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The effect of histamine resulted from decarboxylase corruption of the diets on non-specific immune response, growth performance and hepatic index of rainbow trout *(Oncorhynchus mykiss)*

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Abstract

In the present study, dietary histamine levels were tested as indices of destructive bacterial activity. Four experimental diets were formulated which were similar in terms of digestible energy, crude protein and fixed dietary components but had different levels of histamine (according to the values of stale fish meal). Dietary histamine levels were determined by high-performance liquid chromatography (HPLC). Control diet contained 3.65 mega cal/kg digestible energy, 40% crude protein and 1.2 mg/100g histamine. Diets 1 to 3 contained histamine levels of 1.6 mg/100g, 2.15 mg/100g and 2.8 mg/100g, respectively. The design of the study was completely randomized with four replications of four treatments in 76 days in 16 pools. 60 rainbow trout with average weight of 150± 9 g were used per pool. The results showed that with increasing dietary histamine levels, a reduction in specific growth rate and an increase in feed conversion ratio were observed (0.05). A_1-antiprotease activity increased in diets 2 and 3 compared with the control diet ($P<0.05$). Total antiprotease activity in diet 3 and serum total protein in all treatments were significantly increased in comparison with the control diet ($P<0.05$). It was observed that dietary histamine levels higher than 1.6 mg/100g stimulated non-specific immune system and decreased specific growth rate. An increase in feed conversion ratio and somatic hepatic index were also visible with increasing dietary histamine levels. No significant differences were observed in growth performance, but significant differences were observed in hepatic somatic index of experimental fish compared with the control ones ($P<0.05$).

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Introduction

Biogenic amines, especially histamine, are formed through decarboxylation of amino acids or by amination and transamination of aldehydes and ketones. In fact, these combinations are organic bases with low molecular weight, but biologically active. They are synthesized through bacterial metabolism of plants and animals and constitute the bulk of total volatile nitrogen of the food. This microbial activity decreases the value of food production used to feed the fish and reduces the productivity of fish farms.

Histamine is the only biogenic amine whose highest levels can be found in food (Ladero *et al.*, 2010). Currently, no complete and comprehensive information is available regarding the toxicity of biogenic amines on aquatic organisms. Chemical analyses of animal by-products like poultry by-product meal, bone meal and fish meal used in feeding poultry as well as aquatic animals have shown that as they were kept in suitable conditions for microbial spoilage, several types of biogenic amines were formed simultaneously and in large quantities. Increase in biogenic amines' concentrations in fish with increasing amounts of these amines in aquatic food can be partly controlled by the hormone system and immune system of the body. The results obtained by Shiozaki *et al.* (2003) regarding exogenous histamine metabolism in rainbow trout indicated that catabolic histamine enzymes (diamine oxidase and histamine-n methyl transferase) were formed and released in rainbow trout tissues after the entry of exogenous histamine. Shiozaki *et al.* (2003) illustrated that changes in the levels of histamine and its metabolites (imidazole acetic acid and 1-methylhistamine) increased in trout tissues after consuming feeds containing histamine. The results of these studies were indicative of the fact that histamine can be blocked in trout's body through two metabolic ways. The main way is the one in which imidazole acetic acid is produced by the intestinal diamine oxidase enzyme. In the other way, convertion of histamine to 1-methylhistamine is performed by hepatic n- methyl transferase. According to these studies, liver was found as the involved organ in the excretion of biogenic amines, especially histamine (Shiozaki *et al.*, 2003).

Fish meal obtained from fish contains high levels of histamine and can be toxic for birds and may result in gizzard corruption (Fairgrieve *et al.*, 1994). In the present study, gastric abnormalities were also observed in fish fed fish meal containing different levels of biogenic amines (Fairgrieve *et al.*, 1994). Feed intake, feed efficiency and growth of the fish fed different experimental diets had no significant difference with that of control group which were fed diets containing fresh fish meal and were without supplements (Fairgrieve *et al.*, 1994).

The results of the study conducted by Tapia-salazar *et al.* (2004) illustrated that survival, food consumption and final biomass of the shrimp fed diets containing stale fish meal were significantly lower than the shrimp fed diets containing fresh fish meal. It was also concluded that adding synthetic biogenic amines had no effect on growth parameters and feed conversion ratio of shrimp.

