Improved Intestinal Membrane Permeability of Hexose-Quinoline Derivatives via the Hexose Transporter, SGLT1

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ABSTRACT: Intestinal membrane permeability is an important factor affecting the bioavailability of drugs. As a strategy to improve membrane permeability, membrane transporters are useful targets since essential nutrients are absorbed efficiently via specific transporters. For example, there are reports that intestinal hexose transporters could be used as a tool to improve permeability; however, there has been no direct evidence that the transporter protein, sodium/glucose cotransporter 1 (SGLT1), is involved in the transport of hexose analogs. Accordingly, we examined directly whether the intestinal membrane permeability of hexose analogs can be improved by utilizing SGLT1. Three hexose-quinoline derivatives were synthesized and their interactions with SGLT1 were evaluated. Among the three derivatives, the glucose-quinoline molecule exhibited an inhibitory effect on D-glucose uptake by both rat intestinal brush-border membrane vesicles (BBMVs) and *Xenopus* oocytes expressing SGLT1. In addition, significant uptake of the glucose-quinoline derivative by *Xenopus* oocytes expressing SGLT1 was observed by both an electrophysiological assay and direct measurement of the uptake of the compound, while the galactose-quinoline derivative did not show significant uptake via SGLT1. Thus, it was directly demonstrated that SGLT1 could be used as a tool for the improvement of intestinal membrane permeability of drugs by modification to the glucose analogs. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:1821–1830, 2008

Keywords: intestinal absorption; hexose transporter; SGLT1; transporters; drug delivery; oral absorption; membrane transport

Abbreviations used: BBMVs, brush-border membrane vesicles; Gal-Q, 4-(β-D-galactosyloxy)-quinoline; Gluc-Q, 4-(β-D-glucosyloxy)-quinoline; IC_{50}, half-inhibitory concentration; HPLC, high-performance liquid chromatography; Man-Q, 4-(β-D-mannosyloxy)-quinoline; SGLT, sodium/glucose cotransporter.

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INTRODUCTION

Permeability across the intestinal brush-border membrane is an important factor affecting the bioavailability of orally administered drugs. Mechanisms of intestinal membrane transport include simple diffusion and carrier-mediated transport. Water-soluble nutrients such as sugars, oligopeptides, and hydrophilic vitamins are absorbed well via their respective transporters. These nutrient transporters, therefore, may be useful targets for improving the intestinal membrane permeability of orally administered drugs.

There are several reports of attempts to enhance the intestinal absorption of drugs by utilizing the intestinal oligopeptide transporter, PEPT1.[1–4] This transporter is one of the best targets to be used for the improvement of the intestinal membrane permeability for poorly absorbable drugs, because PEPT1 possesses high capacity and broad substrate selectivity. This strategy was applied to improve the intestinal absorption of amino acid-like compounds such as L-dopa by derivation to L-dopa-L-phe and the β-lactam antibiotic, cefixime, via PEPT1.[1,5] In the present study, we investigated whether another nutrient transporter, that is, the glucose transporter, SGLT1, can be used as a tool to improve the permeability of quinoline by derivation to the hexose-quinoline.

Previously, it was reported that hexoses modified with aromatic groups (e.g., 1- or 2-naphthyl glycoside, *p*-nitrophenyl glycoside) or a tetrapeptide glycosylated with α- or β-D-glucopyranoside were transported via the glucose transporter (GLUT) in the rat small intestine using a modified everted sac technique and isolated intestinal brush-border membrane vesicles (BBMVs).[6–12] However, there are two types of hexose transporters in the human and rat small intestine, the sodium/glucose cotransporter (SGLT) and the sodium independent GLUT. It was reported that SGLT1, 3, 4, and 6, and GLUT2, 5, 9 and 12 were expressed in the human small intestine.[13,14] SGLT1, the first sodium dependent GLUT to be identified, mainly participates in the absorption of nutritional D-glucose and D-galactose in the small intestine across the apical membrane of epithelial cells.[15] The K_m values of D-glucose and D-galactose for human SGLT1 are 0.5 and 0.6 mM, respectively.[16] SGLT3 is not a GLUT, but rather a glucose sensor in the plasma membrane of cholinergic neurons and other tissues.[17] SGLT4 exhibits sodium-dependent transport of α-methyl-D-glucopyranoside with an apparent K_m value of 2.6 mM and it can transport mannose, 1,5-anhydro-D-glucitol and fructose.[18] SGLT6 transports *myo*-inositol and D-glucose.[13] GLUT2 is expressed at basolateral membrane of the small intestine and the K_m values of D-glucose, D-galactose, D-mannose, and fructose are 17, 92, 125, and 76 mM, respectively, while GLUT 5 is expressed at the apical and lateral membranes in the small intestine and mainly transports fructose ($K_m = 6$ mM).[14] At present, the localization of GLUT 9 and GLUT12 are unknown in the small intestine.

Among those hexose transporters expressed in the small intestine, we selected SGLT1 as the target hexose transporter in the present study, since it is well understood to contribute to the intestinal apical membrane permeation of hexoses. In addition, β-naphthyl-D-glucoside may also be transported by SGLT1 based on voltage clamp experiments in *Xenopus* oocyte expressing SGLT1.[19] Although several previous studies suggested that those glycosides are absorbed by SGLT1, there was no direct evidence that SGLT1 transported those hexose derivatives, since those studies used intestinal tissues which express several hexose transporters as the experimental methods. Therefore, we examined whether SGLT1 can transport the hexose-derivatives and improve their intestinal absorption using hexose analogs synthesized newly in the present study.

This study focused on quinoline, an antimalarial drug, as the model compound to examine its interaction with SGLT1 after derivation to hexose analogs (Fig. 1). Quinoline-hexose analogs were chosen, since glucose is the primary energy source for the malaria parasite,[20] which makes use of the GLUT for efficient intake of sugars.[21] Accordingly, the final purpose of our research is to deliver drugs for malaria via the malarial hexose transporter. In the present study, the aim was to directly demonstrate whether SGLT1 could transport hexose derivatives of quinoline for the purpose of the improvement in the intestinal membrane permeability of hexose derivatives.

EXPERIMENTAL

Materials

[^{3}H]D-Glucose (740 GBq/mmol) was purchased from American Radiolabeled Chemicals, Inc. (St.

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