Effects of Particle Size and Physical Form of Diets on Mast Cell Numbers, Histamine, and Stem Cell Factor Concentration in the Small Intestine of Broiler Chickens

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ABSTRACT The aim of this study was to investigate the hypothesis that particle size and diet form may affect the growth of mast cells and histamine release from the small intestine of broiler chickens. A total of 288, day-old male broiler chicks were randomly allocated to 1 of 4 corn-soy diets in a 2 × 2 factorial design. The factors included particle size (coarse vs. fine) and physical form (mash vs. pellet). The birds were housed in 90 × 60 cm pens containing 12 birds, and each treatment contained 6 replicate pens of birds from d 1 to 22. On d 22, 6 broilers from each treatment were slaughtered. Tissues from the small intestine (duodenum, jejunum, and ileum) were obtained to quantify mast cells using the toluidine blue staining technique. The results showed that mast cells in the jejunum were concentrated in the upper part of the villus in birds fed the coarsely ground mash diet, whereas mast cells were evenly distributed throughout the intestine in birds fed the other 3 diets. The number of mast cells was significantly lower in the duodenum ($P = 0.04$), jejunum ($P < 0.01$), and ileum ($P = 0.01$) of birds fed coarsely ground diets compared with finely ground diets, and there was no difference in mast cell numbers between birds fed mashed or pelleted diets at any site in the intestine. The histamine content ($P = 0.02$) and stem cell factor concentration ($P = 0.03$) were markedly lower in the jejunum of birds that were fed coarsely ground diets compared with finely ground diets. The stem cell factor concentration in the duodenum ($P < 0.01$) and jejunum ($P = 0.05$) was higher in birds fed pelleted compared with mash diets. The overall results of this experiment suggest that particle size and diet form affect mast cell number and histamine content in the small intestine by regulation of stem cell factor concentration.

Key words: particle size, diet form, mast cell, histamine, broiler

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INTRODUCTION

The effects of particle size and diet form on the performance, digestibility, and gastrointestinal functions of animals have been extensively evaluated (Choi et al., 1986; Nir et al., 1994a,b; Engberg et al., 2002; Svihus et al., 2004). Although grinding and pelleting generally improve broiler performance, there are some disadvantages connected to these processing methods. For example, a correlation has been found between feeding pelleted diets and the occurrence of certain metabolic diseases such as ascites and tibial dyschondroplasia (Havenstein et al., 1994; Nir et al., 1995; Engberg et al., 2002).

Mature mast cells within all layers of the gut wall play a role in intestinal peristalsis, inflammatory processes, and the immune response (Golkar and Bernhard, 1997; de Jonge et al., 2002; Schneider et al., 2002). Histamine is a chemical mediator released by mast cells, and it is considered to be an important cellular messenger in the gastrointestinal tract (Rangachari, 1992). Stem cell factor, a growth factor of mast cells (Karimi et al., 1999; Lorentz and Bischoff, 2001), has been shown to increase histamine synthesis in mice (Karimi et al., 1999).

It has not been established whether particle size and diet form can regulate the intestinal expression of stem cell factor or the growth of mast cells and histamine synthesis. This could be one of the potential mechanisms whereby feed structure affects intestinal function in broiler chickens. Therefore, the aim of this study was to investigate the hypothesis that particle size and diet form may affect the growth of mast cells and histamine release from the small intestine of male broiler chicks.

MATERIALS AND METHODS

This experiment was conducted under protocols approved by the China Agricultural University Animal Care and Use Committee. The birds and diets used in the present experiment were the same as those used in the experiments of Huang et al. (2006).

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Experimental Birds

This study was performed with 288, day-old male Arbor Acre broiler chicks. All birds were raised in an environmentally controlled room with continuous light (10 to 20 lux). According to normal management practices, the room temperature was maintained at 33°C from d 0 to 5 and then gradually reduced to 22°C by the end of the experiment. Feed and water were supplied ad libitum throughout the experiment.

Experimental Design and Diets

The broilers were randomly allocated to 1 of 4 dietary treatments in a 2 × 2 factorial design. The factors included particle size (coarse vs. fine) and diet form (mash vs. pellet). The birds were housed in 90 × 60 cm pens containing 12 birds, and each treatment was fed to 6 pens of birds from d 1 to 22 of age.