Tapia-salazar *et al.* (2004) also measured Polyamine concentrations of hepatopancreas and the whole body at the end of their experiment. No significant differences were observed for different concentrations of biogenic amines of the experimental diets, but hepatopancreas Cadaverine levels of the shrimp fed stale fish meal were higher. It is worth noting that the available information about biogenic amines and their values in marine species are more than that of fresh water fish (Křížek *et al.*, 2011).

One important factor influencing the growth of bacterial colonies and consequently increasing decarboxylation of free amino acids is temperature. Rise in temperature directly correlates with increased concentrations of total volatile nitrogen of the food (Ayesh *et al.*, 2012).

Ayesh *et al.* (2012) stated that increased concentration of biogenic amines is even evident in case of frozen fish before processing. They believed

that the main reason of the toxicity of these products is an increase in histamine concentration.

According to Masamuto *et al.* (2000), yellowtail fish fed heated protein sources containing histamine showed no signs of disordered stomach, but at the same time had lower feed intake and specific growth rate compared with the control diet.

As it was shown by Opstvedt *et al.* (2000), growth, feed intake and feed efficiency of Atlantic salmon fed diets containing stale herring fish meal were decreased. In addition, histological changes were also observed in the liver and intestine of fish fed stale herring fish meal which was not visible in those fish fed diets containing fresh fish meal. Opstvedt *et al.* (2000) believed that adding synthetic biogenic amines to diets containing fresh herring fish meal not only had no effect on fish production performance, but also did not lead to pathological changes in the gastrointestinal tract. They also showed that in addition to biogenic amines, other compounds should also exist in total volatile nitrogen of stale herring fish meal which reduces the palatabilityof the diets containing stale fish meal (Opstvedt *et al.*, 2000).

Al Bulushi *et al.* (2009) observed that sometimes histamine alone is not capable of causing food poisoning and other biogenic amines like putrescine and cadaverine are also needed.

The main aim of the present study was to investigate the adverse effects of histamine resulted from decarboxylase corruption of dietary fish meal on non-specific immune response, growth performance and somatic hepatic index of rainbow trout *(Oncorhynchus mykiss)*.

Materials and method

In the present study, 960 rainbow trout with average weight of 150 ±9 were used (60 in each pond). The Fish were kept in 16 octagon concrete ponds (1×1×1m) with inlet water of 1.5-2 lit sec^{-1}. The water temperature was 14.5° C with the pH level of 7.3. The dissolved oxygen of water was 7.5 mg/lit. Feeding was three times a day according to NRC (1999) and was based on 2.5% of the body weight.

Chemical analysis of the experimental diets was done as follows:

The crude protein of the diets was determined by Kjeldalh (kjeltec Analyzer unit 2300 Foss Model), fat by solvent extraction, ash by placing the samples in a muffle furnace (550°C) for 12 h, fiber by placing the samples remaining in a muffle furnace (600°C) for 6 h after acid and alkali hydrolysis and moisture by drying (105°C) until constant weight has been attained. Nitrogen free extract was calculated by subtracting the values of protein, fat, fiber and ash from the dry matter. The amount of histamine of stale fish meal used in the present study along with dietary histamine levels and amino acid profile of the experimental diets were determined using high-performance liquid chromatography (HPLC, Knauer/smatline Model, Germany). All methods are based on those described in the Association of Official Analytical Chemists, (AOAC, 1990) and modified as described in Aksnes *et al.* (2006).

In the present study, four isonitrogenous (40% crude protein) and isocaloric (3650 kcal/kg digestible energy) diets which differed in terms of histamine levels were formulated considering the nutrient requirements for cold water fish (NRC,1999) (Tables 1&2). Control diet was based on fresh fish meal and contained 1.2 mg/100g histamine, diet 1 contained 25/66% fresh fish meal, 24/34% stale fish meal and 1.6 mg/100g histamine, diet 2 contained 12/5% fresh fish meal, 37/5% stale fish meal and 1.8 mg/100g histamine and diet 3 was free from fresh fish meal and had 50% stale fish meal along with 2.15 mg/100g histamine. The pellet sizes were 3-3.5 mm.

Growth performance

Average weight gain, specific growth rate, condition factor and feed conversion ratio as the most important factors of growth performance along with Hepatic Somatic Index (HIS) were measured in the current study (Espe *et al.*,2008).

Weight gain (gr) = final weight – initial weight

Specific growth rate =

$$\frac{(\text{Ln final weight} - \text{Ln initial weight}) \times 100}{\text{Experimental period (days)}}$$

Condition factor = weight / (length)^3 × 100

Feed conversion ratio = food consumption (gr)/ weight gain (gr).

