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Altered Uric Acid Levels and Disease States

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Abbreviations: UA, uric acid; MS, multiple sclerosis; EAE, experimental allergic encephalomyelitis; NO, nitric oxide; SOD, superoxide dismutase; NOS, nitric oxide synthase; PD, Parkinson’s disease; AD, Alzheimer’s disease; ATP, Adenosine 5'-triphosphate; MRP4, multidrug resistance protein 4

Abstract

Altered serum uric acid concentrations, both above and below normal levels, have been linked to a number of disease states. An abnormally high uric acid level has been correlated with gout, hypertension, cardiovascular disease, and renal disease, while a reduced uric acid concentration has been linked to multiple sclerosis, Parkinson's disease, Alzheimer's disease, and optic neuritis. Historically, uric acid has been considered a marker of these disease states. Recent studies, however, have provided evidence that uric acid may actually play a role in the development or progression of such diseases. As a result, the manipulation of uric acid concentrations is now either included in, or being investigated for, the treatment of a variety of disease states.

Introduction

Uric acid (UA; 7,9-dihydro-1H-purine-2,6,8(3H)-trione) has been implicated as a risk factor and cause of numerous disease states. Some disease states, such as gout, hypertension, and cardiovascular disease, have been shown to result when UA levels in the blood are too high. Other conditions, such as neurodegenerative diseases, may be caused by reduced serum UA levels. Consequently, the manipulation of serum UA levels has become a popular strategy in the treatment of a variety of diseases (Table 1). One approach in the treatment of gout, for example, is to reduce the overall serum UA concentration. This is either accomplished through dietary and lifestyle changes or through treatment with UA reducing drugs (Emmerson, 1996; Choi et al., 2005).

Alternatively, increasing UA levels has been proposed as a therapy for the treatment of neurodegenerative diseases, such as multiple sclerosis (MS), as well as in the treatment of both spinal cord injury and stroke because of UA's neuroprotective properties. UA has been found to both prevent and alleviate the symptoms of experimental allergic encephalomyelitis (EAE), the animal model of MS, in mice (Hooper et al., 2000). The administration of inosine, a UA precursor, has been shown to have a similar therapeutic effect in the treatment of EAE (Scott et al., 2002). Some success was reported using inosine to treat MS patients as a method of raising the serum UA concentration (Spitsin et al., 2001a). Similarly, both UA and inosine have recently been implicated as possible treatments following spinal cord injury. Our laboratory has recently reported that the administration of UA following a simulated spinal cord injury *in vitro* resulted in a decrease in secondary neuronal damage (Du et al., 2007). This result is in agreement with *in vivo* studies by Hooper and colleagues that showed that UA protects when administered before spinal cord injury (Scott et al., 2005). A related result by Ju and colleagues found that inosine also protects spinal cord neurons from secondary damage (Liu et al., 2006).

The adjustment of UA levels as a treatment strategy has proven to be successful for a number of disorders; however, since disease states result from both high and low UA levels, the manipulation of UA levels above or below normal levels could possibly lead to unwanted side effects. Ideally, decreasing UA levels to treat a disease caused by an elevated UA level should not leave a patient more susceptible to the development of a condition that may result from a reduced UA level. This review will outline the variety of disease states that have been shown to, or are believed to, result from altered serum UA levels. It will also briefly summarize some of the mechanisms by which altered UA levels can lead to such conditions.

Uric Acid Balance

Uric acid is a weak acid distributed throughout the extracellular fluid as sodium urate. The amount of urate in the blood depends on the dietary intake of purines, urate biosynthesis, and the rate of urate excretion. Plasma UA levels are regulated by a four component renal transport system involving glomerular filtration, reabsorption, secretion and postsecretory reabsorption (Mount et al., 2006). A number of kidney urate transporters are involved in the regulation of plasma urate levels. These include urate transporter 1 (URAT1), which is responsible for the reabsorption of urate, a number of organic ion transporters (OAT) such as OAT1 and OAT3, and ATP-dependent urate export transporter MRP4, all of which are likely involved in urate secretion. In humans, approximately 90% of the filtered urate is reabsorbed. Thus, because of its involvement in urate reabsorption, URAT1 is believed to be critical in the regulation of plasma urate levels (Hediger et al., 2005; Anzai et al., 2007).

