Sodium-Dependent Phosphate Cotransporters: Lessons from Gene Knockout and Mutation Studies

KEN-ICHI MIYAMOTO,[1] SAKIKO HAITO-SUGINO,[1] SHOJI KUWAHARA,[1] AKIKO OHI,[1] KENGO NOMURA,[1] MIKIKO ITO,[1,2] MASASHI KUWAHATA,[1,3] SHINSUKE KIDO,[1] SAWAKO TATSUMI,[1] ICHIRO KANEKO,[1] HIROKO SEGAWA[1]

[1]Department of Molecular Nutrition, Institute of Health Biosciences, University of Tokushima Graduate School Tokushima 770-8503, Japan

[2]Department of Food Science and Nutrition, University of Hyogo School of Human Science and Environment, Hyogo 670-0092, Japan

[3]Department of Food Sciences and Nutritional Health, Graduate School of Life and Environmental Sciences, Kyoto Prefectural University, Kyoto 606-8522, Japan

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ABSTRACT: Inorganic phosphate (Pi) is an essential physiological compound, highlighted by the syndromes caused by hypo or hyperphosphatemic states. Hyperphosphatemia is associated with ectopic calcification, cardiovascular disease, and increased mortality in patients with chronic kidney disease (CKD). As phosphate control is not efficient with diet or dialysis, oral Pi binders are used in over 90% of patients with renal failure. However, achieving tight control of serum Pi is difficult, and lower levels of serum Pi (severe hypophosphatemia) do not lead to better outcomes. The inhibition of sodium-dependent Pi (NaPi) transporter would be a preferable method to control serum Pi levels in patients with CKD or patients undergoing dialysis. Three types of NaPi transporters (types I–III) have been identified: solute carrier series SLC17A1 (NPT1/NaPi-I/OATv1), SLC34 (NaPi-IIa, NaPi-IIb, NaPi-IIc), and SLC20 (PiT1, PiT2), respectively. Knockout mice have been created for types I–III NaPi transporters. In this review, we discuss the roles of the NaPi transporters in Pi homeostasis. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:3719–3730, 2011

Keywords: membrane transporter; solute transporters; phenotype; renal reabsorption intestinal secretion/transport; renal excretion

INTRODUCTION

Inorganic Phosphate Homeostasis and Sodium-dependent Inorganic Phosphate (NaPi) Cotransporters

Inorganic phosphate (Pi) is an essential nutrient for several biological functions, including intracellular signal transduction, the production and function of cell membranes, and energy exchange.[1,2] The maintenance of constant circulating levels of Pi depends on the coordinated activity of three major organs: the intestine, the kidney, and the bones.[1,2] To achieve these functions, a transport system is required to transfer Pi across hydrophobic cell membranes.[1,2] Pi (re)absorption in the renal proximal tubules and small intestine is important for Pi homeostasis.[1,2] The kidney is the major regulator of Pi homeostasis, and its Pi reabsorptive capacity change to accommodate the body's need for Pi. Considerable effort has been devoted to the study of Pi transport in the kidney. Up to 70% of the filtered Pi is reabsorbed in the proximal tubule, in which Na^+-dependent Pi transport systems (NaPi) in the brush border membrane (BBM) mediate the rate-limiting step in the overall Pi reabsorption process.[1,3]

Three types of NaPi transporters have been identified: solute carrier series SLC17, SLC34, and SLC20 types I–III, respectively (Fig. 1 and Table 1).[3] SLC17A1 (NPT1) is expressed in the liver and the kidney.[3] However, the role of the NPT1 in Pi homeostasis is unclear. The type II transporter (NaPi-II) is thought to be the most important transporter of Pi.[3,4] The third type of NaPi cotransporter, type III, was

Correspondence to: Ken-ichi Miyamoto (Telephone: +81-88-6337081; Fax: +81-88-6337082; E-mail: miyamoto@nutr.med.tokushima-u.ac.jp)