All experimental corn-soy diets were formulated to meet or exceed the nutrient requirements of the NRC (1994). The coarse mash diet was prepared by mixing corn and soybean meal ground through a 5-mm screen with all other ingredients to yield a final particle size of 953 μm. The fine mash diet was prepared by mixing corn and soybean meal ground using a 3-mm screen and then mixed with other dietary ingredients to yield a final particle size of 594 μm. The actual particle size of each diet was determined by a standard method (Ensor et al., 1970). The pelleted diets were processed at a temperature of 85°C in a pellet mill (Muyang Corp., Yangzhou, China) using a 38-mm thick die with 2-mm diameter holes.

Sample Collection

On d 22, six birds per treatment (1 bird/pen) were selected randomly and slaughtered by cervical dislocation. Segments of the intestine were removed from the duodenum (5 cm from the pylorus), jejunum (5 cm posterior to the yolk stalk), and ileum (2 cm anterior to the ileocecal valve). The intestinal contents were removed by flushing with saline.

One sample of each of the intestinal tissues, about 2 cm in length, was fixed immediately by immersion in Carnoy's fluid (60 mL of 100% ethanol, 30 mL of chloroform, and 10 mL of glacial acetic acid) and kept at room temperature for 12 h until needed for histochemistry staining. Another sample of each intestinal tissue, about 10 cm in length, was immediately immersed in liquid N and preserved at −80°C for later histamine and stem cell factor analysis.

Histochemistry Staining

The intestine samples previously fixed in Carnoy's fluid were dehydrated in a graded series of alcohol and xylene and then embedded in paraffin wax. Paraffin sections (6 μm thick) were made and mounted on poly-L-Lys-coated slides, dewaxed in xylene and then rehydrated. Two or 3 copies of each paraffin-embedded segment were rinsed with 0.5 *M* HCl (pH 0.5) for 5 min and stained with toluidine blue (Gurr, Poole, UK). The sections were then dehydrated and mounted (Xu et al., 2001).

Mast cells were observed using a Microcheck Grid (Wuhan Optical Ltd, Wuhan, China), following the procedures described by Xu et al. (2001). The average number of mast cells in a single intestinal villus was acquired by randomly counting more than 10 intestinal villi per section. For the measurement of mast cell numbers in the intestinal serosa, stained mast cells of the whole serosa were counted using 3 sections per sample (Xu et al., 2001) in high-power fields (×40) with a Microcheck Grid containing 100 microchecks (0.25 mm^2). Mast cell numbers in the intestinal serosa were expressed as a cell number per squared millimeter of the intestine serosa.

HPLC Determination of Histamine in the Small Intestine

The HPLC method used for the determination of histamine was that described by Veciana-Nogues et al. (1995). Following tissue homogenization and extraction, the samples transited a cation exchange column (Symmetry, C^{18}, 5 μm, 4.6 × 150 mm, Waters Ireland, Dublin) and were eluted by a gradient elution program at a flow rate of 1 mL/min. The eluate was then reacted with o-phthalaldehyde (Sigma, Chicago, IL) at 40°C and examined using a fluorescence detector (Waters 2475 Multi$^{\lambda}$ Fluorescence Detector, Waters Ireland) at excitation 340 nm and emission 450 nm. The data were analyzed using a data integrator (Waters TM 600, Waters Ireland). All reagents were filtered through a 0.45-μm dialyzer and degassed before use. Postcolumn derivatizating reagents were prepared fresh daily and protected from light.

ELISA Detection of Stem Cell Factor Protein in the Small Intestine

Samples of the different intestinal segments weighing approximately 0.5 g were homogenized at 4°C in 1 mL of a buffer containing 1 *M* NaCl-Tris, 0.25% Triton X-100, and protease inhibitors, as described by Gaça et al. (1999). Samples were then centrifuged for 10 min at 10,000 × *g* at 10°C, and the supernatant was obtained. Stem cell factor protein concentrations were measured in duplicate using a commercial ELISA kit (enzyme immunoassay for the quantitative determination of goat anti-chicken stem cell factor, Dalianfanbang Biochemical Technology Ltd, Dalian, China) according to the manufacturer's instruction. Sensitivity was 45 pg/mL. Intra- and interassay CV were 6.8 and 11.0%, respectively. The recovery was 98 to 110%.