UA is produced from purines by the enzyme xanthine oxidase via the purine metabolism pathway (Figure 1 and Waring et al., 2000a). In the majority of mammals, UA is further degraded to allantoin via the urate oxidase (uricase) enzyme. Allantoin is then freely excreted from the body in the urine (Waring et al., 2000a). However, during the Miocene epoch, two separate mutations occurred that resulted in a non-functioning uricase gene. Consequently, humans, apes and certain New World monkeys have higher UA levels (>2 mg/dl or 120μmol/L) as compared with other mammals (<2 mg/dl) (Johnson et al., 2003).

A range of serum UA concentrations has been defined for both hyperuricemia and hypouricemia. Hyperuricemia has been defined for men as a UA concentration greater than 386 μmol/L in one study (Klemp et al., 1997) and greater than 420 μmol/L in a separate study (Johnson et al., 2003). For women, most studies define hyperuricemia as a concentration greater than approximately 360 μmol/L (Klemp et al., 1997; Johnson et al., 2003). Hypouricemia is generally defined as a UA concentration of less than approximately 120 μmol/L (Hisatome et al., 1996). Thus, the normal range of UA concentration falls somewhere between 120 μmol/L and 380 μmol/L, varying slightly depending on gender.

Elevated Uric Acid Levels

Elevated serum UA levels can result from a number of factors including both acute and chronic causes. Acute causes of hyperuricemia include the intake of large amounts of alcohol, tumor lysis syndrome (a complication of cancer chemotherapy), and a diet that is high in purines or proteins. Alternatively, chronic hyperuricemia can result from conditions that cause a reduction in the glomerular filtration rate, a decrease in the excretion of UA, or an increase in overall tubular absorption (Johnson et al., 2003; Choi et al., 2005). Hyperuricemia has been shown to be linked to a number of diseases and conditions including gout, hypertension, cardiovascular disease, myocardial infarction and stroke, and renal disease (Jossa et al., 1994; Freedman et al., 1995; Kang et al., 2002; Choi et al., 2005; Bos et al., 2006). It remains unclear, however, whether an increased UA level is the cause or a consequence of some of these conditions.

Hyperuricemia, Gout and Kidney Disease

A number of studies have found a link between hyperuricemia and gout (Lin et al., 2000; Choi et al., 2005), an inflammatory arthritis that results from the crystallization of UA within the joints (Choi et al., 2005). A direct positive association between serum urate levels and a future risk for gout has been reported. Specifically, as urate concentration increases, the risk for crystal formation increases, raising a patient's susceptibility to the development of gout (Lin et al., 2000). Approximately 20 to 60% of patients with gout also have mild or moderate renal dysfunction, indicating a possible link between an elevated UA level and renal disease (Berger and Yu, 1975). While hyperuricemia may simply be a marker of renal disease, there are some studies that suggest that elevated UA levels might contribute to the development and progression of renal dysfunction (Saito et al., 1978; Kang et al., 2002). An epidemiological study of patients with normal renal function found that a serum UA concentration of > 8.0 mg/dl, as compared with a serum UA concentration of < 5.0 mg/dl, is associated with a 2.9 times increased risk of the development of renal deficiency in men and a 10 times increased risk in women within 2 years (Saito et al., 1978). Furthermore, a study that induced hyperuricemia in rats with the remnant kidney model of progressive kidney disease found that a mild elevation in serum UA concentration led to a significant increase in the progression of renal disease. Specifically, an increase in a number of conditions associated with renal disease was reported, including renal hypertrophy, hypertension, proteinuria (an excess of protein in the urine), glomerulosclerosis and interstitial fibrosis. A possible mechanism by which UA may worsen the progression of kidney disease is by the activation of the renin angiotensin system (RAS). The RAS has been identified as a contributor to the progression of renal disease by increasing both systemic and glomerular pressure and by directly causing the fibrosis of renal and vascular cells (Kang et al., 2002). A recent study that indirectly quantified RAS activation through the measurement of renal vasoconstriction in response to the administration of angiotensin II found that renovascular responsiveness to angiotensin II, and therefore RAS activation, is independently associated with plasma UA concentration. However, while this association is now fairly well established, the underlying mechanism through which an elevated UA concentration stimulates RAS remains unclear (Perlstein et al., 2004).

