Pflügers Archiv - European Journal of Physiology (2019) 471:1–6
https://doi.org/10.1007/s00424-018-2245-6

EDITORIAL

Phosphate transport: from microperfusion to molecular cloning

Heini Murer[1] · Jürg Biber[1] · Ian C. Forster[2] · Andreas Werner[3]

Received: 3 December 2018 / Accepted: 4 December 2018 / Published online: 19 December 2018

Inorganic phosphate (P_i) is a constituent of important biological molecules (e.g., nucleic acids and phospholipids) and is essential for cellular energetics and signaling, and protein synthesis as well as skeletal development in all mammalian organisms. Inadequate P_i supply causes bone malformations such as rickets and spinal deformations, whereas an excess in P_i is linked to vascular calcification or ectopic CaP_i deposits. In general, whole-body P_i homeostasis is maintained by transepithelial transport mechanisms in the small intestine and kidney where P_i is absorbed from the diet and reabsorbed from the glomerular filtrate, respectively. The renal proximal tubule is the main locus of P_i regulation so that under "steady-state" physiological conditions, renal P_i-excretion corresponds approximately to dietary P_i intake.

Membrane transport proteins belonging to the SLC34 solute carrier family[1] lie at the heart of maintaining P_i homeostasis. In the small intestine, NaPi-IIb (SLC34A2) mediates luminal P_i uptake together with a paracellular component, whereas the renal isoforms NaPi-IIa (SLC34A1) and NaPi-IIc (SLC34A3) are responsible for P_i reabsorption in the proximal tubule. This Special Issue focusing on phosphate transport mediated by SLC34 proteins was conceived to coincide with an important milestone in renal physiology: the expression cloning of the first member of the SLC34 family (NaPi-IIa) just over a quarter of a century ago [33]. This, together with the subsequent identification of the other two SLC34 isoforms [24, 42], has paved the way for a deeper understanding of the molecular basis of P_i homeostasis, many aspects of which are the subject of dedicated reviews in this issue. Whereas the pivotal role of SLC34 cotransporters in maintaining P_i homeostasis is undisputed, other carriers such as PIT-1 and PIT-2 (SLC20 family) may also contribute to epithelial transport of P_i in the intestine and the kidney. However, their respective contributions to

[1] Historically, the nomenclature of the cloned, mammalian P_i transporters followed a strictly chronological convention, beginning with the type 1 (NaPi-I) [10, 53] (since shown to be related to an anion conductance and not directly mediate Na-dependent P_i transport [8]); the type II (NaPi-II [33] or npt2) and the type III (NaPi-III [28, 29], or Pit-1,2). The widely used solute carrier (SLC) nomenclature [22] assigns the type I transporters to the SLC17 gene family; type II Na-P_i transporters to SLC34 and type III transporters to SLC20, respectively. The SLC system is increasingly used, i.e., SLC34A1, SLC34A2, and SLC34A3 for the human type II transporters NaPi-IIa, NaPi-IIb, and NaPi-IIc, respectively. The structurally similar isoforms are grouped into the same sub-family (SLC34A) with individual indices (1, 2, 3). This nomenclature is easily applicable to most vertebrates; it only becomes less clear in the case of fish that have undergone genome duplications followed by lineage specific gene losses.

This article is part of the special issue on Phosphate transport in Pflügers Archiv – European Journal of Physiology

✉ Jürg Biber
juergbiber@access.uzh.ch

Heini Murer
Heini.murer@grc.uzh.ch

Ian C. Forster
Ian.forster@florey.edu.au

Andreas Werner
Andreas.werner@ncl.ac.uk

[1] Department of Physiology, University of Zurich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

[2] Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia

[3] Epithelial Research Group, Newcastle University, Institute for Cell and Molecular Biosciences, Newcastle, UK

overall P_i balance remain to be clarified and will not be the main focus of the present Special Issue.

Following the cloning of NaPi-IIa [33], the phosphate physiology field has progressed rapidly, benefitting from advances in molecular and cell biology, imaging, and biophysical assays, as exemplified by the invited articles. Therefore, it is easy to overlook how key aspects of our present knowledge of P_i handling had already been established prior to 1993. A brief reflection on the main findings of these earlier studies seems appropriate to set the scene for the developments that have taken place over the past 25 years.