Statistical Analysis

Data were analyzed by ANOVA using the GLM procedures of SAS (SAS Institute Inc., Cary, NC) appropriate for a 2 × 2 factorial design. The statistical model included the effects of diet particle size (coarse vs. fine), diet form

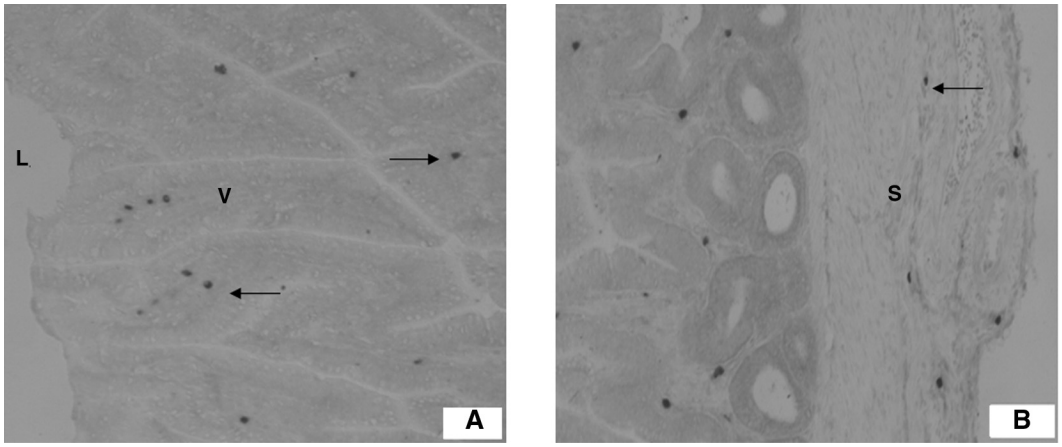

Figure 1. Mast cells in the jejunum of the birds fed the finely ground mash diet that are evenly distributed throughout the intestine. Mast cells visualized in the mucosa, submucosa (panel A), and serosa (panel B) by toluidine blue staining. L = lumen; V = villus; S = serosa. Original magnification ×100.

(mash vs. pellet), and their interactions. Differences between treatments were analyzed using a *t*-test following a significant *F*-test. Results were expressed as least squares means and SEM. Probability values of <0.05 were considered to be significant.

RESULTS

The Distribution of Mast Cells in the Small Intestine of Broilers

Particle size affected the location and quantity of mast cells in the intestinal villi. Mast cells in the intestinal villi of broilers fed the finely ground mash diet were distributed relatively evenly throughout the intestine, with mast cells visualized in the mucosa, submucosa, and serosa (Figure 1). In contrast, mast cells in the intestinal villi of birds fed the coarsely ground mash diet were clustered in the upper end of the villi (Figure 2). Diet form did not affect the distribution of mast cells in the small intestine of birds. Mast cells were observed throughout the intestine for both finely ground and coarsely ground pelleted diets with the pattern similar to that observed for the finely ground mash diet (Figures 3 and 4).

Mast Cell Numbers in the Duodenum, Jejunum, and Ileum of Broilers

There was a significant ($P = 0.02$) particle size × diet form interaction for the number of mast cells in the duodenum, with the number of mast cells dramatically greater in finely ground mash diets compared with coarsely ground mash diets (4.65 vs. 1.95), whereas the number of mast cells was similar for coarsely and finely ground pelleted diets (3.15 vs. 3.01). In addition, there was a remarkable effect of particle size on mast cell numbers in the small intestinal villus, whereby the number of mast cells in the duodenum ($P = 0.04$), jejunum ($P < 0.01$), and ileum ($P = 0.01$) was higher in birds given finely ground diets compared with coarsely ground diets (Table 1). Diet form had no effect ($P > 0.05$) on the number of mast cells in the small intestinal villus at any of the 3 sites tested. Neither particle size nor diet form affected the number of mast cells in the intestinal serosa of broilers ($P > 0.05$).

