Influence of Dietary Histidine on Basophil Release, Circulating Concentration, and Urinary Excretion of Histamine in Domestic Felines

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ABSTRACT

Dietary histidine has been shown to elevate circulating free histidine and plasma histamine concentration in murine models as much as 6- fold. Bladder mastocytosis is a hallmark of feline interstitial cystitis, and histidine is stored in mast cells and converted to histamine for signaling and inflammation by the enzyme histidine decarboxylase. Elevated dietary histidine may represent a risk factor for heightened mast cell responses. Nine healthy adult female shorthair cats were used in random crossover experiment with fixed treatment sequences to test the effects of dietary histidine (0.6, 1.0, and 1.4% DM) on histamine in blood and urine. The dry-extruded test foods were fed in sufficient amounts to maintain ideal body weight. Each experimental period was preceded by a 7-day wash out period, in which the 0.6% histidine diet was fed, followed by a 14-day feeding period of the appropriate food. Two 24-hr total urine collections were performed (d13: acidified, day 14: un-acidified; immediately iced) and blood was collected on day 14. Dry matter intake ($P \geq 0.09$) and BW ($P \geq 0.58$) were not affected by treatment. Plasma histidine concentration increased with dietary supply of histidine (linear, $P=0.02$). Urine output ($P \geq 0.42$), NH3 ($P \geq 0.53$) and titratable acidity of urine ($P \geq 0.31$) were similar across treatments. However, urine pH was lower in cats fed 1.4% histidine compared with 0.6 or 1.0% histidine (quadratic, $P=0.02$). Urinary histamine:creatinine was greater for the

Table 1. *Ingredient composition of experimental diets (DM basis).*

	% Dietary histidine		
Ingredient (%)	0.6	1.0	1.4
Brewers rice	47.77	46.77	46.52
Corn gluten meal	26.10	26.10	26.10
Choice white grease	11.00	11.00	11.00
Pork by-product meal	3.67	3.67	3.67
Fish meal	2.30	2.30	2.30
Lamb meal	2.24	2.24	2.24
Fish oil	0.80	0.80	0.80
Palatability enhancer	1.50	1.50	1.50
Histidine-HCl	---	1.00	1.25
L-Threonine	0.40	0.40	0.40
Taurine	0.25	0.25	0.25
DL-Methionine	0.15	0.15	0.15
L-Lysine-HCl	0.13	0.13	0.13
L-Tryptophan	0.05	0.05	0.05
Potassium chloride	1.00	1.00	1.00
Calcium sulfate	0.70	0.70	0.70
Choline chloride	0.53	0.53	0.53
Salt, Iodized	0.35	0.35	0.35
Dicalcium phosphate	0.30	0.30	0.30
Potassium sulfate	0.18	0.18	0.18
Vitamin E	0.31	0.31	0.31
Vitamin E premix (29% vitamin E)	0.10	0.10	0.10
Mineral premix	0.10	0.10	0.10
Preservative	0.07	0.07	0.07

1.4% histidine treatement (linear, P=0.03) compared to other diets, whereas urinary histamine concentration (P=0.17) and excretion (P≥0.68) and plasma histamine concentration (P≥0.17) were unaffected by treatment. Differences were not detected among treatments in total histamine, cellular + noncellular,(P≥0.18) or antigen-induced histamine release (P≥0.65) in whole blood. Increase in dietary histidine elevates circulating concentrations of histidine without affecting circulating concentrations of histamine or antigen-induced histamine release in whole blood. However, urinary histamine excretion may be responsive to dietary histidine supply.

INTRODUCTION

In male rats, it has been demonstrated that dietary histidine affects free histidine and histamine concentrations in tissue (brain, kidney, muscle, and stomach.[1] For example, in stomach tissue an increase from 0.1% to 0.8% dietary histidine increased tissue histamine 6-fold.[1] Although debate exists as to the extent of exogenous histamine absorption from the GIT, it is known that histidine is converted to histamine via pyridoxal phosphate containing, L-histidine decarboxylase (HDC).[1] Variable amounts of histamine can be formed in the intestine by bacteria; up to the equivalent of 18% of dietary histidine.[2]

The term feline interstitial cystitis (FIC) was coined because of the similarities

