Original Research

Fecal Concentrations of N-methylhistamine in Common Marmosets (*Callithrix jacchus*)

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Chronic lymphocytic enteritis (CLE) is a frequent disease in common marmosets. However, no diagnostic test for early detection of CLE is available. Mast cells have an important role in gastrointestinal disease. The purpose of this study was to measure fecal concentrations of N-methylhistamine (NMH), a breakdown product of histamine metabolism, in common marmosets. A previously established NMH gas chromatography–mass spectrometry assay for canine feces and urine was used, and partial validation was performed. The reference intervals ($n = 30$) established for fecal NMH concentrations in common marmoset were 118.2 ng/g or less for a single fecal sample, 121.7 ng/g or less for the 3-d mean, and less than or equal to 167.5 ng/g for the 3-d maximum. Considerable day-to-day variation was observed in fecal NMH concentrations; the mean %CV was 42.2% (minimum, 7.1%; maximum, 141.4%). Fecal NMH concentrations were measured in 14 marmosets for which necropsy reports were available; 7 of the 8 marmosets with CLE and the 1 animal with lymphoma and ulcerative enteritis had increased fecal NMH concentrations. Increased fecal NMH concentrations may serve as a potential marker for CLE; however, further studies exploring the role of mast cells in marmosets with CLE are needed.

Abbreviations: CLE, chronic lymphocytic enteritis; NMH, N-methylhistamine

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Common marmosets (*Callithrix jacchus*) are a New World monkey employed in biomedical research since the early 1960s. Their popularity has increased over the years,¹ particularly because of their small size, lower cost for maintenance compared with larger NHP, easy husbandry, rapid reproductive turnover, and decreased susceptibility to various human pathogens.¹³

Inflammatory diseases of the gastrointestinal tract, particularly of the large intestine, have been described in marmosets since their initial use in biomedical research.^{6,7,22} Inflammatory bowel disease, particularly chronic lymphocytic enteritis (CLE), has been a consistent finding in *C. jacchus* colonies, with prevalence rates as high as 60.5% of all marmosets used as controls in various studies at one center.¹² No specific etiology has been identified; however, many etiologic factors, including gluten sensitivity, dietary protein deficiency, and the pancreatic spirurid nematode *Trichospirura leptostoma*, have been suspected. Clinically, failure to thrive in juveniles and weight loss with or without diarrhea in adults are observed. Diffuse to segmental lymphocytic enteritis is seen on histology.¹²

Currently, antemortem diagnosis of CLE in common marmosets is made on the basis of clinical signs, a history of weight loss, and a decreased serum albumin concentration.⁴ No proven effective treatment exists, and a final diagnosis usually is made only at necropsy.¹⁶ Newer markers like fecal calprotectin,¹⁴ fecal α_1 -PI,¹⁸ serum matrix metalloproteinases,²⁵ serum IgA antibodies

to gliadin and related proteins¹¹ are being investigated and may serve as markers of CLE in the future. In addition, treatment with steroids¹⁷ or tranexamic acid²⁶ may have promise.

Mast cells in the gastrointestinal tracts of dogs⁸ and humans¹⁹ have been described and have been investigated in chronic enteropathies of dogs^{3,5} and inflammatory bowel disease in humans.¹⁵ The role of mast cells has not been determined in marmoset CLE. Mast cells can be missed on routine hematoxylin–eosin staining, and their detection requires either special staining with toluidine blue or immunohistochemistry for mast cell tryptase.^{3,5} In addition, rather than absolute numbers of cells seen on histology, markers of mast cell activation have been suggested as a better method for measuring their activity. Histamine is stored primarily in mast cells and serves as marker of mast cell degranulation. Rapid metabolism of released histamine leads to N-methylhistamine (NMH) and imidazole acetaldehyde.²¹ Fecal concentrations of NMH were found to be increased in a subset of dogs with chronic enteropathies, suggesting that mast cell–mediated inflammation plays a pathogenic role.^{3,5}

We hypothesized that fecal concentrations of NMH are increased in marmosets with CLE and that this metabolite could be used as a marker of intestinal inflammation in these patients. Therefore, the aim of this study was to measure NMH concentrations in fecal samples collected from healthy marmosets, establish a reference interval for fecal NMH in common marmosets, and compare the concentrations from healthy marmosets with those from marmosets with CLE.