Histamine Content in the Small Intestine of Broilers

The effects of particle size and diet form on histamine content are presented in Table 1. There were effects of particle size on the histamine content in the jejunum ($P = 0.02$), with histamine content significantly higher in finely ground diets than coarsely ground diets. In addition, higher concentrations of histamine were detected in the small intestine of all pellet-fed birds compared with mash-fed birds, although the effects were not statistically sig-

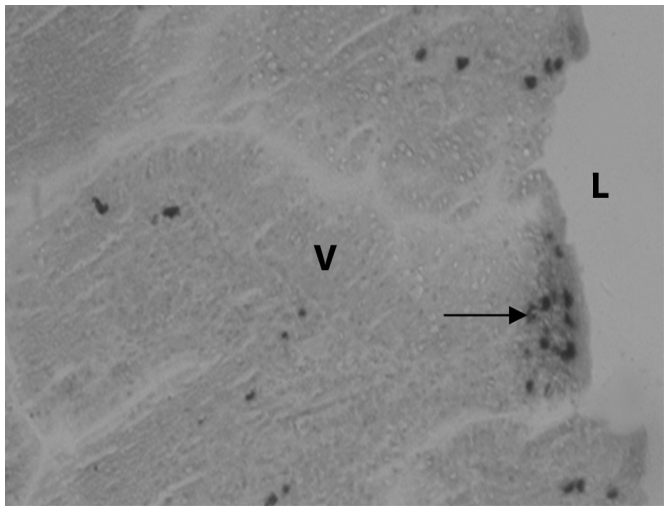

Figure 2. Mast cells in the jejunum of birds fed the coarsely ground mash diet that are clustered in the upper end of the villi. L = lumen; V = villus. Original magnification ×100.

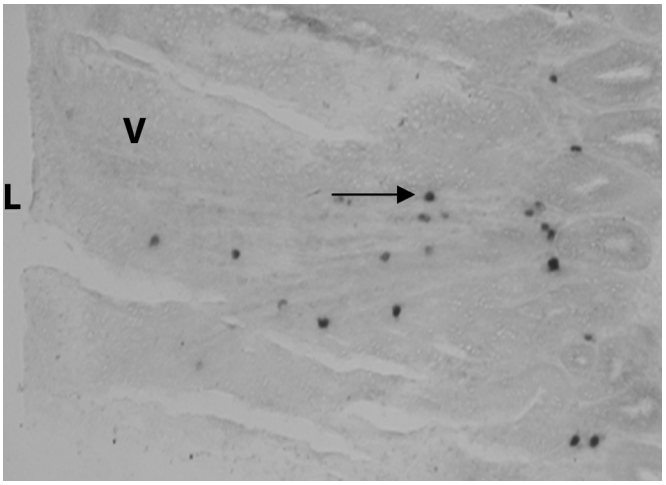

Figure 3. Mast cells in the jejunum of birds fed the finely ground pellet diet that are evenly distributed throughout the intestine. L = lumen; V = villus. Original magnification ×100.

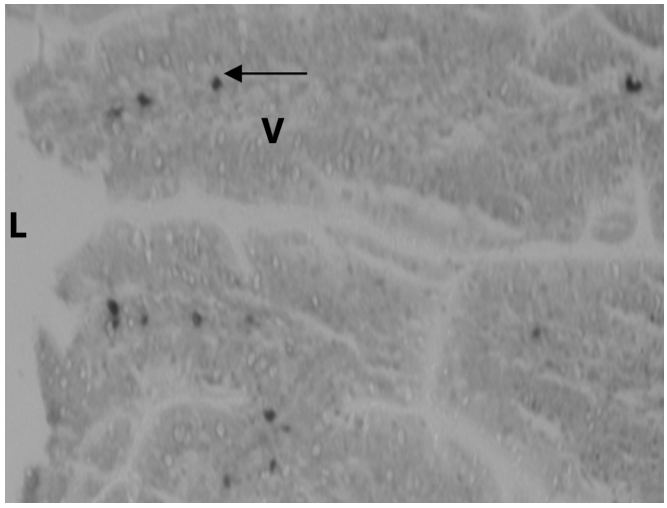

Figure 4. Mast cells in the jejunum of the birds fed the coarsely ground pellet diet that are evenly distributed throughout the intestine. L = lumen; V = villus. Original magnification ×100.

nificant. No significant interaction occurred between particle size and diet form for histamine concentration at any site in the small intestine of broilers.

Stem Cell Factor Protein Concentrations in the Small Intestine of Broilers

The effects of particle size and diet form on stem cell factor concentrations in the small intestine are shown in Table 1. With regard to particle size, birds fed finely ground diets had higher stem cell factor concentrations in the jejunum ($P = 0.03$) than coarsely ground-fed birds, whereas no differences were observed in the duodenum and ileum. The stem cell factor concentrations in the duodenum ($P < 0.01$) and jejunum ($P = 0.05$) of birds fed pelleted diets were higher than those in birds fed mash diets. No particle size × diet form interactions were observed.

