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Review Article

Transporter-mediated natural product–drug interactions for the treatment of cardiovascular diseases

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ABSTRACT

The growing use of natural products in cardiovascular (CV) patients has been greatly raising the concerns about potential natural product–CV drug interactions. Some of these may lead to unexpected cardiovascular adverse effects and it is, therefore, essential to identify or predict potential natural product–CV drug interactions, and to understand the underlying mechanisms. Drug transporters are important determinants for the pharmacokinetics of drugs and alterations of drug transport has been recognized as one of the major causes of natural product–drug interactions. In last two decades, many CV drugs (e.g., angiotensin II receptor blockers, beta-blockers and statins) have been identified to be substrates and inhibitors of the solute carrier (SLC) transporters and the ATP-binding cassette (ABC) transporters, which are two major transporter superfamilies. Meanwhile, *in vitro* and *in vivo* studies indicate that a growing number of natural products showed cardioprotective effects (e.g., gingko biloba, danshen and their active ingredients) are also substrates and inhibitors of drug transporters. Thus, to understand transporter-mediated natural product–CV drug interactions is important and some transporter-mediated interactions have already shown to have clinical relevance. In this review, we review the current knowledge on the role of ABC and SLC transporters in CV therapy, as well as transporter modulation by natural products used in CV diseases and their induced natural product–CV drug interactions through alterations of drug transport. We hope our review will aid in a comprehensive summary of transporter-mediated natural product–CV drug interactions and help public and physicians understand these type of interactions.

1. Introduction

Natural products have been widely used among patients with cardiovascular (CV) diseases [1] and many patients often combined natural products with CV medications [2]. However, accumulating clinical evidence indicates that the combination use of natural products and conventional medicines has been paralleled by high risk of harmful natural product–drug interactions [3]. For instance, the patients given anticoagulant

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agents are at a higher risk of bleeding due to unwanted natural product–drug interactions when co-administered with natural products, such as ginkgo and danshen [4]. Despite increasing recognition of these types of natural product–drug interactions, improved understanding of the underlying mechanisms remain a pressing need for guiding the rational use of such combinational therapies.

Transporter-mediated natural product–drug interactions are increasingly acknowledged to play an important role in changing drug absorption and disposition and thus determine the efficacy and safety of drugs [5]. Generally, two transporter superfamilies including the solute carrier (SLC) transporters and the ATP-binding cassette (ABC) transporters are of considerable pharmacological significance [6]. Potential drug–drug interactions mediated by these two types of transporters are of clinical and regulatory concern [6]. In recent years, a large number of CV drugs have been identified as substrates of both SLC and ABC transporters [6–8]. Altered functions and expressions of these transporters may cause marked changes in the pharmacokinetics of these CV drugs, and many cases have either documented or suspected clinical relevance for patients with CV diseases [7,8]. In parallel, many natural products and their active ingredients were found to display modulatory effects on different drug transporters [5], and some transporter-mediated natural product–CV drug interactions have already shown to have clinical relevance. Aside from metabolizing enzymes [9,10], it is now well established that also modification of transport function is involved in natural product–drug interactions.

Therefore, this paper focuses on the recent understanding regarding transporter-mediated natural product–drug interactions for the treatment of CV diseases. We first briefly summarize the current knowledge on two major transporter families (ABC and SLC transporters) and their role in CV therapy. We then review transporter modulation by natural products used in CV disease and their induced natural product–drug interactions through affecting transporter expressions and functions. Lastly, a brief summary along with future perspectives for studying natural product–drug interactions is presented.

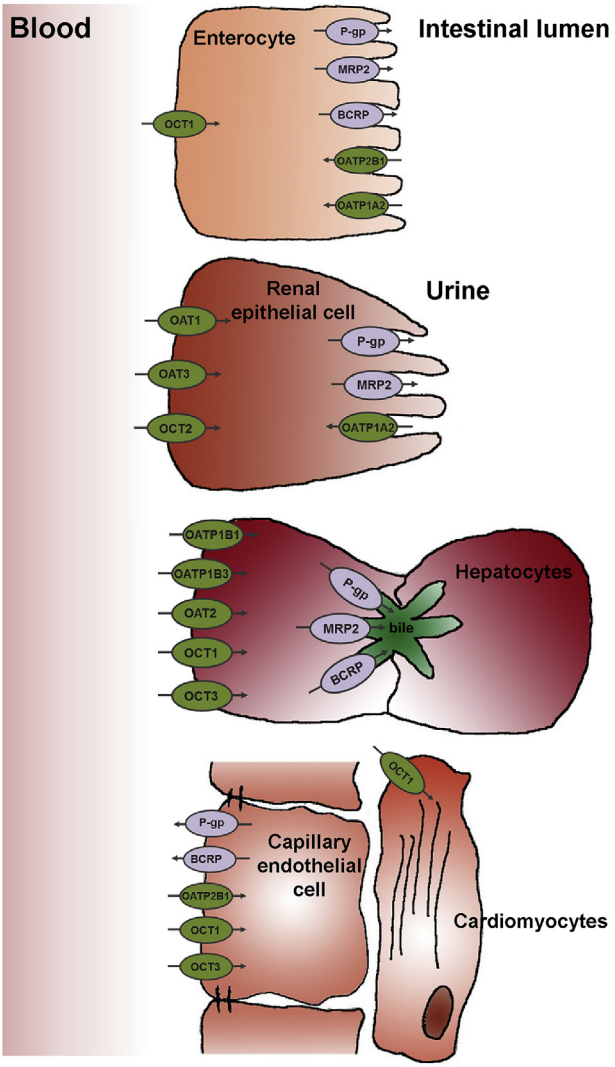

Fig. 1 – Major SLC and ABC transporters expressed in human enterocytes, renal epithelial cells, hepatocytes, heart capillary endothelial cells and cardiomyocytes.

2. Role of drug transporters in cardiovascular therapy

There are more than 400 membrane transporters that have been discovered until now, and generally fall into two classes of transporter proteins: the ABC (efflux) and the SLC (generally influx) transporters [11]. ABC and SLC transporters share a wide distribution in the body, and mediate the influx or bidirectional movement of drugs across the cell membrane. Since the intestine, liver, and kidney are the prime organs that determine drug absorption, distribution, and excretion, and the heart is one of principal target organs in CV diseases, this review focuses on the drug transporters expressed in these organs (Fig. 1).

The role of drug transporters in CV therapy received great interest because many CV drugs with a narrow therapeutic range, such as antiarrhythmic and anticoagulant agents, interacted with the drug transporters [7]. As demonstrated in Table 1, ATP binding cassette (ABC) transporters, organic anion transporting polypeptides (OATPs), organic anion transporters (OATs), and organic cation transporters (OCTs) are four major drug transporters involved in the efflux and uptake of CV drugs.

Numerous *in vitro* and *in vivo* experiments have lead to the identification of many of currently marketed CV drugs including angiotensin receptor blockers, antiarrhythmics, anticoagulants, antihypertensive agents, statins, antiplatelets, beta-blockers, calcium channel blockers, and endothelin receptor antagonist as P-glycoprotein (P-gp, also known as ABCB1 or MDR1) substrates and inhibitors [7,12–14]. Most of statins including atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin are substrates and inhibitors of multidrug resistance-associated protein 2 (MRP2, also known as ABCC2) [15]. Furthermore, MRP2-mediated transport of enalapril, fosinopril, eprosartan, olmesartan, and valsartan has also been shown [16–20]. In addition, five CV drugs

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