Materials and Methods

Sample collection. Fecal samples were collected from a total of 30 healthy marmosets maintained at the Southwest National

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Primate Research Center (Texas Biomedical Research Institute, San Antonio, TX) and the Marmoset Aging Center (MAC), The University of Texas Health Science Center, San Antonio, TX. Collection of fecal samples was approved from both institutional IUCAC (animal use protocols 1259CJ for Texas Biomed and 06120X for the University of Texas Health Science Center, San Antonio). Three consecutive naturally passed fecal samples were collected from each marmoset by using fecal collection tubes (101 × 16.5 mm; Fecal Collection Tube with Spatula, Sarstedt, Nümbrecht, Germany) and frozen immediately. Marmosets sampled did not have had any clinical signs of gastrointestinal disease and were not part of any research studies during the sampling process.

In addition, single-time–point fecal samples were collected rectally from 16 marmosets at necropsy. These marmosets died or were euthanized at the New England Primate Research Center (Boston, MA); these samples were frozen immediately after collection. The necropsy and sample banking were part of routine colony management procedures and included sick and healthy marmosets. The investigators were blinded to the final postmortem diagnoses of these animals when the assays were run. Where available, samples of gastrointestinal tissue were obtained from these animals for additional staining for mast cells.

All of the fecal samples were shipped overnight on dry ice to the Gastrointestinal Laboratory at Texas A and M University. Fecal samples were stored at –80 °C until extraction. Fecal extracts were stored at –80 °C until NMH analysis.

Preparation of fecal samples. A fecal NMH extraction protocol similar to that previously described for domestic dogs²⁰ was used. Briefly, fecal samples were extracted in a 1:5 solution of PBS (BupH Phosphate Buffered Saline, Thermo Scientific, Rockford, IL) and newborn calf serum (Sigma-Aldrich, St Louis, MO), followed by vigorous shaking in an automated shaker for 20 min. The fecal tubes were then centrifuged at 3000 × *g* for 20 min and filtered by using a serum filter (Fisherbrand Serum Filter System, Fisher Scientific, Pittsburgh, PA). The resultant supernatant (fecal extract) was used for the assay.

NMH assay. NMH in the marmoset fecal extracts was measured by using stable isotope dilution gas chromatography–MS as previously described for those from domestic dogs.²⁰ Briefly, 50 pg of trideuterated NMH (CDN Isotopes, Pointe Claire, Quebec, Canada) was added as an internal standard to 200 µL of fecal extract. Then 200 µL of sodium borate buffer (pH 9, 10 mM) was added. The sample was vortexed and then applied to a solid-phase silica extraction column (Sep-Pak Cartridge, Waters, Milford, MA). The columns were washed with changes of chromatography-grade water, and then the sample was eluted by using 0.1 N HCl acidified methanol (VWR, West Chester, PA). The eluted samples were placed in a heating block and evaporated to dryness by using nitrogen. The dried sample was reconstituted with 300 µL of 20% methanol in chloroform (VWR) before application to the second solid-phase silica extraction column. The column was washed with 150 µL of 20% methanol in chloroform (VWR). The sample was eluted by using four 1-mL volumes of methanol:chloroform: ammonium hydroxide (25:25:1, v/v) and dried as described earlier. Derivatization was achieved by adding 200 µL ethyl acetate (Sigma-Aldrich), 40 µL pyridine (Thermo Fisher Scientific, Waltham, MA), and 100 µL pentafluoropropionic anhydride (Sigma-Aldrich) to the sample and incubating at 64 °C for 40 min. The samples were evaporated to complete dryness as described. In the next partitioning step, 500 µL of 0.5 M Tris buffer was added to each sample, followed by 1.5 mL of hexane (Sigma-Aldrich). The samples were

vortexed for 1 min and centrifuged at 574 × *g* for 1 min. The hexane (upper) layer was collected, another 1.5 mL of hexane was added to each sample, and the process was repeated. The 2 hexane fractions were combined and evaporated to dryness. Before its transfer to a gas chromatography–MS autosampler vial, the residue was reconstituted with 30 µL of ethyl acetate and vortexed. The gas chromatography–MS analysis was performed by using a gas chromatograph (model 690N, Agilent, Santa Clara, CA) and mass selective detector (model 5975C, Agilent) with a dimethylpolysiloxane capillary column; all other conditions (temperature, carrier gas, gradient, and pressure) used were similar to what has been described in the earlier fecal NMH assay in dogs.²⁰ A standard curve from 0 to 5000 pg/µL was processed prior to each run, to evaluate assay performance. NMH and deuterated isotopes were quantified by using the ions at an *m/z* of 417 and 420, respectively. Fecal concentrations of NMH were back-calculated for the wet weight of the sample and reported as nanograms per gram of feces.

