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Original Article

Expression Profile of Circulatory Adiponectin and Plasma Variables in Broilers

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ABSTRACT

Adipokines serve as a human clinical biomarker and they regulate mammalian metabolic functions. Research on adipokine regulation of metabolic function in avian species is limited. The current study is to investigate the profile of plasma adiponectin and several biochemical variables in broilers, to establish the pattern of development.

A total of one hundred and fifty-two 1-day-old Arbor Acres broilers were separated by different gender and homogenously divided into 2 groups (male and female), with 6 replicate pens and at least 12 chickens per pen. The data for body weight, plasma variables, and feed consumption were collected at days 3, 7, 14, 21, 28 and 35 after hatching. Plasma monomer adiponectin, high-molecular weight (HMW) adiponectin and biochemical variables, including triacylglycerol, total cholesterol, glucose, high-density lipoprotein and low-density lipoprotein were quantified. Monomer adiponectin was highly correlated with age in a negative fashion and with HMW adiponectin in a positive fashion in both genders in broilers. Moreover, body weight was highly correlated with monomer adiponectin in a negative fashion and positively correlated with HMW adiponectin in growing chickens.

It was concluded that monomer adiponectin and HMW adiponectin have highly correlation with age, body weight and biochemical variables in chickens and further investigation is needed for physiological or nutritional functions.

INTRODUCTION

In the late 20th century, many adipokines and their physiological functions were discovered (Lago *et al.*, 2007). White adipose tissue is the main energy store of the body, but is also a source of cytokines that modulate metabolic and immune functions. Although many adipokines are well known in mammals, information about them is lacking in non-mammalian species. Adiponectin is a cytokine secreted from adipocytes consisting of a single peptide with a collagen-like domain and a globular domain (Okamoto *et al.*, 2006). Exogenous administration of adiponectin to mammals decreases blood biochemical variables, such as glucose, free fatty acids and triglycerides; increases muscular fatty acid oxidation and induces weight loss (Fruebis *et al.*, 2001). Reduced adiponectin levels and actions are associated with obesity and type 2 diabetes. Increasing adiponectin signaling and actions reduces diet-induced obesity, inflammation, insulin resistance, cardiovascular diseases, and type 2 diabetes (Turer & Scherer, 2012; Li *et al.*, 2012). This suggests a promising approach for the treatment of metabolic dysregulation diseases.

The chicken adiponectin cDNA is composed of 735 nucleotides and has 65% to 68% homology with mammals (Maddineni *et al.*, 2005;

Yuan *et al.*, 2006). Adiponectin receptors in chicken have high homology with mammals (from 76% to 83%) (Ramachandran *et al.*, 2007). In addition to the chickens, turkeys and geese also express adiponectin and adiponectin receptors (Cao *et al.*, 2015; Diot *et al.*, 2015). There is basic information on the genome of poultry (Burt, 2006). However, the physiological function of adiponectin is still unclear. It is important to explore the function or correlation among adiponectin, chicken manifestations and biochemical values. Our hypothesis is that chicken adiponectin or HMW adiponectin have a correlation with biochemical variables and physiological manifestations, such as body weight and ages. The goal of the current study is to investigate the profiles of plasma adiponectin and its relationship to plasma biochemical variables in growing chickens.

MATERIALS AND METHODS

Animals, treatments, diets and sampling

All chicken experiments were exerted in accordance with animal welfare guidelines and approved by the Institutional Animal Care and Use Committee at Tunghai University (THU, approval no. 106-15).

A total of one hundred and fifty-two 1-day-old Arbor Acres broilers were separated by different gender and homogenously divided into 2 groups (male and female), with 6 replicate pens and at least 12 chickens per pen. The feeding strategy was adapted from the Broiler Management Manual (Arbor Acres, 2012). At each stage (days 3, 7, 14, 21, 28 and 35 after hatching), twelve chickens (both genders) were randomly selected from each pen (2 chickens per pen) and weighed at feeding. The composition and nutrient levels of diets at different stages are presented in table 1. At each stage chickens were sacrificed and plasma was collected for measurement of monomer adiponectin, HMW adiponectin, glucose, total cholesterol, triacylglycerol, high-density lipoprotein and low-density lipoprotein. Peripheral tissues including thigh muscle, abdominal fat and liver were harvested to measure mRNA expression of adiponectin and adiponectin receptor by real-time PCR analysis. Total RNA was extracted and converted to cDNA which procedure was modified by Lin *et al.* (2013).

