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The complex interplay of purines in health and disease

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Abstract: Since the 1940s, purines have been known predominantly for two functions as both nucleic acid building blocks for the genetic material in cells, and as substances which break down to produce urate, and potentially elevate the risk for gout, an arthritis-like ailment or gouty arthritis with an excruciatingly painful presentation in joints There are two extant pathways of purine nucleotide synthesis, the De Novo synthesis pathway and the salvage pathway. The former is the major nucleotide synthesis pathway and the latter is the one essential in brain and bone marrow. The quantity of salvage of certain purines by animals is linked to the related intestinal or bacterial population containing elevate nucleic acid levels. Allopurinol inhibits the enzyme xanthine oxidase and decreases uric acid synthesis, and is broadly applied in the treatment of the excessive production of gout and uric acid.

Key words: purines, uric acid, de Novo synthesis, salvage pathway, Lesch-Nyhan disease, allopurinol

INTRODUCTION

Since the 1940s, purines have been known predominantly for two functions as both nucleic acid building blocks for the genetic material in cells, and as substances which break down to produce urate, and potentially elevate the risk for gout, an arthritis-like ailment or gouty arthritis with an excruciatingly painful presentation in joints (1). A purine (2) consists of a heterocyclic aromatic compound made up of a pyrimidine ring inextricably attached to an imidazole ring; and include substituted purines and their tautomers, i.e. isomers of organic compounds which readily interconvert (3). Purines occur at elevated levels in meat and meat-related products and meat derivatives, particularly internal organs, such as kidney and liver; but are low in plant-formulated diets (4). Purines are essential for life and occur in all plant and animal cells. They consist of adenine, guanine, hypoxanthine, xanthine and caffeine. The others, excepting caffeine, in cooperativity with pyrimidines constitute the genetic codes, DNA and RNA as well as energy molecules, such as ATP,

GTP and coenzyme A. Purine metabolism, specifically their breakdown in the liver forms uric acid, that is an antioxidant with beneficial impacts as a free-radical scavenger. The overproduction of uric acid accumulates to an elevated level in the blood culminating in certain health-related aberrations, and gout i.e. an arthritis-simulated disorder that manifests as accumulated uric acid crystals in joints, with exceptional presence in the big toe.

There are two extant pathways of purine nucleotide synthesis, the De Novo synthesis pathway and the salvage pathway. The former is the major nucleotide synthesis pathway and the latter is the one essential in brain and bone marrow. The particular instances of certain forms of gout and the Lesch-Nyhan syndrome whereby a deficiency of hypoxanthine-guanine phosphoribosyltransferase results in elevated PRPP concentrations, and an accelerated de novo purine biosynthesis is indicative that PRPP supply is a limiting factor for the de novo pathway. This is consistent with the low intrinsic PRPP amidotransferase affinity for PRPP, $S_{0.5}$0.06-0.47mM (5); and the competitive characteristics of the nucleotide inhibitions regarding PRPP (6), as well as conclusively undergirds the premise that a principal function of hypoxanthine-guanine phosphoribosyltransferase is the balance convergence between purine biosynthesis and biodegradation. Introduction of purine bases to intact bacterial suspensions (7) and animal (8) cells causes the accelerated inhibition of de novo purine synthesis; this finding is perspicuous by production of PRPP amidotransferase nucleotide feedback inhibition. There is an ostensible contradiction between the decreased concentrations of purine bases necessary for the inhibition of intact cell de novo synthesis, 4-20 umoles (8), and the relatively feeble nucleotide inhibitions derived via isolated PRPP amidotransferase (5). It is suggested that in vitro determination affinities are not representative of the in vivo event. Furthermore, a contributing factor in the demonstrated de novo purine synthesis inhibition is PRPP limitation emanating as a requirement for the purine phosphoribosyltransferase reaction. It is reasonable to state that any tissue augmented with exogenous purine bases portends energy conservation by switching off de novo synthesis.

