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Genetic Variation in Resistance to Inflammation and Infectious Disease

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1. Introduction

Genes determine functions of the neuroendocrine and immunological systems that affect an animal's ability to cope with stress, resulting in resistance or susceptibility to infection and inflammation. In this study, genetic variation in responses to lipopolysaccharide (LPS) challenge was examined in chicken lines divergently selected for high (HGPS) and low (LGPS) group productivity and survivability resulting from cannibalism and flightiness in colony cages and in a Dekalb XL (DXL) commercial line selected individually for egg production. Six-week-old chicks were randomly assigned to control or experimental groups and were injected intravenously with *Escherichia coli* LPS (5 mg/kg BW) or distilled saline (control). Sickness responses were measured at 6, 12, 24, 48, and 72 h following injection (n=10/at each point in time for each line). Although LPS induced widespread sickness symptoms in all of the treated chicks, the reactions were in a genotypic- and phenotypic-specific manner. Compared to both LGPS and DXL chicks, HGPS chicks had acute, transient behavioral and physical changes with less effect on body weight (BW) gain and organ development as well as core temperature, which were in the order HGPS<DXL<LGPS. The effects of heritable factors and LPS challenge on the differential responses among the present lines may reflect each line's unique adaptability to stress and resistance to infection and inflammation. The results suggest that the present chicken lines may provide a new animal model for biomedical investigation on the effects of genetics, epigenetics, and gene-environmental interactions on physiological homeostasis in response to stress and inflammatory disorders as well as infectious disease.

2. Aging and inflammation

Aging is a complex biological process characterized by decline of the functions of various biological systems through the lifetime in an organism. Especially, the decline in the functions of the immune system results in an immune-senescence status (i.e., the coexistence of inflammation and immunodeficiency), with a low-grade chronic inflammation (so called inflamm-aging effect) (Franceschi et al., 2000; Gruver et al., 2007; Salvioli et al., 2006). In humans, inflamm-aging is characterized by the up-regulation of the inflammatory response, resulting in over expressing pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-12, tumor necrosis factor (TNF)-alpha, and interferon (IFN)-alpha and IFN-beta

(Bruunsgaard and Pedersen, 2003; Salvioli et al., 2006). The aging process also causes an increase in cortisol concentrations due to over activation of the hypothalamus-pituitary-adrenal (HPA) axis by various specific and non-specific stressors (Sergio, 2008). Aging-associated changes in immunity and stress reaction systems increase the risk of infection and promote inflammation, which underlies the biological mechanisms of age-related inflammatory diseases (Agrawal et al., 2010; Cevenini et al., 2010; Chung et al., 2011). Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the elderly for the treatment of fever, headache, pain, and pain associated with inflammation (Table 1). However, aging-associated physiological changes, such as alterations in pharmacokinetics and impaired homeostasis, and drug interactions, lead to worse the side-effects profile of NSAIDs (Bennett, 1999; Buffum and Bufum, 2000).

Common drugs	Characteristics of Aging	Common treatments	Impact of NSAIDs during aging ^{1,2}
Nonselective NSAIDs	a low-grade systemic	Pain, fever, headache	Gastrointestinal tract: ulcers and bleeding
Salicylates	Inflammation with increased	Inflammation in rheumatoid	Renal tract: acute renal impairment
Propionic acid derivatives	Pro-inflammatory cytokines	Arthritis and osteoarthritis	Liver: hepatotoxicity
Acetic acid derivatives	such as IL-1, -6, -12, TNF-α	Neuromuscular disorder	Others: cardiovascular, hematological
Enolic acid derivatives	and overexpression of free	Musculoskeletal conditions	and CNS effects and photosensitivity
Fenamic acid derivatives	Radicals, such as NO and ROS	and Alzheimer’s disease	
Selective NSAIDS	and CRP, contributing to		
Celecoxib	Neurodegenerative diseases		

¹, The common side-effects of NSAIDs in the elderly persons, resulting from, a few examples, age-related alterations in pharmacokinetics, impaired homeostasis, and drug interactions.
², The information presented in the table is summary from the following references: Bennett, 1999; Buffum and Buffum, 2000; Candore et al., 2010; Capone et al., 2010; Gruver et al., 2007; Johnson and Day, 1991; Lipton et al., 2007; Maroon et al., 2010; McGeer and McGeer, 2004; Menkes, 1989; Salvioli et al., 2006; Sastre and Gentleman, 2010; Sherman et al., 2005; Tiihonen et al., 2008.
COX = cyclooxygenase; CRP = C-reactive protein; IL = interleukin; NO = Nitric oxide; NSAIDs = Nonsteroidal anti-inflammatory drugs; ROS = Reactive oxygen species.