Indeed, in the three decades that preceded the NaPi-IIa cloning, ground-breaking studies using ex vivo and in vivo preparations revealed fundamental properties of P_i transport physiology that are still valid today, including the location of active sites of absorption and reabsorption, the energetic basis of the transport mechanism, and the identification of some of the key physiological regulators. One of the first attempts to identify the site of renal P_i reabsorption involved micropuncture of intact kidneys to compare samples of fluid from the renal tubules in normal and P_i-loaded rats [45]. It was shown that the reabsorption of filtered P_i occurs primarily in the proximal tubules and furthermore, it was concluded that this process probably involves an active transport process [45]. Later, using the standing droplet method and simultaneous microperfusion of the peritubular capillaries performed in situ on superficial renal tubules (e.g., [40]) (Fig. 1A), Ullrich and colleagues at the MPI in Frankfurt established unequivocally that P_i is reabsorbed from the primary

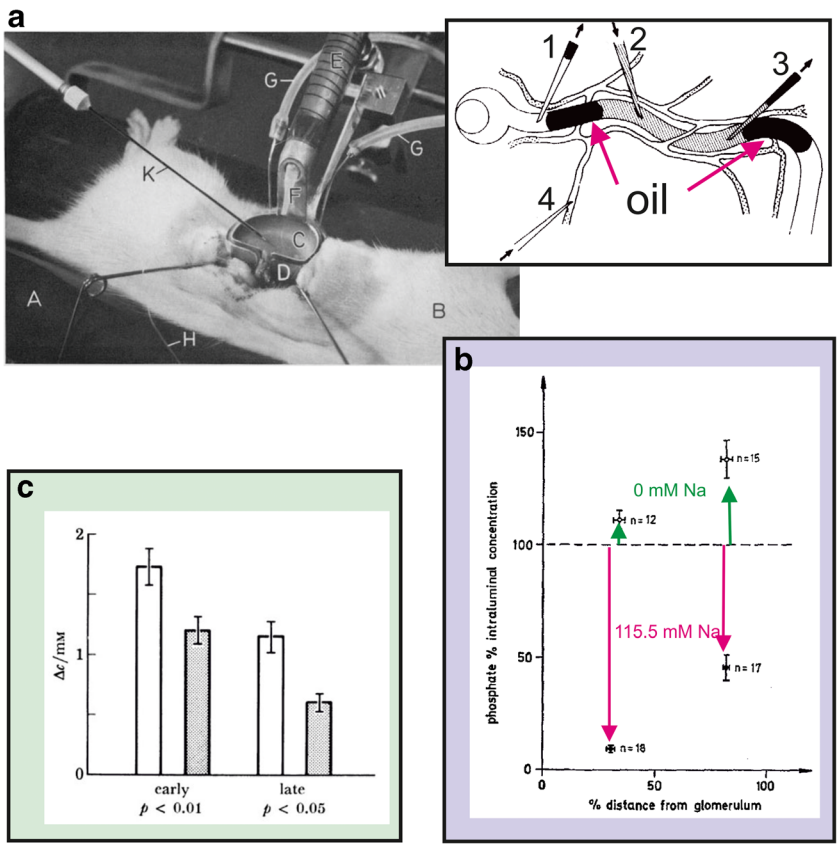

Fig. 1 Evidence for transepithelial P_i transport in renal tissue demonstrated by microperfusion assays on the intact kidney. A) General features of the experimental setup to perform microperfusion of superficial renal proximal tubules. Photograph shows the rat preparation: A: animal table; B: rat; C: inner kidney cup; D: outer kidney cup; E: outer cup holder; F: perfusion tube; G: suction; H: catheter in ureter; K: oil-filled micropipette (adapted and modified from [49]). *Inset* summarizes different aspects of micropuncture techniques showing pipettes for collection of tubule fluid (1, 3) tubule perfusion (2), and perfusion of peritubular capillaries (4). In the standing oil droplet approach, an oil droplet is first injected using a double-barrelled pipette (not shown) and the droplet split (black areas) by injection of the test solution that also contains a non-reabsorbable solute. Modified from Fig. 1, ref. [40]. B) Transport of P_i is Na^+-dependent determined at two positions along the proximal tubule: in the presence of Na^+ on either side of the epithelia, achieved by means of double microperfusion involving continuous perfusion of peritubular capillaries and stop flow microperfusion of the proximal tubule [2]. The intraluminal P_i concentration (expressed as a % of the initial 2 mM concentration after 45 s exposure) is significantly reduced, whereas in the absence of Na^+, there is a small increase in P_i. Data taken from [2]. C) Effect of parathyroid hormone (PTH) on P_i transport in the early and late rat proximal tubule using the double microperfusion method as in B). The luminal perfusate contained initially 2 mM P_i; hence, a concentration difference (Δc) of maximally 2 mM could be detected indicating that all P_i is reabsorbed. When PTH was given intravenously, this led to ~ 40% decrease of P_i transport in both early and late tubules within minutes (maximum at 15 min). Empty bars represent control and filled bars show effect of PTH given intravenously. Data taken from [51]