Table 2. *Chemical composition of experimental diets (DM basis).*

	% Dietary histidine		
Analyte (%)	0.6	1.0	1.4
Crude protein	28.48	30.13	30.40
Crude fat	17.40	16.66	16.36
Crude fiber	<0.21	0.43	0.43
Ash	5.23	5.29	5.31
Amino acids			
Alanine	2.06	2.10	2.13
Arginine	1.22	1.21	1.20
Aspartate	1.82	1.83	1.84
Cystine	0.43	0.43	0.44
Glutamate	5.07	5.14	5.21
Glycine	1.26	1.25	1.27
Histidine	0.57	1.01	1.36
Isoleucine	1.06	1.06	1.07
Leucine	3.44	3.54	3.58
Lysine	0.96	0.96	0.96
Methionine	0.91	0.91	0.93
Phenylalanine	1.47	1.50	1.50
Proline	2.06	2.09	2.12
Serine	1.24	1.28	1.27
Threonine	1.33	1.34	1.35
Tryptophan	0.30	0.29	0.28
Tyrosine	0.98	1.03	0.96
Valine	1.30	1.30	1.32
Minerals			
Calcium	0.77	0.79	0.75
Chloride-soluble	0.97	1.12	1.14
Magnesium	0.06	0.06	0.06
Phosphorus	0.70	0.70	0.67
Potassium	0.85	0.85	0.85
Sodium	0.33	0.33	0.31
Sulfur	0.68	0.68	0.66
DCAD, meq/ga	-0.311	-0.341	-0.336

between the feline condition and the human condition primarily seen in adult women: interstitial cystitis (IC). Interstitial cystitis has been described as a lower urinary tract syndrome characterized by painful, pollakiuria, and the clinical signs will often resolve in 3 to 7 days with variable and unpredictable recurrence[3, 4]. The similarities between the feline and human diseases are notable and include:

- Adult onset
- Severity
- Spontaneous remission
- Increased urination frequency
- Pain
- Urgency

Table 3. *Effects of dietary histidine on biochemical analytes in plasma and urine.*

	% Dietary histidine			P Value[a]		
	0.6	1.0	1.4	SEM[b]	Lin	Quad
Body Weight (kg)	4.2	4.2	4.2	0.15	0.58	0.67
Dietary Intake (g/24 h)	37.8	38.4	38.6	2.02	0.09	0.91
Urine						
Output (g/24h)	38.6	35.9	35.3	8.02	0.42	0.89
pH	6.24	6.30	5.98	0.12	0.001	0.02
Titratable Acidityc	0.34	0.25	0.40	0.10	0.31	0.61
Creatinine (mg/dL)	339.8	318.7	326.4	24.92	0.42	0.46
NH3 (mmol/L)	347.8	326.6	331.5	24.8	0.83	0.53
Histamine (ng/mL)	156.7	137.1	174.7	22.7	0.17	0.93
Histamine:Creatinine[d,e]	4.6	4.3	5.3	0.42	0.03	0.57
Histamine (ng/24 h)	6122	5055	5536	1319	0.68	0.73
Plasma Histamine (ng/mL)	1.7	0.7	0.9	0.4	0.27	0.17

a Probability of larger F-statistic.
b n = 9.
c mL of 0.1 N NaOH / mL of urine.
d Ratio of concentrations of histamine and creatinine.
e Value x 10-9.

- Diagnosis based on clinical signs and history
- Sterile urine
- Exclusion of other diseases
- Bladder mastocytosis
- Increased histamine excretion
- Increased bladder permeability
- Decreased glycosaminoglycans (GAG) excretion[4].

Bladder mastocytosis is a hallmark of feline idiopathic cystitis.[5] Increased concentrations of mucosal mast cells have been identified in detrusor muscle and mucosa of bladder of interstitial cystitis (IC) patients (analogous human disease).[6] Histidine is stored in mast cells and converted to histamine for signaling and inflammation by the enzyme histidine decarboxylase. In contrast to allergic or anaphylactic mast cell degranulation, IC mast cells possess electron dense granules in different stages of dissolution when observed microscopically for ultra-structural characteristics.[5] This unique degranulation mechanism is characteristic of differential release of secretory mediators. Elevated dietary histidine may, therefore, represent a risk factor for heightened mast cell responses and altered histamine dynamics in plasma and urine. This experiment tested the hypothesis that increased dietary histidine would result in elevated histamine in blood and or urine.