Table 1. The impact of common anti-inflammation dugs during aging and age-related inflammatory disorders

2.1 Inflammation and stress

Inflammation has been termed as: a localized protective response to various harmful stimuli, such as tissue injury or pathogens invasion, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissue. Recently, inflammation has also been

defined as a balanced biological process between apoptosis ('Yin') and wound healing ('Yang') for acute inflammation; and lost of the balance for chronic inflammation, i.e., mismatched the biological signals during apoptotic and wound healing processes, resulting in disrupting the protective mechanisms of the immune system (Khatami, 2008, 2011). In general, inflammation, as a part of the evolutionary program, is a critical defense mechanism to pathogenic viruses and bacteria; and inflammatory response is a non-specific response of the tissues of an organism. Normally, inflammation facilitates the organism to return to physiological homeostasis to permit survival while uncontrolled inflammatory response contributes to chronic conditions of pathophysiological changes seen during aging (Vasto et al., 2007).

Stress is defined as: any disruption of an animal's homeostatic equilibrium requiring the animal to make some response to maintain its psychophysiological integrity (Hurnik et al., 1995). Stress and inflammatory response evoke the similar somatosensory pathways to signal the brain, and then the brain sends integrated information to the subcortical centers, such as the hypothalamus, regulating final active organs, such as immune cells (T and B lymphocytes and macrophages) and the adrenal glands to regulate the organism's immune and stress responses (Carrier et al., 2005; Sternberg, 2006; McNaul et al., 2010).

Inflammatory response has been considered as a part of stress response. There is a bilateral communication between the immune and neuroendocrine systems (Turnbull et al., 1999; Cohen and Cohen, 1996). For example, various internal and external specific and non-specific stressors induce an increase in releasing cytokines from immune cells during the aging process. The released cytokines bind to their receptors on neurons, affecting the activity of the HPA axis, causing an increase in cortisol concentrations with age. Cortisol, at a physiological level, acting as a potent immune regulator and an anti-inflammatory agent, is necessary for reducing tissue damage and injury. Age-related increase in cortisol concentrations, causing an imbalance between inflammatory response and anti-inflammatory networks, is a major determinant of immune-senescence observed during aging (Bauer, 2008). Immune-senescence, resulting from lifelong chronic antigenic load (allostatic load), leads to a low-grade chronic pro-inflammatory status. Previous studies have evidenced that the antigenic load to individuals exposed throughout lifetime impacts greatly on immune performance and stress response in late life (Pawelec and Larbi, 2008). Due to inherent differences in the capability to maintain physiological homeostasis in response to internal and external stimuli, the interaction of environmental factors with genetic variations determines the phenotypes of the aging process in organisms.

2.2 Inflammation and genetic characters

Aging process and rate of age-associate diseases in humans and other animals is not uniform. It is depended on internal (genetic heterogeneity) and external (environment) factors (Vogt et al., 2008; Turko et al., 2011). There are two types of genetic variations affecting the aging process and susceptibility, progression, and severity of aging diseases: 1) the gene sequence (genotype or phenotype) and 2) the modifications of DNA and DNA associated proteins (epigenetics).

Genes regulate patterns of cellular processes and determine the functions of the immune and neuroendocrine systems in controlling an animal's coping strategy and productivity. There are genetic basis in variations of the polymorphism in the promoter regions of the genes encoding pro-inflammatory cytokines and inflammatory mediators (Loktionov, 2003;

Naumova et al., 2004; Pes et al., 2004). Genetic background has been proposed as a major contributor for the differences in stress response within and among species (intra- and inter-individuals' difference) (Knight, 2005; Pastinen and Hudson, 2004). Molecular basis of low-grade, sub-clinical inflammation is a major risk factor for exacerbating the aging process and its associated disease.