Hepatic somatic index = (liver weight/carcass weight) × 100.

Blood sampling

At the end of the experiment, 7 fish per tank were euthanized and bled from the caudal vein. Blood samples were transferred into Eppendrof tubes and allowed to clot at room temperature for 1 h. Then samples were kept at 4 ^oC for 5 h. The sera were separated by centrifugation (1500 × g for 5 min at 4 ^oC). The sera samples were stored at -80 ^{C} until required for analysis of immune parameters.

Immune parametrs

In order to evaluate immune parameters the method described by Cuesta *et al.* (2005) was used. 135 µl of HBSS without Ca^{+2} or Mg^{+2} was added to 15 µl of serum sample in each well plate. Finally 50 µl of 20 mM 3, 30, 5, 50-tetramethylbenzidine hydrochloride (TMB) (Sigma) and 5 mM H_2O_2 was added. The color-change reaction was stopped after 2 min by adding 50 µl of 2 M sulfuric acid and the optical density values were read at 450 nm by ELISA reader.

Serum bactericidal activity was measured by slight modification of the method described by Villamil *et al.* (2003). 10^8 ml^{-1} bacterial suspension of *Yersinia ruckery* was prepared in Tryptone soy broth (TSB) and 100 µl of suspension was dispersed into each well plate. After adding 33 µl of serum in triplicate in each well, the mixture was incubated at 18^{o}C for 6 h. For 10 min plate was shaken slightly and then supernatant was discarded. 100 µl of 3-(4, 5-dimethylthiazol-2-yl) 2,5-diphenyltetrazolium bromide (MTT) (0.5 mg ml^{-1}) was added to each well. After 15 min in the dark, the optical density (600 nm) of the viable bacteria was measured.

The level of serum α_1-antiprotease was measured according to Rao and Chakrabarti (2005) with some modifications. In tubes 10 µl of serum sample was diluted with 20 µg of trypsin dissolved in 100 µl of Tris-HCl (50 mM, pH 8.2). All tubes were made up to 200 µl with Tris-HCl and incubated at room temperature for 1 h. Then, 2 ml of 0.1 mM substrate, BAPNA (Na-benzoyl-DL-arginine-p-nitroanilide HCl, Sigma) dissolved in Tris-HCl (containing 20 mM calcium chloride), was added to all tubes and incubated for a further 15 min. Finally the color-change was stopped by adding 500 µl of 30% acetic acid and the optical density was read at 410 nm in a UV-visible spectrophotometer, Spectronic 2OD.

Finally the color-change was stopped by adding 500 µl of 30% acetic acid and the optical density was read at 410 nm in a UV-visible spectrophotometer, Spectronic 2OD.

The level of serum total antiprotease was measured according to Rao and Chakrabarti (2005) with some modifications. In tubes 10 µl of serum was diluted with 20 µg of trypsin dissolved in 100 µl of PBS (pH 7.4). All tubes were incubated at room temperature for 30 min. Then, 1 ml of casein dissolved in PBS (2.5 mg ml^{-1}), was added to all tubes and incubated for a further 15 min. Finally the color-change was stopped by adding 500 µl of 10% trichloroacetic acid. All tubes were centrifuged at 3800 rpm for 10 min to remove the precipitate. The optical density was read at 280 nm in a UV-visible spectrophotometer, Spectronic 2OD and trypsin inhibition was checked.

Serum lysozyme activity was measured using a turbidometric microtitre plate technique according to Tukmechi *et al.* (2011) with slight modification. Briefly, a standard suspension of *Micrococcus lysodeikticus* (75 µg ml^{-1}) was prepared with 0.1 M phosphate citrate buffer, pH 5.8. Rainbow trout serum (25 µl) was added to 75 µl of *Micrococcus lysodeikticus* suspension and the decrease in absorbance after 4 and 9 min at 450 nm. One unit of

lysozyme activity was defined as reduction in absorbance of 0.001 per min.

Plasma total immunoglobulin was determined following the method of Siwicki *et al.* (1994). The difference in total protein content prior to and after precipitation of the immunoglobulin component with 12 % polyethylene glycol (PEG, Sigma) was determined by Bradford method.

Statistical analyses

The effects of experimental diets on growth performance, hepatic indexes and non-specific immune parameters of Rainbow trout were studied using a completely randomized design with four replications of four treatments. The obtained data were analyzed using GLM procedure of SAS software (9.1) and mean comparison was performed using Duncan test.