Hyperuricemia and Hypertension

Hyperuricemia also predicts the development of hypertension in the general population, and an independent positive correlation between UA levels and the occurrence of hypertension has been reported (Jossa et al., 1994). The elevated UA level may be caused by the decrease in renal blood flow that develops in the early stages of hypertension. A reduced renal blood flow could alter the balance between medullary and cortical circulation, possibly resulting in a decrease in urate secretion. This could ultimately lead to an overall increase in the serum UA level (Messerli et al., 1980). Hypertension can also lead to microvascular disease that can cause local tissue ischemia (Puig and Ruilope, 1999). Tissue ischemia can then lead to an increase in the synthesis of UA, ultimately resulting in an increased serum UA level (Friedl et al., 1991). These mechanisms indicate that the increase in the plasma UA level may be a consequence rather than a cause of hypertension.

Hyperuricemia and Cardiovascular Disease

Hyperuricemia may also be a risk factor for cardiovascular disease (Freedman et al., 1995), myocardial infarction, and stroke (Bos et al., 2006). Bos and colleagues found a significant positive association between serum UA levels and the risk of both heart disease and stroke (Bos et al., 2006). Elevated UA levels were also found to be an independent risk factor for overall cardiovascular mortality (Fang and Alderman, 2000).

Furthermore, serum UA levels were found to be significantly higher in patients with established coronary heart disease as compared with healthy patients (Torun et al., 1998). The association of high serum UA levels with cardiovascular disease may be due to uric acid's role as an antioxidant (Ames et al., 1981; Davies et al., 1986), as an elevated serum UA level may be a defense mechanism against atherosclerosis. UA concentrations may increase in an attempt to block lipid peroxidation and other related phenomena (Nieto et al., 2000). This again suggests that elevated UA levels are a consequence of disease. On the other hand, increased UA levels may instead contribute to the development of cardiovascular disease by exerting a negative effect on the endothelium. There is some evidence that serum UA could possibly promote, rather than prevent, oxygenation of low-density lipoprotein cholesterol and lipid peroxidation (De Scheerder et al., 1991). This can lead to an increase in platelet adhesiveness, resulting in thrombus formation that can contribute to the development of atherosclerosis, increasing the likelihood of the development of cardiovascular disease. High UA levels can also stimulate the release of free radicals, which have been shown to be involved in adhesion molecule expression by inflammatory cells as well as in inflammatory cell activation and adherence to the damaged endothelium (Waring et al., 2000a). This ultimately results in endothelial injury, again increasing the risk of cardiovascular disease development. This mechanism is supported by the positive correlation found between elevated UA levels and chronic inflammation in chronic heart failure (Leyva et al., 1998). In addition, an elevation in plasma UA concentration is associated with an increased level of C-reactive protein that has been identified as an important indicator of myocardial infarction, stroke, and vascular death (Kang et al., 2005).

Elevated Serum Uric Acid Concentration: Cause or Consequence of Disease?

As stated, it remains unclear whether an elevated UA concentration contributes to the development of these conditions or whether it is simply a marker of them. Additional evidence that UA is a consequence rather than a cause of these conditions includes the many studies that have failed to identify UA as an independent risk factor of disease development. An increase in serum UA concentration could simply be an indication of other risk factors of cardiovascular disease, hypertension, and renal disease that are themselves associated with elevated serum UA levels such as obesity, glucose intolerance (Lee et al., 1995), or hyperlipidemia (Puig et al., 1991). However, numerous other studies found UA to be an independent risk factor of disease development even after adjusting for these other factors (Jossa et al., 1994; Bos et al., 2006). Thus, there remains a strong possibility that UA could play a pathogenic role in hypertension, cardiovascular disease, and renal disease. In addition, recent studies have found that an elevated serum UA concentration as a child is associated with an increased blood pressure as an adult and is likely to contribute to the development of early onset essential hypertension.(Alper et al., 2005)

Numerous studies have investigated the effects of directly increasing plasma UA levels. These findings provide added support that elevated UA levels are at least partly responsible for the development of a number of disease states. Maxwell and colleagues found that increasing UA levels in healthy humans resulted in impaired acetylcholine-induced vasodilation in the forearm (Waring et al., 2000b). This suggests an alteration in the release of nitric oxide, as nitric oxide is an important mediator of arterial vasodilation as a means of increasing blood flow. Furthermore, increasing serum UA levels in animal models has been shown to inhibit the nitric oxide system in the kidney (Johnson et al., 2003). In other studies, mild hyperuricemic rats developed hypertension and an increase in blood pressure after several weeks (Mazzali et al., 2001; Sanchez-Lozada et al., 2002). In these studies, the hypertension and blood pressure increase could be prevented by maintaining UA levels in the normal range with the administration of allopurinol (Mazzali et al., 2001). Animal models of chronically hyperuricemic rats have resulted in a persistent afferent arteriolopathy resulting in an increased media: lumen ratio (Watanabe et al., 2002). Finally, renal injury was also reported in hyperuricemic rats and these changes could again be prevented by maintaining serum uric acid levels in the normal range (Sanchez-Lozada et al., 2002).