urine along the proximal tubule with highest rates occurring in the early part of the tubule [2]. These in vivo epithelial transport assays demonstrated that reabsorption of P_i in the proximal tubules is strictly dependent on the presence of sodium ions in the luminal medium (Fig. 1B). Importantly, the Frankfurt group provided the first insights into the regulation of renal P_i reabsorption. Their experiments revealed that parathyroid hormone (PTH) downregulates the rate of P_i reabsorption and that the reabsorption rate is influenced by dietary P_i [50, 51] (Fig. 1C). From such in vivo studies, it became clear that proximal tubular reabsorption of P_i was indeed *not* paracellular, but rather involved a first transport step through the apical (brush border) membrane of the epithelia and a subsequent exit step across the basolateral membrane [37, 50]. In the following years, the interest focused on functional aspects of the transport mechanism at the cell membranes facing either the tubular lumen or the peritubular interstitium. A novel technique, free-flow electrophoresis, allowed the isolation of brush-border and basolateral membrane vesicles simultaneously and enabled a direct comparison of the two transport steps [21, 25]. However, the isolated basolateral membranes (BLMV) were of random orientation and represented a mix of "inside out" and "outside out" vesicles, thus making the basolateral P_i exit step challenging to investigate [18]. The findings obtained with free-flow separated vesicles were complemented by transport studies with basolateral membrane vesicles isolated by Percoll gradient [18]. These seminal experiments established that the Na^+ dependent step is localized at the brush border membrane and the basolateral translocation of P_i is Na^+ independent [19]. Thus, proximal tubular reabsorption of P_i could be described as a classical secondary active transport process that relies on the Na/K-ATPase to establish the necessary electrochemical driving force. To conceptualize these findings, a model was proposed whereby the transmembrane Na^+ gradient drives the reabsorption of P_i via a Na^+-coupled P_i cotransporter system (Fig. 3). A Na^+-independent mechanism (possibly an anion-exchanger) would then complete the net transcellular P_i movement from the primary urine to the peritubular space. Whereas the identity of the apical transport protein was soon to be established in Zurich, the membrane proteins mediating the basolateral step

