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P-GLYCOPROTEIN – A REVIEW

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ABSTRACT

P-glycoprotein (P-gp), an efflux transporter aimed to pump hydrophobic toxins and xenobiotics thus preventing their toxicity. It is widely distributed in most body tissues and belongs to the ATP-binding cassette family of transporter molecules. It has major implications in pharmacokinetics, pharmacodynamic, chemotherapeutic drug resistance, drug interactions genetic polymorphism and diseases. This review summaries the various aspects of this P-gp implication.

KEYWORDS: P-glycoprotein, induction, inhibition.

INTRODUCTION

P-gp is a member of ATP binding cassette super family and encoded by MDR1 gene.[1] It is an efflux transporter that limits the bio-availability of various drugs by pumping them out of cells. It is highly expressed on the surface of biliary canalicular hepatocytes, epithelial cells of liver, pancreas, jejunum, colon, intestine, kidney and capillary endothelial cells of BBB.[2] In gut it decreases the oral bioavailability of drug in the intestine, by decreasing absorption of drugs in intestine and increasing drug excretion into bile and urine.[3] The high concentration of P-gp substrate in the intestinal lumen can saturate the transporter and hence these P-gp substrate does not show significant decrease in drug absorption. Brain exposure to anticancer drugs, antiviral, antibiotics and steroids is limited by presence of P-gp in blood-brain barrier.[4] P-gp drug transporter is modulated by the genetic polymorphism, drug and fluidity of the membrane. Its transcription is up regulated in cellular stress response to stimuli such as carcinogens, shock, inflammation, hypoxia, and ionizing radiation.

Consequences of p-glycoprotein modulation

Numerous single nucleotide polymorphisms and insertions/deletions in the P-gp has been established. P-gp polymorphisms might influence drug treatment by affecting expression of the transporter. It may modulate the susceptibility to diseases such as colon cancer, renal cancer, inflammatory bowel disease, (Table. 1) Parkinson's disease and metabolic diseases.[5]

Table 1: Effect of p-glycoprotein on drug action and diseases.

Diseases	P-gp	Causes	References
Cancer	Increases efflux of anti-cancer drugs.	Multi-drug resistance for anticancer drugs.	(lehne G).[6]
Ulcerative colitis	Decreases the expression of P-gp	It which lead to produce toxicity due to uptake of mesalamine.	(Sehirli AO).[7]
Rheumatoid arthritis (RA)	Increases P-glycoprotein function.	Multi drug resistance to DMARDs.	(Marchette S).[8]
Systemic lupus erythematosus (SLE)	Increases P-glycoprotein function.	Resistance for using SLE drugs.	(Kansal A).[9]
Epilepsy	Increases the expression of P-glycoprotein.	Resistance to anti-epileptic drugs.	(Tishler DM).[10]
Alzheimer's disease (AD)	Decreases P-gp function in blood brain barrier.	Reduces the clearance of βeta-amyloid peptide.	(Lam F).[11]
Parkinson's disease (PD)	Decreases P-gp function.	Dysfunction of P-gp in BBB, one of the main causes of PD.	(Bartels A).[12]

Anticancer drugs confer resistance in two ways, firstly due to resistance of cancer cells due to genetic and epigenetic reason. Secondly inhibition of anticancer drug transport to these cells. P-gp transporters contribute to chemotherapeutic resistance drugs[13] and inhibitors of P-gp are currently being studied widely as a strategy to overcome anticancer drug resistance[14] with significant decrease in drug systemic toxicity.

Induction of P-gp will reduce the bioavailability of drugs which lead to therapeutic failure and inhibition of P-gp will produce toxicity by increasing the bioavailability of drugs. For instance, rifampicin will induce P-gp efflux, decrease digoxin, tacrolimus bioavailability due to increased renal clearance. Carbamazepine induces P-gp efflux and decreases fexofenadine bioavailability.

Drugs that inhibit drug transporters leads to accumulation of drug substrates in cells and a reduction in drug dose is often necessary to avoid toxicity. Especially drug-drug interactions

(DDIs) involving anti-cancer drug are associated with life threatening toxicity. DDIs can cause the inhibition of P-gp transport and lead to increase penetration and culmination of drug in brain leading to detrimental consequences.[15] Also, its inhibition can lead to retention of endogenous substances such bile acids which lead to the development of cholestatic drug-induced liver injury.[5] Similarly drug interaction of P-gp substrate drug is possible when taken along with foods or herbal supplements containing flavonoids or St. John's Wort.

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