MATERIALS & METHODS

Animals

Nine domestic shorthaired spayed female cats (4.2 ± 0.15kg BW) between 3 to 4 years of age were utilized in this experiment. Cats were housed in individual cages at Spindletop Research Unit (University of Kentucky, Lexington, KY) and maintained at an ambient temperature of 25°C with a 16 hr light:8 hr dark cycle. Animals were confined to cages during feeding periods, and at night. Enrichment and social time was provided between feeding periods. Felines had ad libitum access to water, and were fed a complete and balanced adult maintenance diet to maintain ideal body weight (Hill's

Table 4. *Effect of dietary histidine on in vitro histamine release in whole blood.*

	% Dietary Histidine			P Value[a]		
	0.6	1.0	1.4	SEM[b]	Lin	Quad
Total release [bc,d]	15.7	15.3	15.9	3.2	0.65	0.72
Spontaneous release [c,e]	3.7	3.5	4.7	1.0	0.68	0.11
Total [c,f]	22.4	16.6	20.5	3.6	0.88	0.18

a Probability of larger F-statistic.
b n = 9.
c ng/mL.
d Total release: histamine released in response to antigen treatment.
e Spontaneous release: non-stimulated release or fractiont "leaked" from cells.
f Total: cellular + noncellular histamine concentration.

Science Diet, Adult Maintenance Formula) prior to each experimental period and during inter-experimental periods. Animals were fed at 0730 and 1930. The experiment was performed as a random cross over design with fixed treatment sequences to test the effects of dietary histidine (0.6%, 1.0%, 1.4% DM; Table 1). Each experimental period was preceded by a 9-day "pre-feed" or "wash out" period, during which time the animals received adult maintenance diet, fed to maintain ideal body weight. Following each "wash-out", a one d dietary transition was performed in which cats were provided 50 percent adult maintenance and 50 percent test diet. The first d after the diet transition was considered day 1 of a 14-day feeding period, during which time the cats received assigned test diet. Refusals were collected at 0730 from the previous d, weighed, recorded, and discarded. After day 14 of each feeding period, animals underwent a one day diet transition day back to adult maintenance diet, and were maintained thusly for 7 days as a "wash out."

Total Urine Collection

On days 12, 13, and 14, cats were confined to their individual cages for urine collection. Urine was collected via Smart Cat Box Collection System (Smart Cat Box, Providence House Mfg. Inc., Seal Rock, OR). This system utilized a grated tray containing polyethylene beads (Smart Cat Box, Providence House Mfg. Inc., Seal Rock, OR), (cat litter substitute), which drained into a lower tray equipped with a funneled floor and drains into center hole. These boxes are fashioned to function with a urine reservoir. However, the needs of this collection required that the urine samples be immediately preserved over ice, post elimination. In order

Table 5. *Effect of dieary histidine on plasma concentrations (nmol/gram) of individual amino acids.*

	% Dietary Histidine			P Value*		
	0.6	1.0	1.4	SEM[a]	Lin	Quad
Valine	118	117	115	5.28	0.61	0.52
Leucine	102	99	99	4.01	0.70	0.94
Isoleucine	55	53	53	2.67	0.80	0.79
Methionine	48	52	49	2.04	0.69	0.94
Threonine	93	101	97	2.85	0.54	0.31
Phenylalanine	76	76	73	2.40	0.38	0.92
Lysine	91	101	94	6.23	0.84	0.17
Histidine	99	106	110	2.65	0.02	0.22
Tryptophan	44	44	46	1.47	0.25	0.97
Alanine	416	458	414	36.82	0.59	0.25
Glycine	502	411	357	93.97	0.24	0.39
Proline	146	156	152	10.93	0.92	0.39
Serine	159	173	177	9.57	0.26	0.32
Aspartate	15	15	15	1.18	0.99	0.51
Glutamate	34	34	35	6.50	0.77	0.40
Glutamine	215	315	315	36.13	0.18	0.05

