



Hyperuricemia in Preeclampsia as an Endothelin Effect

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ABSTRACT

Although the etiology of the elevated serum uric acid levels observed in preeclampsia remains unknown, much is actually known of uric acid metabolism in general. One aspect of uric acid metabolism that may be relevant to understanding its involvement in preeclampsia is that, in the human, cells in only a few organs have been found to be actually capable of producing uric acid. These organs are: the liver (probably responsible for most of uric acid production), the small bowel, as well as (probably) the endothelium, the placenta, and lactating mammary epithelial cells. Cells of all other organs lack xanthine oxidase (which is an enzyme necessary for the conversion of xanthine to uric acid). Given that the liver, placenta, and endothelium are known to be involved in preeclampsia, it is plausible to assume that a process that increases purine catabolism in cells of these organs could explain the increased serum uric acid levels. In this paper are discussed mechanisms whereby activation of endothelin-1 receptors on cells of these organs (which are known to have endothelin-1 receptors) will tend to result in increased purine catabolism in them.

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Introduction

Serum uric acid elevations in women with preeclampsia traditionally have been ascribed to diminished renal excretion, yet some have considered this to be an inadequate explanation. If diminished excretion is not the sole cause, then overproduction of uric acid is implied [1,2].

Uric acid is the end product of purine catabolism. In the human, although purine catabolism would be expected to occur to some extent in any living cell, most cells are incapable of producing uric acid. This is because xanthine oxidase, which is required to convert xanthine to uric acid, is not present to an appreciable degree in the cells of most tissues. Cells in the liver and in the small bowel most consistently have been found to contain the most significant amounts of xanthine oxidase [3, 4], and there is also evidence that endothelial cells, mammary gland epithelial cells [5, 6], and placental trophoblastic cells contain the enzyme as well.

Given this, and given that preeclampsia is known to involve the liver and the endothelium, as well as the placenta, it would be most plausible to consider a process causing increased purine catabolism in these organs (as well as, possibly, in the others mentioned above) as a cause of increased serum uric acid

production in preeclampsia and also, as a likely significant aspect of the etiology of preeclampsia. In this paper are presented intracellular mechanisms whereby endothelin-1 can be seen as tending to promote purine catabolism in these organs (as well as in cells of the small bowel [7] and placenta which also have endothelin-1 receptors) [8].

Additionally, a study is referenced that demonstrated “a remarkably close correlation” between plasma endothelin levels and plasma uric acid levels in women with preeclampsia.

Literature Review

A recent review article (extensively quoted below) on hyperuricemia has divided the causes into three categories [9]:

- Under excretion
- Overproduction
- Combined causes

Known causes of under excretion

- Idiopathic
- Familial juvenile gouty nephropathy
- Kidney insufficiency

Kidney failure is one of the more common causes of hy-

peruricemia. In chronic kidney disease, the uric acid level does not generally become elevated until the creatinine clearance falls below 20ml/min, unless other contributing factors exist. This is due to a decrease in urate clearance as retained organic acids compete for secretion in the proximal tubule. In certain kidney disorders, such as medullary cystic diseases and chronic lead nephropathy, hyperuricemia is commonly observed even with minimal kidney insufficiency.

- Metabolic syndrome

This syndrome is characterized by hypertension, obesity, insulin resistance, dyslipidemia, and hyperuricemia, and is associated with a decreased fractional excretion of urate by the kidneys.

- Drugs

Causative drugs include diuretics, low-dose salicylates, cyclosporine, pyrazinamide, ethambutol, levodopa, and nicotinic acid.

- Hypertension

- Acidosis

Types that cause hyperuricemia include lactic acidosis, diabetic ketoacidosis, alcoholic ketoacidosis,

- Preeclampsia and eclampsia

The elevated uric acid associated with these conditions is a key clue to the diagnosis because in healthy pregnancies, uric acid levels are lower than normal.

- Hypothyroidism

- Hyperparathyroidism

- Sarcoidosis

- Lead intoxication (chronic)

History may reveal occupational exposure (e.g., lead smelting, battery and paint manufacture) or consumption of moonshine (i.e., illegally distilled corn whiskey) because some, but not all, moonshine was produced in lead-containing stills.

- Trisomy 21

Known causes of overproduction

- Hypoxanthine Guanine Phosphoribosyl Transferase (HGPRT) deficiency (Lesch-Nyhan Syndrome).

- Partial deficiency of HGPRT (Kelley-Seegmiller Syndrome).

This is also an X-linked disorder. Patients typically develop, gouty arthritis in the second or third decade of life, have a high incidence of uric acid nephrolithiasis, and may have mild neurologic deficits.

- Increased activity of PRPP synthetase, a rare X-linked disorder.

- Diet (diet rich in high purine meats and legumes).

- Increased nucleic acid turnover (such as hemolytic ane-

mia and hematologic malignancies such as lymphoma, myeloma, or leukemia).

- Tumor Lysis Syndrome

- Glycogenoses III, V, VII

- Exposure to persistent organic pollutants (e.g. Organochlorine pesticides).

Known combined causes

- Alcohol

Ethanol increases the production of uric acid by causing increased turnover of adenosine nucleotides. It also decreases uric acid excretion by the kidneys, which is partially due to the production of lactic acid.