Results

As it is shown in table 2, statistical analyses of the data revealed that with increasing histamine levels from 1.2 mg/100g to 2.8 mg/100g, no significant differences were observed in weight gain, feed intake and condition factor. On the other hand, feed conversion ratio increased with increasing histamine level and showed significant difference in diet 3 compared with the control diet ($P<0.05$). Specific growth rate is one of the important traits in assessing growth performance of the fish which decreased in experimental diets with increasing histamine level and revealed a significant difference in diet 3 compared with the control diet ($P<0.05$).

Table 1. Composition of experimental fish diets.

	Experimental diets			
Ingredients	(Control)	1	2	3
Fresh Fish Meal	50	25.66	12.5	0
Stale Fish Meal	0	24.36	37.5	50
Fish Oil	7	7.75	9	9.71
Corn	12.48	12	9.62	8.40
Wheat	10	8	8.48	9.64
Soybean Meal	17.27	19	19.65	19
Mineral Premix[1]	0.5	0.5	0.5	0.5
Vitamin Premix[2]	0.5	0.5	0.5	0.5
D-Methionine	0.5	0.5	0.5	0.5
L- Lysine	0.5	0.5	0.5	0.5
Anti Oxidant[3]	0.1	0.1	0.1	0.1
Colin Chloride	0.15	0.15	0.15	0.15
Binder[4]	1	1	1	1
Histamine level				
Histamine (mg/100g)	1.2	1.6	1.8	2.15
Amino acid composition				
Arginine (%)	2.58	2.51	2.4	2.38
Histidine (%)	1.02	1.02	1	0.8
Lysine (%)	3.2	3.1	3.02	3.02
Leucine (%)	3.08	3	3	3
Isoleucine (%)	1.87	1.87	1.86	1.86
Cysteine and Methionine (%)	1.95	1.92	1.93	1.9
Phenylalanine (%)	1.74	1.7	1.6	1.61
Tryptophan (%)	0.93	0.91	0.92	0.9
Valine (%)	2.03	2.01	2.02	2

[1] Mineral Premix (g/kg): zinc, 12.5 g; iron, 26 g; manganese, 15.8 g; copper, 4.2 g; cobalt, 0.48 g; selenium, 2 g; iodine, 1 g.

[2] Vitamin Premix: (mg or IU/kg of diet) Vitamin A (as acetate) 1600000 IU; vitamin D3, 400000 IU; choline chloride.12000; niacin, 4000; riboflavin, 8000; pyridoxine, 4000; folic acid, 2000; vitamin B12, 8000; biotin, 1; inositol, 20000; vitamin C, 60000; vitamin H2, 2.4; vitamin B2, 8000; vitamin K3, 2000; vitamin E,40000.

[3] Butil Hydroxi Anisol

[4] Lignosulfate.

Somatic hepatic index increased with increasing histamine level and differed significantly in diet 3 (P<0.05). According to table 2, levels of lysozyme, peroxidase, antibacterial activity and total immunoglobulin were not affected by experimental diets, but α-antiprotease activity in diets 2 and 3 had a significant difference with that of the control diet (P<0.05). With increasing histamine level, total antiprotease also increased and significantly differed in diet 3 compared with the control diet (P>0.05). Significant increases were also observed in serum total protein so that significant differences became visible in diets 1, 2 and 3 in comparison to the control diet (P<0.05).

Table 2. Nutritional composition of experimental diets.

	Experimental diets			
Ingredients	Control	1	2	3
Dry Matter (%)	90.96	90.98	90.98	91.52
Crude Protein(%)	40.3	40.2	40	40
Crude Fat (%)	16.54	16.98	17.73	20.6
Crude Fiber (%)	2.3	2.98	3.48	3.85
Nitrogen Free extract (%)	24.82	23.52	21.27	17.77
Crude Ash (%)	7	7.3	8.5	9.3
Digestible Energy (Kcal/Kg)	3650	3650	3650	3650

Discussion

In the present study, increasing histamine levels had no significant effect on feed intake, weight gain and condition factor. In other words, these traits were not affected by using stale fish meal containing high levels of histamine. The results of the present study were in accordance with the findings of Fairgrieve *et al.* (1994). It should be taken into account that the decrease in specific growth rate can be due to the withdrawal of essential amino acids such as histidine from bacterial decarboxylation activity of the diets containing stale fish meal.

Table 3. Weight gain, feed intake, feed conversion ratio, specific growth rate and condition factor for rainbow trout fed different diets for 76 days.