The function of blood in purine transport: It is perspicuous that erythrocytes are incapable of synthesizing purines de novo (9); thus, any purine nucleotide turnover in red cells is derived from the continual purine ingress and egress. An accumulated nucleotide turnover of circa 3300 umoles per 24h corresponds to 1280 mg or 450 mg of purine base, i.e. approximately 6mg of base per kg body weight (10). These values are anecdotal due to nucleotide content variations (11) and turnover rates; it is clear that appreciable amount of purines enter and depart the red cell nucleotide pool. The red cell ATP concentration decreases with senescence (12), but it can be determined that the ostensible adenine nucleotide turnover is not merely due to dilution effect from senescence of labeled red cells and their replacement by reticulocytes having unlabeled ATP. On the assumption of a life span of 127 days for human erythrocytes (13), within 9 days, 7% of the labeled cells undergo replacement by reticulocytes having about double ATP as erythrocytes (12); consequently, the maximum adenylate pool dilution could be circa 14% encompassing this period.

The diverse sources of purines: The quantity of salvage of certain purines by animals is linked to the related intestinal or bacterial population containing elevate nucleic acid levels (14). The high activities of excreted pancreatic ribonuclease in rodents, ruminants and herbivorous marsupials is necessary for bacterial RNA salvage and resultant phosphate and nitrogen conservation (14). The importance of

salvage from the diet is not very clear, although, as Man and other mammals are capable of being indefinitely sustained on purine-free diets (15). However, the elevated nucleic acid value of yeast may be relevant regarding the single-cell protein usage in human nutrition. Yeast consumption by Man enhances plasma uric acid contents (16), suggesting that daily yeast nucleic acid intake should not be in excess of 2g in order to minimize the resultant impact of stone formation.

The liver assumes the main dietary source of purines (17); the specific presentation of the purine released from liver and taken up by the erythrocyte is not clear as nucleotides do not appreciably transverse the cell membrane intact (18); and the initial step definitely involves nucleotide production, catalyzed by the 5'-nucleotidase of liver plasma membranes (19). Purines enter and leave rabbit erythrocytes as free bases instead of nucleosides, with the feature of the transported purine varying between species as related to the activities of xanthine oxidase and guanase in blood cells. Human blood does not contain xanthine oxidase in either erythrocytes or serum (20) with consequential human plasma containing detectable values of 0.01 – 0.04mM of both hypoxanthine and xanthine (21, 22). The absence of guanine in plasma, and the presence of guanase in blood (23) indicates that the predominant purine available to be converted into nucleotide by human erythrocytes is hypoxanthine. The existence of free hypoxanthine in the blood of several other species is not conceivable due to the elevated xanthine oxidase activities (20). 5-phosphoribosyl transfer from PRPP to hypoxanthine, with IMP production, is catalyzed by hypoxanthine/guanine phosphoribosyltransferase (20, 24). In rabbit erythrocytes, the IMP produced can undergo conversion into either adenine or guanine nucleotides (25), but human erythrocytes are unable to convert IMP into AMP (26), with implication that adenosine is a nucleotide source for these cells by reaction with adenosine kinase as demonstrated by adenine nucleotide turnover in human erythrocytes (27). The other explanation entails adenine salvage, but supplies of this compound in animal tissues are limited in scope, otherwise there may be an extant genetic aberration culminating in adenine phosphoribosyltransferase deficiency. Cases have been detected in partial adenine phosphoribosyltranferase deficiency in red blood cells exhibiting conventional rates of uric acid formation and normal values of PRPP (28). In rabbit cells, the main purines released from prelabeled cells are hypoxanthine and xanthine with purine release from erythrocytes increased by anomalies of elevated oxygen concentrations. Issues concerning the PRPP supply necessary for hypoxanthine salvage by erythrocytes indicate that the PRPP level in rabbit red blood cells is approximately 20 mmoles per ml of cells (29) and the PRPP Km in reaction with hypoxanthine/guanine phosphoribosyl transferase is 0.2mM (30). This necessitates an incessant PRPP supply to sustain albeit a slow rate of IMP production. Animal tissue PRPP synthetase has an absolute requirement for inorganic phosphate. The augmented requirement in intact cells is perhaps linked to surmount PRPP synthetase feedback inhibition by ADP, GDP, and 2,3-diphosphoglycerate (29). It has been shown that minimal nucleotide production from base is derivable in whole human blood (31). The probable manner in which erythrocytes make sufficient amount of PRPP for nucleotide synthesis in the presence of low phosphate values is that inosine is made available to the erythrocytes whereby IMP is generated in sequential reversible steps initiated via inosine + phosphate through non-reversible PRPP + hypoxanthine → IMP + pyrophosphate. The scheme presents that PRPP synthesis occurs at low phosphate levels, with compartmentalization within the erythrocyte or release of PRPP synthetase feedback inhibition in the sequential reactions. There are suggestions that inosine is a better