DISCUSSION

Previous studies have shown the performance of broiler chickens to be improved by decreasing particle size as well as pelleting (Nir et al., 1994a,b; 1995). Feed structure may contribute to the improved performance of broiler chickens via effects on the gastrointestinal tract, because it has been reported that feed structure has a strong influence on the physiological functions of the digestive tract in broiler chickens (Engberg et al., 2002).

In this study, we evaluated intestinal tissues and found that there were abundant numbers of mast cells in the small intestine wall of birds and that the mast cells were located mainly in the mucosa and submucosa. Mast cells originate from bone marrow-derived progenitor cells, which enter the tissue via the blood circulation and then complete their differentiation and maturation locally (Galli, 1990; Li and Krilis, 1999).

Mast cells have significant potential to modulate gut function. Mast cell recruitment and proliferation has been suggested to play a role in the alterations of motility-related gastrointestinal symptoms (Golkar and Bernhard, 1997; de Jonge et al., 2002). In addition, an increase in mast cell numbers may result in an increase in the production and release of active mediators that regulate the movement of intestinal smooth muscle. Mast cells release large amounts of active mediators including histamine, prostaglandin, 5-hydroxytryptamine, leukotriene, and other cytokines (Lorentz and Bischoff, 2001; Marshall, 2004). It has been reported that 5-hydroxytryptamine and leukotriene induce the shrinkage of smooth muscle. Receptor antagonists of serotonin could interdict the change of intestinal motility mediated by allergen (Grider et al., 1998; Dahlén et al., 2004). Nakajima et al. (1997) also reported that serotonin increased the gastrointestinal contraction in vivo. In addition, leukotriene can affect smooth muscle adrenoceptor populations, which are likely to contribute to the change of intestinal motility (Martinolle et al., 1995).

Mast cells are widely distributed in areas such as the epithelial surfaces of the skin, respiratory system, and the gut. All of these areas easily come into contact with foreign substances and allow the mast cell to fulfill various regulatory, protective, and inflammatory functions (Nilsson et al., 1994; Golkar and Bernhard, 1997). Some researchers have reported that enteric bacterial infection, parasitic infection, and other antigen stimulation could induce the number of mast cells in the small intestine to increase (Mathan and Mathan, 1986; Ashida and Denda, 2003).

An important finding of the current study is that the number of mast cells in the villi in the duodenum, jejunum, and ileum of birds fed finely ground diets was greater than that of birds fed coarsely ground diets. Mast cell-mediated inflammatory and subsequent mucosal immune responses (innate and adaptive) would not be energetically favorable to performance gains, unless they successfully eliminated an enteric pathogen that was decreas-

Table 1. The number of mast cells in the small intestinal villus (no./single intestinal villus) and serosa (no./mm^2), histamine content (μg/g), and stem cell factor concentration (pg/g) of duodenum, jejunum, and ileum of broilers as affected by particle size (PS) and diet form (DF)

	PS		DF			*P*-value		
Items	Coarse	Fine	Mash	Pellet	SEM	PS	DF	PS × DF
Mast cell no. in villus (no./single villus)								
Duodenum	2.55[a]	3.83[b]	3.30[ab]	3.08[ab]	0.34	0.04	0.70	0.02[1]
Jejunum	1.77	4.31	3.03	3.05	0.45	<0.01	0.98	0.48
Ileum	2.26	4.72	2.96	4.02	0.51	0.01	0.25	0.45
Mast cell no. in serosa (no./mm^2)								
Duodenum	51.1	46.0	46.7	50.4	4.03	0.53	0.65	0.09
Jejunum	29.8	31.6	33.3	28.1	1.85	0.63	0.18	0.48
Ileum	35.7	30.3	30.3	35.6	2.55	0.29	0.29	0.11
Histamine content (μg/g)								
Duodenum	4.18	4.05	3.48	4.76	0.40	0.87	0.13	0.69
Jejunum	4.22	6.97	4.51	6.68	0.63	0.02	0.06	0.70
Ileum	4.30	6.49	4.51	6.27	0.64	0.09	0.17	0.75
Stem cell factor concentration (pg/g)								
Duodenum	829.4	931.4	474.7	1,286.1	108.7	0.40	<0.01	0.55
Jejunum	634.9	910.6	644.9	900.6	70.7	0.03	0.05	0.38
Ileum	731.7	956.5	719.4	968.7	77.9	0.15	0.11	0.68

[a,b]Values with different superscripts are different at $P < 0.05$.