Inheritance is not restricted to DNA sequence. Epigenetics plays a key role in producing viable offspring by passing epigenetic information to progeny (Migicovsky and Kovalchuk, 2011). Similarly, during aging process, a chronic low-grade inflammation status is also related to a trans-generational gene expression via heritable epigenetic mechanisms (vel Szic et al., 2010). Epigenetics means 'above the genetics', used to define the change in gene expression occurring without a change in primary DNA sequence (Lu et al., 2006; Duff, 2007; Mill J 2011). There is growing evidence that epigenomic variability mediates the variation in susceptibility to various diseases during the aging process (Hatchwell and Greally, 2007; Tang and Ho, 2007). Several epigenetic mechanisms associated with phenotypic variations have been identified, including DNA methylation (epimutations), histone modifications, and RNA-mediated pathways from non-coding RNAs, notably silencing RNA (siRNA) and microRNA (miRNA) expression (Wilson 2008; Baccarelli and Bollati, 2009; Krishna et al., 2010). Epigenetic changes are heritable across generations and under environmental influence. Environmental factors, such as lifestyle choices, may result in conflict with the programmed adaptive changes or genomic imprinting made during early development, leading to disease in later life, especially those involving the inflammatory diseases (Petronis, 2001; Pearce et al., 2006; Bayarsaihan, 2011).

2.3 Lipopolysaccharide (LPS) and inflammation

Lipopolysaccharide (LPS) is an integral component of the outer membrane (cell wall) of Gram-negative bacteria. Lipopolysaccharide as an endotoxin, is ubiquitous in the external environment; and, as a "hormone", is released from the gastrointestinal tracts in response to a variety of stressors. In a host, LPS, invaded from outside or absorbed from the gastrointestinal tracts, binds to the host's plasma proteins, such as albumin and soluble CD14, to form monomeric particles. The monomeric particles interact with specific surface receptors of host cells, such as Toll-like receptor 4 (TLR4), to activate the intracellular signaling pathways to initiate gene transcription to disrupt the host's innate immune system, resulting in local and or systemic inflammatory reactions (Alexander and Rietschel, 2001; Fessler et al., 2002). Previous studies have shown that LPS induces release of pro-inflammatory cytokines, adhesion molecules, and acute phase reactants from various cells of the innate immune system, stress hormones, such as CRF and cortisol, from the HPA axis, and catecholamines, i.e., epinephrine and norepinephrine, from the autonomic nervous system (the sympathetic and parasympathetic systems) to facilitate the resolution of inflammation (Black and Garbutt, 2002; Marshall, 2005).

Lipopolysaccharide has been implicated as the bacterial product which is responsible for the clinical syndrome of inflammation and infectious disease. Experimentally, administered LPS causes sickness symptoms including fever, reduction of weight gain and food intake as well as changes of behavior in animals including birds (Xie et al., 2000; Koutsos and Klasing, 2001). In mammals, LPS-induced acute phase response is species and individual dependent (Leininger et al., 1998). Recent findings suggest that birds show many similar response patterns to LPS-immune challenge as mammals (Xie et al., 2000; Koutsos and Klasing 2001). In my lab, chicken has been used as an animal model for detecting the effect of genetic variation on animals' stress response and disease resistance.

2.4 Chicken as an animal model for genetic basis of variations in Inflammation

Chickens is a useful animal models in the assessment of the effects of genetic-environmental interactions on psychopathological stress and inflammation, since a chicken can have more than three hundred offspring with similar genetic characteristics within a lifespan of approximately 60 weeks. In addition, the chicken's immune and HPA systems display similar functions in pathogenic and stress response as those in mammals (Larson et al., 1985; Savory and Mann, 1997). Chickens have been used as animal models in various clinical and psychopharmacological studies (Norman, 1990; Johnson, 1998; Dubousset and Machida, 2001). Functional integrations among behavior, physiology, and morphology may create suites of traits that are simultaneously acted upon by selection. Recently, a selection program termed "group selection" was introduced (Muir, 2005; Muir and Schinckel, 2002; Cheng and Muir, 2005). The advancement of the program is that it allows selection on production traits but takes into account competitive interactions in a group setting. The program focuses on gene(s), environment, and genetic-environmental interactions, by which, it turns "survival of the fittest" with emphasis on the individuals to "survival of the adequate" with emphasis on the group, by which antisocial behaviors are overcome.