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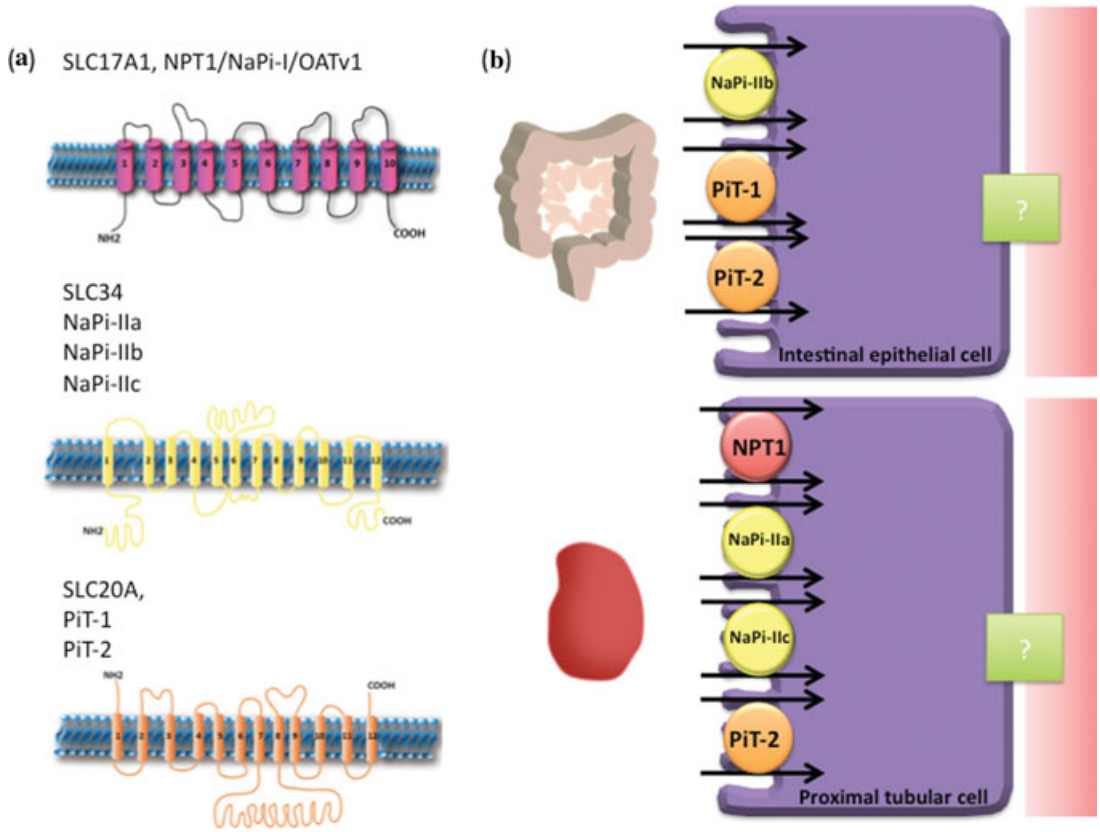

Figure 1. Sodium dependent inorganic phosphate (NaPi) cotransporters. (a) Membrane topology of the NaPi transporters. Three types (types I–III) of NaPi cotransporters have been identified: solute carrier series SLC17A1 (NPT1/NaPi-I/ OATv1), SLC34 (NPT2a, NPT2b, NPT2c), and SLC20 (PiT1/2), respectively. (b) Localization of the NaPi transporters in the intestine and the kidney. SLC34A2 (NaPi-IIb), SLC20A1 (PiT-1/), and SLC20A2 (PiT-2) are localized on the apical side of the intestinal epithelial cells. SLC34A1 (NaPi-IIa), SLC34A3 (NaPi-IIc), and SLC20A2 (PiT-2) are localized on the apical side of the renal proximal tubule cells.

originally identified as a family of cell-surface receptors for gibbon ape leukemia virus and murine amphotropic retrovirus.[3,5] In contrast to the type I and II, the type III NaPi transporters are expressed ubiquitously in several species.[5] Parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 are also regulators of Pi homeostasis,[4,6] and recent studies have identified other factors that contribute to the maintenance of Pi homeostasis, including phosphatonins [fibroblast growth factor (FGF) 23, secreted frizzled-related protein 4, matrix extracellular phosphoglycoprotein, etc.).[4,6] These factors regulate the levels of NaPi transporters in various organs including the kidney (Fig. 2).[4,6]

Genetic knockouts of various NaPi transporters have been used to understand the physiological roles of these transporters.[6] These models have also been and are still used to study the *in vivo* functions of Pi influx. However, given the extensively overlapping substrate specificities of the NaPi transporters, it is often difficult to unravel their separate roles or to understand the significance of this functional overlap using single knockout mice.[6] For example, when one transporter is absent, another transporter may partly or completely compensate for its loss. Consequently, mice in which a single transporter gene is knocked out will often fail to manifest a discrete phenotype. In this review, which aims to identify the target molecule of a new drug, we discussed the roles of the types I–III NaPi cotransporters on body Pi homeostasis.

Type I Sodium-dependent Phosphate Transporter

The bulk reabsorption of filtered Pi occurs along the renal proximal tubule.[3,4,7–9] SLC17A1 (NPT1/NaPi-I/OATv1) was identified in an expression cloning study using *Xenopus laevis* oocytes based on the NaPi transport, and it was also localized to the apical side of the proximal tubules (Table 2).[3,10] Follow-up *in vitro* studies indicated that this transporter is involved in the proximal tubule transport of organic anions rather than Pi.[11–13] However, the role of NPT1 in organic anion or Pi homeostasis *in vivo* remains unclear. Oocytes expressing rabbit NPT1 also take up neutral red and benzylpenicillin.[14] HEK

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