[1]Value means the number of mast cells dramatically greater in finely ground mash diets compared with coarsely ground mash diets (4.65 vs. 1.95), whereas the number of mast cells was similar for coarsely and finely ground pelleted diets (3.15 vs. 3.01).

ing performance in an infected animal. However, an activity of mast cells on motility could directly be associated with increased performances in chickens. The fact that mast cells within the gut wall play a role in intestinal peristalsis, inflammatory processes, and the immune response (Golkar and Bernhard, 1997; de Jonge et al., 2002; Schneider et al., 2002), could partially explain the improved performance of birds fed these types of diets.

Another novel finding of the current study was that mast cells in the intestinal villi of broilers fed the coarsely ground mash diet were always clustered in the upper end of the intestinal villi. In contrast, the mast cells in the intestinal villi of birds fed the finely ground mash and pelleted diets were more evenly distributed throughout the intestine. The physiological significance of this finding is unclear.

Histamine is a multifunctional biogenic amine produced when histidine is decarboxylated by a special histidine decarboxylase (Jutel et al., 2002; Schneider et al., 2002). Histamine-containing mast cells were numerous in chickens (Rangachari, 1992). Histamine exerts secretory, contractile, and immune effects on the intestine. This amine enhances the shrinkage of smooth muscle in pigs, guinea pigs, and humans and is mediated by histamine H1 and H2 receptors (Bolton and Clark, 1981; Panettieri et al., 1989; Hill, 1990; Schneider et al., 2002). In addition, histamine H3 receptor, as a presynaptic receptor, affects gastrointestinal functions via regulating nerve center and release of peripheral acetylcholine, norepinephrine, 5-hydroxytryptamine, and other mediators (Ishikawa and Sperelakis, 1987; Arrang et al., 1991).

The results of the current study show that the histamine contents in the jejunum of broilers fed finely ground diets were higher than those of broilers fed coarsely ground diets. In addition, the histamine content in the duodenum, jejunum, and ileum was correlated with the number of mast cells in these tissues. As the quantity of mast cells increased, the histamine content also increased in the small intestine of broilers. These results are consistent with those reported by other researchers (Hiragun et al., 1998; Yamamoto et al., 2000; Ashida and Denda, 2003).

The development, survival, and final maturation of mast cells in tissues are dependent upon stem cell factor, also called mast cell growth factor, which is a chemoattractant candidate and the ligand for the protooncogene product c-kit (Lemura et al., 1994; Nilsson et al., 1994; Lorentz and Bischoff, 2001). Stem cell factor expression has been observed in mast cells of various types and sources according to Welker et al. (1999). In addition, mast cells, which abundantly express the receptor for stem cell factor, might immediately bind stem cell factor once it is released, with subsequent autocrine stimulation of the cells, enhancing their secretory function, i.e., releasing histamine (Welker et al., 1999). Interestingly, our results demonstrate that stem cell factor protein concentrations in the small intestine of the birds fed the finely ground and pelleted diets were increased, which was consistent with the observation of increased numbers of mast cells and an increase in histamine content.

Increased production of endogenous stem cell factor may contribute to the expansion of mast cell populations that has been observed by other researchers (Lemura et al., 1994). The mechanism involved in the increase of the number of mast cells induced by a decrease of dietary particle size and pelleting remains to be investigated. However, it is most likely that the finely ground and pelleted diets enhanced mast cell growth through upregulation of the stem cell factor concentrations in the small intestine.

There is accumulating evidence to suggest that stem cell factor promotes mast cell function as well as mast cell growth (Kawasaki et al., 1995; Hiragun et al., 1998). Also, there is evidence that stem cell factor treatment increases histamine synthesis in mice based on in vitro

assays (Karimi et al., 1999). The current study provides further evidence associating mast cells with histamine and stem cell factor in broiler chickens.

In conclusion, the results of the current study show that reducing particle size and pelleting enhances the number of mast cells and increases histamine synthesis. These effects are likely mediated through increasing stem cell factor concentration and stem cell factor expression in the small intestine in broiler chickens.

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