precursor than glucose for nucleotide synthesis in ascites turnover cells (32); and that IMP is synthesized in good yield from inosine in the absence of phosphate (33).

The significance of purine salvage is the enabling ambient for purines synthesized in a specific tissue to be made available to other requiring tissues. An appropriate PRPP dissemination between de novo synthesis and salvage, in cooperativity with feedback control mechanisms of the de novo pathway ensures a regulated purine formation rate. The precise and specific operative regulatory attributes of the de novo synthesis of purine nucleotides, the release of bases and nucleotides with their resultant hepatic reutilization, and blood uptake for dissemination to other tissues, or oxidation to urate need enhanced investigation activities for further studies. Diet may be connected with hyperuricaemia and gout development, but the association between dietary factors and hyperuricaemia is not clear, and a paucity of investigations has directed relationships between food intake and hyperuricaemia (34). Consumption of animal protein and seafood had been linked with elevated hyperuricaemia prevalence, whereas soy product consumption was related with decreased hyperuricaemia prevalence among middle-aged Chinese men (34). Uric acid concentrations accelerated following fructose-rich food intake, that triggers uric acid formation by accelerating ATP degradation to AMP, a urate precursor (35) including an enormous quantity of purine intake (36). Purine-rich food consumption is connected with both the incident and acute gout events. Prolonged purine consumption via the augmentation of uric acid concentrations may accumulate in gout. Based on the slow progression of both nucleation and MSU crystal growth and development, a transient elevation in uric acid values may not be an aberrant feature. Purine may constitute an innocuous participant in acute events of gout, which are liable to be elicited by, for instance, free fatty acids in certain purine-rich foods (37).

Characterization of purine metabolism in the central nervous system (38) is exhibited by decreased de novo purine synthesis (39), accelerated HPRT activity (40) and lack of detectable xanthine oxidase functionality (20, 41). These demonstrate that rather than uric acid, the end-products of purine nucleotide degradation in the CNS are hypoxanthine for adenine nucleotides and xanthine for guanine nucleotides (40, 42). Conversely, HPRT hyperactivity is ostensibly relevant to salvage a significant quantity for purine nucleotide synthesis. Hypoxanthine transport to the brain from blood presents a possible source for purine nucleotide synthesis in the CNS (43, 44). The aberrant neurological presentations of absolute HPRT deficiency depict that hypoxanthine salvage is essential for optimum neuronal functionality (45).

Human peripheral blood leucocytes were investigated for the detection and the regulatory attributes of de novo synthesis pathway of purine nucleotides (46). The result suggests that ribose-5-phosphate availability is perceptibly not limiting to generate PRPP under physiological ambient. Furthermore, the results depicted peripheral human leukocytes, the availability of the entire pathway of the de novo synthesis of purine nucleotides and the presentation in these cells of the biochemical implications of hypoxanthine-guanine phosphoribosyltransferase deficiency as augmented presence of PRPP and accelerated purine synthesis de novo. The findings present the suitability of the leukocyte as a model tissue to investigate human purine metabolism (46). Human B lymphoblast lines grossly lacking in hypoxanthine-guanine phosphoribosyltransferase, HGPRT wre selected for resistance to 6-thioguanine from cloned normal and phosphoribosylpyrophosphate, PP-Rib-P