Partial validation. Because the assay had not been validated for use in common marmosets, we performed a partial validation to assess linearity and accuracy. Linearity was determined by calculating observed:expected ratios for 3 pooled (due to lack of sufficient volume) fecal extracts serially diluted 1:2 and 1:4. Accuracy was measured by calculating observed:expected ratios for 3 pooled fecal extracts that were spiked with 3 different NMH concentrations (125, 500, and 1250 pg/µL; equivalent to assay standards).

Establishment of the reference interval in healthy marmosets. Single-time–point, 3-d mean, and 3-d maximal concentrations for fecal NMH were measured and used to establish the reference interval for healthy marmosets. The coefficient of variation between the 3-d collections was calculated. A reference interval was established by calculating the upper 95th percentiles of the single time point, 3-d mean, and 3-d maximal fecal NMH concentrations. For the single-time–point reference interval, the sample from the 1st day of collection was used.

Necropsy results fecal NMH concentrations. Complete necropsy data, including gross findings, microscopic findings, and a summary from the pathologist were obtained for the 16 marmosets at the New England Primate Research Center from which fecal samples were collected and analyzed. Fecal NMH concentrations were correlated to the postmortem findings.

Histology and mast cell counts. Where available, samples of gastrointestinal tissue (stomach, small intestine, and large intestine) collected at necropsy were obtained and stained with hematoxylin–eosin and toluidine blue by using routine protocols. Sections stained with hematoxylin–eosin were not evaluated but were assessed to ensure that they were full-thickness sections and contained mucosa, submucosa, and muscularis propria. Only full-thickness sections were considered for the toluidine blue staining. Sections stained with toluidine blue were evaluated by a single board-certified anatomic pathologist (RL), and the mast cells in 4 high-power fields (magnification, 400×) per tissue were counted.

Statistical analysis. Statistical computation was performed by using a commercial software package (PRISM 5.0 (GraphPad Software, La Jolla, CA), and statistical significance was set at a *P* value less than 0.05. In addition, the coefficient of variation (CV% = [SD / mean] × 100%) was used to determine the variability in the fecal concentrations of NMH from the 3-d samples. Sensitivity and specificity were calculated by using an online calculator (https://www.medcalc.org/calc/diagnostic_test.php).

Results

During the partial validation of the assay, 1 of the 3 samples failed to go through the column as expected and had to be excluded. For assessment of the linearity, the observed:expected ratio was 137.1% and 124.6% for one sample at dilutions of 1:2 and 1:4, respectively, and 101.4% and 76.3%, respectively, for the other sample at the same dilutions. The accuracy observed:expected ratio for the 2 fecal extracts that were spiked with 3 NMH concentrations (125, 500, and 1250 pg/ μ L; equivalent to assay standards) were 84.5%, 85.2%, and 76.1%, respectively, for one sample and 74.1%, 80.7%, and 72.8%, respectively, for the other.

Overall, 30 healthy marmosets were used to establish the reference interval. Of these, 16 animals were from the Southwest National Primate Research Center, and 14 were from the Marmoset Aging Center. These marmosets ranged in age from 1 to 9 y (median, 2 y) and included 20 females and 10 males. The concentrations of NMH detected in marmoset fecal extracts ranged from undetectable to 216.1 μ g/g of feces. By using the upper 95th percentile, the reference intervals were determined to be less than or equal to 118.2 ng/g of feces for a single fecal sample, less than or equal to 121.7 ng/g for the 3-d mean, and less than or equal to 167.5 ng/g for the 3-d maximum. The median interday coefficient of variation from each subject was 42.2% (minimum, 7.1%; maximum, 141.4%).

Only 14 of the 16 single-time-point fecal samples collected from marmosets undergoing postmortem examination (Table 1) were available for analysis. Conditions included CLE ($n = 7$), healthy controls ($n = 2$), renal failure ($n = 2$), lymphoma with ulcerative enteritis ($n = 1$), enteropathogenic *E. coli* ($n = 1$), and adenocarcinoma ($n = 1$). The diagnosis of CLE was established histologically. Overall, 7 of the 14 marmosets had fecal NMH concentrations greater than the upper limit of the reference interval, and 6 of these 7 animals had CLE; the remaining animal had been diagnosed with lymphoma and ulcerative enteritis. For diagnosis of CLE from a single fecal sample by using a diagnostic cutoff of 118.2 ng/g, the sensitivity of this assay is 86% (95% CI, 42% to 100%) and the specificity was 86% (95% CI, 42% to 100%).