Methods for Reducing Serum Uric Acid Levels

As a result of the established role of UA in the development and progression of gout, as well as its potential contribution to hypertension, cardiovascular disease, and renal disease, various treatment strategies for reducing a person's overall serum UA concentration have been developed. Initially, dietary and lifestyle changes are encouraged, as many of the causes of hyperuricemia are correctable and the use of drugs to lower UA levels is often life-long. These include decreasing the consumption of protein, purines, and alcohol, as well as reducing obesity. There are two types of drugs that are used to treat chronic hyperuricemia. Xanthine oxidase inhibitors, such as allopurinol, inhibit the production of UA by blocking the final two steps of urate synthesis. As a result, there is an increase in the production of the urate precursors xanthine and hypoxanthine. Xanthine oxidase inhibitors are primarily used in patients who have an increased urate production. Alternatively, if the elevated UA concentration is caused by a low urate clearance, uricosuric drugs, such as probenecid, sulfinpyrazone and benzpromarone, are used to reduce the serum UA concentration through the inhibition of the URAT1 transporter, resulting in an increase in UA excretion (Emmerson, 1996; Choi et al., 2005).

Reduced Uric Acid Levels

Serum uric acid levels that are below normal concentrations have also been linked to a variety of disease states including multiple sclerosis, optic neuritis, Parkinson's disease, and Alzheimer's disease (Church and Ward, 1994; Toncev et al., 2002; Knapp et al., 2004; de Lau et al., 2005; Kim et al., 2006). In these inflammatory diseases, a decreased UA concentration may not be able to prevent the toxicity by reactive oxygen and nitrogen species that form as a result of the inflammation. Peroxynitrite, in particular, is believed to have a significant negative impact on cellular function and survival (Pacher et al., 2007).

The Role of Peroxynitrite in Inflammation

Peroxynitrite ($ONOO^-$) is formed by the reaction of nitric oxide (NO) with superoxide (O_2^-) whenever the two are within a few cell diameters of one another. The reaction is diffusion limited due to nitric oxide's ability to move between cells and through cell membranes. Thus, the production of NO and superoxide do not necessarily have to occur within the same area or even within the same cell in order for a reaction to occur and result in the formation of peroxynitrite (Pacher et al., 2007). Individually, neither NO nor superoxide are especially toxic *in vivo*. Superoxide is quickly removed by the scavenging enzyme superoxide dismutase (SOD) and NO is removed by rapid diffusion into the red blood cells where it is converted via a reaction with oxyhemoglobin to nitrite. Due to the high concentration of NO that is produced *in vivo*, along with the rapid reaction rate of NO with superoxide, NO is able to outcompete SOD for reaction with superoxide whenever both species are present (Beckman, 1996).

Peroxynitrite is a strong oxidant that can react directly with electron rich groups of a number of biological molecules, leading to oxidative damage. It reacts relatively slowly with most biological molecules due to its unusual stability. As a result, peroxynitrite is able to collide with billions of biological molecules without undergoing a reaction, allowing it to be selective in the biological molecules that it does react with (Beckman, 1996). Under normal physiological conditions, there is a low production of peroxynitrite, resulting in a minimal amount of oxidative damage. A small increase in NO and superoxide production, however, produces a much larger increase in peroxynitrite formation. Even a slight increase in peroxynitrite production can result in substantial oxidation that can lead to tissue destruction and can damage a number of processes that are critical for normal cellular function (Pacher et al., 2007). Peroxynitrite toxicity results from a number of different mechanisms including the nitration of amino acids such as tyrosine and cysteine (Ischiropoulos et al., 1992) and DNA mutations and breakages resulting from oxidation modifications that ultimately lead to cell death via necrosis or apoptosis (Inoue and Kawanishi, 1995). Tyrosine nitration can lead to the alteration and inactivation of a number of enzymes as well as to modifications in the cytoskeletal organization. Structural proteins have an abundance of tyrosine residues, making them an attractive target for nitration. The nitration of structural proteins can have significant consequences because the alteration of one subunit can result in the improper formation of the entire structure (Pacher et al., 2007). Peroxynitrite can also inhibit the mitochondrial electron transport chain (Radi et al., 1994) by altering the permeability of the mitochondrial outer membrane (Pacher et al., 2007). This can result in a state of cellular energy deficiency and can damage a number of cellular components including lipids, proteins and nucleic acids, again resulting in cell death (Smith et al., 1999). Peroxynitrite can also activate cell death by altering essential signal transduction pathways (Pacher et al., 2007).