synthetase superactive cell lines and compared with particular parental cell lines as related to growth and PP-Rib-P and purine nucleotide metabolism (47). At the blocking of purine de novo synthesis by 6-methylthioinosine or aminopterin, it was found that growth inhibition of all HGPRT-deficient cell lines was refractory to increased amount of Ade at values which restored appreciable growth to parental cell lines. Ade-resistant growth inhibition of parent cell lines with 6-methylthioinosine resulted in Ado-deaminase inhibition , insufficiently generated IMP and consequently, guanylates to undergird lymphoblast growth deficient in HGPRT activity and blocked in purine synthesis de novo explicated that a paramount trajectory to interconvert AMP to IMP is associated with the reaction sequence: AMP…Ado…Ino…Hyp…IMP. The generation of PP-Rib-P and purine nucleotide triphosphate pools were unaltered by the release of HGPRT deficiency into normal lymphoblast lines, undergirding the aspect that accelerated purine synthesis de novo in this deficiency emerged from augmented PP-Rib-P presence for the pathway. Cell lines with double aberrant enzyme features did not vary from PP-Rib-P synthetase superactive parent lines of PP-Rib-P and purine synthesis rates nothwithstanding 5- to 6-fold increment in PP-Rib-P values, excretion of circa 50% newly synthesized purines, and lowered GTP levels. Fixed rates of purine synthesis de novo in PP-Rib-P synthetase-superactive cells ostensibly depict saturated rate-limiting amidophosphoribosyltransferase reaction for PP-Rib-P. Cooperativity with accelerated purine excretion, enhanced channeling of newly produced purines into adenylates, and aberrant conversion of AMP to IMP, fixed rates of purine synthesis de novo are liable to condition cell lines with impairments in HGPRT and PP-Rib-P synthetase to diminished GTP culminating in growth retardation (47).

Nucleotides are relevant for an expansive array of biological processes and invariably synthesized de novo in all cells (48). With the proliferation of cells, increased nucleotide synthesis is required for DNA replication and for RNA formation to undergird protein synthesis at diverse stages of the cell cycle when these events are regulated at multiple stages, as the synthesis of the precursor nucleotides is also significantly regulated at multiple steps (49). An investigation of the reutilization of DNA nucleotide bases in the liver and spleen of young and adult mice showed that the re-dissemination of 14C-thymidine is highly evident in adult mice, particularly following partial hepatectomy, and is not suppressed by splenctomy and administration of hydrocortisone (50).

The influence of ammonia on purine and pyrimidine biosynthesis was determined in rat liver and brain in vitro (51). The results indicated that excessive quantities of ammonia could cause interference with purine nucleotide biosynthesis by inducing the formation of carbamoyl phosphate via mitochondrial synthetase, with the excess carbamoyl phosphate also augmenting pyrimidine nucleoside synthesis de novo and reducing the available phosphoribosyl pyrophosphate required for biosynthesis. The relative functionalities of purine de novo synthesis and of purine salvage have been respectively evaluated in various tissues by the actions of amidophosphoribosyltransferase and HPRT. Alterations in purine de novo synthesis as measured by [14C]formate incorporated into cellular purines were demonstrated in the amidophosphoribosyltransferase activities (50). The potential of various tissues to synthesize purines de novo is expansive and the action of the liver as the major locus of purine de novo synthesis in vivo and transporting purines to other tissues is ostensibly controversial. Regulatory or control mechanisms are more likely to be tissue specific.

