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Renal Handling of Urate and Oxalate: Possible Implications for Urolithiasis

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Summary. Both urate and oxalate are organic acids of considerable clinical interest, owing to their limited solubility. Calcium oxalate is the most frequent constituent of renal calculi and occasionally precipitates in body fluids. Urate precipitations are common in the kidney and in various other tissues. In this paper, a short outline of the present knowledge of renal handling of these substances will be followed by some conclusions as to the possible relevance of this knowledge for the understanding of urolithiasis and intrarenal precipitation. Direct (micropuncture) data are available for urate in the rat (1, 6, 7, 10, 21, 23, 28, 36, 42), rabbit (35), dog (34) and cebus monkey (33) and in the rat only for oxalate (11, 15, 20).

Key words: Urate, Oxalate, Renal Handling, Precipitation.

Since considerable species differences in the renal handling of urate are encountered, renal clearance data from animals cannot be safely extrapolated to man (9). However, the bulk of indirect evidence available favours the view that in most mammals similar mechanisms are involved, are governed by the same parameters and are influenced by the same manoeuvres.

RENAL HANDLING OF URATE (Fig. 1)

Mechanisms involved in renal handling of urate are glomerular filtration, tubular secretion and tubular reabsorption.

Glomerular filtration is virtually complete. Free urate, as a relatively small molecule, easily passes the glomerular filter. Urate bound to protein, however, would escape glomerular filtration. Although a considerable portion of urate is bound to proteins at low temperatures, at 37°C protein binding of urate is negligible (8). Therefore, the filtered load (L) of urate in man approximates L = GFR x P, where GFR is the filtered volume per time unit, and P is the plasma concentration. Hence glomerular filtration rate and plasma concentration are the two parameters determining the filtered load of urate.

Tubular reabsorption of urate is limited to the proximal tubule including the pars recta and possibly the thin limb of the loop of Henle (7, 21, 23, 36, 42). Only minimal (22) or no reabsorption (10, 28) was found in the distal nephron. The reabsorptive process appears to be saturable; however the maximal transport rate is very high and affinity for urate very low (12, 25). As a result, increasing urate loads enhance re-

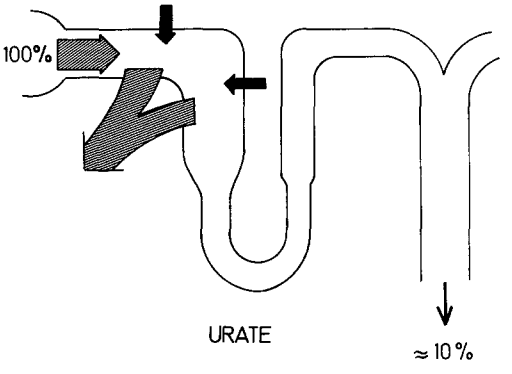

Fig. 1. Renal handling of urate. Complete glomerular filtration, and bidirectional transport limited to the proximal nephron. Because of predominating reabsorption, only some 10% of filtered load is excreted in the urine

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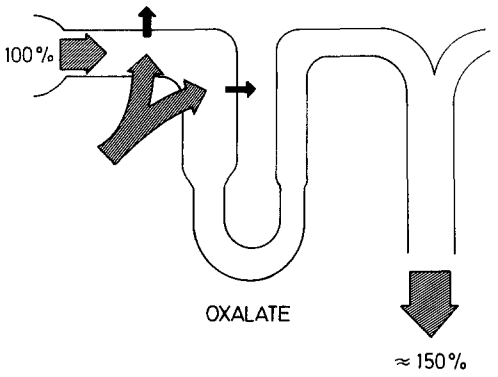

Fig. 2. Renal handling of oxalate. Complete glomerular filtration and bidirectional transport limited to the proximal tubule. Because of predominant secretion, more than filtered load is excreted in the urine

absorptive rate. However, the rate does not increase in linear proportion to the load, and the fraction of urate which escapes reabsorption increases as well. Therefore, a slight increase of renal urate clearance is encountered with the rise of plasma concentration.

An important determinant of urate reabsorption is the luminal flow rate, especially in the loop of Henle (7). Increasing luminal flow rate drastically reduces urate reabsorption and thus enhances excretion. This factor is most likely responsible for the fact that in renal insufficiency, urate clearance often remains within normal limits (3, 5, 26, 32): In this situation, the luminal flow rate of the remaining nephrons is greatly increased and urate reabsorption minimised.

