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Human organic cation transporter 2 (hOCT2): Inhibitor studies using S2-hOCT2 cells

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ABSTRACT

Highly expressed in kidney and located on the basolateral membrane, human organic cation transporter 2 (hOCT2) can transport various compounds (*i.e.* drugs and toxins) into the proximal tubular cell. Using cultured proximal tubule cells stably expressing hOCT2 (*i.e.* S2-hOCT2 cells), we sought to probe different compound classes (*e.g.* analgesics, anti-depressants, anti-psychotics, disinfectant, herbicides, insecticides, local anesthetic, muscarinic acetylcholine receptor antagonist, sedatives, steroid hormone, stimulants and toxins) for their ability to inhibit ^{14}C-TEA uptake, a prototypical OCT2 substrate. Aconitine, amitriptyline, atropine, chlorpyrifos, diazepam, fenitrothion, haloperidol, lidocaine, malathion, mianserin, nicotine and triazolam significantly inhibited ^{14}C-TEA uptake; IC_{50} values were 59.2, 2.4, 2.0, 20.7, 32.3, 13.2, 32.5, 104.6, 71.1, 17.7, 52.8 and 65.5 μM, respectively. In addition, aconitine, amitriptyline, atropine, chlorpyrifos, fenitrothion, haloperidol, lidocaine, and nicotine displayed competitive inhibition with K_i values of 145.6, 2.5, 2.4, 24.8, 16.9, 51.6, 86.8 and 57.7 μM, respectively. These *in vitro* data support the notion that compounds pertaining to a wide variety of different drug classes have the potential to decrease renal clearance of drugs transported *via* hOCT2. Consequently, these data warrant additional studies to probe hOCT2 and its role to influence drug pharmacokinetics.

1. Introduction

Renal tubular transporter proteins are well known to excrete and/or reabsorb endogenous (*e.g.* urate, mercapturic acids) and exogenous compounds (*e.g.* drugs, toxins) (Koepsell et al., 2003; Koepsell and Endou, 2004; Jonker and Schinkel, 2004; Wright and Dantzler, 2004). Since organic anions and cations do not readily penetrate cell membrane lipid bilayers, transporters are required to actively secrete compounds into and out of the proximal tubules (Wright and Dantzler, 2004). Albeit not all-inclusive, Fig. 1 provides a renal transporter summary. The first secretion step requires that a drug or metabolite cross the basolateral membrane (*i.e.* blood–cell interface). For example, organic cation transporter 2 (OCT2) is a solute carrier 22A (SLC22A2) transporter family member and known to transport various clinically useful drugs (Bendayan, 1996; Wright, 2005). OCT2 can mediate organic compound (400–600 amu) cellular uptake and elimination throughout the body (Jonker and Schinkel, 2004; Wright, 2005). OCT2 was first reported in rat (rOCT2; Okuda et al., 1996) followed by pig (pOCT2; Grundemann et al., 1997), human (hOCT2; Gorboulev et al., 1997) and mouse (mOCT2; Mooslehner and Allen, 1999). The genes encoding hOCT2 have been identified in chromosome 6q26 (Koehler et al., 1997) and encode 555 amino acids (Boom et al., 1992). Regarding tissue distribution, human liver highly expresses hOCT1 while kidney predominately exhibits hOCT2 (Fig. 1; Motohashi et al., 2002; Koepsell, 2004); hOCT2 expression has also been detected in central neurons, intestine, placenta and spleen (Gorboulev et al., 1997; Busch et al., 1998; Koepsell et al., 2003). In humans, hOCT2 mediates organic cation renal translocation *via* facilitative diffusion (Inui et al., 2000; Motohashi et al., 2002) with most substrates being monovalent (*e.g.* tetraethylamine: TEA. Fig. 2; Koepsell et al., 2007) and designated "Type 1" (Meijer et al., 1999; Wright, 2005). Functional studies have demonstrated that OCTs have overlapping substrate and inhibitor specificities (Koepsell, 1998; Inui et al., 2000; Urakami et al., 2001, 2002). Drugs known to be transported by OCT2 (Fig. 2) include histamine receptor antagonist cimetidine (Barendt and Wright, 2002), anti-diabetic drugs metformin and phenformin (Dresser et al., 2002; Kimura et al., 2005), the anti-Parkinson's disease drugs amantadine and memantine, the neurotoxin 1-methyl-4-phenypyridinium (Busch et al., 1998) and the anti-neoplastic drug cisplatin (Ciarimboli et al., 2005). Moreover, hOCT2 accepts endogenous monoamines such as dopamine, histamine, norepinephrine and serotonin (Busch et al., 1998). Hence, due to the fact that

