular configuration. The brain capillary endothelial cells (BMECs) sealed by tight and adherent junctions are in dynamic interaction with the pericytes that share the basal membrane with the BMECs and the astrocyte end-foot processes with the neuron axonal projections that almost entirely surround the brain microvessels. These specific features make the endothelial cells of the brain microvessels very different from those of peripheral tissues. The tight junctions restricts paracellular diffusion and the presence of specific transport proteins make the BBB a physical and a biochemical barrier that controls the entry of endogenous and exogenous compounds into the brain. The BCSFB is composed of a tight monolayer of cuboidal epithelial cells known as choroid plexus epithelial cells, which function as a barrier in the choroid plexus (CP). The CP is a highly vascularized structure located in the four brain ventricles and its blood capillaries are relatively permeable due to the non-tight junction architecture [10]. Also, the arachnoid barrier, a brain membrane envelope formed by a multilayered epithelium with tight junctions between the cells, is a barrier which only allows CSF movement out of the brain to blood; as it is non-vascularized, the arachnoid membrane is not an important route for the transport of molecules into the brain [11]. The ABC transporter superfamily is responsible for the efflux of xenobiotics from the brain into the bloodstream, making some ABC transporters key elements in controlling the brain penetration of many drugs and thus their central nervous system (CNS) effects [11-13]. Typically, ABC transporters display low substrate specificities which enable them to extrude a large number of structurally unrelated substrates. Therefore, the BBB not only acts as a passive barrier, but also actively efflux a large number of molecules from the brain. In this review we will focus on recent data concerning the expression, relative abundance and activity of ABC transporters in the human BBB.

2. HUMAN ABC TRANSPORTER GENES, PROTEINS AND ACTIVITIES IN THE BBB

2.1. Classification, Nomenclature, Structure and General Functions of Human ABC Transporters

ABC transporter superfamily members are grouped into subfamilies based on their amino acid sequence similarities and

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