Extra tissue for mast cell counts was available from only 6 of these 14 marmosets (Table 2). Given the small number of animals, no statistical analysis was done.

Discussion

Because CLE is a common disease in marmoset colonies, having a minimally invasive diagnostic test would be beneficial. In the current study, fecal NMH concentrations were increased in 7 of the 8 common marmosets with CLE, thus suggesting that this test may have diagnostic utility.

Given the limited number of samples tested, the linearity and accuracy of the NMH gas chromatography–MS assay seem adequate for the assessment of marmoset fecal samples. The linearity and accuracy seem comparable to when this assay was used for the measurement of NMH in dog fecal samples (dilutional parallelism observed:expected, 88.6% to 115.0%; mean spiking recovery observed:expected, 104.2%).²⁰

The concentrations of NMH detected in marmoset fecal extracts ranged from undetectable to 216.1 μ g/g of feces. Undetectable NMH concentrations have also been reported in dogs.²⁰ The reference intervals established for common marmoset fecal samples are comparable to canine reference intervals of less than or equal to 191 μ g/g feces for the 3-d mean NMH concentration and less than or equal to 334 μ g/g feces for the 3-d maximum.⁵

To account for day-to-day variations in fecal NMH concentrations, 3-d mean or 3-d maximal concentrations have been used in other studies⁵ and may be more appropriate than single time point samples in common marmosets, given the broad intraindividual variation in the current study.

The observed increases in fecal NMH concentrations for marmosets with CLE compared with controls and the estimated diagnostic sensitivity and specificity suggest that this metabolite may be useful for noninvasive diagnosis of this disease in marmosets. However, further studies involving a larger number of animals are needed. Currently, the ‘gold standard’ for diagnosis of CLE in marmosets is postmortem examination, and establishing a definitive diagnosis antemortem is difficult. Therefore, a noninvasive test may allow earlier and more accurate diagnosis of this common disease of marmosets. Fecal NMH was normal in a single marmoset with CLE, this finding might represent a separate subtype of the disease, disease severity, issues with sample handling, or the broad intraindividual variation observed in the study. In addition, increased concentration of fecal NMH was present—unexpectedly—in a case of lymphoma and ulcerative enteritis. Increased mast cell activation currently known as ‘mast cell activation syndrome’ has been reported to occur during chronic inflammatory or neoplastic disorders.² What leads to this increase is unknown, and no histologic sections were available for evaluation of mast cells numbers in the gastrointestinal tract of these animals. Previously, fecal NMH concentrations were shown to be increased in some dogs with chronic enteropathies.^{3,5} In addition, fecal NMH was increased more often in dogs with moderate intestinal inflammation and only sporadically in dogs with mild inflammation.

Canine and human studies have used urine NMH:creatinine ratios as indicators of active disease^{3,5,23} or endoscopically diagnosed disease.²⁴ In our study, feces were used because the samples were already available and were easier to collect than urine samples. In addition, some authors believe that fecal histamine concentrations do not reflect a human’s systemic burden but rather luminal active histamine.⁹ Therefore feces may be a better marker of mast cell activation in CLE—another reason why we used fecal samples rather than urine for our study.

To our knowledge, mast cells have not been described in the marmoset gastrointestinal tract. Previous studies evaluating mucosal mast cell numbers in dogs¹⁰ and humans^{15,23,24} have reported mixed results. Staining techniques—particularly those using toluidine blue—may be inaccurate because they stain intact mast cell granules only, whereas immunohistochemical stains targeting mast cell tryptase cross-react with residual enzymes from degranulated cells. We decided to pursue toluidine blue staining in our study because metachromatic stains are significantly cheaper than immunohistochemical staining. Furthermore, patchy distribution of mast cells throughout the gastrointestinal tract, nonrepresentative biopsies, and ongoing degranulation of mast cells resulting in their depletion have been suggested as potential reasons for why mast cell counts may not be a true representation of the disease process.⁵ These factors potentially could explain the variation seen in the mast cell counts for the same gastrointestinal location in the same marmoset in our study. In one healthy animal, reported mast cell counts in the colon were 3 and 21, and in a marmoset with CLE, they were 0, 23, and 38, thus raising concerns regarding patchy distribution. However, no conclusions can be based on these findings, given the small number of animals.