Peroxynitrite and Disease

Peroxynitrite has been shown to have a negative impact in a number of diseases and conditions. These include cardiac diseases, vascular diseases, local inflammation, cancer, stroke, neurodegenerative disorders (including multiple sclerosis, Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer's disease and Huntington's disease) and diabetes (Pacher et al., 2007). The inflammation that occurs in neurodegenerative diseases directly encourages the production of NO and superoxide, leading to a vast increase in peroxynitrite formation (Radi et al., 1991). A number of studies have documented the involvement of peroxynitrite and other reactive nitrogen species in multiple sclerosis (MS). Nitrotyrosine has been identified in the cells surrounding the plaque areas of postmortem brains of MS patients (Spitsin et al., 2001b). An increase in the levels of inducible nitric oxide synthase, an enzyme involved in the production of NO, has also been found in the macrophages, microglia, and astrocytes of demyelinating plaques of MS patients (Bagasra et al., 1995). Furthermore, elevated NO concentrations were measured in mice with EAE (Hooper et al., 1995). Evidence of oxidative stress was also identified in postmortem studies of patients with Parkinson's disease (PD) (Jenner, 2003). Specifically, an increased accumulation of nitrotyrosine was found in both Lewy bodies, a structure often found in the brains of Parkinson's patients, as well as in polymophonuclear cells (Gatto et al., 2000).

Peroxynitrite, along with other free radicals, is believed to be involved in the inflammation, demyelination, and axonal injury that occur during MS (Toncev et al., 2002). Free-radical production can increase inflammation and lead to tissue damage. Peroxynitrite is thought to play a role in the demyelination that occurs during MS because of its ability to induce lipid peroxidation of the highly fatty myelin sheath that surrounds the oligodendrocytes (van der Veen et al., 1997). Pathological studies have shown that axonal damage in MS is most prevalent in regions with increased inflammation and demyelination, suggesting that axonal damage is also a result of the actions of free radicals and cytokines (Ferguson et al., 1997). Oxidative stress resulting from an excess of free radicals is also implicated in the pathogenesis of Alzheimer's disease (AD) (Jenner, 2003). An increased neuronal nitric oxide synthase expression has been reported in both neurons with neurofibrillary tangles in the hippocampus and cortex and in reactive astrocytes close to amyloid plaques in AD patients, suggesting that both neurons and astrocytes are affected by peroxynitrite (Thorns et al., 1998; Simic et al., 2000). In PD, oxidative damage to lipids, proteins, and DNA has been identified (Gatto et al., 2000; Jenner, 2003). In addition, toxic products of oxidative damage, such as 4-hydroxynonenal, have been shown to impair cell viability in patients with PD through their reaction with various proteins (Jenner, 2003).

Uric Acid and Neuroprotection

Uric acid is a natural antioxidant, accounting for up to 60% of the free radical scavenging activity in human blood (Ames et al., 1981). UA can scavenge superoxide, the hydroxyl radical, and singlet oxygen (Ames et al., 1981; Davies et al., 1986). UA may assist in the removal of superoxide by preventing against the degradation of superoxide dismutase, the enzyme that is responsible for clearing superoxide from the cell (Pacher et al., 2007). Removal of superoxide helps to prevent its reaction with NO, blocking the formation of peroxynitrite (van der Veen et al., 1997). UA is also very effective at preventing peroxynitrite from nitrating the tyrosine residues of proteins, thereby preventing the inactivation of cellular enzymes as well as the modification of the cytoskeleton (i.e. Pacher et al., 2007). UA also has the ability to bind iron and inhibit iron-dependent ascorbate oxidation, preventing an increased production of free radicals that can further contribute to oxidative damage (Davies et al., 1986). Thus, a reduced UA concentration may decrease the body's ability to prevent peroxynitrite and other free radicals from acting on cellular components and damaging the cell. There are some recent studies, however, that suggest that this may not be UA's sole method of neuroprotection. Interestingly, Pryor and colleagues found that at normal human levels, peroxynitrite binds with carbon dioxide 920 times faster than it does with UA, questioning whether UA plays a significant role in the reduction of peroxynitrite toxicity *in vivo* (as discussed in Du et al., 2007). Furthermore, our laboratory recently found that astroglia must be present for UA to protect spinal cord neurons in a cell culture model of spinal cord injury (Du et al., 2007). UA acts upon astroglia and upregulates protein levels of EAAT-1, a glutamate transporter, to protect spinal cord neurons from glutamate-induced toxicity. When astroglia are not present, UA can no longer protect neurons, suggesting that UA does not act passively by merely binding reactive oxygen species. Thus, UA acts to protect cells through a more direct, astroglia-mediated mechanism (Du et al., 2007).