[a] *Probability of larger F-statistic.*
[b] *n = 9.*

to achieve this, the central hole which would normally drain to a urine reservoir was permanently attached to a 33mm laboratory funnel. Funnel was fitted to 46cm BARD urine collection tubing (C.R. BARD, Inc., Covington, GA). Tubing exited the cage into a Styrofoam cooler, through a hole drilled into the side, approximately 5 -10cm from the bottom of the cooler. The tubing was attached to a 265mL BARD Urine Collection bag (C.R. BARD, Inc., Covington, GA), inside the cooler, preserved on ice. Samples were collected such that starting on day 12; cats were given 24 hr to void urine. If after 24 hr, no void was produced, the first urinary elimination was collected and considered to be the first 24 hour urine void. After the first sample was collected, urine collection bags were acidified with 5mL of 6N HCl and were preserved over ice. Acidified urine samples were collected in the same manner as those, not acidified, with 24 hr provided, and if no sample produced after 24 hr, the first elimination considered the second 24 hr urine void.

Non-acidified urine samples were assessed immediately for pH, and titratable acidity. Titratable acidity was determined from aliquots of urine sample and titrated via the addition of 0.1M NaOH until a sustained pH of 7.4 was attained. The amount of NaOH required to titrate the sample was recorded and reported as a proportion of the aliquot size (mL NaOH/ mL urine). Acidified urine samples were aliquoted into 12x75mm polyethylene tubes or 1.5mL micro-centrifuge tubes and stored at -20°C until assayed.

Chemical Analysis of Diets

Diets were analyzed for moisture (930.15), ash (942.05), crude fat (954.02), crude fiber (962.09), calcium (968.08), sodium (968.08), potassium (968.08), magnesium (968.08), chloride (969.10), sulfur (923.01), and phosphorus (965.17) content according to the AOAC[7]. Crude protein content of the diets was determined using a Leco CN2000 nitrogen analyzer (Leco Corp., St. Joseph, MI). Dietary amino acid content was determined by hydrolyzing a representative sample of each diet according to methods 988.15 (sulfur and regular) and 994.12 (tryptophan) of the AOAC (1995). Subsequent solutions were derivatized with 6-aminoquinolyl-N-hydrosuccinimidyl carbamate and amino acid concentration determined by reverse phase liquid chromatography using Millipore Waters AccQ·Tag System, as described previuosly.[8]

Blood Sampling and Handling

On d14 of experimental period, cats were sedated with Torbugesic (0.01mg / kg BW, Fort Dodge, Pfizer Animal Health,Wyeth) and Dormitor (40 µg/ kg BW, Pfizer Animal Health, Exton, PA). Blood samples (8mL) were drawn from the jugular vein, placed into heparinized (23.5 IU per mL heparin sulfate) tubes, with a 1 mL aliquot was placed into a 1.5 mL micro-centrifuge tube and maintained at room temperature for 1-2 hr for histamine release ELISA, while the remaining 7mL were stored on ice until centrifuged at 7,000 x g for 15 minutes and plasma harvested, and stored (-20 ºC) for analysis.

Histamine ELISA

Histamine ELISA kits (Ref #: BA 10-1000; Rocky Mountain Diagnostics, Colorado Springs, CO) were utilized for the determination of histamine concentration of plasma, urine, and whole blood. Urine samples were diluted 1:9 with provided diluent. Plasma samples were de-proteinized with 1% Tricholoacetic acid solution; 0.150 mL plasma and 0.150 mL 1% TCA combined in micro-centrifuge tube, vortexed for 30 seconds, and submerged in an ice water bath for 5 minutes. Samples were centrifuged at 18,000 x g for 10 min at 4 °C. Supernatant was utilized for determination of histamine in plasma. Histamine Release kits (Ref #: BA 10-1100; Rocky Mountain Diagnostics,Colorado Springs, CO) were utilized in conjunction with Histamine ELISA kit for determination of histamine release capacity in heparinized whole blood. Total histamine (intracellular + extracellular) was measured in heparinized whole blood

and represented the total concentration (mg/dL) of histamine in a representative sample. Total histamine release was determined by incubating whole blood in releasing buffer in the presence of anti-IgE. Spontaneous release was determined by incubating whole blood in releasing buffer without the addition of anti-IgE. Because basophilic granulocytes are the primary cells in blood that contain and release histamine[9], total histamine release represents the basophilic releasable pool and spontaneous release is that faction that is released or leaked from cells in the absence of antigen.