- Fructose sweetened soft drinks.

Fructose raises serum uric acid levels by accentuating degradation of purine nucleotides and increasing purine synthesis, and epidemiologic studies have documented a link between sugar-sweetened soft drink intake and serum uric acid levels in several populations. More recently, Lecoultre et al. found that fructose-induced hyperuricemia is associated with a decreased uric acid excretion by the kidneys.

- Exercise

Exercise may result in enhanced tissue breakdown and decreased kidney excretion due to mild volume depletion.

- Deficiency of aldolase B (fructose-1-phosphate aldolase).

This is a fairly common inherited disorder, often resulting in gout.

- Glucose-6-phosphatase deficiency (glycogenosis type 1, von Gierke Disease).

Discussion

None of these causes provides a specific explanation for the intrinsic association of elevated serum uric level elevations with preeclampsia. This would suggest that the cause of serum uric level elevations in preeclampsia is likely a previously undescribed etiology and also that, as such, it likely is peculiar to preeclampsia. In this paper is presented a description of the capacity of endothelin-1 to cause increased uric acid production in cells with both endothelin receptors and with adequate xanthine oxidase content (which include hepatocytes, cells in the small bowel, placental trophoblastic cells, and endothelial cells). Endothelin-1 has been suspected of playing a role in the etiology of preeclampsia since its discovery and recent research has implicated it as possibly the cause of the blood pressure elevations in preeclampsia [10, 11] and also of the oxidative stress which occurs in endothelial cells in preeclampsia [12]. Additionally, it potentially is the cause of prostaglandin and calcium aberrancies noted in preeclampsia [13].

Endothelin-1 activation of its receptors, as they are G protein-coupled receptors, can cause increased production of uric acid within such cells by these mechanisms:

By activation of the cyclic cAMP cascade, in which ATP is converted to cAMP, which will decrease the (ATP)/(ADP) ratio, which in turn will stimulate the catabolism of adenosine to uric acid. Evidence of this is provided in a recent paper, in which it was demonstrated that “uric acid production by hepatocytes is a very sensitive index of ATP depletion irrespective of whether cell P: is lowered or raised. This suggests that raised plasma uric acid may be a marker of compromised hepatic ATP homeostasis [13, 14].”

Activation of the phosphatidylinositol 4,5 bisphosphate cascade results in the formation of inositol 1,4,5 triphosphate, which brings about the rapid release of calcium from intracellular storage sites (such as the endoplasmic reticulum). This increases the cytoplasmic calcium concentration, which will bring about the activation of ATP-dependent calcium pumps to pump calcium into the extracellular fluid and also back into the intracellular storage sites, which will also decrease the (ATP)/(ADP) ratio and thus also promote the catabolism of adenosine to uric acid [13].

Additionally, there is evidence that intracellular accumulation of fatty acids can result in increased uric acid production [15]. In one study, accumulation of free fatty acids has been noted in incidental liver biopsies in 100% of 41 women with preeclampsia [16]. This study also noted a positive relationship between the degree of hepatocytic fat accumulation and serum uric acid levels (which, of course, is also consistent with a common etiology). Abnormally increased activation of endothelin-1 receptors would be expected to result in such intracellular accumulation of fatty acids [17].

A study of plasma endothelin levels has demonstrated “a remarkably close correlation” between plasma endothelin levels and plasma uric acid levels in women with preeclampsia [18]. This, of course, supports the hypothesis that increased activation of endothelin-1 receptors, specifically on hepatocytes, in cells in the small bowel, possibly in endothelial cells, and possibly in placental trophoblastic cells could be the source for the elevations in uric acid levels noted with preeclampsia.

Elevated serum endothelin-1 levels have been noted in several studies of women with preeclampsia [18-21], yet these studies have also demonstrated detectable serum levels in women with normal pregnancies as well. If, actually, the elevations in uric acid levels in women with preeclampsia are due to increased activation of endothelin-1 receptors in hepatocytes and in endothelial cells (and, possibly, in small bowel cells and in placental trophoblastic cells), then it would be expected that the degree of these activations is significantly greater than what occurs in normal pregnancies. Although the observed el-

evations in serum endothelin-1 levels are consistent with suspicions of its involvement with preeclampsia, yet, as a paracrine substance, serum concentrations would not be expected to provide a reliably accurate estimation of its systemic biologic activity; however, systemic endothelin receptor saturation studies likely could [22,23].

Conclusion

In this article is presented the hypothesis that, in preeclampsia, the increased uric acid production is occurring in the same organs (liver, small bowel, and possibly endothelium) as in non-pregnant adults (and, possibly, also in the placenta) and that the increase in production is stimulated by the same biochemical processes (increased purine catabolism), as well. What may be peculiar to women with preeclampsia is suggested to be a significant increase in the degree of endothelin-1 receptor activation in these organs (and systematically, as well). Although increased serum levels have long been noted in women with preeclampsia, what would be most helpful in studying this possibility would be to perform systemic endothelin-1 receptor saturation studies. Should such studies demonstrate a significant difference between results in women with preeclampsia relative to those with normal pregnancies, then it would be plausible to consider increased systemic endothelin-1 activity to be an appropriate target for therapeutic intervention.

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Conflict of Interest Statement

All authors have no conflicts of interest.

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