Health Consequences of Catabolic Synthesis of Hippuric Acid in Humans

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Abstract: Hippuric acid has been a major human metabolite for years. However, there is no well-known documented health benefit associated with it except for excretion of environmental-toxic exposures of aromatic compounds such as toluene, or from dietary protein degradation and re-synthesis by intestinal microflora metabolism of quinic acid *via* the shikimate pathway. Thus hippuric acid can appear in humans as an excretory product from natural or unnatural sources. It has been believed over the years that the major source of urinary hippuric acid levels in humans has come from environmental toxic solvent exposures. However, more recently it was been shown that approximately 1-2 mM hippuric acid is excreted daily in the urine, even in the absence of organic solvent exposure, signalling abundant metabolic dietary sources of hippuric acid are also apparent. One of these has been dietary proteins. The other is from the well-documented presence of quinic acid in healthy colored foodstuffs. Quinic acid is a key metabolite associated with the shikimate pathway existing only in plants, and it is responsible for essental amino acid biosynthesis such as tryptophan, phenylalanine and tyrosine. Here we review the evidence that the human gastrointestinal tract microflora are responsible for quinic acid metabolism not only to hippuric acid, but more importantly to efficacious antioxidant amino acids and vitamins.

Key Words: Hippuric acid, quinic acid, tryptophan, nicotinamide, antioxidant metabolism.

INTRODUCTION

Hippuric acid is not found in plant material nor is it metabolzied by higher plants. It is recognized by reference in the scientific literature as an excretory product found in highest concentrations in urine with no known well-defined health effect [1-5]. Hippuric acid is known to be catabolically synthesized from benzene-type aromatic compounds usually believed to be originating from environmental exposures [6] but also from basic human liver metabolism of protein catabolism [7], or from the cyclic sugar type-compound, quinic acid, which in turn leads to all aromatic plant biosynthesis *via* the shikimate pathway in the gastrointestinal tract [8-15]. The reason for excreting hippuric acid, is apparently because plants need aromatic amino acids, steroidal hormones and other key aromatics for their survival, and must get them from their own biosynthetic pathways, whereas animals are not food sources for plants. Thus plants can utilize aromatic-type compounds within their own biosynthetic pathways and excretion of them is not necessary for survival. On the other hand, animals must eat food plants in order to provide the essential aromatic ingredients for life (e.g. aromatic amino acids and hormones such as tryptophan and nicotinamide). Thus, the key aromatic signal transducing compounds of plant and animal life are produced from plant aromatics, but both plants and animals are mutually dependent on their synthesis from plants for survival.

HISTORICAL PERSPECTIVE OF THE PHARMACOLOGICAL LINKS BETWEEN HIPPURIC AND QUINIC ACIDS

Millions of people in India and China including the world famous Gandhi practiced urine therapy; i.e. drinking their own urine on a regular basis. Urine contains about 4 % hippuric acid and any health benefit related to this historical practice could be from its hippuric acid content. It has been known for at least hundreds of years, but still today there has been no known health benefit documented from consumption of hippuric acid.

However, because of the early documentation in1940 [10] that benzoic acid was converted to hippuric acid in human liver slices, together with the explosion of industrialized societies since then, there has been great concern that the human population has exposed itself to unnaturally high levels of benzene-type solvents . Because these compounds can be converted to benzoic acid, and eventually to be excreted as hippuric acid, then environmental exposures to toxic organic solvents, could be easily monitored by estimating hippuric acid levels in humans. This approach has now been utilized by many scientists, and it is generally accepted to be a useful tool in monitoring hazardous exposures to many aromatic compounds in human populations [16-18].

Recently it has been reported that after >70 years of having relative no or extremely minor scientific discoveries made around hippuric or quinic acids, Pero *et al.* [19] proposed that quinic acid was indeed a natural occurring nutrient of many foods, especially well-known healthy food sources such as multi-colored fruits and vegetables [7, 20-23]. This well documented dietary information has in turn suggested to control subjects not known to be exposed to environmental toxic organic solvents, where they also had urinary hippuric acid levels dose dependently increase whether achieved by supplementation or not (Fig. **1**) [19]. Thus these data have suggested hippuric and quinic acid levels in urine were primarily attributed not only to each other but also to food consumption.