Urine Creatinine

Acidified urine samples were used in an enzymatic method to determine concentration of creatinine in which creatinine was converted to creatine under the activity of creatininase. Creatine is then acted upon by creatinase to form sarcosine and urea. Sarcosine oxidase converts sarcosine to glycine and hydrogen peroxide, and the hydrogen peroxide is reacted with a chromophore in the presence of peroxidase to produce a colored product that was measured at 546 nm (secondary wavelength = 700 nm; Roche/Hitachi Modular Analytical System, Roche, Basel, Switzerland).

Urine Ammonia

Previously acidified urine samples were thawed and vortexed thoroughly. Samples were diluted 500:1 with distilled water in 10mL polyethylene test tubes and vortexed for 30 seconds. Ammonia concentration was determined enzymatically using glutamate dehydrogenase on a Konelab Analyzer (Thermo Electron Corp., Vantaa, Finland).

Determination of Total Amino Acids in Plasma

Plasma amino acids were determined by isotope dilution with gas chromatography-mass spectrometry (GC-MS) as previously described [10, 11]. To a known weight (0.5g) of fresh plasma was added an equal known weight of a solution containing 0.2 mg hydrolyzed [U-13 C] algae protein powder (99 atoms %; Martek Biosciences, Columbia, MD), 100 nmol [indole-2H5] tryptophan, 200nmol [5- 15N] glutamine, 25nmol [methyl-2H3] methionine, and 3 μmol [15N2] urea, and the samples stored frozen (-80°C). Thawed samples were de-proteinized by addition (1mL) of sulfosalicylic acid (15% w:v), the supernatant desalted by cation (AG-50, H+ form) exchange, and amino acids and urea eluted with 2 M NH_4OH followed by water. Eluate was lyophilized to dryness, and amino acids converted to their t-butyldimethylsilyl derivative. Under electron impact mode, the following ions (m/z) were monitored: urea 231, 233; alanine 260, 263; glycine 246, 248; valine 288, 293; isoleucine 302, 308; praline 286, 291; methionine 292, 295; serine 390, 393; threonine 404, 408; phenylalanine 234, 242; aspartate 302, 304; glutamate 432, 437; lysine 300, 306; histidine 440, 446; glutamine 168, 169; tyrosine 302, 304; and tryptophan 244, 249. For leucine isotope enrichment and concentration, ions at 302, 303 ([l-13C] leucine), 305 ([2H3] leucine), and 308 ([13C6] leucine, internal standard) were monitored. Calibration curves were generated from gravimetric mixtures of labeled and unlabeled amino acid.

For leucine: Correction was also made for spillover of [l-13C] leucine (m/z 303) into [2H3] leucine (m/z 305), and spillover of [2H3] leucine into [13C6] leucine (m/z 308). All enrichments were expressed as atoms percent excess (APE) relative to background natural abundance [11].

Statistical Analysis

Data were analyzed as a random crossover design with fixed treatment sequences using the MIXED procedure of SAS (version 8.0, SAS Institute, Cary, NC). A backward stepwise regression was performed using actual intake of histidine, where second order model (Quadratic) was tested and if not significant, the analysis was repeated with a first order (Linear) model. All data are presented as Least Squares Means ± SEM. Effects were considered significant at $P \leq 0.05$ and a tendency for significance at $P \leq 0.10$.

RESULTS

Dry matter intake tended (P≥0.09) to increase linearly with increasing dietary histidine. However, body weight (P≥0.58) was not affected by treatment (Table 2). Urinary output (P≥0.42), NH_3 concentration (P≥0.53), and titratable acidity (P≥0.31) were similar across treatments. Urine pH was affected by treatment in a quadratic (P=0.02) fashion with the highest dietary histidine treatment yielding the lowest urine pH value (6.24, 6.30, 5.98, respectively). Urinary concentrations of histamine and creatinine were similar across treatments. Likewise, urinary histamine excretion (P≥0.68) and plasma histamine concentration (P≥0.17) were also unaffected by dietary treatment. However, when urinary histamine concentration was normalized to creatinine concentration, a linear (P = 0.03) increase was seen with increasing dietary histidine.