Reduced Serum Uric Acid Concentration and Disease

There is an abundance of evidence that suggests that low UA levels are associated with the development and progression of a variety of diseases. A number of studies have found an independent negative correlation between serum UA levels and MS (Spitsin et al., 2001b; Toncev et al., 2002; Rentzos et al., 2006). In epidemiological studies, both

Toncev and colleagues and Rentzos and colleagues found that patients with MS have significantly lower serum UA levels as compared with healthy subjects (Toncev et al., 2002; Rentzos et al., 2006). Studies that measured UA levels in sets of mono- and dizygotic twins in which one of the twins has MS also found a significantly lower UA level in the siblings with MS (Spitsin et al., 2001b). There are also some studies that have found a correlation between serum UA levels and disease activity as well as between serum UA levels and BBB dysfunction. MS patients with BBB disruption were found to have significantly lower UA levels than those with no disruption. Also, MS patients with relapse had significantly lower UA levels than those in remission (Toncev et al., 2002). A correlation was also found between UA levels and optic neuritis, an inflammatory demyelinating disease of the optic nerve that is often the first symptom of MS. Persons with optic neuritis were found to have lower serum UA levels than age and sex matched controls (Knapp et al., 2004). Similarly, associations between serum UA levels and the risk of disease were also reported in both AD and PD. A significant reduction in serum UA concentration was found in AD patients as compared to healthy controls (Kim et al., 2006). In PD, higher serum UA levels correlated with a significant decrease in the risk of disease (de Lau et al., 2005). Additionally, diminished levels of UA were found in the substantia nigra of PD patients (Church and Ward, 1994). Lastly, there is some recent evidence that suggests that a reduced UA concentration in the saliva may contribute to the development of tumors in the upper part of the stomach. UA is believed to be involved in defending against the nitrogen species that are generated from the reaction of salivary nitrite with acidic gastric juices. Saliva that is deficient in antioxidants, such as urate and ascorbic acid, may not be able to prevent against the potentially harmful reactive nitrogen species that can promote tissue damage and mutagenesis (Pietraforte et al., 2006).

Reduced Serum Uric Acid Concentration: Cause or Consequence of Disease?

There is some uncertainty as to whether low serum UA levels are a cause or consequence of these neurodegenerative diseases. It is possible that persons with low serum UA levels are unable to prevent against free-radical toxicity, leading to the development of inflammation and the destruction of tissues. However, it is also possible that the inflammation that occurs in MS leads to the consumption of UA to scavenge the excess free-radicals produced, resulting in a lower UA level (Drulovic et al., 2001). The results of the direct administration of UA, and subsequent increase in serum UA concentration, in mice with an acute, aggressive form of EAE provides support that low UA levels are a cause and not a consequence of disease. Hooper and colleagues found that the administration of UA promoted long-term survival of mice with EAE when given either before or after the symptoms of EAE had appeared (Hooper et al., 1998). Specifically, the treatment prevented against the invasion of inflammatory cells into the CNS by maintaining the integrity of the BBB (Kean et al., 2000). Furthermore, a recent clinical study found that the administration of inosine, a UA precursor, stopped the progression of MS in all 11 patients that received the drug and improved some of the symptoms of the disease in 3 of the patients (Spitsin et al., 2001a). In PD animal models, the administration of UA was found to diminish oxidative stress and prevent against cell death (Duan et al., 2002). In addition, an evaluation of epidemiological studies found that MS and gout are virtually mutually exclusive, as there were no reported cases of a patient with both MS and gout, suggesting that the increased serum UA level associated with gout can protect against MS. This again implies that low UA levels have a causal role in MS (Hooper et al., 1998).

