3736490 SCPS/D : MAJOR : PHYSIOLOGY ; Ph.D. (PHYSIOLOGY)
KEY WORDS : ORGANIC ANION TRANSPORTER/ NONSTEROIDAL ANTI-INFLAMMATORY DRUGS/ PROSTANOIDS/ EXCHANGER

NOPPORN APIWATTANAKUL : TRANSPORT PROPERTIES OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND PROSTANOIDS BY ORGANIC ANION TRANSPORTER 1. THESIS ADVISORS : SAMAISUKH SOPHASAN, Ph.D. CHUMPOL PHOLPRAMOOL, Ph.D. PAWINEE PIYACHATURAWAT, Ph.D. PIYARAT GOVITRAPONG, Ph.D. WATTANA WATANAPA, M.D., Ph.D. 176 p. ISBN 974-662-862-3

The organic anion transporter 1 (OAT1) has recently been cloned from rat kidneys (23). OAT1 is considered to be dicarboxylate/organic anion exchanger of proximal tubules and to play the central role in the excretion of various anionic drugs from the body. The present study was aimed at characterizing the exchanger and multispecific property of OAT1 using both *Xenopus laevis* oocyte and stable mouse renal proximal tubule S_3 cell line expression systems. OAT1 exhibited nearly the same transport characteristics in [^{14}C] para-aminohippurate (PAH) uptake by both systems. Preincubation with glutarate or PAH enhanced the subsequent [^{14}C] PAH uptake. All 21 tested drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs) and some other analgesic drugs, with different chemical structures, and prostanoids were shown to inhibit OAT1-mediated PAH uptake. When 7 of these NSAIDs and 2 other analgesic drugs were further studied, the kinetics of all of them showed competitive inhibition. Radiolabelled acetylsalicylate, salicylate, and indomethacin were taken up by OAT1. The uptake rate of these NSAIDs was enhanced by the outwardly-directed dicarboxylate gradient. The efflux of the preloaded [^{14}C] PAH from OAT1-expressing oocytes was trans-stimulated by hydrophilic substrates. In contrast, for hydrophobic NSAIDs, the efflux was concentration dependent. At high concentration, efflux was suppressed, whereas it was stimulated at lower concentration. Noticeably, paracetamol, meclofenamate, and diclofenac exerted higher cytotoxicity toward OAT1-expressing S_3 cells than non-expressing S_3 cells. Furthermore, all prostanoid tested, PGE_1, PGE_2, PGD_2, PGI_2, TxB_2 and 6-keto $PGF_{1\alpha}$, inhibited [^{14}C] PAH uptake. [^{3}H] PGE_2 was proved to be transported by OAT1. Similarly, the induction of [^{14}C] PAH efflux by PGE_2 was also concentration dependent. The present study clearly showed that OAT1 is a multispecific transporter and is not only responsible for renal uptake and secretion of the unchanged form of NSAIDs and prostanoids but also drug induced cytotoxicity. This transporter also functions as an exchanger. Hydrophilic substrates are likely to be transported by OAT1. In contrast, transport of hydrophobic substrates by OAT1 may be concentration dependent. At high substrate concentration, exchanging activity of OAT1 may be inhibited. From this study, it was concluded that OAT1 functions as an exchanger; it can interact with all drugs tested and can transport some NSAIDs tested and PGE_2. OAT1 may be one of the important transporter in the kidney responsible for elimination of the tested substances from the body.