Dietary histidine level did not affect total histamine, cellular + non-cellular, (P≥0.18) or antigen-induced (P≥0.65) histamine release in whole blood (Table 3). Plasma concentrations of individual amino acids were largely unchanged by dietary histidine level; exceptions being histidine and glutamine (Table 4). A linear increase (P = 0.02) in plasma histidine concentration was seen with increasing dietary histidine. In contrast plasma glutamine concentration increased when dietary histidine increased from 0.6 to 1.0%, but was unchanged when dietary histidine was increased from 1.0 to 1.6% (quadratic; P = 0.05).

DISCUSSION

Dry matter intake was controlled in this experiment to maintain ideal body weight, However, DMI tended to increase linearly with level of dietary histidine. The maximal difference in DMI between treatments was less than 1g. Thus it is unlikely that any observed differences are attributable to DMI. As by design, body weight was not affected by treatment.

Although all pH values were consistent with reference values for adult female cats[12], the observed values were inconsistent with prediction of urine pH based on dietary cation-anion difference.[13] All diets were formulated to promote urine acidity. However, due to the inclusion of histidine-HCl, dietary cation-anion difference was lower for the intermediate (-13.1meq) and high (-13.0 meq) histidine diets compared with the low (-11.8 meq) histidine diet. Accordingly, it was expected that urine pH would be lower for the 1.0% and 1.4% histidine diets than the 0.6% histidine diet. However, observed urine pH was only reduced in cats receiving the 1.4% histidine diet and was similar between those receiving low and intermediate histidine diets; despite the latter representing the extremes in dietary cation-anion difference. Titratable acidity of the urine was not affected by treatment. However, it was numerically consistent with the above findings in that it was inversely related to pH. The reason why the current data does not conform to studies which have shown a significant correlation between dietary cation-anion balance and urine acidity in cats is not apparent. Nevertheless, it is important to note that among studies which have reported a correlation, only 36% to 73% of the variation in urine pH was accounted for by dietary cation-anion balance (15); thereby indicating that other factors contribute to urine acidity.

Previous studies in mice have shown that intestinal histidine transporter activity is enhanced with greater dietary supply of amino acids or protein.[14] There are a variety of pathways by which histidine can be stored or metabolized, and the fate of this amino acid is determined by its homeostasis in the organism. Histidine can be catabolized in the liver via L-histidine ammonia lyase (histidase) or stored in the tissues.[15] Circulating histidine in plasma can also be converted in the renal tubules to histamine without entering circulation.[2] Histidine can be stored in mast cells and converted to histamine for signaling and inflammation by the enzyme histidine decarboxylase. In contrast to allergic or anaphylactic mast cell degranulation, interstitial cystitis (IC) mast cells possess electron dense granules in different stages

of dissolution when observed microscopically[5]. This unique degranulation mechanism is characteristic of differential release of secretory mediators. Further support of differential secretion lies in the ability of the mast cell to secrete specific mediators such as biogenic amines and cytokines without degranulation.[16] For example, IL-6 release can be induced by exposure of mast cells to lipopolysaccharide (LPS) without release of histamine.[17] IL-6 and histamine concentrations were significantly higher in IC urine, suggesting greater mast cell degranulation products being exposed to bladder tissue than in controls.[18] Thus, elevated dietary histidine may therefore represent a risk factor for heightened mast cell responses and altered histamine dynamics in plasma and urine.

Urinary histamine has been characterized as having four possible sources: ingested histamine, histamine formed by bacterial decarboxylation of histidine in the intestine, histamine produced via mammalian histidine decarboxylase and excreted without being bound, and histamine formed by mammalian decarboxylase and stored within vesicles in the tissue.[2] In the current experiment, increasing dietary histidine supply increased plasma concentrations of histidine, but did not affect plasma concentrations of histamine. This suggests that if greater amounts of histidine were decarboxylated to form histamine, then histamine was either readily metabolized in tissues or excreted in urine. Simailary, differences were not detected among treatments in total histamine, cellular + non-cellular histamine, or antigen-induced histamine release in whole blood suggesting that dietary histidine does not affect the capacity for histamine degranulation from basophilic leukocytes, at least within the parameters of this experiment.