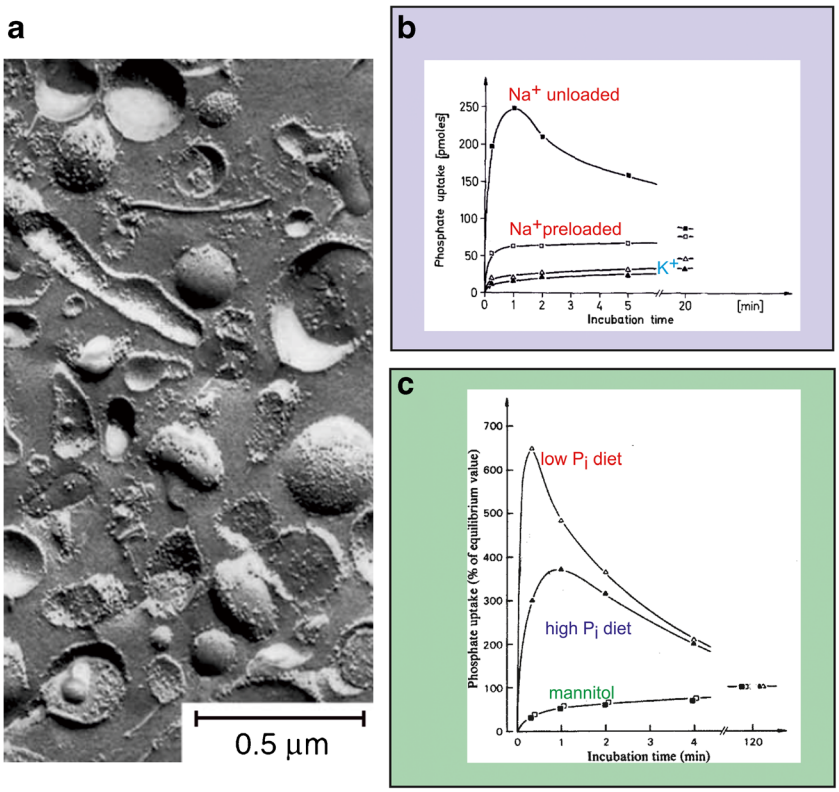

Fig. 2 P_i transport assays performed with isolated proximal tubular brush border membrane vesicles (BBMVs). A) Freeze fracture micrograph of BBMVs prepared from rat renal BBMVs. See [6, 18] for details and methodology. B) Effect of ion gradients on P_i transport. If the intravesicular space is Na^+-free, $^{32}P_i$ uptake initially overshoots and falls to an equilibrium value as the vesicles become loaded with Na^+ (Na^+ unloaded). No overshoot is observed with vesicles preloaded with Na^+ (Na^+ preloaded). With a K^+ gradient uptake is significantly reduced and not affected by preloading (open vs filled triangles). For more details, see original reference [25]. C) Time dependence of $^{32}P_i$ uptake into BBMVs demonstrating the effect of dietary P_i on BBMV activity. As in B) the uptake peaks and decreases as the vesicles become loaded with substrate, and the uptake eventually reaches an equilibrium exchange condition identical to the mannitol control. For vesicles prepared from animals on a low P_i diet, the peak uptake is significantly enhanced, consistent with having greater number of carriers expressed, as would be later shown by immunostaining of proximal tubules and protein analysis (e.g., [37]). Data modified from [44]

are still poorly understood, although the recent emergence of the retrovirus receptor (XPR1) as a candidate for this role appears most promising [1, 16].

The pre-cloning P_i transport studies were advanced significantly by means of a modified procedure to isolate the proximal tubular brush border membrane vesicles (BBMVs). This was adapted from a protocol developed from rabbit renal BBMV [7] and yielded pure and abundant BBMV and involved only a few differential centrifugation steps [6]. The isolated (renal) BBMV were of "right side out" orientation [18] and allowed the study of the transport characteristics in considerable detail in terms of kinetics and regulation. The first studies of P_i transport performed in the Ullrich laboratory (MPI, Frankfurt) using renal and intestinal tissue [5, 25] and later by the Saktor laboratory (NIH, Baltimore) using renal tissue [41] established kinetic hallmarks of the transporter that would later serve as reference values for the cloned transporters. These laboratories confirmed the strict Na^+-dependence of transport and measured an apparent half-maximum concentration (K_m) of approximately 0.1 mM [25, 41] (Fig. 2). Furthermore, it was confirmed that P_i influx into BBMV was pH dependent; however, there was no indication of a net movement of charge (i.e., electrogenic transport) [25, 41]. Indeed, by having an excess of positive charge (i.e., 3 Na^+ to 1 divalent P_i) as would be eventually shown experimentally [9, 14], the cotransport rate mediated by NaPi-IIa and NaPi-IIb would be enhanced by the inside negative membrane potential to provide an additional driving force. Meanwhile, these BBMV studies also allowed the investigation of various inhibitors of Na/P_i-cotransport, such as phosphonoformic acid [46, 47]. In addition, dietary or hormonal interventions prior to BBMV isolation confirmed the inhibitory effect of PTH and the influence of dietary P_i as observed in microperfusion studies [36, 44] (Fig. 2). Importantly, the inhibitory/stimulatory effects were conserved in isolated membrane vesicles, i.e., independent of the cellular/organ context, and were manifest as changes in maximal transport rate (V_{max}) but not K_m [31]. These observations underpinned the fundamental property of BBMV P_i transport, namely that the rate of P_i reabsorption was most likely proportional to the number of active transporters and not dependent on functional changes in the transporter itself.