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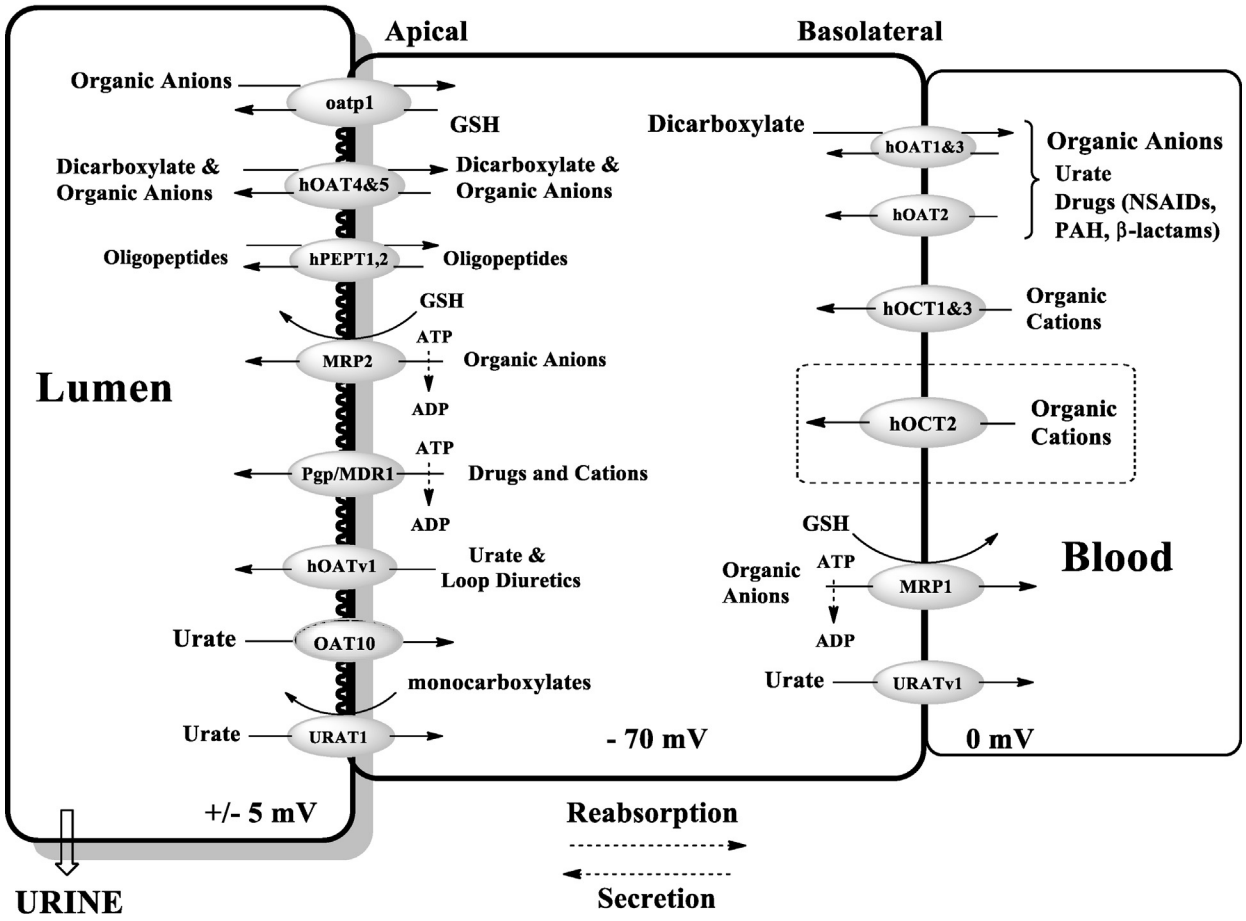

Fig. 1. Renal tubular cell transporters. Human renal tubular cell transporter protein summary.

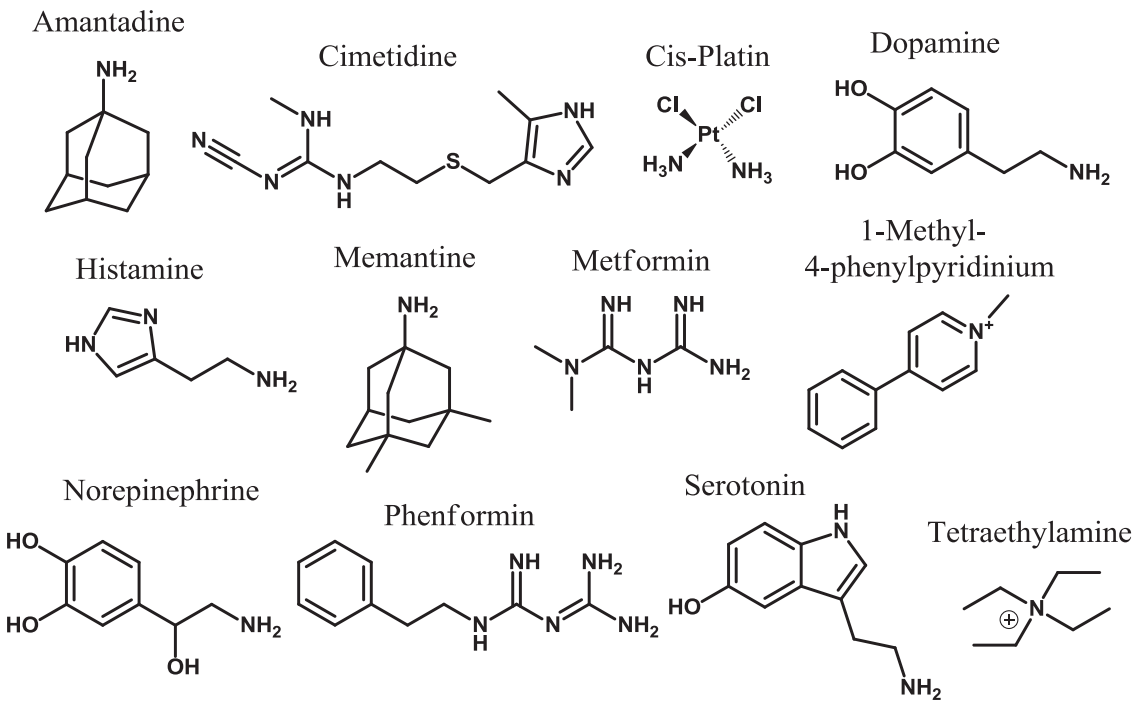

Fig. 2. Chemical structures of known OCT substrates.