Previous studies in rats, using both intravenous and oral administration of C14 L-histidine, indicate that the primary source of urinary histamine is from the decarboxylation of histidine in the kidney and that this pool of histamine does not enter the circulation.[2] Accordingly, experiments in humans have shown that C14 L-histidine loading results in elevated histamine levels in urine, but not plasma[19]. Similar studies in guinea-pigs have shown that urinary histamine increases in response to oral L-histidine administration.[20] However, others have reported that oral administration of L-histidine in humans resulted in no pronounced or consistent effect on excretion of histamine or histamine metabolites in urine[21].

Still other studies in pigs have reported that the majority of the radiolabel in urine following oral administration of C14-histidine, was recovered as a methylated metabolite of histamine (N tau-methylimidazoleacetic acid), with only a very small fraction as histamine.[22] In the current experiment 24 hr urinary histamine excretion was not affected by dietary histidine. However, normalization of histamine concentration to creatinine concentration resulted in a higher urinary histamine:creatinine ratio for the 1.4% histidine diet compared with that of the 0.6% histidine diet. Creatinine is a metabolite of creatine metabolism in skeletal muscle and is freely filtered across the glomerulus and is not reabsorbed, secreted, or metabolized by any cell type in the nephron, and is used for normalization of renal filtered or excreted analytes[23]). Thus, the greater histamine:creatinine ratio for the 1.4% histidine diet is suggestive of a greater histamine excretion rate. The reason(s) for the conflicting results between 24 hr histamine excretion and histamine:creatinine data is not apparent. However, recovery and frequency of urine voiding may have complicated measures of 24 hr excretion rate. Not all cats voided during the 24 hr urine collection period and thus the first subsequent voiding was used as the 24 hr output. Previous efforts using 14C-labelled inulin, a non-metabolized and rapidly excreted compound, indicate that multiple days of urine collection are necessary for accurate quantitative measures of urinary metabolite excretion in cats.[24] Because the histamine:creatinine ratio was only greater for the 1.4% histidine diet, and not the 1.0%

histidine diet, our data are not conclusive on the relationship between dietary histidine supply and urinary histamine excretion. However, only histamine was measured in the current study, thus the possibility that dietary histidine was excreted via metabolites of histamine and not the parent molecule (e.g. 4(5)-imidazoleacetic acid, N-τ Methylhistamine) cannot be excluded[25].

Plasma amino acid concentrations were comparable to those found in felines fed to 100% minimum amino acid requirement[26]. The linear increase in plasma histidine with increasing dietary histidine is consistent with results seen in rats, pigs, chicks, and humans, which demonstrate that an increase in dietary essential amino acid above requirement results in an increase in respective plasma amino acid concentration[27-35]. These results suggest a relationship between post-absorptive plasma histidine and dietary histidine concentration. When graded levels of histidine between 0 and 0.57% were incrementally added to chick diets between 3 and 20 days post hatching, plasma histidine remained low until reaching a level of 0.41%. At this level and above, plasma histidine increased linearly with increasing dietary histidine[28]. The observed treatment differences in plasma glutamine are difficult to explain. There is no obvious explanation to account for such differences. There is a potential consequence of differing N intakes between dietary treatments that may account for such an effect, but it would be expected that other amino acids would reflect such an influence, and this was not seen.

CONCLUSIONS

This study demonstrates that dietary inclusion of up to 1.4% histidine increases circulating concentrations of histidine in cats without affecting circulating concentrations or basophilic release of histamine. Quantitative measures of urinary histamine excretion showed that histamine excretion was not responsive to dietary histidine. Contrariwise, the observed increase in urinary histamine:creatinine for the 1.4% histidine suggests that urinary histamine excretion may have been increased. Thus, results from this study are equivocal as to the influence of excess dietary histidine on urinary histamine excretion. Overall, it appears unlikely that dietary histidine, at least within range of 0.6% to 1.4%, significantly alters histamine dynamics in healthy female cats.

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