The biosynthesis of quinic acid by the shikimate pathway has been known to occur in microorganisms since 1932 [9-

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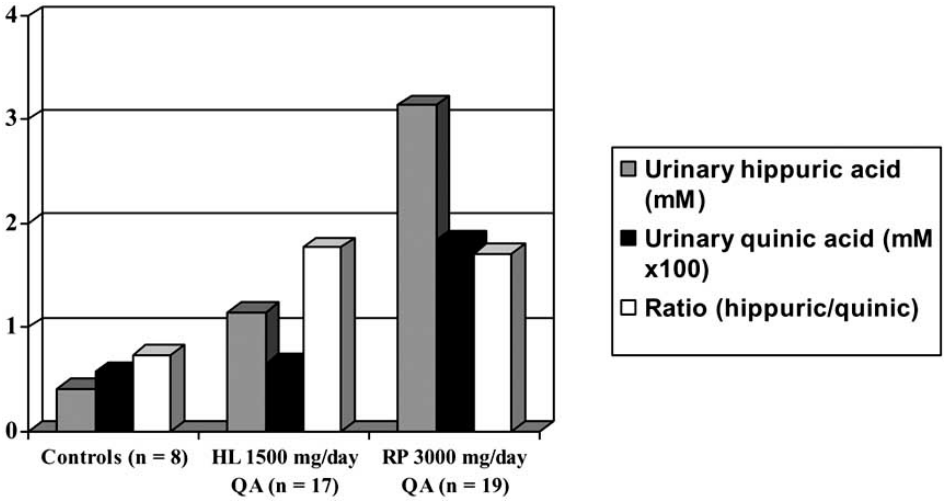

Fig. (1). Dependence of urinary levels of hippuric acid, the primary known metabolite of quinic acid, on the urinary level of quinic acid in untreated individuals and in subjectstreated with 1500 mg/day and 3000 mg/day Aqua Bimini for 36 day, then followed for an additional 8 month immediately after treatment. The data used here were recorded as the individual values represented by the sample dates and summarized as mean values presented in Table 1 herein. These data were statistically analyzed by linear regression of the total sample (n = 45) involving both treated (n = 36) and controls (n = 9), where hippuric acid values versus quinic acid values collected from urine at the same time in the same subject gave $y = 0.0157x + 0.1839$, $r = 0.60$, $p < 0.001$. Both hippuric acid and quinic acid values were thus collected at the same time from the same urine samples, and hence may be directly compared. Figure and data reproduced from [19].

15]. After the topic had been reviewed in the 1960s [9], it was quite apparent quinic acid was ubiquitous, and only produced from plant origin, as the only metabolic pathway for biosynthesis of natural occurring aromatic compounds. Moreover, it was also not until 1960 [24] that a major significant advance in the understanding of quinic/hippuric acid metabolism was made. It was discovered that aromatization and excretion occurred in man only after oral administration, but not after intraperitoneal administration. Furthermore, the aromatization seen after oral dosage was prevented when the normal gaetrointestinal (GI) tract microflora were inhibited by co-administration of neomycin (antibiotic). Thus, these data were strong evidence that GI tract microflora could convert quinic acid to benzoid-type type compounds, and finally to hippuric acid for excretion. Presumably this conversion required a functional shikimate metabolic pathway for the quinic acid catabolism, since only GI tract microflora could have produced hippuric acid from quinic acid by the oral route that by-passes any metabolic involvement of the liver.

It has taken about another 50 years to fully confirm this hypothesis. The shikimate pathway is presented in (Fig. **2**) [14,15]. It predicts that a fully functional GI shikimate path-

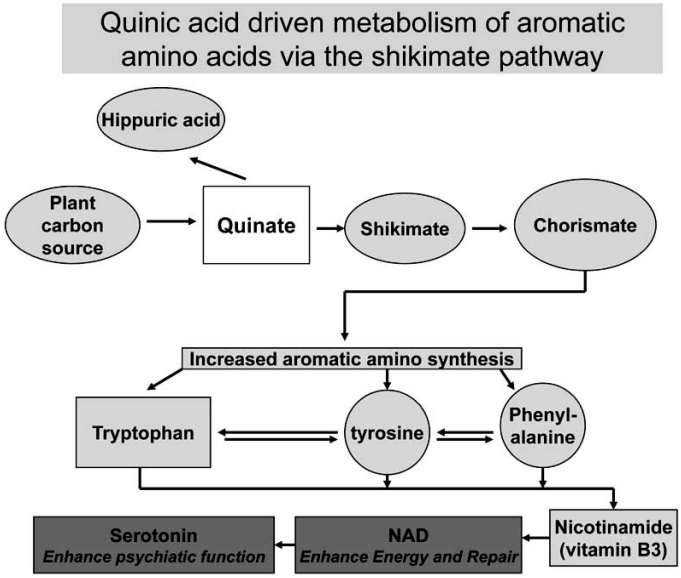

Fig. (2). Digramatic representation of how animal gastrointestinal (GI) tract microflora can metabolize quinic acid to an array of nutritents essential for maintenance of life. Although hippuric acid can also be synthesized in human liver from protein catabolism or organic solvent exposures, only GI tract microflora can produce aromatic amino acids essential to life [14,15].