Given that all the necropsy samples were from the same institution, where primate necropsies and histology are a common practice performed by boarded anatomic pathologists,

Table 1. Summary of data regarding fecal NMH concentrations in 14 marmosets

Marmoset	Sex	Weight (g)	Age (d)	Clinical history	Diagnosis based on gross and microscopic examination at necropsy	Fecal NMH ($\mu\text{g/g}$)
1	Female	415.7	1243	Control for clinical study	Normal animal	18.0
2	Male	456.8	1400	Control for clinical study	Normal animal	35.0
3	Female	336.7	3757	Suspected chronic lymphocytic enteritis, wasting, and poor health	Chronic lymphocytic enteritis	994.8
4	Male	398.9	Unavailable	None	Chronic lymphocytic enteritis	396.6
5	Male	292.8	5372	Suspected mass in abdomen	Chronic lymphocytic enteritis	219.5
6	Female	485.5	Unavailable	Diabetes and lymphocytosis	Chronic lymphocytic enteritis	228.6
7	Female	353.1	Unavailable	Suspected mass in abdomen	Chronic lymphocytic enteritis	106.7
8	Female	305.6	2346	Suspected chronic lymphocytic enteritis, wasting, and poor health	Lymphoma and ulcerative enteritis	1540.0
9	Female	307.0	5170	Suspected <i>E. coli</i> infection	Enteropathogenic <i>E. coli</i>	24.4
10	Female	302.0	3796	Doing poorly	Adenocarcinoma	111.4
11	Male	456.0	3654	Chronic diarrhea	Chronic lymphocytic enteritis	256.7
12	Female	400.5	3838	Chronic diarrhea	Chronic lymphocytic enteritis	236.5
13	Male	272.9	6304	Weight loss	Renal failure	83.4
14	Male	357	4667	Renal failure	Renal failure	23.8

NMH, N-methyl histamine

All marmosets were euthanized, except for animal 4, which was found dead.

Table 2. Distribution of mast cells in the gastrointestinal tracts of 6 marmosets

Marmoset	Necropsy diagnosis	Stomach	Total number of mast cells in four 20 $\times$ fields from each slide			
			Duodenum	Small intestine Jejunum	Ileum	Large intestine Cecum-Colon
1	Normal control	42	14	4, 14	NA	3, 6, 7 ^a
2	Normal control	NA	11	27, 46	7, 21 ^b	3, 21 ^b
4	Chronic lymphocytic enteritis	169	12	21, 51	93	0, 23, 38
5	Chronic lymphocytic enteritis	NA	23	78, 110	109	47, 69
10	Adenocarcinoma	NA	NA	26, 38	NA	5, 21
13	Renal failure	33	NA	43	NA	46, 57, 82

NA, not available

Numbers separated by commas indicate that multiple slides were available.

^aOnly 3 fields counted.^bOnly 2 fields counted.

no attempts were made to reevaluate the diagnosis of CLE in these samples. A report from a study in dogs³ suggested that increased numbers of intestinal mast cells were seen in animals responding to diet or antimicrobial therapy compared with immunosuppressive medications. This information would have been valuable if any such increases were detected in our study,

because it would have helped to guide treatment in the marmosets; unfortunately, this evaluation could not be done due to low sample numbers.

The major limitations in our study were the small sample size ($n = 30$) for establishing the reference interval, as well as the small number of animals ($n = 14$) that underwent necropsy and

could subsequently be used to estimate diagnostic accuracy. No laboratory data were available to see whether these animals also had low albumin concentrations or were anemic, as described in previous studies.^{4,12,17} Given the small number of samples ($n = 6$) available for specific staining of mast cells, no association between the presence of mast cells and NMH concentrations could be demonstrated. Furthermore, optimal fecal sample handling and storage conditions were not assessed in this study. In particular, fecal samples were collected from the necropsied animals after death, and the effect of that technique on fecal NMH concentrations is unknown. It also is possible that the marmosets with increased fecal NMH concentrations and histologic evidence of CLE were terminally ill and therefore euthanized. Consequently, the utility of fecal NMH in healthy colonies or as an early marker of CLE remains uncertain.

Even with the given the limitations, the study findings do suggest that common marmosets with CLE may have increased fecal NMH concentrations. Further studies in a larger number of common marmosets are warranted to better evaluate the role that mast cells play in CLE and to fully evaluate the utility of this test.

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