The age-associated alterations in the activity respectively, of the purine de novo synthesis and

purine salvage pathways in the brain suggest physiologic actions of the developed brain in lieu of cell division and organogenesis which necessitate an increased level of purine salvage compared to purine de novo synthesis. This undergirds the aspect that purine de novo synthesis can singly meet the requirements for augmented purine nucleotides that involves an unclear mechanism of lectin-induced lymphocyte transformation (52).

pH Effects : The influence of pH, P_{o2} and inorganic phosphate on red blood cell uptake and metabolism of hypoxanthine and inosine-5'-monophosphate, IMP accumulation were observed to be significantly elevated at acid pH, elevated extraneous phosphate levels and reduced $P_{o2.}$ Accumulated IMP release as hypoxanthine resulted at alkaline pH levels and reduced extraneous phosphate values. Ambient conducive to IMP accumulation resulted in non-availability of hypoxanthine to a consequential elevation in 5'-phosphoribosyl-1-pyrophosphate intracellular phosphate values were remarkably dependent on pH. These allosteric effectors act in opposing directions, two enzymes influencing IMP accumulation, i.e. 5'-phosphoribosyl-1pyrophosphate synthetase and 5'-nucleotidase, thus suggesting the role of red blood cells in hypoxanthine elimination from anoxic tissue (53). The interconversion rate of alpha- to beta-phosphoribosylamine as a pH function was observed by saturation- and inversion-transfer NMR techniques (54). The generation rate of 5-phosphoribosylamine, PRA from ribose-5-phosphate and NH3 and its degradation rate as a pH function were demonstrated with a glycinamide ribonucleotide synthetase trapping system aligned with other studies (55).

The safety and efficacy of allopurinol : The purine transfer via hematoencephalic barrier is not clearly pellucid. Allopurinol causes the inhibition of the enzyme xanthine oxidase and elevates xanthine and hypoxanthine plasma concentrations, but it should not elevate the cerebrospinal fluid, CSF contents of these purines due to the non-appearance of xanthine oxidase in the central nervous system, CNS. An evaluation of the plasma and CSF levels of uric acid, hypoxanthine, xanthine and inosine in the baseline state, and following seven days of the administration of allopurinol, 5-19mg/kg/24h in four patients with hypoxanthine phosphoribosyltransferase, HPRT deficiency depicted that the CSF uric acid concentration correlated with its plasma content, $r = 0.93$, $p < 0.01$ (56). The CSF hypoxanthine and xanthine levels were respectively, as a mean five and ten times higher in patients having HPRT deficiency than in four control patients. As hypoxanthine usually derives from guanine nucleotides, the finding suggests that in patients with CNS deficient HPRT, there exists an elevated degradation level in adenine nucleotides than in guanine nucleotides. Allopurinol respectively augmented plasma content of hypoxanthine, xanthine and inosine in magnitude of four, ten and three times in comparison to baseline values. The average CSF elevation in hypoxanthine and xanthine values was respectively, 17.5 mumol and 7.7 mumol, whereas inosine value remained unaltered. These findings suggest that there are transferred hypoxanthine and xanthine to the brain barrier in the presence of HPRT deficiency (56).

HPRT represents a genetic disorder of purine metabolism culminating in excess production of uric acid. Allopurinol inhibits the enzyme xanthine oxidase and decreases uric acid synthesis, and as broadly applied in the treatment of the excessive production of gout and uric acid. An analysis of the long-run efficacy and safety of allopurinol in HPRT deficient individuals was conducted in nineteen subjects of which thirteen has Lesch-Nyhan syndrome and six had partial HPRT deficiency were allopurinol treated, mean dose, 6.4mg/kg body weight/24h of range 3.7 – 9.7 mg/kg body

weight/24h with a follow-up of not less than twelve months with a mean follow-up of 7.6 years. Allopurinol efficacy was evaluated by serial determination of purine metabolic parameters and renal functionality including clinical observations or presentations (57). Assessment of safety was done by observing adverse presentations. Allopurinol treatment controlled and normalized serum urate values in all patients with resultant average decrease in 47% serum urate with an associated allopurinol treatment of an average 74% decrease in urinary uric acid:creatine ratio. Conversely, allopurinol treatment respectively augmented mean hypoxanthine and xanthine urinary excretion rates, 5.4 – and 9.5-fold in comparison to baseline values. The reduction in uric acid excretion in full-blown and inchoate HPRT-deficient subjects was unaccompanied by a stoichiometric substitution or replacement of hypoxanthine and xanthine excretion rates. It was determined that allopurinol was efficacious and safe in uric acid overproduction treatment in HPRT deficiency patients. In the event of the development of xanthine lithiasis due to allopurinol treatment, it is suggested that dose adjustment is palliative (57).