way should increase the urinary levels of hippuric acid, quinic acid, tryptophan, phenylalanine, and tyrosine as well as other key compounds such as nicotinamide. The data presented in Table **1**, clearly confirm that indeed urinary levels of hippuric and quinic acids were increased by quinic acid supplementation, but as would be predicted by the shikimate pathway, there would also be substantial increases in urinary tryptophan and nicotinamide. These data establish a potentially profound health benefit from increases in urinary quinic acid that lead directly to corresponding increases in typtophan and nicotinamide, and not to just increases in hippuric acid generated from toxic benzoid-type exposures, protein metabolism or the shikimate pathway.

The aromatic amino acids (tryptophan, tyrosine and phenylalanine) are essential to all life forms, plants or animals. A key reason is that they need to come from the diet of humans and other animals to support protein synthesis. Therefore, the breakdown and re-synthesis of proteins in the GI tract is because of the primary demand for tryptophan in our GI tract; i.e. to make new proteins even if at the expense of older or not yet consumed ones [25] (Fig. **3**). However, immunity *via* indolediamine oxygenase (IDO) modulation [26] or energy production *via* NAD [27-29] are secondary health mechanisms, but nevertheless are crucially linked to tryptophan metabolism in the GI tract *via* the shikimate pathway [14,15] as displayed in (Fig. **3**).

There is strong support for the medical hypothesis that there exists natural sources of quinic acid in our diet that lead in turn to elevated levels of urinary hippuric acid, that are free from metabolic influences generated from toxic organic solvent exposures such as toluene, benzene, styrene, etc. Firstly, as shown in Table **1** there was about 1 mM urinary hippuric acid and 60 mM quinic acid present in 10 individuals representing a broad range of the population from 12-86 years, 6 males and 3 females, having no known exposure to organic solvents. In another study [30] urinary samples from 195 people (99 women and 96 men) between the ages of 17-46 years, and that also had no known organic solvent exposures, had similar values of urinary hippuric acid (i.e. 2.06 mM). In addition, the levels of quinic acid and hippuric acid in urine were strongly correlated to each other (Fig. **1**). Hence, in the absence of any toxic exposures the

Table 1. Level of Quinic Acid Metabolites in Urine During and Estimated Immediately After Oral Administration of Either 3000 mg/day or 1500 mg/day Aqua Bimini (Quinic Acid Ammonium Chelate) for 30 Consecutive Days Followed by a Dryout (no Treatment) Period for an Additional 8 Months. Mean ± S.D. Values are Shown for Each Group. Further Experimental Details and Data are Found in [19]

Clinical Treatment	n	Tryptophan µM	Nicotinamide µM	Hippuric Acid mM	Quinic Acid µM
1. Controls					
(no supplement)	9	10 ± 4	23 ± 23	1.1 ± 2.0	60 ± 42
2. RP 3000 mg/day					
(30 days duration)	5	13 ± 5	21 ± 1	2.6 ± 4.0	231 ± 181
3. RP first 4 months					
dryout	11	22 ± 7**	71 ± 44**	3.6 ± 3.0 *	160 ± 57**
4. RP second 4 months					
dryout	3	19 ± 6	71 ± 63	2.5 ± 0.6	194 ± 70*
5. Total RP trial data					
treatment+ dryout	19	19 ± 7**	58 ± 46**	3.1 ± 3.0 *	184 ± 103 **
6. HL 1500 mg/day					
(30 days duration)	5	18 ± 5**	163 ± 91**	1.4 ± 0.8	86 ± 52
7. HL first 4 months					
Dryout	6	30 ± 8**	453 ± 139**	1.5 ± 2.0	84 ± 52
8. HL second 4 months					
dryout	6	17 ± 7	24 ± 7	0.5 ± 0.5	30 ± 17
9. Total HL trial data					
treatment + dryout	17	22 ± 9**	216 ± 210**	1.2 ± 1.0	65 ± 49