Growth Performance	Experimental Diets			
	Control	1	2	3
Weight gain (gr)	354.93±9.31	361.95±2.35	366.88±9.25	370.77±15.63
Feed Intake (gr)	222.09±5.02	221.37±5.37	224.28±3.18	235.10±8.67
Feed Conversion Ratio	$1.00\pm0.032^{b*}$	1.09 ± 0.07^{ab}	1.13 ± 0.03^{a}	1.20 ± 0.047^{a}
Specific Growth Rate (%)	1.67 ± 0.044^{a}	$1.47\pm.086^{ab}$	$1.43\pm.086^{ab}$	1.34 ± 0.051^{b}
Condition Factor	1.420±0.196	1.385±0.070	1.400±0.077	1.530±0.130
Hepatic Somatic Index (%)	1.385 ± 0.023^{b}	1.387 ± 0.043^{b}	1.425 ± 0.065^{b}	1.595 ± 0.027^{a}

* In each row, the means with different letters have significant differences (P<0.05). Values are means± SE for three replications.

In the current experiment, reduced palatability of the food did not result in a decrease in feed intake. To put it another way, increasing biogenic amines such as histamine up to 2.8 mg/100g did not affect feed intake. So, the main cause of the decrease in specific growth rate and increase in feed conversion ratio can be due to amino acid imbalance resulted from bacterial decarboxylation activity. The results of the

present study are in accordance with the findings of Masamuto *et al.* (2000) who investigated the specific growth rate and feed intake of yellow tail fish fed heated fish meal.

The findings of Shiozaki *et al.* (2003) indicated that liver is the involved organ in the excretion of large amounts of dietary histamine and this was what the present study also concluded.

Increasing dietary histamine levels increased somatic hepatic index and a significant difference was observed in diet 3 compared with the control diet and diets 1 and 2 ($P<0.05$). Urinary excretion of high amounts of histamine requires converting histamine to metabolites such as 1-methylhistamine and imidazole acetic acid in liver. As it was seen in the current study, excretion of histamine and its metabolites increases liver function and hepatocytes and as a result leads to an increase in somatic hepatic index.

Table 4. Immune parameters for rainbow trout fed different diets for 76 days.

Immune Parameters	Experimental Diets			
	Control	1	2	3
Peroxidase content (450 nm)	$0.282 \pm 0.005^{a*}$	0.275 ± 0.005^{a}	0.268 ± 0.005^{a}	$0.268 \pm 0.004^{a*}$
Bactericidal activity (600 nm)	0.797 ± 0.042^{a}	0.662 ± 0.025^{a}	0.746 ± 0.032^{a}	0.727 ± 0.039^{a}
α_1-antiprotease (410 nm)	0.037 ± 0.002^{b}	0.045 ± 0.003^{ab}	0.049 ± 0.002^{a}	0.047 ± 0.005^{a}
Total antiprotease (280 nm)	2.370 ± 0.013^{b}	2.387 ± 0.015^{b}	2.431 ± 0.017^{ab}	2.484 ± 0.015^{a}
Total protein (mg ml^{-1})	37.6 ± 1^{c}	41.8 ± 1^{b}	41.5 ± 0.8^{b}	48.3 ± 1.5^{a}
Total Ig (mg ml^{-1})	4.8 ± 0.33^{a}	4.68 ± 1.15^{a}	4.27 ± 0.8^{a}	4.94 ± 0.8^{a}
Lysozyme (U ml^{-1})	3 ± 0.363^{a}	3.111 ± 0.504^{a}	3 ± 0.370^{a}	2.944 ± 0.526^{a}

* In each row, the means with different letters have significant differences ($P<0.05$). Values are means± SE for three replications.

It can be said that increased activity of hepatic catabolism for converting biogenic amines especially histamine resulted in an increase in energy efficiency and consequently a decrease in specific growth rate and an increase in feed conversion ratio.

It should be noted that infected nutrients are directed preferentially toward the immune system. This way, the amino acids are distributed to the liver to synthesize proteins such as proteases and compensate for the low levels of nutrients before infection leads to impairment of the immune response (Brandsen *et al.,* 2001).

In the present study, as a result of using stale dietary fish meal, bio amines such as histamine were increased in fish blood and as a consequence allergic symptoms were observed in fish.

In other words, increasing histamine level in blood had positive feedback on stimulation of the immune system. These stimulations resulted in significant increases in serum total protein as well as α-antiprotease and total antiprotease ($P<0.05$).

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