DISCUSSION AND CONCLUSION

Purine metabolic requirements and those of their cognate bases are available by both dietary intake and/or synthesis de novo via low relative molecular mass precursors. The potential to salvage purines from sources within the body ameliorates whatever the nutritional needs for purines, thus the purine bases are not required in the diet, per se. The salvage pathway constitutes a principal purine source for the synthesis of DNA, RNA and enzyme co-factors. The liver is the main site of purine synthesis; and both the salvage and de novo synthesis pathways of purine biosynthesis culminate in the formation of nucleoside-5'-phosphates by means of the usage of an activated sugar intermediate and the phosphoribosyltransferases.

Research has now focused on purines as not only promoters of health, but also as "purinergic signaling" which influence the blood circulatory system, cardiovascular functionalities, alimentary system, pain and inflammatory responses (58). Uric acid constitutes the metabolic endproduct of human purine metabolism, with antioxidant attributes which may confer protection, but is capable of being pro-oxidant in relation to its microambient. Hyperuricemia culminates in perturbation via urate crystal production and establishment, and has been associated with, but not aet6iologically related with hypertension, atheriosclerosis, insulin resistance and diabetes. Urate is a weak organic acid with pKa of 5.75, and occurs mainly as monosodium urate, MSU at physiological pH levels. SLCZAg encodes the glucose transport family isoform Glut9 is a principal determinant of plasmic uric acid concentrations and development of gout (59).

Purines and nucleotides are subunits of nucleic acids, principal energy carriers and precursors for the synthesis of nucleotide co-factors, such as NAD and SAM. Purines are involved in several significant functions in the cell, such as the constitution of the monomeric precursors of nucleic acids RNA and DNA. Purines contribute to influence energy metabolism and signal transduction as well as structural components of certain coenzymes which have been demonstrated to feature appreciably in the physiology of platelets, muscles and neurotransmission. Cells need a n approximate amount of purines for growth and development, proliferation and survival. With the favourable ambient, the enzyme associated in purine metabolism sustain within the cell a balanced ratio between their synthesis and degradation. Urate is the ultimate compound of purine catabolism in humans. All other mammals contain the enzyme

uricase that catalyzes urate to allantoin that is consequently excreted via urine. Urate overproduction that results from purine metabolism presents emerging role in human disease. Serum uric acid elevation is inversely related with disease augmentation and magnitude, particularly associated with cardiovascular events (60).

The inherited deficiency of the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase, HPRT results in three encompassing clinical syndromes influenced by the magnitude of residual enzyme activity. Patients presenting with a minimum of 8 per cent residual enzyme activity depict substantial urate overproduction with concomitant hyperuricaemia, nephrolithiasis and gout. Patients having 1.5 to 8 per cent residual activity present urate overproduction with neurologic morbidity that differs from minor clumsiness to perturbative extra-pyramidal and pyramidal motor aberrations. Patients having less than 1.5 per cent reduced activity present with urate overproduction, inimical neurologic disability or deficit, diverse magnitudes of cognitive impairment, disability and behavioural aberrations which include impulsive and self-injurious behaviours. This latter and most debilitating aspect of the disorder is referred to as Lesch-Nyhan disease, LND (61, 62). The metabolic basis for the excess urate production in HPRT deficiency emanates from alterations in the regulation of purine synthesis and degradation. The urate overproduction (62, 63) can be blocked by effective allopurinol administration to ameliorate the risk of nephrolithiasis nd gout in the compromised patients; but allopurinol has no efficacy has no efficacy on the neurobehavioural characteristics or presentations.

Although, much research has been conducted regarding the perspicuous significance and relevance of purines, a lot needs to be unraveled about how these nucleotides are synthesized and metabolized by various organisms. These are pertinent in their complex interplay of health and disease in genetic analysis (48) for the baseline evaluation and monitoring of the function/activities of specific enzymes in the absence and presence of purines.

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