** two way t-test = $p < 0.05$ versus controls; *one way t-test = $p < 0.05$ versus controls.

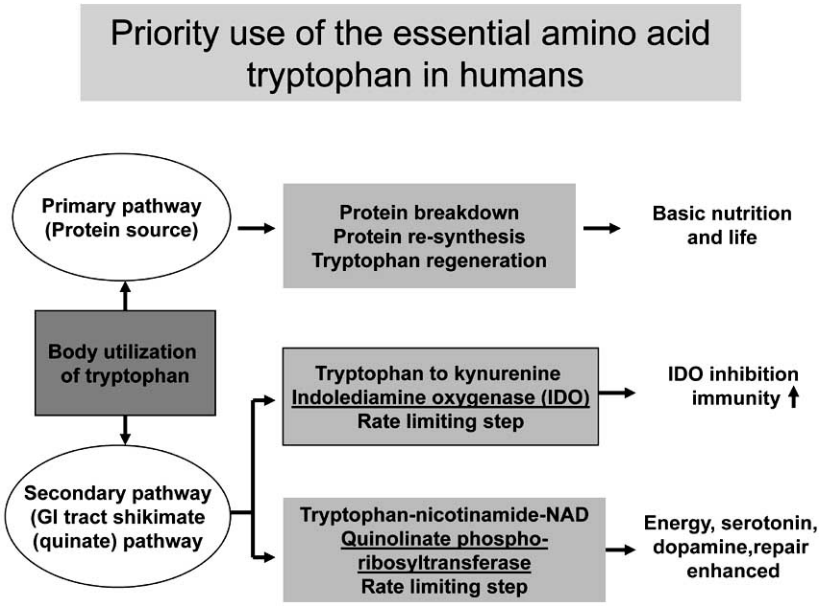

Fig. (3). Scheme of how the GI tract digests and absorbs dietary proteins with the net movement of nitrogenous substances from the gut lumen into the body. Tryptophan plays a key role balancing dietary production from protein breakdown with new synthesis *via* the shikimate pathway and microflora metabolism [26-29].

levels of hippuric/quinic acids in urine reflect a natural dietary balance, and a natural origin of these compounds. Secondly, this interpretation is further supported by literature that suggests vegetarians also have higher levels of at least hippuric acid in urine [31, 32].

EFFICACY-RELATED METABOLISM OF HIPPURIC/ QUINIC ACIDS FINALLY DESCRIBED

The health benefits for estimating hippuric / quinic acid ratios in urine in the absence of toxic environment exposures to organic solvents are far reaching, because both metabolites signal a bioactive GI tract shikimate pathway that also can produce tryptophan, phenylalanine, tyrosine, nicotinamie, NAD, and serotonin, all of which adds enormous nutritional health benefit to the individual. Here we review the clinical evidence that supports this medical hypothesis, which has remained scientifically undocumented for over the last 50 years.

It was in the beginning of 1998, before water extracts of cat's claw (Uncaria tomentosa) were shown to possess DNA repair and immune modulating properties [33-44]. Later on these extracts were delineated to have as the bioactive components; i.e. first carboxy alkyl esters (CAEs) [35-40], and then further identified to quinic acid esters [41,42], and finally shown to be quinic acid [42,43].

Additional nutritional support for positive health effects to be associated with quinic acid, was because most well-known healthy foodstuffs [7,20-23], contained quinic acid in known efficacious amounts of brightly colored foods (i.e yellow, green, orange, red). Hence, we propose that quinic acid and its end-product catabolite, hippuiric acid, are not in themselves efficacious, but they can be in turn characterized as indicating a pro-metabolite synthesis that leads to production of efficacious levels of nicotinamide and tryptophan as antioxidants by GI tract microflora *via* the Shikimate Pathway not otherwise existing inside the human body.

Further proof of an association between dietary quinic acid/hippuric acids and antioxidant properties were recently shown using human serum thiol status as a surrogate measure of individual DNA repair [44]. The pertinent data are presented in Table **2**. Here it can be seen that as the clinical response to quinic acid (Quinmax, Aqua Bimini) supplementation improves, so does the DNA repair index estimated by changes in serum thiol status. It was concluded that the individual antioxidant status estimated by having more reduced serum thiols in serum was paralleled by enhanced clinical responses to appetite, skin quality, joint pain, fatigue; self-perceived health, and energy [44].

DISCUSSION

Finally, it has been shown that both tryptophan and nicotinamide are well known therapeutic agents at higher doses than exist naturally. The scientific data pertaining to tryptophan's use as a therapeutic agent and in relation to quinic acid supplementation are presented in Table **3**. Here it can easily be seen that tryptophan doses known to be therapeutic have urinary levels of around 1.5 mg/liter tryptophan in urine, whereas the corresponding tryptophan values after quinic acid supplementation were about 4.5 mg/ml (Table **3**). Here the implication is very strong that quinic acid nutritional intervention can achieve even greater efficacious therapy than high dose tryptophan supplementation by itself.

