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Special Invited Article

Organic solute carrier 22 (SLC22) family: Potential for interactions with food, herbal/dietary supplements, endogenous compounds, and drugs

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ABSTRACT

Many drugs, hormones, components of herbal medicines, environmental pesticides and toxins are Solute Carrier family 22 (SLC22) substrates. The last twenty years has seen great progress in determining SLC22 tissue expression profiles, membrane localization, energetics, substrate profiles and biopharmaceutical significance. However, much still remains to be answered in terms of SLC22 family member's roles in 'normal' physiology as compared to pathophysiological states, as well as in drug interactions that impact pharmacokinetics, efficacy and toxicity. This review begins with a brief synopsis of SLC22 family discovery, function and tissue expression. Subsequent sections provide examples establishing a role for SLC22 transporters in food-drug, herbal supplement-drug, endogenous substrate-drug and drug–drug interactions.

1. Introduction

Over the last few decades increasing numbers of people have turned to herbal/dietary supplements, often with a rich history in traditional Chinese medicine (TCM), to alleviate illness, treat pathological conditions, enhance cognitive ability, boost self-confidence, etc. With their branding of being "natural," the use of herbal and dietary supplements has gained popularity worldwide as complementary therapy to conventional medicines, giving rise to emerging concerns of herb–drug interactions (HDIs) [1]. Use of herbal products by populations of developed countries has been steadily increasing, ranging between 31 and 71% in a recent survey, with as much as 66% of the population of Norway reporting the combined use of herbal products with prescribed medications [2,3]. According to the 2012 National Health Interview Survey, nearly 20% of American adults were using herbal products [4]. A recent comprehensive study concluded that amongst herbal product users in the United States, 38% were also taking prescription medications and 42% were also using over-the-counter products [5]. Thus, there is increasing potential for unintended interactions between components of herbal products, active pharmaceutical ingredients and their metabolites, and

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endogenous molecules that are competing for the same cellular transport pathways. Exacerbating this potential is the fact that, due to their perception as being innocuous, herbal medicines and dietary supplements are produced, marketed and consumed with little to no regard for quality or regulatory control [1,6].

Standardization is problematic on a number of levels. Unlike most approved medications which contain only one or two active ingredients, herbal supplements are often composed of a mixture of several different plant components that each contain multiple active compounds (regardless of whether or not they produce a therapeutic effect) leading to variations in the amounts and combinations of pharmacologically active ingredients in any given lot of product, for both a single manufacturer and between manufacturers [7,8]. A consequence of this is that the extremely limited data in the literature regarding plasma concentrations of components of herbal medicines/supplements after oral dosing do not accurately represent any marketed product(s). Indeed, often the studies do not actually use a marketed product at all, but rather custom prepared extracts that contain components believed to be the active ingredients in marketed products. Additional challenges associated with herbal medicines include scientific misidentification, product adulteration, active ingredient instability, as well as failure of patients to disclose their use to providers [9]. Given the dearth of randomized clinical trial data, efficacy and toxicity data for herbal remedies are difficult to obtain making the assessment of their claimed benefits challenging. Currently, adverse reactions associated with herbal supplement use, including HDIs, are likely to be underreported, and are likely to occur at increasing rates as long as these products continue to be sold to consumers [10–12]. As a culprit for synergizing, augmenting, antagonizing or neutralizing the effects of conventional medications, HDIs are responsible for a number of undesirable clinical outcomes as conveyed in several case reports [8,11–15]. Besides potentiating toxicity, pharmacokinetic drug interactions may also cause loss of pharmacotherapeutic efficacy of the victim drugs [16]. Consequently, it is paramount that increased effort be directed toward controlled studies characterizing the biological mechanisms that underlie HDIs.

Herbal components may affect the activity and function of endogenous metabolic enzymes and/or transporters and thus lead to changes in systemic levels and the extent of organ distribution of concomitant drugs. In conjunction with the well-established role of enzymes (*e.g.*, cytochrome P450s and uridine diphosphate-glucuronosyltransferases) in drug metabolism and clearance, increasing evidence has shown involvement of drug transporters in HDIs [8,17–24]. Drug transporters are known to be responsible for the translocation of both endogenous and exogenous compounds across cellular membranes affecting their absorption, distribution and elimination [25–29]. As a result, there is potential for both, disruption in the 'normal' distribution and elimination of endogenous compounds (*e.g.*, neurotransmitters, toxic waste products of metabolism) as well as HDIs involving pharmacologically active phytochemicals in herbal products interacting with drug transporters leading to clinically significant pharmacokinetic changes when taken concurrently with prescribed medicines, particularly medications with narrow therapeutic windows [30]. Therefore, the intent of this review is to explore recent evidence for potential contribution of members of the solute carrier 22 (SLC22) family to drug-food, -herbal supplement, -endogenous compound, and -drug, as well as possible herbal supplement/endogenous compound, interactions.

2. SLC22 transporter family

Almost a quarter century has passed since the cloning of the first member of what is now recognized as the SLC22 organic cation/anion/zwitterion transporter family. Currently, the Human Genome Organization Gene Nomenclature Committee recognizes some 50 SLC families (http://www.genenames.org/cgi-bin/genefamilies/set/752) with the SLC22 family containing 23 proposed members (Oat5 [Slc22a19] and Oat6 [Slc22a20] are currently rodent specific) [31]. Within this group, eight members are extensively understood in terms of transport function, substrate specificity and driving forces; OCT1 (SLC22A1), OCT2 (SLC22A2), OCT3 (SLC22A3), OAT1 (SLC22A6), OAT2 (SLC22A7), OAT3 (SLC22A8), OAT4 (SLC22A11) and URAT1 (SLC22A12). While SLC22 family members are expressed in virtually every barrier membrane within the human body (including the blood-testis barrier, blood-brain barrier, blood-cerebrospinal fluid barrier, and various CNS cell types) expression and function in kidney, liver and intestine has received the most attention (Fig. 1).

Positively and negatively charged hydrophilic organic molecules of low molecular weight enter cells through the organic cation and organic anion transport systems first identified well over a half-century ago [27]. Experiments with renal membrane vesicles, tissue slices and intact tubules demonstrated that the inside negative membrane potential of a cell drives the uptake (cellular entry) of organic cations [32]. That is, cellular entry of organic cations mediated by SLC22 family members is driven by facilitated diffusion, which is 'powered' by the membrane potential difference and chemical gradient (Fig. 2). The driving force for cellular exit mediated by this transport system was found to be a three-step process ending in organic cation/proton (H^+) exchange [32]. Initially, Na^+/K^+-ATPase directly hydrolyzes ATP and pumps Na^+ out of the cell to establish an inwardly directed Na^+ gradient, which is subsequently used by Na^+/H^+ exchanger 3 to establish an inwardly directed H^+ gradient, that ultimately serves to power cellular exit of organic cations via an organic cation/H^+ antiporter (Fig. 2).

For organic anions, cellular entry mediated by SLC22 family members requires energy input to drive their movement against the membrane potential (Fig. 2). Experiments utilizing the above-mentioned systems demonstrated that uptake was coupled to established ion gradients (*e.g.*, Na^+, α-ketoglutarate) and not to direct ATP hydrolysis [32]. That is, cellular entry of organic anions mediated by SLC22 family members is driven by a three step process (similar to exit of organic cations) in which Na^+/K^+-ATPase establishes the inwardly directed a Na^+ gradient, the Na^+/dicarboxylate symporter 3 utilizes the movement of Na^+ ions down their concentration gradient (into the cell) to power entry of α–ketoglutarate into the cell (maintaining an outwardly directed gradient) and,

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