The effect of diuretic agents on urate transport has been reviewed extensively (24). In short, a variety of diuretic states may enhance urate clearance acutely, probably because luminal flow rate is increased in the reabsorbing segments (proximal nephron including the loop of Henle). With chronic administration of highly effective diuretics, however, the picture is reversed (40, 41): Volume contraction stimulates fluid reabsorption in the proximal nephron. Despite increased urinary flow rates, luminal flow rate in the proximal nephron is reduced and urate reabsorption enhanced. In addition, diuretic agents may inhibit tubular secretion of urate by competition at the tubular transport step.

Urate excretion is increased following the administration of alkali loads (13). This observation has been interpreted as indicative of nonionic diffusion for urate. In micropuncture experiments, nonionic diffusion, however, has been ruled out as a mechanism of urate reabsorption (25). Therefore, other mechanisms must account for this finding, e. g. increased flow rate in the proximal nephron due to reduced bicarbonate reabsorption.

Various drugs are known to inhibit urate reabsorption. Some of them, e. g. probenecid, benzbromarone and sulfinpyrazone are used to enhance urate elimination in hyperuricaemic patients. The application of uricosuric agents in hyperuricaemic patients appears logical, because the majority of patients with hyperuricemia yield low renal clearances and normal endogenous production (26). Nevertheless, intrarenal precipitation and stone formation are possible hazards, as will be discussed below.

Tubular secretion of urate is located in the proximal convolution, probably including the pars recta. Although the distal tubule was originally believed to be the site of urate secretion (4, 45), both direct and indirect evidence (10, 19, 28, 31, 46), has been accumulated which indicates that the distal nephron does not significantly contribute to urate elimination.

Tubular secretion rate in the rat has been found to increase in proportion to plasma concentration. Saturation was not apparent in a wide range of concentrations (23).

The coexistence of tubular reabsorption and secretion leads to a continued increase of secreted urate, whereas urate filtered at the glomerular level is reabsorbed almost completely during tubular passage. Therefore, in general, excreted urate is derived almost completely from secretion. Furthermore indirect evidence suggests that variations in endogenous urate clearances are mainly due to variations in urate secretion. As a matter of fact, most patients with hyperuricemia or gout appear to have reduced urate secretion (26).

Decreased urate secretion possibly accounts for the antiuricosuria in metabolic acidosis due to fasting (29, 37), diabetes mellitus (30) and stress (27). It may be speculated that free fatty acids, acetoacetate or β-hydroxybutyrate may compete with urate secretion, thus producing antiuricosuria in these situations.

As a result of the above mechanisms, some 10% of filtered urate is excreted in the urine (26). Considerable variations occur between different individuals and between male and female patients.

RENAL HANDLING OF OXALATE (Fig. 2)

As for urate, glomerular filtration, tubular secretion and reabsorption are the mechanisms involved in renal handling of oxalate.

Glomerular filtration of oxalate is virtually complete (11) so that oxalate concentration is almost identical in ultrafiltrate and plasma.

A small but significant reabsorptive flux is demonstrable in the proximal tubule of the rat (11, 15, 43). No reabsorption is apparent beyond the proximal tubule, and again the distal nephron appears to be impermeable to oxalate (11, 43). Since reabsorptive rate is minimal, it has been concluded that this constitutes a merely passive event. A decreased oxalate reabsorption probably accounts for the enhancement of oxalate clearance in the dog during mannitol diureses (2). Other determinants of oxalate reabsorption are note known.

Meanwhile general agreement exists that tubular secretion of oxalate clearly exceeds tubular reabsorption (11, 15, 16, 43, 44). However, free flow micropuncture experiments led to contrasting conclusions as to the site of the secretory process. On the one hand, oxalate recoveries in proximal and distal tubules, consistently below both filtered load and excreted amount, suggested that the secretory process is located in the distal nephron (15). On the other hand, oxalate recoveries in proximal tubules, significantly above filtered load and not different from excreted amount, indicated a proximal site of oxalate secretion (43). In addition, oxalate secretion is inhibited by PAH and urate (11, 20). Since both substances are secreted in the proximal and not in the distal nephron, it appears likely that oxalate secretion is indeed located in the proximal nephron. An interesting observation is the reduction of oxalate secretion during volume expansion (11). It might be feasible that oxalate secretion like PAH secretion (14) is in some way related to sodium reabsorption and thus is reduced when sodium reabsorption is decreased.

As a result of tubular transport, oxalate excretion exceeds the filtered load by some 20% in the rat. In man, the fraction of oxalate secreted might be even higher and excreted oxalate might exceed filtered load by 60% (18). The lack of chemical methods sufficiently specific and sensitive for the measurement of endogenous oxalate plasma concentrations (17) necessitates the use of radioactive tracers for determination of oxalate clearances which is not possible on a large scale.