In addition to the kidney, absorption of P_i along the small intestine also contributes to whole body P_i homeostasis [35]. Studies using isolated small intestinal membrane vesicles provided evidence for a Na^+-dependent and a Na^+-independent pathway across the brush border and basolateral membranes of enterocytes [11, 38]. Interestingly, the Na^+-dependent component showed a divergent pH dependence compared to the renal transporter with significant transport activity at pH < 7. Thus, for both, proximal tubules and small intestine, it was assumed that a single renal and intestinal Na^+-dependent transport system at the brush border membrane was being observed. Figure 3 depicts a schematic of the hypothesized single pathway of P_i through the apical membrane of proximal tubules. Based on the experimental evidence at the time, this model proposed a 2 Na^+:1 P_i stoichiometry and an allosteric regulation by protons that compete with the interaction of the Na^+ ions [17]. As divalent P_i is the prevalent form at physiological pH, it was also assumed that the transport process was electroneutral, contradicting previous studies with intact renal tubules in which electrogenicity was observed [15]. This model has since undergone several revisions as detailed in [13].

The molecular identity of the proteins involved in P_i transport was a pressing question and attempts were undertaken to identify the transporter by biochemical means in the pre-cloning era. For example, given that PTH affects renal P_i reabsorption and Na^+/P_i-cotransport in BBMVs in a cAMP-dependent manner, phosphorylation studies were performed with isolated BBMVs. These studies demonstrated cAMP-dependent changes of BBMV protein-phosphorylation, but the identity of those phospho-proteins remained unknown [20].

The cloning of NaPi-IIa [32, 33] heralded a new era in the field by enabling the study of the transport mechanisms/characteristics in isolation after injection of cRNA into oocytes of *Xenopus laevis* [13]. By knowing the amino acid sequence, specific antibodies could be raised to enable specific in situ protein detection of each isoform. Studies using these antibodies allowed the detailed

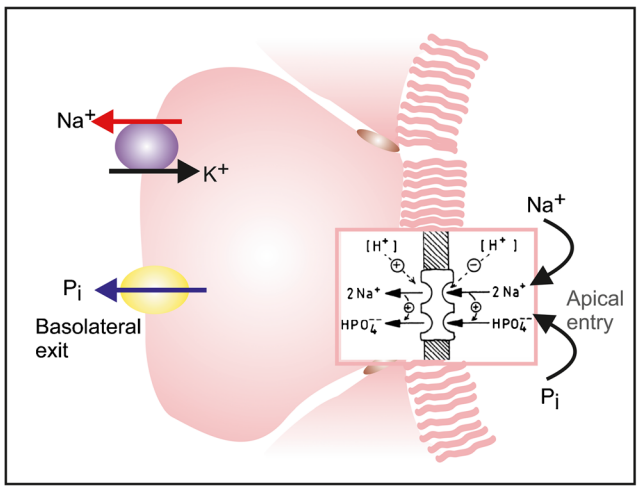

Fig. 3 Pre-cloning model of the molecular mechanism from 1986 of renal proximal tubular Na-dependent P_i reabsorption that accounts for apical entry of P_i [17]. At the apical membrane the interaction of 2 Na^+ ions from the external medium allows divalent P_i to bind and be translocated by means of a secondary active carrier. Protons compete with Na^+ ions to account for the pH dependence of transport. Studies on the cloned transporter have led to the revision of this model (see [13]). Basolateral exit of P_i was proposed to be mediated by Na^+-independent anion carrier (yellow) and the Na/K-ATPase maintains the driving force (purple)

characterization of the cellular mechanisms that are involved in the physiological regulation by an increasing number of hormones. It was also possible to answer questions regarding the interaction with other proteins that are involved in the cellular regulation of Na^+/P_i-cotransport.