Measurement of plasma adiponectin profiles and biochemical variables

Blood was drawn from the brachial wing using EDTA as anticoagulant. Plasma samples were prepared by centrifugation (2,000 x g for 15 min, 4 °C). The supernatant fraction was collected and stored at - 80 °C for ELISA analysis. Plasma samples were diluted to appropriate concentrations with saline, and levels of glucose (#3150, Fujifilm, Kanagawa, Japan) triacylglycerol (TG) (#1650, Fujifilm, Kanagawa, Japan), total cholesterol (CHOL) (#1450, Fujifilm, Kanagawa, Japan), high-density lipoprotein (#2650, Fujifilm, Kanagawa, Japan) and low-density lipoprotein (#3450, Denka Seiken, Niigata, Japan) were measured by biochemistry automatic analyzer (FUJI DRI-CHEM NX 500i, Fujifilm Co., Japan). Chicken monomer adiponectin (ADP) and HMW adiponectin were analyzed by commercial ELISA kits according to manufacturer's directions (Ch ADP, E12A0125, and; Ch MADP, E12M0038, Shanghai, BlueGene Biotech). The intra and inter assay coefficient of variability for the adiponectin kits were smaller than 10%.

Table 1 – Diet composition and calculated nutrition levels.

Ingredient (%)	Diet (0-21 days)	Diet (22-35 days)
Yellow corn	51.22	58.80
Soybean meal	40.00	33.00
Soybean oil	4.5	4.49
Choline	0.15	0.15
BHT	0.02	0.02
Dicalcium phosphate	1.65	1.21
Calcium carbonate	1.63	1.60
DL-methionine	0.18	0.08
NaCl	0.35	0.35
Vitamin premix[1]	0.15	0.15
Mineral premix[2]	0.15	0.15
Total	100	100
Calculated value		
ME (kcal/kg)	3340.31	3384.34
Crude protein (%)	23.16	20.41
Total lipid (%)	6.99	7.16
Lysine (%)	1.33	1.14
Methionine (%)	0.60	0.39
Methionine+Cysteine (%)	0.95	0.78
Calcium (%)	1.00	0.91
Nonphytate phosphorus (%)	0.45	0..36

[1]Provided per kg of diet (vitamin): vitamin A, 10,000 IU; vitamin D_3, 2,000 IU; vitamin E, 15 mg; vitamin K, 4 mg; thiamine, 2 mg; riboflavin, 6 mg; pyridoxine, 4 mg; vitamin B_{12}, 0.02 mg; pantothenate, 12 mg; niacin, 40 mg; folate, 1 mg; biotin, 0.02 mg.

[2] Provided per kg of diet (mineral): Zn, 90 mg; Mn, 100 mg; I, 1 mg; Cu, 15 mg; Fe, 90 mg; I, 200 mg; Se, 0.15 mg; Co, 0.25 mg.

Statistical analysis

Data were analyzed using Statistical Analysis Systems software (Version 8.2, SAS Institute, Cary, NC, USA, 2001). Correlation between monomer adiponectin, HMW adiponectin with days of age on both gender was analyzed by Pearson's method. Correlation between monomer adiponectin, HMW adiponectin and biochemical variables were analyzed by Spearman's correlation coefficients. $p \leq 0.05$ (*), $p \leq 0.01$ (**) or $p \leq 0.001$ (***) were considered significant. Data of age with an analysis of covariance (ANCOVA) are presented as mean ± SEM. ANCOVA analysis were used to determine whether gender and body weight have an effect on each variable. Table 2, table 3 and figure 1 were assessed by a one-way ANOVA procedure. The Tukey's multiple comparison test was used to evaluate differences among means. A significant difference was considered at $p \leq 0.05$.

RESULTS

The expression profile of plasma adiponectin in growing broilers

Body and liver weight varied with age, as expected (Table 2). Liver weight increased with age and the ratio of liver weight (LW)/body weight (BW) decreased with age (Table 2).

The plasma level of monomer adiponectin ranged from 2 to 8 μg/mL and HMW adiponectin ranged from 1.5 to 13 μg/mL in growing broilers (Figure 1). The concentration of monomer adiponectin gradually decreased with age, whereas the level of HMW adiponectin increased with age. It should be noted that genders showed that there was no significant effect of blood variables by ANOVA analysis in this trial (data not shown).

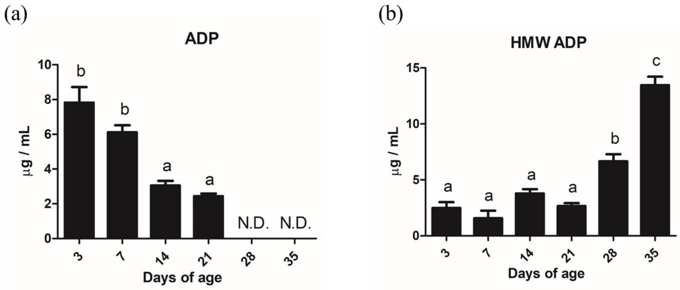

Figure 1 – Chicken plasma levels of adiponectin (a) and HMW ADP (b) in broilers. Data indicated as mean with S.E. represented by vertical bars. Different letters indicate statistical significance. N.D.= non-detectable. (n=25-27).

Table 2 – Body weight, liver weight and ratio of LW/BW in various with age.

Male						
Days of age	3	7	14	21	28	35
N	13	12	12	12	12	12
Body weight (g)	57.26±7.54ᵃ	135.68±20.69ᵃ	400.17±54.64ᵇ	746.50±79.46ᶜ	1220.70±91.60ᵈ	1838.71±208.59ᵉ
Liver weight (g)	2.65±0.48ᵃ	6.21±1.40ᵃ	12.06±1.50ᵇ	19.50±2.46ᶜ	33.98±5.12ᵈ	49.12±2.56ᵉ
Ratio (LW/BW)	0.046±0.006ᵃ	0.046±0.009ᵃ	0.030±0.004ᵇ	0.026±0.002ᵇ	0.029±0.004ᵇ	0.027±0.002ᵇ
Female						
Days of age	3	7	14	21	28	35
N	14	13	13	13	13	13
Body weight(g)	59.74±6.15ᵃ	149.86±20.77ᵃ	369.77±61.51ᵇ	758.00±99.98ᶜ	1124.77±142.54ᵈ	1674.67±168.95ᵉ
Liver weight(g)	3.03±0.38ᵃ	6.17±1.19ᵃ	11.50±1.87ᵇ	18.68±4.65ᶜ	36.59±5.16ᵈ	47.86±8.13ᵉ
Ratio (LW/BW)	0.050±0.006ᵃ	0.042±0.008ᵇ	0.031±0.003ᶜ	0.026±0.005ᶜ	0.033±0.004ᶜᵈ	0.029±0.004ᶜᵈ

Data are expressed as mean ± SE. Different letters indicate statistical significance.

The correlation of plasma adiponectin and biochemical parameters

Table 3 indicated the plasma biochemical values for TG, TCHO, GLU, HDL and LDL at different ages.

Plasma TG decreased with age and then increased at older ages. Plasma TCHO was only elevated at day 3. Plasma glucose was constantly stable. Plasma HDL was elevated at day 3 and again at day 21 and 35. Plasma LDL was elevated at day 3, 28 and 35.

Table 3 – The level of blood biochemical values at different days of age.

Days of age	Blood biochemical values, mg/dL					
	N	TG[1]	TCHO[2]	GLU[3]	HDL[4]	LDL[5]
3	27	156.783±17.6ᵃ	224.870±11.3ᵃ	268.739±10.2ᵃ	68.087±1.3ᵃᵇᶜ	87.000±3.0ᵃ
7	25	108.238±15.7ᵃ	116.810±3.9ᵇ	263.238±12.5ᵃ	65.857±1.5ᵃᵇ	63.095±2.2ᵇ
14	25	73.958±8.0ᵇ	125.208±4.3ᵇ	296.250±11.3ᵃ	64.667±1.3ᵃ	56.750±1.2ᵇᶜ
21	25	59.833±7.0ᵇ	123.625±4.5ᵇ	266.375±8.2ᵃ	74.125±2.3ᵇ	50.875±1.2ᶜ
28	25	143.091±18.9ᵃ	127.182±4.4ᵇ	292.727±4.2ᵃ	62.682±2.4ᵃᶜ	85.773±1.4ᵃ
35	25	164.111±16.8ᵃ	133.05±6.6ᵇ	291.778±5.6ᵃ	67.944±2.2ᵃᵇᶜ	87.778±1.5ᵃ

Values are given as mean ± standard error (SE). [1]TG, triglycerides; [2]TCHO, total cholesterol; [3]GLU, glucose; [4]HDL, high-density lipoprotein; [5]LDL, low-density lipoprotein. Data are expressed as mean ± SE. Different letters indicate statistical significance.

Body weight was highly negatively correlated with monomer adiponectin (r value= -0.8291) and positively correlated with HMW adiponectin (r value=0.7482) (Table 4).

The ratio of liver weight to body weight (LW/BW) was positively correlated with monomer adiponectin (r=0.3304) and negatively correlated HMW adiponectin (r=-0.3202) (Table 4). Plasma TG (r value=-0.3834), GLU (r value=-0.3303) and LDL (r value=-0.6138) were negatively correlated with monomer adiponectin. In contrast, HMW adiponectin was positively correlated with TG (r=0.2869), GLU (r=0.2481) and LDL (r=0.5180) (Table 4).

ANCOVA analysis were used to determine whether gender and body weight have an effect on each variable. The data of ANCOVA are shown in supplemental table 1.

Table 4 – The correlation of ADP, HMW ADP and blood biochemical values.

	LW	TG	TCHO	GLU	HDL	LDL	ADP	HMW ADP	ratio
BW	0.9759**	0.3001**	0.2012*	0.3212**	0.1361	0.4884**	-0.8291**	0.7482**	-0.5521**
LW		0.3519**	0.1966*	0.3564**	0.0988	0.5088**	-0.8439**	0.7405**	-0.4253**
TG			0.2420**	0.4674**	0.0166	0.6233**	-0.3834**	0.2869**	0.1697
TCHO				0.2806**	0.2080*	0.1809	-0.1397	0.0804	-0.0913
GLU					0.0027	0.3041**	-0.3303**	0.2481**	-0.04290
HDL						0.0490	0.0636	-0.0044	-0.2635**
LDL							-0.6138**	0.5180**	0.1341
ADP								-0.6777**	0.3304**
HMW ADP									-0.3202**

BW, body weight; LW, liver weight; TG, triglycerides; TCHO, total cholesterol; GLU, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ADP, adiponectin; HMW ADP, high-molecular weight adiponectin; ratio, LW/BW.

*$p \leq .05$; ** $p \leq .01$

DISCUSSION

Adiponectin functions have been elucidated for two decades in rodents and mammalian species (Scherer *et al.*, 1995). The characteristics of adiponectin and its signaling are also defined, but these features are still unclear in avian species. A study on profiles of adiponectin and plasma variables in growing broilers has not been reported before. We hypothesized that chicken monomer adiponectin or HMW adiponectin have a correlation with biochemical variables and physiological manifestations, such as body weight and ages. And such correlation has been confirmed by our results. These findings can provide a view of the regulation of the basic physiological functions in chicken. The level of circulatory adiponectin is similar to mammalian species (from 1.5 to 13 μg/mL in broilers), and the high molecular weight forms of adiponectin were dominant; consistent with a previous study (Chou *et al.*, 2014; Hendricks *et al.*, 2009). Since adiponectin is secreted by adipose tissue (Okamoto *et al.*, 2006), as the age of the animal increases the amount of fat increases which indicate that adiponectin may have strong correlation with fat mass (Baéza and Bihan-Duval, 2013; Guo *et al.*, 2011). Regarding the fat mass, we did not collect all the fat tissue in the chicken. And according to previous literature, the fat mass increased with age (Baéza and Bihan-Duval, 2013; Guo *et al.*, 2011). Interestingly, we found that the monomeric adiponectin decreased, while the oligomeric HMW form adiponectin increased with age. The fat disulfide-bond-A oxidoreductase-like protein (DsbA-L) is a regulator involved in adiponectin multimerization. Our previous study found that the mRNA expression of DsbA-L increased by high-fat diet feeding which means a larger amount of adipose tissue may have higher HMW adiponectin production (Chen *et al.*, 2018). And young birds are existing monomeric adiponectin majority, which may also impact by DsbA-L. In the current study, we did not observe obvious abdominal fat deposition in chicks within seven days of age which may indicate that the secretion of monomeric adiponectin may be secreted by other adipose tissue, such as jugular subcutaneous fat, femoral subcutaneous fat, heart coronary adipose tissue or gastric adipose tissue. However, the secretory profile of monomeric adiponectin needs to be further analyzed to clarify.

Adiponectin receptors in chicken are expressed in various tissues, such as adipose tissue, skeletal muscle, liver, diencephalon, and reproductive glands (Ocon-Grove *et al.*, 2008; Ramachandran *et al.*, 2013). Chicken Adiponectin receptor 1 is mainly expressed in skeletal muscle, fat and diencephalon; whereas, Adiponectin receptor 2 is predominantly found in adipose tissue. In the current study, we have evaluated the expression profile of adiponectin receptor 1 and 2. However, we did not find the specific pattern of thigh muscle, abdominal fat and liver tissue (data not shown). In addition to the chickens, other poultry species such as turkey and goose also have adiponectin and adiponectin receptors (Cao *et al.*, 2015; Diot *et al.*, 2015). Adiponectin is expressed in varying degrees at different egg production stages of turkeys. At the early stage of spawning, the expression levels of adiponectin and its receptors were relatively higher; the concentration of circulating adiponectin decreased significantly as the egg production decreased during the late egg production stage (Diot *et al.*, 2015).

Broiler chickens grow fast with high feed efficiency, but an adverse effect is obesity with excessive fat accumulation accompanied by poor energy efficiency and consequent increased costs; Laying hens are prone to develop hemorrhagic fatty liver of the peak of egg production, similar to human fatty liver symptoms. Fat accumulation in the liver is a serious problem, causing a decrease in egg production (Tsai *et al.*, 2017). Previous researches use various nutrients to regulate chicken performance and promote energy efficiency. The level of vitamin E in blood is negatively correlated with obesity (Laight *et al.*, 1999; Mayer-Davis *et al.*, 2002). Both vitamin E and adiponectin function to ameliorate insulin resistance (Costacou *et al.*, 2008; Lara-Castro *et al.*, 2007). Treatment with glycine enhances expression of adiponectin in 3T3-L1 cells (Garcia-Macedo *et al.*, 2008). In mammals, adiponectin is regarded as an anti-inflammatory cytokine and improves type 2 diabetes, obesity and atherosclerosis (Oh *et al.*, 2007). Glycine is also an important antioxidant and improves adiponectin expression (Tataranni and Ortega, 2005). There are few reports on the effects of nutrients or feeding strategy on adiponectin signaling in chickens. Regardless, we speculate that there are nutrients that can regulate adiponectin signaling and improve the health of chickens. Restricted feeding (feeding every other day) cause broiler weight loss and a decrease in abdominal fat and adiponectin levels, but these effects are not maintained at 49 days of age (Tahmoorespur *et al.*, 2010). Moreover, a low protein diet (16.3%) increases the expression of adiponectin in 32-day-old broilers, but not in broilers at 49 days of age; raising the energy supply in the diet also increases the expression of adiponectin in abdominal fat (Tahmoorespur *et al.*, 2010). The mRNA expression of adiponectin is decreased in fat, liver and brain tissues after 48 hours fasting in broilers (Maddineni *et al.*, 2005). In this study, we analyzed the profile of mRNA expression in peripheral tissues, including fat, liver and muscle tissues but found no specific pattern for adiponectin related signaling (data not shown).

In general, chicken adiponectin and its receptors have a high degree of homology for DNA and amino acid sequences with mammals, but there are many differences in physiological function (Ramachandran *et al.*, 2007; Chen *et al.*, 2018). The current study supplies values for adiponectin at various stages of growing broilers and further analyzed plasma biochemical variables and their correlation with plasma adiponectin.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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