



Current Drug Metabolism

ISSN (Print): 1389-2002

ISSN (Online): 1875-5453

VOLUME: 12

ISSUE: 8

DOI: 10.2174/138920011798357024 **Price:** \$58

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Interplay of Drug Metabolizing CYP450 Enzymes and ABC Transporters in the Blood-Brain Barrier

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Pages 732-741 (10)

Abstract:

The recent identification of drug-metabolizing enzymes cytochrome P450 (CYP) in the human blood-brain barrier (BBB) raises the question of whether these enzymes act in concert with ATP-binding cassette (ABC) transporters to limit the brain distributions of drugs. We recently demonstrated several CYP genes in freshly isolated human brain microvessels; the main isoforms expressed were CYP1B1 and CYP2U1. Many studies using different experimental approaches have revealed that P-glycoprotein (P-gp, ABCB1), breast cancer resistance protein (BCRP, ABCG2) and the multidrug resistance-associated protein 4 (MRP4, ABCC4) are the main ABC transporters in the human BBB. The first part of this review covers recent studies on the expression, regulation and function of CYP450 and ABC transporters in the rodent and human BBBs. The second part focuses on the possible interplay between some CYPs and certain ABC transporters at the BBB, which makes it a determining element of brain drug concentrations and thus of the effects of centrally acting drugs.

Keywords:

ATP-binding cassette transporters, blood-brain barrier, cytochromes P450, expression, interplay, regulation, brain microvascular endothelial cells (BMECs), first-pass effect, abluminal plasma membranes, CAR

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