The collection of invited reviews in this Special Issue gives a comprehensive summary of the impressive progress that has been made in the P_i field since the early cloning days. It is our hope that these articles will provide a useful overview for experts and non-experts alike and stimulate continued research in the P_i field. The reviews have been grouped according to five themes: *Molecular and Mechanistic Aspects*, including interacting proteins [12, 13, 23, 43], *Physiological Regulation* [26, 27, 48], *Human Mutations/Clinical Aspects and Diseases* [4, 30], *Non-renal Roles for SLC34 Proteins* [3, 34], and *Comparative Aspects* [39, 52].

References

1. Ansermet C, Moor MB, Centeno G, Auberson M, Hu DZ, Baron R, Nikolaeva S, Haenzi B, Katanaeva N, Gautschi I, Katanaev V, Rotman S, Koesters R, Schild L, Pradervand S, Bonny O, Firsov D (2016) Renal Fanconi syndrome and hypophosphatemic rickets in the absence of xenotropic and polytropic retroviral receptor in the nephron. J Am Soc Nephrol. https://doi.org/10.1681/ASN.2016070726
2. Baumann K, de Rouffignac C, Roinel N, Rumrich G, Ullrich KJ (1975) Renal phosphate transport: inhomogeneity of local proximal transport rates and sodium dependence. Pflugers Arch 356:287–298
3. Beck L (2018) Expression and function of Slc34 sodium–phosphate co-transporters in skeleton and teeth. Pflugers Arch. https://doi.org/10.1007/s00424-018-2240-y
4. Bergwitz C, Miyamoto KI (2018) Hereditary hypophosphatemic rickets with hypercalciuria: pathophysiology, clinical presentation, diagnosis and therapy. Pflugers Arch. https://doi.org/10.1007/s00424-018-2184-2
5. Berner W, Kinne R, Murer H (1976) Phosphate transport into brush-border membrane vesicles isolated from rat small intestine. Biochem J 160:467–474
6. Biber J, Stieger B, Stange G, Murer H (2007) Isolation of renal proximal tubular brush-border membranes. Nat Protoc 2:1356–1359. https://doi.org/10.1038/nprot.2007.156
7. Booth AG, Kenny AJ (1974) A rapid method for the preparation of microvilli from rabbit kidney. Biochem J 142:575–581
8. Broer S, Schuster A, Wagner CA, Broer A, Forster I, Biber J, Murer H, Werner A, Lang F, Busch AE (1998) Chloride conductance and Pi transport are separate functions induced by the expression of NaPi-1 in Xenopus oocytes. J Membr Biol 164:71–77
9. Busch A, Waldegger S, Herzer T, Biber J, Markovich D, Hayes G, Murer H, Lang F (1994) Electrophysiological analysis of Na^+/P_i cotransport mediated by a transporter cloned from rat kidney and expressed in Xenopus oocytes. Proc Natl Acad Sci U S A 91:8205–8208
10. Busch AE, Schuster A, Waldegger S, Wagner CA, Zempel G, Broer S, Biber J, Murer H, Lang F (1996) Expression of a renal type I sodium/phosphate transporter (NaPi-1) induces a conductance in Xenopus oocytes permeable for organic and inorganic anions. Proc Natl Acad Sci U S A 93:5347–5351
11. Danisi G, Murer H, Straub RW (1984) Effects of pH and sodium on phosphate transport across brush border membrane vesicles of small intestine. Adv Exp Med Biol 178:173–180
12. Fenollar-Ferrer C, Forrest LR (2018) Structural models of the NaPi-II sodium-phosphate cotransporters. Pflugers Arch. https://doi.org/10.1007/s00424-018-2197-x
13. Forster IC (2018) The molecular mechanism of SLC34 proteins: insights from two decades of transport assays and structure-function studies. Pflugers Arch. https://doi.org/10.1007/s00424-018-2207-z
14. Forster IC, Loo DD, Eskandari S (1999) Stoichiometry and Na^+ binding cooperativity of rat and flounder renal type II Na^+-P_i cotransporters. Am J Physiol 276:F644–F649
15. Fromter E (1979) The Feldberg Lecture 1976. Solute transport across epithelia: what can we learn from micropuncture studies in kidney tubules? J Physiol 288:1–31
16. Giovannini D, Touhami J, Charnet P, Sitbon M, Battini JL (2013) Inorganic phosphate export by the retrovirus receptor XPR1 in metazoans. Cell Rep 3:1866–1873. https://doi.org/10.1016/j.celrep.2013.05.035
17. Gmaj P, Murer H (1986) Cellular mechanisms of inorganic phosphate transport in kidney. Physiol Rev 66:36–70. https://doi.org/10.1152/physrev.1986.66.1.36
18. Haase W, Schafer A, Murer H, Kinne R (1978) Studies on the orientation of brush-border membrane vesicles. Biochem J 172:57–62
19. Hagenbuch B, Murer H (1986) Phosphate transport across the basolateral membrane from rat kidney cortex: sodium-dependence? Pflugers Arch 407(Suppl 2):S149–S155
20. Hammerman MR (1986) Phosphate transport across renal proximal tubular cell membranes. Am J Phys 251:F385–F398. https://doi.org/10.1152/ajprenal.1986.251.3.F385
21. Hannig K (1982) New aspects in preparative and analytical continuous free-flow cell electrophoresis. Electrophoresis 3:235–243. https://doi.org/10.1002/elps.1150030502
22. Hediger MA, Romero MF, Peng JB, Rolfs A, Takanaga H, Bruford EA (2004) The ABCs of solute carriers: physiological, pathological and therapeutic implications of human membrane transport proteins.Introduction. Pflugers Archiv Eur J Physiol 447:465–468
23. Hernando N (2018) NaPi-IIa interacting partners and their (un)known functional roles. Pflugers Arch. https://doi.org/10.1007/s00424-018-2176-2
24. Hilfiker H, Hattenhauer O, Traebert M, Forster I, Murer H, Biber J (1998) Characterization of a murine type II sodium-phosphate cotransporter expressed in mammalian small intestine. Proc Natl Acad Sci U S A 95:14564–14569
25. Hoffmann N, Thees M, Kinne R (1976) Phosphate transport by isolated renal brush border vesicles. Pflugers Arch 362:147–156
26. Hu MC, Shi M, Moe OW (2018) Role of aKlotho and FGF23 in regulation of type II Na-dependent phosphate co-transporters. Pflugers Arch. https://doi.org/10.1007/s00424-018-2238-5
27. Jacquillet G, Unwin RJ (2018) Physiological regulation of phosphate by vitamin D, parathyroid hormone (PTH) and phosphate (Pi). Pflugers Arch. https://doi.org/10.1007/s00424-018-2231-z
28. Kavanaugh MP, Kabat D (1996) Identification and characterization of a widely expressed phosphate transporter/retrovirus receptor family. Kidney Int 49:959–963
29. Kavanaugh MP, Miller DG, Zhang W, Law W, Kozak SL, Kabat D, Miller AD (1994) Cell-surface receptors for gibbon ape leukemia virus and amphotropic murine retrovirus are inducible sodium-dependent phosphate symporters. Proc Natl Acad Sci U S A 91:7071–7075
30. Lederer E, Wagner CA (2018) Clinical aspects of the phosphate transporters NaPi-IIa and NaPi-IIb: mutations and disease

assocations. Pflugers Arch. https://doi.org/10.1007/s00424-018-2246-5
31. Levi M, Kempson SA, Lotscher M, Biber J, Murer H (1996) Molecular regulation of renal phosphate transport. J Membr Biol 154:1–9
32. Magagnin S, Werner A (2018) Expression cloning human and rat renal cortex Na/Pi cotransporters: behind the scenes in the Murer laboratory. Pflugers Arch. https://doi.org/10.1007/s00424-018-2198-9
33. Magagnin S, Werner A, Markovich D, Sorribas V, Stange G, Biber J, Murer H (1993) Expression cloning of human and rat renal cortex Na/P_i cotransport. Proc Natl Acad Sci U S A 90:5979–5983
34. Marks J (2018) The role of SLC34A2 in intestinal phosphate absorption and phosphate homeostasis. Pflugers Arch. https://doi.org/10.1007/s00424-018-2221-1
35. Marks J, Debnam ES, Unwin RJ (2010) Phosphate homeostasis and the renal-gastrointestinal axis. Am J Physiol Renal Physiol 299: F285–F296. https://doi.org/10.1152/ajprenal.00508.2009
36. Murer H, Evers C, Stoll R, Kinne R (1977) The effect of parathyroid hormone (PTH) and dietary phosphate on the sodium-dependent phosphate transport system located in the rat renal brush border membrane. Curr Probl Clin Biochem 8:455–462
37. Murer H, Hernando N, Forster I, Biber J (2000) Proximal tubular phosphate reabsorption: molecular mechanisms. Physiol Rev 80: 1373–1409
38. Murer H, Hildmann B (1981) Transcellular transport of calcium and inorganic phosphate in the small intestinal epithelium. Am J Phys 240:G409–G416. https://doi.org/10.1152/ajpgi.1981.240.6.G409
39. Muscher-Banse AS, Breves G (2018) Mechanisms and regulation of epithelial phosphate transport in ruminants: approaches in comparative physiology. Pflugers Arch. https://doi.org/10.1007/s00424-018-2181-5
40. Quamme GA, Dirks JH (1986) Micropuncture techniques. Kidney Int 30:152–165
41. Sacktor B, Cheng L (1981) Sodium gradient-dependent phosphate transport in renal brush border membrane vesicles. Effect of an intravesicular greater than extravesicular proton gradient. J Biol Chem 256:8080–8084
42. Segawa H, Kaneko I, Takahashi A, Kuwahata M, Ito M, Ohkido I, Tatsumi S, Miyamoto K (2002) Growth-related renal type II Na/Pi cotransporter. J Biol Chem 277:19665–19672
43. Sorribas V, Guillén N, Sosa C (2018) Substrates and inhibitors of phosphate transporters: from experimental tools to pathophysiological relevance. Pflugers Arch. https://doi.org/10.1007/s00424-018-2241-x
44. Stoll R, Kinne R, Murer H (1979) Effect of dietary phosphate intake on phosphate transport by isolated rat renal brush-border vesicles. Biochem J 180:465–470
45. Strickler JC, Thompson DD, Klose RM, Giebisch G (1964) Micropuncture study of inorganic phosphate excretion in the rat. J Clin Invest 43:1596–1607. https://doi.org/10.1172/JCI105035
46. Szczepanska-Konkel M, Yusufi AN, Lin J-T, Dousa TP (1989) Structural requirement of monophosphates for inhibition of Na+-Pi cotransport in renal brush border membrane. Biochem Pharmacol 38:4191–4197
47. Szczepanska-Konkel M, Yusufi AN, VanScoy M, Webster SK, Dousa TP (1986) Phosphonocarboxylic acids as specific inhibitors of Na+-dependent transport of phosphate across renal brush border membrane. J Biol Chem 261:6375–6383
48. Tatsumi S, Katai K, Kaneko I, Segawa H, Miyamoto KI (2018) NAD metabolism and the SLC34 family: evidence for a liver-kidney axis regulating inorganic phosphate. Pflugers Arch. https://doi.org/10.1007/s00424-018-2204-2
49. Ullrich KJ, Frömter E, Baumann K (1970) Micropuncture and microanalysis in kidney physiology. In: Passow H, Stämpfli R (eds) Laboratory techniques in membrane biophysics. Springer, Heidelberg, pp 106–129
50. Ullrich KJ, Fromter E, Murer H (1979) Principles of epithelial transport in the kidney and intestines. Klin Wochenschr 57:977–991
51. Ullrich KJ, Rumrich G, Kloss S (1977) Phosphate transport in the proximal convolution of the rat kidney. I. Tubular heterogeneity, effect of parathyroid hormone in acute and chronic parathyroidectomized animals and effect of phosphate diet. Pflugers Arch 372: 269–274
52. Verri T, Werner A (2018) Type II Na+-phosphate cotransporters and phosphate balance in teleost fish. Pflugers Arch. https://doi.org/10.1007/s00424-018-2239-4
53. Werner A, Moore ML, Mantei N, Biber J, Semenza G, Murer H (1991) Cloning and expression of cDNA for a Na/Pi cotransport system of kidney cortex. Proc Natl Acad Sci U S A 88:9608–9612