IMPLICATIONS FOR UROLITHIASIS

The following discussion cannot deal with the various factors favouring or preventing urinary and intrarenal precipitation of urate, uric acid or oxalate. Instead, the discussion will focus on the question of the way the renal handling of these substances may contribute to the occurrence of urolithiasis.

Three issues will be discussed: (a) Is renal handling responsible for urinary excretion of enhanced amounts of urate or oxalate, thus provoking urolithiasis, (b) could renal transport contribute to peak concentrations in a non-steady state, and (c) where is intrarenal precipitation expected to occur?

In a steady state, renal and extrarenal (mainly enteric) elimination of urate or oxalate must equal uptake and endogeneous production. In other words, extrarenal factors (production, uptake and extrarenal elimination) determine the amount excreted in the urine. If renal clearance increases, plasma concentration decreases; if renal clearance decreases, plasma concentration increases, until the amount of urate or oxalate excreted again equals production plus uptake minus extrarenal elimination. Thus, we may conclude that the kidney accounts for gout but not for stones.

This statement, however, must be qualified: Enhanced renal clearance decreases plasma concentration. If decreased plasma concentration reduces extrarenal elimination, a greater portion of urate or oxalate produced or taken up must be excreted in the urine. Nevertheless, most of both urate and oxalate produced or taken up is excreted in the urine (18, 39); and alterations of extrarenal elimination probably have little influence on renal urate excretion. The kidney does influence the amount of urate excretion in non steady state situations, which is the state we are usually in. Plasma urate concentration and urate clearance undergo certain diurnal rhythms, which alter the amount of urate excreted at a given time. Usually fractional urate excretion, i. e. urate clearance over GFR, is lowest during the night. This behaviour makes sense because antidiuresis prevails during night hours and precipitation may follow, if normal amounts of urate are excreted into the reduced urine volume. Another nonsteady state encountered daily is the dietary purine load after meals. If affinity of the reabsorptive process were high and maximal transport rate low, the increase of plasma concentration would be followed by immediate excretion of the additional load. As a result, peak concentrations of urate would favour precipitation, which possibly could not be dissolved during the intervals of low urate output.

These two examples show that the kidney may indeed be responsible for stone formation even if the daily excretion of urate is normal. The same may hold for oxalate although we know less about saturability of its transport systems and diurnal rhythms. In any case the highly efficient renal elimination of oxalate may keep plasma oxalate concentration low at the expense of great fluctuations in urinary concentration.

For this discussion, a few conclusions may be added on the use of uricosuric agents. If uricosuric agents are utilised in hyperuricaemic patients, three points must be consid-

ered: First, although most patients with hyperuricaemia show normal production, this should be confirmed in each single patient before the drug is used (urate excretion in 24 h should be less than 800 mg or 5 mmol). Second, the drug should be administered in the morning. If the drug is given in the afternoon or evening, peak uricosuria, e. g. 4-12 hours after administration of Probenecid (26) will be during the night, when urine volume is low. Third, some patients are antidiuretic even if they are given plenty of water to drink. Fasting patients especially may produce very little urine volumes despite good hydration. In these patients uricosuric agents may be hazardous. Similarly, patients with hyperuricaemia due to diuretic therapy may have intervals of severe antidiuresis. One should make sure that peak uricosuria does not fall within those intervals.

The knowledge of the site of urate or oxalate transport may explain the site of intrarenal precipitation. For both substances, urate and oxalate, tubular transport is limited to the proximal nephron. Since some 90% of fluid is reabsorbed beyond the loop of Henle, the concentration of the substances in the loop of Henle, approximates some 10% of that in antidiuretic urine. It appears unlikely that nonionised uric acid precipitates in the loop of Henle (pH is 6.8 and 90% of uric acid is ionised). However, both for oxalate and urate ions tubular fluid in the loop may – under certain conditions – be more critical than final urine: Sodium and calcium concentrations are far higher than in urine, thus precipitation of sodium urate or calcium oxalate are favoured. If a crystal is formed, this crystal is not washed away easily, because the loop of Henle is very long and has an extremely narrow lumen. Thus, a crystal may easily block the lumen thus facilitating further precipitation. In hyperuricaemic rats (due to oxonate), urate precipitates blocking loops of Henle may be seen, while collecting ducts are free of precipitates.

In summary, we conclude that knowledge about sites and parameters of urate and oxalate transport in the kidney may indeed contribute to the understanding of urolithiasis and intrarenal precipitation. Unfortunately, experimental and clinical data on this topic are scarce and the discussion must be based on hypotheses rather than facts. It is hoped, however, that this discussion will stimulate experimental and clinical efforts to prove or to disprove our assumptions.

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