Tubular handling and regulation of sulphate

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Sulphate, the fourth most abundant anion in human plasma, is known to play an essential role in a variety of biochemical processes [1]. The importance of sulphate has been demonstrated recently by the identification of mutations in a sulphate transport protein (diastrophic dysplasia sulphate transporter; DTDST) in three different types of osteochondrodysplasia, diastrophic dysplasia, type IB achondrogenesis and type II osteochondrodysplasia [2–4]. In these osteochondrodysplasias, undersulphation of cartilage proteoglycans is associated with abnormalities affecting the organization of collagen fibrils, the tinctorial properties of proteoglycans and the number and morphology of chondrocytes. The severity of the phenotype appears to be correlated with the predicted effect of the mutations on the residual activity of the DTDST protein [4]. Despite their potential importance, sulphate levels are almost never measured in clinical practice, and little is known about the factors that regulate sulphate homeostasis in mammals.

The kidney plays a crucial role in maintaining sulphate homeostasis. Sulphate is filtered freely at the glomerulus and reabsorbed in the proximal tubule. Only 5–20% of the filtered load is excreted in urine. Tubular sulphate uptake from lumen to blood depends on the activity of a sodium-coupled sulphate transport (co-transport at the luminal membrane) [5]. Once sulphate has been accumulated within the tubular epithelial cell, its exit across the peritubular face of the cell is mediated by anion exchange. Recently, two sulphate transporters, a NaSi-1 co-transporter and a sulphate/oxalate–bicarbonate anion exchanger (Sat-1) have been identified [6–8] and implicated in this physiological process. The NaSi-1 co-transporter and Sat-1 protein have been localized to the apical and basolateral membrane of the proximal tubule, respectively [9–11]. In addition to the proximal tubule, NaSi-1 co-transporter is expressed in the ileum [12], while Sat-1 is also expressed in the liver [7]. These two transporters are thought to be responsible for inorganic sulphate entry into and exit from the proximal tubular cells.

We have been interested in the possibility that vitamin D status regulates sulphate metabolism. Indeed, several considerations raise the possibility that certain of the skeletal abnormalities seen in vitamin D deficiency could result from abnormal sulphate metabolism. First, a number of the pathological features seen in 1,25(OH)\textsubscript{2}D deficiency states are not easily explained solely by changes in calcium and phosphate metabolism. Thus, although hypocalcaemia and hypophosphataemia easily account for the impairment in mineral deposition typical of rickets and osteomalacia [13], the disorganization of the chondrocyte columns seen in rachitic cartilage and the presence of abnormalities in the maturation of chondrocytes [13,14] are more difficult to attribute to this mechanism. Furthermore, changes in the physical properties of proteoglycan aggregates in rachitic rat bone [15], and a reduction in sulphate fixation in the matrix of growth plate cartilage in vitamin D-deficient rats have also been reported [16], findings that are consistent with the presence of abnormalities of sulphate metabolism in 1,25(OH)\textsubscript{2}D deficiency. Finally, the intestine and kidney, two of the principal target organs for 1,25(OH)\textsubscript{2}D action, are also known to represent the two most important tissues implicated in the regulation of extracellular concentrations of inorganic sulphate [5]. Nevertheless, no direct evidence for abnormalities in the circulating levels of sulphate in vitamin D-deficient animals has been reported.

To explore the possibility that vitamin D status regulates sulphate homeostasis, plasma sulphate levels, renal sulphate excretion and the expression of the renal NaSi-1 and Sat-1 sulphate transporters were evaluated in vitamin D-deficient (D\textsuperscript{−}\textsuperscript{−}) rats and in D\textsuperscript{−}\textsuperscript{−} rats rendered normocalcaemic by either vitamin D or calcium/lactose supplementation [17]. D\textsuperscript{−}\textsuperscript{−} rats had significantly lower plasma sulphate levels than control animals (0.93 ± 0.01 and 1.15 ± 0.05 mM, respectively, \(P<0.05\)), and fractional sulphate renal excretion was \(~3\)-fold higher comparing D\textsuperscript{−}\textsuperscript{−} and control rats. A decrease in renal cortical brush border membrane (BBM) NaSi-1 co-transport activity, associated with a parallel decrease in both renal NaSi-1 co-transport protein and mRNA content (78 ± 3% and 73 ± 3% decreases, respectively, compared with control values), was also observed in D\textsuperscript{−}\textsuperscript{−} rats. The expression of Sat-1 (mRNA and protein) in the kidney and in the liver, and of NaSi-1 (mRNA) in the ileum were not...
significantly changed by vitamin D deficiency. Vitamin D supplementation resulted in a return to normal of plasma sulphate, fractional sulphate excretion and both renal NaSi-1 co-transport mRNA and protein. In contrast, renal sulphate excretion and renal NaSi-1 co-transport activity, protein abundance and mRNA remained decreased in vitamin D-depleted rats fed a diet supplemented with lactose and calcium, despite the fact that these rats were normocalcaemic, and had significantly lower levels of parathyroid hormone (PTH) and 25(OH)- and 1,25(OH)$_2$-vitamin D levels than the vitamin D-supplemented groups. These results demonstrate that vitamin D modulates renal NaSi-1 sulphate co-transport and sulphate homeostasis. The ability of vitamin D status to regulate NaSi-1 co-transport appears to be a direct effect, and is not mediated by the effects of vitamin D on plasma calcium or PTH levels. Thus, vitamin D status, by modulating renal NaSi-1 co-transport, and thereby sulphate homeostasis, may influence the amount of inorganic sulphate available for intracellular sulphatation of intracellular components, such as proteoglycans, and contribute to producing some of the abnormalities observed in rickets and osteomalacia. 

Subsequently, renal NaSi-1 co-transporter has been shown to be regulated in various physiological and pathophysiological alterations of sulphate homeostasis. Regulation of the NaSi-1 mRNA and protein by dietary sulphate intake has been demonstrated [18,19]. Regulation of the NaSi-1 co-transporter gene and protein has also been demonstrated in hypothyroidism [20], metabolic acidosis [21], chronic hypokalaemia [22] and ibuprofen administration [23]. In a recent study, we have shown that both NaSi-1 and Sat-1 expression are altered in chronic renal failure, which may provide at least a partial explanation for the hypersulphaetaemia observed in renal insufficiency (personal unpublished results).

Thus, these studies demonstrated that the NaSi-1 co-transporter plays a major role in sulphate homeostasis by modulating the renal reabsorption of the anion. Sat-1 could also contribute to the maintenance of sulphate homeostasis, although few data are available on the regulation of this transporter in health and disease. In conclusion, the recent cloning of two sulphate transporters has allowed us to examine by molecular techniques the mechanisms involved in the physiology and pathophysiology of sulphate homeostasis, and this may contribute of abnormalities in sulphate metabolism to the pathogenesis of human diseases.

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References