DRUG TRANSPORT IN THE CARDIOVASCULAR SYSTEM
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Cardiovascular diseases are the leading cause of death worldwide. The hallmark of treatment is chronic drug therapy. In order to reach their therapeutic targets (eg, heart, blood vessels or peripheral cells) cardiovascular drugs have to pass multiple biomembranes. Successful therapy by the oral route, for example, requires uptake into the enterocyte, transfer to the vascular system and subsequent uptake into target tissue. It has been assumed for a long time, that these transfer processes are governed by biophysical properties of the respective compounds. Within the last decade, however, a significant number of in vitro experiments, animal studies and clinical trials pointed out that drug-transporting proteins are important modifiers along the entire process of a cardiovascular drug reaching its site of action.

Following oral administration drugs reach the intestinal wall as its first absorption barrier. The process of drug absorption is rather complex and modulated by active and passive uptake processes, mucosal metabolism and efflux transport. One of the first studies addressing the influence of the ABC-transporter P-gp on pharmacokinetics of digoxin was carried out by Greiner et al (1) and indicated that intestinal expression of P-gp predicts oral bioavailability of digoxin. Subsequent work unravelled a similar role for other proteins such as MRP2 (2). Both in the GI-tract and in the liver coordinated action of uptake and elimination transport modifies intracellular drug concentrations. At the basolateral membrane of hepatocytes predominately members of the solute carrier superfamily (SLC), the organic anion and cation transporters (OATs and OCTs; both SLC22A family) as well as organic anion transporting polypeptides (OATPs; SLCO family) are expressed (for review see 3). It has been demonstrated that single nucleotide polymorphisms in the SLCO1B1 gene, encoding for OATP1B1, markedly affect the in vitro transport activity as well as the pharmacokinetics and the lipid-lowering response to statins, eg pravastatin in humans. Most recently, a population based trial indicated, that a genetic variant in the SLCO1B1 predicts myopathy of statins, a major side effect of this class of drugs (4).

Other cardiovascular compartments have not been thoroughly investigated with respect to the role of intracellular pharmacokinetics and its modification by transport proteins. In human heart, P-gp and bcrp have been identified in the endothelial wall of both cardiac arterioles and capillaries (5, 6). Unlike P-gp and bcrp, MRP5 is expressed not only in the endothelium, but also in smooth muscle cells and cardiomyocytes. Moreover, it has been demonstrated that its expression is enhanced by ischemic cardiomyopathy. (7). Several uptake transporters have been identified in cardiac tissue. For example, the cation transporter OCTN2 has been localized in the endothelial wall of cardiac blood vessels and in vitro studies revealed a possible involvement of this transporter in the uptake of drugs such as verapamil and spironolactone (8). Another SLC transporter expressed in human heart is OATP2B1 and its cardiac expression is again mainly restricted to the endothelium and unaffected by cardiac diseases such as ischaemic or dilated cardiomyopathy (9). However, there are some in vitro and in vivo indications that statins, especially atorvastatin, reduce the expression of OATP2B1.

Peripheral cells of the cardiovascular system express transport proteins. Jedlitschky et al identified MRP4 in human platelets by immuno blotting and immuno fluorescence (10). These data indicate a function of MRP4 in platelet mediator storage. Therefore, inhibition of MRP4 may represent a novel mechanism for inhibition of platelet function by some anti-inflammatory drugs.

In summary, drug transporters are expressed throughout the entire cardiovascular system thereby modulating intracellular concentrations and hence actions of drugs.

References:


