UNIVERSITI PUTRA MALAYSIA

ACUTE PHASE PROTEINS, HEAT SHOCK PROTEIN AND OTHER BLOOD PARAMETERS AS PHYSIOLOGICAL INDICATORS OF STRESS IN POULTRY

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By

PARDIS NAJAFI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirement for the Degree of Doctor of Philosophy

February 2016

DEDICATION

I dedicate this thesis to my husband, Faraz, for his remarkable patience, unconditional love and support during the challenges of my research, and also for the unlimited helps of daddy day care to our beautiful son, Ryan, during my last months of writing. This work is also dedicated to my beloved parents for their endless support and encouragement at my life. Without whom I would have struggled to find the inspiration and motivation needed to complete this thesis.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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Chair: Professor Zulkifli Idrus, PhD
Institute: Institute of Tropical Agriculture

Experiments were conducted to explore physiological aspect of stress in chickens. Acute phase proteins (APPs), heat shock protein (HSP) 70 and other blood parameters responses to various stressors were investigated. Activation of APPs by nonpathogenic stimulus is still unclear in poultry species. Thus, this research was conducted to elucidate the relationship between stress and APPs response in poultry. In Chapter 3, an experiment was conducted to determine the effect of corticosterone (CORT) administration on serum ovotransferrin (OVT), α1-acid glycoprotein (AGP), ceruloplasmin (CP), and IL-6 concentrations, and brain heat shock protein (HSP) 70 expression in broiler chickens. From 14 to 20 day (d) of age, equal numbers of birds were subjected to either (i) daily intramuscular injection with CORT in ethanol:saline (1:1, vol/vol) at 6 mg/kg of BW, or (ii) daily intramuscular injection with 0.5 mL ethanol:saline (1:1, vol/vol; control). Blood samples were collected before CORT treatment (14 d old), 3 and 7 d after CORT injections, and 4 d after cessation of CORT administration for determination of serum levels of CORT, OVT, AGP, CP, and IL-6. Brain samples (whole cerebrum) were collected to measure HSP70 density. Although CORT administration significantly increased feed intake, weight gain was significantly decreased. Administration of CORT also increased CORT, OVT, CP, AGP, IL-6, and HSP70 expression. Four days following cessation of CORT administration, OVT declined to the basal level but not CP and AGP. An elevation in CORT can induce an APR and HSP70 expression. In Chapter 4, effect of feed deprivation on serum CORT, OVT, AGP and CP concentrations in broiler chickens was investigated. At 21 days of age, birds were subjected to one of five feed deprivation periods: (i) 0 h (*ad libitum*) (AL), (ii) 6 h, (iii) 12 h, (iv) 18 h, (v) 24 h, and (vi) 30 h. Upon completion of the deprivation period, blood samples were collected to determine CORT, OVT, AGP and CP. Results showed that feed deprivation for 24 h or more caused a marked elevation in CORT when compared to AL. However, significant increases in AGP, CP and OVT were only noted following 30 h of feed deprivation. Thus, elicitation of AGP, CP and OVT response may represent a more chronic stressful condition than CORT response in assessing the well-being of broilers. In Chapter 5, effect of different stocking densities

on serum CORT, OVT, AGP and CP concentrations, brain HSP70 expression and performance in broiler chickens exposed to unheated and heated conditions was determined. Day-old chicks were stocked at 0.100m2/bird (low density (LD)) or 0.063m^2/ bird (high density (HD)), in battery cages and housed in environmentally controlled rooms. From 21 to 35 days of age, birds from each stocking density group were exposed to either 24 or 32 °C. Growth performance was recorded during the heat treatment period, and blood and brain samples were collected to determine CORT, OVT, AGP, CP and HSP70 levels on day 35. Heat treatment but not stocking density was detrimental to growth performance. There were significant temperature×density interactions for CORT, CP and OVT on day 35. Although HD elevated CORT, CP and OVT when compared to LD, the effects of the former were more obvious under heated condition. Both temperature and density had significant effect on AGP and HSP70. In conclusion, irrespective of temperature, high stocking density was physiologically stressful to broiler chickens, as indicated by CORT, AGP, CP, OVT and HSP70, but not detrimental to growth performance and survivability. So AGP, CP and OVT could be useful biomarkers to determine the effect of overcrowding and high temperature on the welfare of broiler chickens. In Chapter 6, an experiment was conducted to determine the physiological response to feed restriction in female broiler breeders using a range of conventional and novel indicators. One hundred female breeders were subjected to one of five feeding regimens from d 28-42 as follows (i) *ad libitum* feeding (AL), (ii-v) 75, 60, 45 and 30% of *ad libitum* feed intake. Blood heterophil to lymphocyte ratio (HLR), and plasma circulating CORT, ghrelin (GHR), serotonin (5-HT) and dopamine (DA), and serum acute phase proteins (APP) concentrations, and brain HSP70 level were measured. The results showed a significant effect of feed restriction on blood HLR and plasma CORT, GHR, 5-HT, DA and brain HSP70 levels. However, feed restriction had no effect on serum levels of APP such as AGP, OVT and CP. Serum levels of 5-HT and GHR varied curvilinearly with the feed restriction level. The relationship between brain HSP70 and level of feed restriction was negligible. However, significant linear relationships between HLR, CORT, DA and level of feed restriction were noted. Thus, these three parameters appear to represent a straight forward relation with severity of feed restriction. In Chapter 7, the effect of inhibiting adrenal steroidogenesis on serum CORT, OVT, AGP and CP, IL-6 concentrations and brain HSP70 expression was elucidated in broiler chickens subjected to feed deprivation for 24 hours. On days 4, 5, and 6, equal numbers of birds were assigned to either *ad libitum* feeding (AL) or (2) 60% of *ad libitum* feed intake (60FR). On day 35, equal number of AL and 60FR birds were subjected to (i) *ad libitum* feeding (ALF), (ii) 48 h feed restriction (SFR), or (iii) 24 hours feed restriction with intramuscular injection of 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethane (DDT) (an adrenal blocker) dissolved in corn oil at 100 mg/kg BW (SFR+DDT). The birds were injected with DDT 12 h prior to feed deprivation. Following feed withdrawal, samples were collected to determine CORT, OVT, AGP, CP, IL-6 and HSP70 levels. The earlier feeding regimen had no significant effect on CORT, AGP, OVT, CP, IL-6 and brain HSP70 concentration on day 36. The CORT, AGP, OVT, CP, IL-6 and brain HSP70 density of SFR birds following 24 h (day 36) of feed deprivation were significantly higher than their ALF and SFR+DDT counterparts. However, both ALF and SFR+DDT birds had similar values. It can be concluded that stress without concurrent elevation in the circulating level of corticosterone may not elicit APP, IL-6 and HSP 70 reactions. The linear relationship between DA and level of feed restriction suggests that this neurotransmitter is a potential marker of stress magnetite in feed restricted breeders. Serum levels of 5-HT and GHR are not clear indicators of feed restriction level.

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ACUTE PHASE PROTEIN, HEAT SHOCK PROTEIN DAN PARAMETER DARAH LAIN SEBAGAI PENUNJUK FISIOLOGI TEKANAN POLTRI

Oleh

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Februari 2016

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Beberapa eksperimen dijalankan untuk mengkaji aspek fisiologi stress pada ayam. Respon penghasilan acute phase protein (APP), heat shock protein (HSP) 70 dan parameter darah lain terhadap pelbagai faktor stress dikaji. Walaubagaimanapun, penghasilan respon acute phase oleh rangsangan bukan patogenik bagi spesies ayam adalah masih tidak jelas. Oleh itu, kajian ini dijalankan untuk menjelaskan hubungan antara stress dengan penghasilan APP dalam ayam. Dalam Bab 3, satu eksperimen telah dijalankan untuk mengkaji kesan suntikan corticosterone (CORT) kepada penghasilan ovotransferrin (OVT), a-1-acid glycoprotein (AGP), ceruloplasmin (CP), IL-6 dan heat shock protein (HSP) 70. Ketika ayam berumur 14 hingga 20 hari, sebilangan ayam dengan jumlah yang sama telah disuntik setiap hari samada (i) dengan CORT dalam larutan ethanol:saline (1:1,vol/vol) sebanyak 6mg/kg berat ayam, atau (ii) dengan 0.5 mL ethanol:saline (1:1,vol/vol;kawalan (control). Sampel darah diambil sebelum CORT disuntik (hari ke-14), dan juga hari ke-3 dan 7 selepas suntikan CORT dilakukan. Sampel otak (keseluruhan serebrum) diambil untuk mengukur penghasilan HSP 70. Walaupun suntikan CORT menyebabkan kenaikan pengambilan makanan, tetapi ia menyebabkan kadar kenaikan berat badan merosot. Suntikan CORT juga telah menambah pengeluaran CORT, OVT, CP, AGP, OVT, IL-6 dan HSP70. Empat hari sebelum terhentinya penyuntikan CORT, penghasilan OVT telah menurun tetapi tidak bagi CP dan AGP. Peningkatan jumlah CORT telah merangsang penghasilan APR dan HSP70. Dalam Bab 4, kesan pengurangan makanan ke atas jumlah CORT, OVT, AGP dan CP telah dikaji. Ayam yang berusia 21 hari telah dibahagikan kepada 5 tempoh sekatan makanan berbeza, iaitu samada selama; (i) 0 jam (*ad libitum*) (AL), (ii) 6 jam, (iii) 12 jam, (iv) 18 jam, (v) 24 jam, atau (vi) 30 jam. Setelah tamat tempoh sekatan, sampel darah diambil untuk mengukur jumlah CORT, OVT, AGP dan CP. Keputusan menunjukkan bahawa sekatan makanan selama 24 jam atau lebih telah menyebabkan kenaikan CORT, berbanding kumpulan AL. Walaubagaimanapun, peningkatan AGP, CP dan OVT hanya dilihat apabila sekatan makanan dijalankan selama 30 jam. Oleh itu, dalam menilai tahap kesejahteraan ayam, respon penghasilan AGP, CP dan OVT dapat menjadi penunjuk bagi stress yang lebih kronik, berbanding dengan respon penghasilan CORT. Dalam Bab 5, eksperimen dijalankan untuk mengkaji kesan kepadatan berbeza terhadap jumlah CORT,OVT, AGP, CP, HSP70 dan prestasi pertumbuhan bagi ayam yang didedahkan

kepada persekitaran biasa dan panas. Ayam berumur satu hari telah ditempatkan di dalam sangkar bersuhu normal dengan kepadatan 0.100 m^2/ekor (kepadatan rendah (LD)) atau kepadatan 0.063 m^2/ekor (kepadatan tinggi (HD)). Ketika berumur 21-35 hari, ayam daripada setiap tahap kepadatan didedahkan samada 24 atau 32 °C. Prestasi pertumbuhan ayam direkod sepanjang tempoh pemanasan dan sampel darah dan otak diambil untuk mengukur jumlah CORT, OVT, AGP, CP dan HSP70 pada hari ke-35. Faktor suhu memberi kesan negatif kepada pertumbuhan ayam, tetapi tidak bagi faktor kepadatan. Terdapat interaksi antara suhu dengan kepadatan bagi CORT, CP dan OVT pada hari ke-35. Walaupun HD telah menyebabkan kenaikan CORT, CP dan OVT berbanding LD. Kedua-dua faktor suhu dan kepadatan telah memberi kesan kepada AGP dan HSP70. Kesimpulannya, kepadatan yang tinggi telah menyebabkan stress fisiologi pada ayam, sepertimana yang telah dibuktikan oleh penghasilan CORT, AGP, CP, OVT dan HSP70, tetapi ia tidak memberi kesan yang memudaratkan kepada pertumbuhan dan kebolehan ayam untuk meneruskan kelangsungan hidup. Dalam Bab 6, eksperimen dijalankan untuk mengkaji respon fisiologi ayam pedaging betina dengan menggunakan pelbagai penunjuk-penunjuk konvensional dan baru. Seratus ekor ayam baka telah dibahagikan kepada 5 cara pemakanan, iaitu samada (i) secara *ad libitum* (AL) (ii-v) *ad libitum* hanya sebanyak 75, 60, 45 dan 30% daripada pengambilan makanan. Ratio heterofil:limfosit (HLR) dan plasma CORT, ghrelin (GHR), serotonin (5-HT) dan dopamine (DA) dan tahap serum APP telah dikaji. Keputusan menunjukkan bahawa sekatan makanan memberi kesan kepada HLR darah dan jumlah plasma CORT, GHR, 5-HT, DA dan HSP70. Walaubagaimanapun, ia tidak memberi kesan kepada jumlah pengeluaran serum APP; AGP, OVT dan CP. Tahap penghasilan 5-HT dan GHR bercanggah secara linear dengan tahap sekatan makanan. Penghasilan HSP70 tiada kaitan dengan tahap sekatan makanan. Walaubagaimanapun, terdapat hubungan linear antara penghasilan HLR, CORT dan DA dengan tahap sekatan makanan. Oleh itu, tiga parameter ini dapat menjadi penunjuk yang agak tepat bagi menerangkan tahap keseriusan sekatan makanan. Dalam Bab 7, kesan penghalangan 'adrenal steroidogenesis' terhadap penghasilan CORT, OVT, AGP, CP, IL-6 dan HSP70 telah dikaji dalam ayam pedaging yang dikenakan sekatan makanan selama 24 jam. Pada hari 4, 5 dan 6, sejumlah ayam telah dibahagikan kepada salah satu cara pemakanan iaitu samada (1) pemakanan secara *ad libitum* (AL) atau (2) *ad libitum* sebanyak 60% daripada pengambilan makanan (60FR). Pada hari ke-35, ayam berjumlah sama daripada kedua-dua kumpulan AL dan 60FR dibahagikan kepada (i) pemakanan secara *ad libitum* (AFL) (ii) sekatan makanan selama 24 jam (SFR) atau (iii) 24 jam sekatan makanan disertai dengan suntikan 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethane (DDT) dalam larutan minyak jagung, iaitu sebanyak 100mg/kg berat ayam (SFR+DDT). Ayam-ayam tersebut telah disuntik dengan DDT, 12 jam sebelum sekatan makanan dijalankan. Selepas makanan dikeluarkan, sampel diambil untuk mengukur CORT, OVT, AGP, CP, IL-6 dan HSP70. Rejim pemakanan yang terdahulu tidak memberi kesan kepada CORT, AGP, OVT,CP, IL-6 dan HSP70 pada hari ke-36. Jumlah CORT, AGP, OVT, CP, IL-6 dan HSP70 bagi ayam SFR ,selepas sekatan makanan selama 24 jam (hari ke-36) adalah lebih tinggi berbanding dengan ayam ALF dan SFR+DDT. Walaubagaimanapun, tiada perbezaan dari segi nilai jika dibandingkan ALF dan SFR+DDT. Dapat disimpulkan bahawa, stres tanpa diikuti dengan kenaikan paras corticosterone tidak dapat merangsang penghasilan APP, IL-6 dan HSP70. Hubungan linear antara DA dan tahap sekatan makanan menunjukkan bahawa neurotransmitter ini adalah penanda berpotensi untuk ayam pembiakbaka yang disekat pengambilan makanannya. Tahap serum 5-HT dan GHR bukan petunjuk jelas untuk tahap sekatan makanan.

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I certify that a Thesis Examination Committee has met on 19th of February 2016 to conduct the final examination of Pardis Najafi on her thesis entitled "ACUTE PHASE PROTEINS, HEAT SHOCK PROTEIN AND OTHER BLOOD PARAMETERS AS PHYSIOLOGICAL INDICATORS OF STRESS IN POULTRY" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U. (A) 106] 15 March 1998. The Committee recommends that the student be awarded the degree of Doctor of Philosophy (PhD).

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LIST OF ABBREVIATIONS

µl	Micro Litter
60FR	60% of *Ad Libitum* Feed Intake
ACTH	Adrenocorticotropic Hormone
AGP	Alpha-1-Acid Glycoprotein
AL	*Ad Libitum*
ALF	*Ad Libitum* Feeding
ANS	Autonomic Nervous System
APP	Acute Phase Protein
APR	Acute Phase Response
BW	Body Weight
CNS	Central Nervous System
CORT	Corticosterone
CP	Ceruloplasmin
CRH	Corticotropin-Releasing Hormone
CRP	C-reactive Protein
DDT	1,1-bis(4-chlorophenyl)-2,2,2-trichloroethane
FB	Fibrinogen
FCR	Feed Conversion Ratio
FR	Feed Restriction
G	Gram
GC	glucocorticoid
GR	Glucocorticoid Receptor
H	Hours
HD	High Density
HLR	Heterophil to Lymphocyte Ratios
HP	Haptoglobin
HPA	Hypothalamic-Pituitary-Adrenal Axis
HSP	Heat Shock Protein
IL-6	Interleukin-6
LD	Low Density
Mg	Mili Gram
Mm	Mili Litter
MR	Mineralocorticoid Receptor
Nm	Nano Meter
OVT	Ovotransferrin
Pig-MAP	Pig-Major Acute Phase Protein
PVN	Paraventricular
RBP	Retinol Binding Protein
ROS	Reactive Oxygen Species
SA	Sympatho-Adrenal
SAA	Serum Amyloid A
SFR	24 Hours of Feed Restriction
SON	Supraoptic Nucleus
TF	Transferrin
TTR	Transthyretin

CHAPTER 1

GENERAL INTRODUCTION

The commercial broiler chickens which have undergone intensive genetic selection for rapid growth are among the fastest-growing farmed animal species. However, selections for rapid growth and heavy musculature have been associated with the risks of behavioral, physiological and immunological problems. The incidences of non-infectious bone and joint disorders, metabolic disorders, and cardiovascular diseases in broiler chickens are related to rapid growth (Julian, 2005; Mench, 2004). In general, the environment of a broiler chicken is a composite of interacting stressors that, in the broadest sense, can include all conditions in which the bird lives - external (temperature, light, social, human-animal interactions), as well as internal (disease organisms, toxins). There are many conditions under which poultry live and the husbandry procedures to which they are subjected may compromise their welfare. Some of the major concerns are feed restriction in meat-type chickens used for breeding stock, overcrowding, handling and transportation, behavioral restriction, and excessive production stress. Hence, there are major issues about the welfare of the intensively-raised broiler chickens.

The welfare of an animal refers to its quality of life, and this involves many different elements such as health, happiness, and longevity, to which different people attach different degrees of importance (Fraser, 1995). Broom (1996) described animal welfare as the state of animal's efforts to cope with the environmental challenges. An animal's success in coping with its environment thus depends on the severity and its physiological ability to respond appropriately. The animal's welfare is at risk when it fails to cope or having difficulty to cope and the term "stress" is used to describe this phenomenon. Stress can be defined as an environmental effect on an individual which over-taxes its control systems and reduces its fitness or seems likely to do (Broom and Johnson, 1993).

A central issue in animal welfare research is how the welfare state of an individual animal can be assessed scientifically. The general methods that can indirectly measure the welfare of farm animals are productivity, health, behavior and physiology. Some measurements are more relevant to evaluate short-term problems, whereas others are more suitable to long-term problems. Physiological assessments are based on a variety of body processes which reflect the function of physiological systems involved in the animal's response to stressors. One of the best known and consistent physiological responses to stress is the activation of the neuroendocrine system which result in increased secretion of glucocorticoids from the hypothalamic-pituitary-adrenal axis (HPA) into the blood and increased activity of the autonomic nervous system, resulting in increased circulating levels of adrenaline and noradrenaline (Zulkifli and Siegel, 1995). Both of these activations are important to prepare an animal to respond to environmental insults. Many researchers have attempted to assess the welfare of poultry by measuring circulating levels of corticosterone (CORT). However, changes in CORT per se may not suggest poor welfare (Barnett and Hemsworth, 1990). It may indicate continuous adjustment to maintain homeostasis. Moberg (2000) stated that only change in normal function as a result of chronic elevation in CORT duri\ng stress may compromise welfare. In their review, Otovic and Hutchinson (2015) concluded that

although determining CORT may provide useful information there were circumstances where changes in the hormone concentration were inconsistent with putative stress levels. Hence, to address questions about animal welfare in a more holistic approach, a combination of several physiological indices and changes at molecular or cellular would be necessary.

When living organisms are exposed to thermal and non-thermal stressors, the synthesis of most proteins is retarded, but a group of highly conserved proteins known as heat shock proteins (HSP) are rapidly synthesized (Soleimani *et al.,* 2011b) . In a heat shock cell, the HSP may bind to the protein to protect them from degradation, or may prevent damaged protein from immediately precipitating and permanently affecting cell viability (Etches *et al.,* 1995). Heat shock proteins have been shown to play a profound role in regulating a key role in regulating protein folding and in coping with proteins affected by heat and other stresses (Gething and Sambrook, 1992). Work in chickens indicated that feed restriction (Zulkifli *et al.,* 2002; 2011 Soleimani *et al.,* 2011b), crating and road transportation (Al-Aqil and Zulkifli *et al.,* 2009), and social isolation (Soleimani *et al.,* 2012b) augmented HSP70 expression.

The acute phase response (APR) is the non-specific and also early systemic response of the inherent immunity reaction to disorders such as infection, trauma, and inflammation that leads to re-establishment of homeostasis and also healing (Gruys *et al.,* 2005; Cray *et al.,* 2009; Pineiro *et al.,* 2007). During the first few hours of an APR, there are measureable changes in the concentration of different plasma proteins named as acute phase proteins (APP) (Gruys *et al.,* 2005). The circulating concentrations of APP may be associated with severity of the disturbance and also the extent of tissue damage.). It is well-known that in humans and experimental animals, psychological and physical stress may increase plasma interleukin-6 (IL-6) and APP levels (Deak et al., 1997; Nukina et al., 2001). Thus, measurement of APP concentration can provide useful prognostic and diagnostic useful information in animals. In poultry, the major APPs included ceruloplasmin (CP), ovotransferrin (OVT) and Alpha-1-acid glycoprotein (AGP). CP is synthesized by hepatocytes and protects different tissues from the iron-mediated free radicals injury and also is associated with various cytoprotective and antioxidant and activities (Patel *et al.* 2002). OVT is classified as positive APPs that increase in response to challenges however, is considered as negative APP. OVT is involved to innate immune system by decomposition of ferric irons that prevents of parasites and pathogens from using nutrients (Law, 2002). AGP is considered as a serum indicator for detection of infection problems in poultry, when the infection severity is aggravate by stress (Holt and Gast, 2002).

Stresses such as transportation, high stocking density weaning, mixing with unfamiliar individuals and housing on slippery floors have been reported to increase serum concentrations of APP in livestock (Alsemgeest *et al.,* 1995; Murata *et al.,* 2004; Pineiro *et al.,* 2007; Qiu *et al.,* 2007; Shakeri *et al.,* 2014). However, to the best of my knowledge, although the avian APR during inflammation and infection has been well documented (Chamanza *et al.*, 1999; O'Reilly and Eckersall, 2014), little information is available on the effect of stress on APP reaction in poultry. Recently, Shakeri *et al.* (2014) reported that overcrowding evoked APP reaction in broiler chickens. Further

studies are necessary to elucidate the relationship between stress and APP response in poultry.

Therefore, the objectives of this study were:

(1) to assess the response of APP and HSP70, in comparison to other physiological, to various environmental stressors in chickens.

(2) to elucidate the underlying respond responsible for the elicitation and regulation pathway of APP in chickens subjected to environmental stressors.

(3) to investigate the onset of change, duration and magnitude of elevation of APP and other physiological parameters in response to environmental stressors.

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