Conclusions

While some alterations in uric acid levels may be a consequence of disease, it is likely that UA also plays an important role in the development as well as in the prevention of many diseases. Thus, it appears that UA is not an inert organic compound, as has historically been believed, but can instead play a role in many biological functions. UA can be both beneficial, as an antioxidant and free-radical scavenger, and deleterious, if present at an elevated level. The manipulation of serum UA levels holds promise in the treatment of a number of diseases. Importantly, however, because both decreased as well as elevated UA levels may contribute to the development and progression of a number of disease states, significant alterations in UA levels that result in above or below normal serum UA concentrations should be minimized.

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Footnotes

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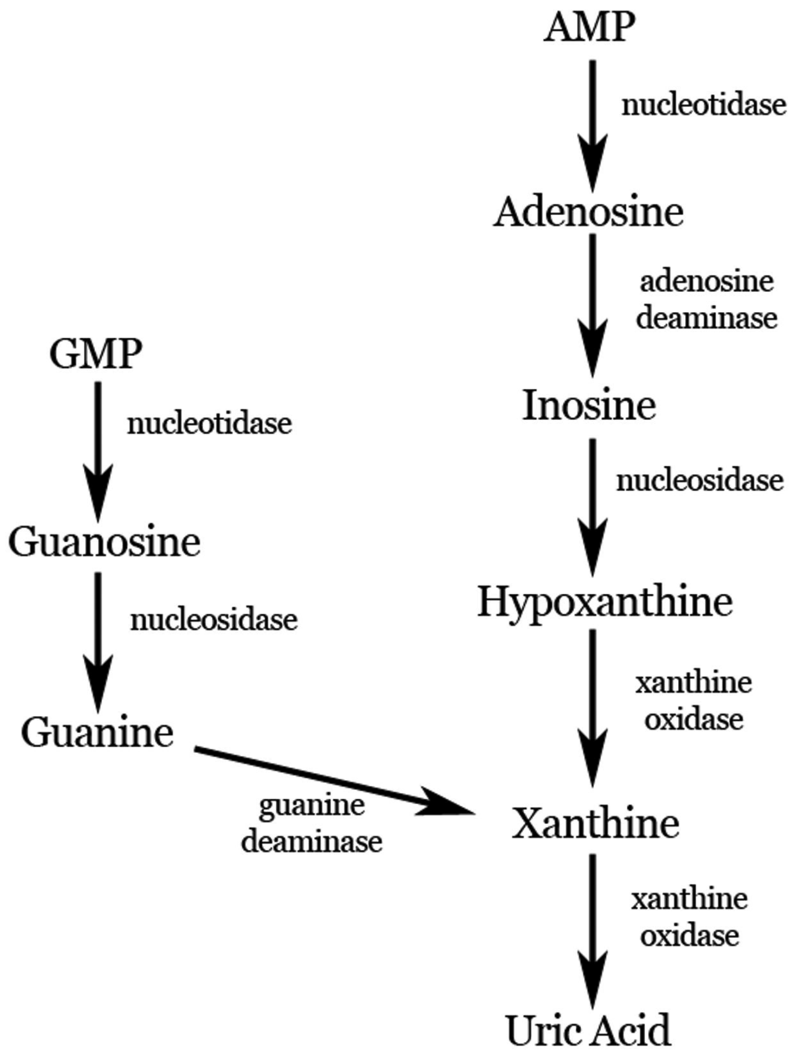
Legends for Figures

Figure 1: Purine metabolism leads to the production of uric acid.

Decreasing Uric Acid Concentrations as a Treatment for:	Increasing Uric Acid Concentrations as a Treatment for:	Diseases Associated with Elevated Uric Acid Levels	Diseases Associated with Reduced Uric Acid Levels
• Gout • Cardiovascular disease • Hypertension • Renal disease	• Spinal cord injury • Multiple sclerosis and other neurodegenerative diseases	• Gout • Kidney disease • Hypertension • Cardiovascular disease	• Multiple Sclerosis • Parkinson's Disease • Alzheimer's Disease • Cancer (tumor development)

Table 1: Treatment with and alterations of UA.

Fig. 1


AMP
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Inosine
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Hypoxanthine
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GMP
nucleotidase
Guanosine
nucleosidase
Guanine
guanine
deaminase