A similar relationship also exists between high dose nicotinamide therapy and therapeutic efficacy. However, the metabolic control of high doses of nicotinamide is strongly regulated so that within 1 day, urinary nicotinamide has returned to about non-supplemented levels (Shibata K J Nutr 1989; 119: 892). Consequently, there were no data available in the literature on urinary levels of high dose nicotinamide over longer peri- ods of time. Nonetheless, high dose nicotinamide has therapeutic value to alter lipid profiles [53-54],

Table 2. Comparison of the DNA Repair Capacity to the Clinical Responses Self-Reported by Subjects Before and After Treatment with Aqua Bimini (AB = Quinic Acid Ammonium Chelate) at 1000 mg/day. Baseline AB is Defined as the Biological and Medical Conditions Existing in the Patient 30 Days Before Starting AB Treatment. The Dryout Period is Defined here as 60-120 Days Reduced AB (500 mg/Day Every 2-3 Days), and then Followed by no Supplementation from 120-180 Days = total of 180 Days Post Treatment. Data and Further Details Reproduced from [44]

		Self Report Clinical Score[b]				
Patient Identity	**DNA Repair Index [a]**	**Baseline Before AB -30 Days**	**After AB+60 Days**	**Ratio After/Base**	**After AB +120 Days of Dryout**	**Ratio After/Base**
A.vdW.	250	13	14	1.07	17	1.31
T.F.	227	8	10	1.25	12	1.50
R.R.	193	10	17	1.70	18	1.80
K.M.	182	16	20	1.25	23	1.44
M.K.	181	16	16	1.00	16	1.00
Mean ± SD	207 ± 31**	13 ± 4	15 ± 4	1.3 ± 0.3	17 ± 4.0	1.4 ± 0.3
T.M.	172	17	20	1.18	21	1.24
J.vdW.	167	20	23	1.15	24	1.24
G.vdM.	164	23	23	1.00	23	1.00
L.S.	158	23	26	1.13	25	1.08
J.B.	141	23	26	1.13	25	1.08
Mean ± SD	160 ± 3	21 ± 3	24 ± 3	1.1 ± 0.1	24 ± 2	1.1 ± 0.1
t-test	0.013**	0.0026**	0.0035**	0.31	0.01**	0.038* (1* or 2** tailed p-value)

[a]DNA Repair Index = Average of 80 % ammonia sulfate precipitated serum protein thiols before (-30 days) and after (60-180 days) treatment with Aqua Bimini expressed as nmoles cysteine / 0.72 ml serum.

[b]Self-Report Clinical Index Score = Appetite previous week bad (1), normal (2), good (3); skin quality poor (1,2,3)or good (4,5); pain previous month yes (1)moderate (2), no (3); fatigue previous month yes (1), moderate (2), no (3); self-perceived health poor (1,2,3,4), and good (5,6,7), energy previous month poor (1), moderate (2), and good (3).

Table 3. Direct Pharmacokinetic Comparison of Orally Administered Quinic Acid Ammonium Chelate (I.) to Doses of Tryptophan Already Known to have Therapeutic Value in Animals (II.) Including Humans (III.)

Nutritional Supplement	**Oral Human Dose Used**	**Urinary Excretion Systemic Metabolic Indicator Daily Sample (avg mg/liter)**	**Clinical Indication**	**Reference**
I. Quinic acid NH4+ [a]	21-42 mg/kg/day (1000-3000 mg/day)	Trypto. = 4.2 mg/liter[b]	Antioxidant DNA repair	Pero [19,44]
III. Therapeutic tryptophan	100 mg/kg (50-200 mg/kg)	Trypto. = 1.3 mg/liter[c]	obesity anarexia	Cavalier [45] Cavalier [45]
			migraine	Gedye [46]
			depress	Chouinard [47]
			insomnia	Brown [48]
			monkeys	
	(50-200 mg/kg)		self-biting	Weld [49]
	(125 mg/kg)		mice	
			depress	Wong [50]
			pigs	
			stress	Li [51]

[a]Abbreviations: QA NH_4 + = Aqua Bimini, quinic acid ammonium chelate (Quinmax), trypto. = tryptophan, avg = average.

[b]Calculated from the average urinary levels of trypophan reported for a 9 month evaluation period in Table 1. Subject RP (3000 mg/day) = 19 ± 7 µM and Subject HL (1500 mg/day) = 22 ± 9 µM; Avg = 20.5 µM or 4.2 mg/liter urine. From Pero *et al*. 2009 [19].

[c]Calculation from literature: Smith [52].

depression [47], HIV [59], renal tumors [60], graft failure [61], migranes [46], and as a antioxidant [62, 63].

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