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COURSE: BCH 408 (PHARMACOLOGICAL BIOCHEMISTRY)

MATRIC NO: 16/SCI03/003

ASSIGNMENT

With the aid of relevant examples, describe drug transport by membrane proteins.

Membrane proteins are common proteins that are part of, or interact with biological membranes. Membrane proteins can either be integral membrane proteins or peripheral membrane proteins. Integral membranes are permanently attached to the membrane and such proteins can be separated from the biological membranes by means of detergents, non polar solvents. Integral proteins are of two basic categories transmembrane proteins that cross the membrane and act as pathways for ion and molecules; monotopic proteins are permanently bounded to the membrane but only from one side. Peripheral membranes proteins are transient proteins attached either to the lipid bilayer or to integral proteins by a combination of hydrophobic, electrostatic, and other non-covalent interactions.

The presence of membrane proteins makes the phospholipid membrane permeable and also enables communication with surrounding cells for the purpose of transporting nutrients into the cell or waste products out of it, or responds to external stimuli. The membrane proteins that are present in a particular membrane determine the substances to which it will be permeable and what signal molecules it can recognize. Transport proteins can be involved in the active absorptive influx of compounds, such as amino acids, oligopeptides, monosaccharides, mono- and di-carboxyic acids, bile acids, and several water-soluble vitamins, from the lumen into the portal bloodstream. Conversely, there are other transport proteins responsible for the active

efflux of drugs and xenobiotics from gut epithelial cells back into the lumen. Molecular characterization of transport proteins present in the gut epithelial plasma membrane has identified a number of transport protein families such as MDR (Watkins 1997), MRP (Kool et al. 1997), OATP (Tamai et al. 2000), OCT (Koepsell 1998) and OAT (Sekine et al. 1999). Pglycoprotein is present on the villus tip of the apical brush border membrane of gut enterocytes and is orientated to pump substrates from inside the cells back into the lumen of the intestine (Watkins 1997). In human studies, cyclosporin provides a good example of the impact of Pglycoprotein on oral absorption. Cyclosporin transport has been shown to be impaired by P-glycoprotein in a variety of P-glycoprotein-containing in vitro systems (Saeki et al. 1993). Similarly, cyclosporin absorption in man is decreased by intestinal P-glycoprotein (Watkins 1997) with a greater decrease in absorption from the colon, plus a concurrent increase in coe • cient of variation in oral blood levels, versus the stomach and jejunum, which appears to correlate with higher relative colonic levels of P-glycoprotein (Fricker et al. 1996). Intestinal P-glycoprotein is thought to contribute significantly to the limited absorption of a range of other drugs such as tacrolimus, digoxin , talinolol , fexofenadine , saquinavir and UK-224,671 (Beaumont et al. 2000).

Major liver sinusoidal and canalicular membrane transporters involved in transport of therapeutic drugs.

S/N	Common name of membrane transport protein	Gene family name	Subcellular location	Known drug substrates
1	MDR1	ABCB1		Cyclosporine, taxol, vincristine,

				vinblastine, doxorubicin, digoxin, talinolol, loperamide, erythromycin.
2	MRP2	ABCC2	canalicular	pravastatin, methotrexate, grepa¯oxacin, cefodizime, irinotecan
3	OATP-C	SLC21A6	sinusoidal	pravastatin, benzylpenicillin, BSP
4	OATP-A	SLC21A3	sinusoidal	fexofenadine, UK-191,005
5	MRP1	ABCC1	lateral membranes	Anticancer agents, anionic conjugates with glutathione, sulfate or glucuronide

Abbreviations

MRP2 multidrug resistance related protein

MDR multidrug resistance

OATP organic anion transporting polypeptide

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