Hyperuricemia and Gout

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Introduction
Significant advances have been made in the knowledge of urate renal handling and in the pathophysiologic mechanisms of acute monosodium urate (MSU) crystal–induced inflammation. Recent evidence that hyperuricemia may play a pathogenic role in hypertension, vascular kidney involvement, and cardiovascular disease emphasizes the important contribution of this metabolite in physiology and pathophysiology.

Hyperuricemia
Pathogenic mechanisms of hyperuricemia include uric acid overproduction or aberrations of renal uric acid handling resulting in underexcretion [1]. All plasma urate is filtered, with greater than 95% of the filtered load undergoing proximal tubular reabsorption. To be reabsorbed, urate crosses the apical membrane of proximal tubules through anion exchangers (Fig. 1). Two anion exchangers have been described in human brush-border membranes, with high and low affinity [2,3], and may have been recently identified at the molecular level [4,5,6]. Subsequently, proximal tubular secretion contributes to the main excreted uric acid before the so-called postsecretory reabsorption. However, this four-step model has been challenged, and some authors suggest a continuous and simultaneous reabsorption-secretion phenomena along the tubule [7].

Pathogenesis of uric acid renal handling
One key issue in hyperuricemia is tubular handling of urate. In many cases, abnormal renal underexcretion results in chronic hyperuricemia and, ultimately, in gout and, eventually, in urate nephrolithiasis. The molecular mechanisms for the reduced excretion of urate were poorly understood, but their knowledge could rapidly improve with recent insights [5,6]. Two molecules are candidates for urate-anion exchange—galectin 9 and urate transporter (URAT1).

From animal studies, Lipkowitz et al. [5] demonstrated two mechanisms for urate transport in the kidney, a voltage-sensitive urate transporter, and a urate-anion exchanger. They isolated and characterized two human urate transporters, human galectin 9, or human urate transporter (hUAT), which is highly homologous to the rat urate transporter, and also a hUAT2, another protein present at a lesser extent in human tissues [5]. These hUATs appear voltage-sensitive. Human urate transporter is a secreted and cytosolic protein, and acts as a highly selective urate ion channel when inserted in lipid bilayers. Expressed in many cells, including kidney and aorta, it is a transmembrane protein with four transmembrane domains. The gene for hUAT is localized on the short arm of chromosome 17 between 17p11.2 and 17p12. They also characterized hUAT2, a highly homologous gene, mapped to a nearby region of chromosome 17. Human urate transporter 2 is present only in a few tissues including colon, prostate, and blood lymphocytes. The mechanism by which uric acid is transported through hUAT is still unknown.

Enomoto et al. [6] hypothesized that the hUAT should belong to the organic anion transporter (OAT) family, and from a systematic survey of the human genome database, they identified a sequence similar to the OAT4 gene in chromosome 11q13. They succeeded in predicting the human sequence of this gene, actually named SLC22A12, and ultimately isolated a circular DNA from human kidney sharing 42% homology with OAT4 [6]. This urate-anion transporter (URAT1) was present at mes-
senger RNA and protein levels in the human kidney. Using *Xenopus* oocytes injected with URAT1 circular RNA, they showed that the expressed protein does not involve a direct sodium\(^+\)-urate cotransport, but is linked to an exchange mechanism for urate, chloride, and organic anions. Urate uptake via URAT1 is trans-stimulated via intracellular anions (lactate and sodium nitrate), depending on an indirect coupling of sodium and urate transport (Fig. 1). As mentioned by Enomoto *et al.* [6\••], chemicals or drugs with affinity for URAT1, such as probenecid, benz bromar one, and nonsteroidal anti-inflammatory drugs (NSAIDs), including salicylic acid and even losartan, will be uricosuric when acting from the lumen, and will perform as antiu ricosuric agents when acting from the intracellular space. Clinical consequences have already been discovered. In one patient with idiopathic renal hypouricemia whom fractional excretion of urate was 95% compared with 10% in normal individuals, a genomic DNA study revealed a homozygous G774A mutation of *SLC22A12*, which leads to a truncated and inactive protein. Additional missense mutations have been found in two other patients with renal hypouricemia. None of these mutations have been found in 180 normal Japanese control individuals. Urate-anion transporter could control urate accumulation in humans compared with other mammals in which the filtrated load is lower than the excreted amount of urate.

**Secondary Hyperuricemia**

**Drug-induced hyperuricemia and gout**

Several medications, such as diuretics, are able to modify uric acid renal handling, which leads to decreased tubular excretion or increased tubular reabsorption, which are two mechanisms that are associated with other tubular functions. Low-dose aspirin has been considered to reduce urate excretion, but new evidence has been brought by Caspi *et al.* [8]. They studied 49 elderly patients (range 61 to 94 years) with normal renal function. Subjects received increased doses of aspirin (75, 150, and 325 mg daily) for 7-day periods. Doses as low as 75 mg daily caused significant decreases in uric acid and creatinine clearances. These effects diminished gradually when aspirin dosing was increased, and there were no more differences at 325 mg per day. Lower serum albumin equals lower creatinine clearance. Concomitant use of diuretics also enhanced renal effects of aspirin. Because low-dose aspirin is widely used in patients with vascular diseases, it can be hypothesized that hypouricemic treatment may lose its effect when prescribed in association. Mechanisms of this interference remain to be determined. Only high-dose aspirin has been evaluated with probenecid, which is a widely used uricosuric drug in the US. Harris *et al.* [9] addressed this question in 11 patients with gout who were receiving probenecid for 3 months. The addition of 325 mg of aspirin did not modify serum uric acid (SUA) levels or 24-hour urinary urate excretion. Other hypouricemic drugs, such as benz bromar one, and lower aspirin should be evaluated in order to confirm the absence of deleterious effect of aspirin on uric acid excretion.

**Bartter’s syndrome, hyperuricemia, and gout**

Over the past 25 years, few cases of gout and Bartter’s (BS) or Gitelman’s (GS) syndromes have been reported in Jewish [10] and Japanese [11] patients. However, the prevalence might be higher, because in the 1970s, Fishel *et al.* [12] reported the presence of hyperuricemia in 50% and gout in 20% of patients with BS. This high prevalence should be confirmed, because other crystal-induced arthropathies, such as calcium pyrophosphate dihydrate disease, are mainly linked to BS and GS. Features include normal blood pressure, hypokalemia, alkalosis, increased potassium excretion, high supine plasma renin activity, and aldosterone concentration. Calcium urine output and magnesium plasma levels are normal in BS and low in GS. The three known molecular defects were defined as type I for renal bumetamine potassium-potassium-2-chloride cotransporter, type II for an adenosine phosphatase–