A genetic basis of differentially regulated behavior and physical indexes, in response to social stress, has been found in the chickens from White Leghorn lines selected for high (HGPS) or low (LGPS) group productivity and survivability in colony cages (Muir and Craig, 1998; Cheng et al., 2001a). Group productivity was based on an average rate of lay whereas survivability was based on days of survival. Chickens were not beak-trimmed and high light intensity was used to provide conditions that allowed expression of aggressive behavior with resulting stress and productivity impacts (Craig et al., 1999). Under these housing conditions, the HGPS line (previously named KGB, the Kinder, Gentler Bird) showed an improved rate of lay, survival and feather score as well as reduced cannibalism and flightiness compared to hens from the non-selected control line, Dekalb XL (DXL) line, and reversed selected LGPS line (Cheng et al., 2001a). HGPS hens also had better and faster adaptations to various stressors such as social, handling, cold, and heat in multiple-hen cages (Hester et al., 1996a, b, and c). In addition, HGPS hens displayed a greater cell-mediated immunity with a higher ratio of CD4:CD8, whereas LGPS hens exhibited eosinophilia and heterophilia and had a greater ratio of heterophil:lymphocyte (H/L) (Cheng et al., 2001b). Both eosinophilia and H/L have been used as stress indicators in animals including chickens (Gross and Siegel, 1983; Woolaston et al., 1996; Hohenhaus et al., 1998). Collectively, genetic selection has created the lines with significantly different phenotypes, each of which has unique characteristics in physical indexes, behavior, immunity and resistance to stressors (Table 2), which are likely due to differential stress adaptation of the HPA axis and immune system. Based on our and others studies we hypothesize that gene(s) and gene-environmental interactions affect immunity and neuroendocrine functions, which in turn alters the animal's stress coping ability and well-being.

In one of our studies, the role of LPS on evoking inflammatory response in those selected lines was examined. One-day-old chicks from the HGPS, LGPS and DXL line were used in the study. Female chicks (n=60 per line), at 6 weeks of age, were randomly divided into saline control and experimental groups. Experimental chickens were injected intravenously with 0.2 mL of sterile saline reconstituted LPS at an approximate dose of 5.0 mg/kg of body weight. The saline control chicks were handled the same as the experimental chicks except that they were injected intravenously with 0.2 mL of sterile saline.

Stressors	Birds			References
	HGPS	LGPS	DXL	
<i>Single-bird cage</i>				
Immunity	high	Low	- ¹	Cheng et al., 2001a
Production	high	Low	-	Cheng et al., 2011b
Mortality	Low	High	-	Cheng et al., 2001b
Level of DA, EP, 5-HT	Low	High	-	Cheng et al., 2001b
<i>Multiple-hen cages²</i>				
Social environment	Great adaptation	-	Low adaptation	Hester et al., 1996a
H/L ratio	No change	-	Increased	Hester et al., 1996a
Handling stress	Low	-	High	Hester et al., 1996b
Production	High	-	Low	Hester et al., 1996b
Cold exposure	Resistant	-	Susceptive	Hester et al., 1996b
Heat exposure	Resistant	-	Susceptive	Hester et al., 1996b
<i>Others</i>				
Social stress	Low	High	High	Cheng, et al., 2002, 2003a,b
Immune challenge	Low	High	High	Cheng et al., 2004a,b
Transportation stress	Low	High	High	Cheng & Jefferson, 2008

¹, Birds were housed in 12 hens per cage without beak trimming.
² -, Did not compare in the studies.
³, Immune reaction followed *Escherichia coli* lipopolysaccharide challenge.
5-HT= Serotonin; DA = Dopamine; DXL = Dekalb XL line; EP = Epinephrine; H/L ratio = Heterophil to lymphocyte ratio, as stress indicator; HGPS (also called KGB; kind, gentle birds, previously) = High group productivity and survivability; LGPS (also called MBB; mean, bad birds, previously).

Table 2. The differences between the selected birds in responses to various stressors.

3. Genetic variations in LPS-induced inflammation

3.1 The LPS-induced different changes in body weight and organ weight in different chicken lines

Present study demonstrated that LPS-induced immune stress differently affected chickens' growth among the HGPS, LGPS, and DXL lines. In DXL chicks, change in body weight (BW) gain exhibited a biphasic pattern, i.e., a greater reduction of BW gain at 6 h post-injection ($P<0.05$) and a tendency for reduction of BW gain at 24 h post-injection ($P=0.08$), followed by a full recovery at 48 h post-injection (Figure 1). Compared to DXL chicks, LGPS chicks, but not HGPS chicks, had a similar biphasic pattern of reduction of BW gain in response to LPS immune challenge. In LGPS chicks, reduction of BW gain was greater at both 6 h and 24 h post-injection ($P<0.05$) and did not reach a positive BW gain at 72 h post-injection. In contrast, HGPS chicks did not have a reduction of BW gain until 24 h post-injection ($P<0.05$), followed by a complete recovery at 48 h post-injection ($P>0.05$), and reached a positive BW gain from 48 h to 72 h post-injection.

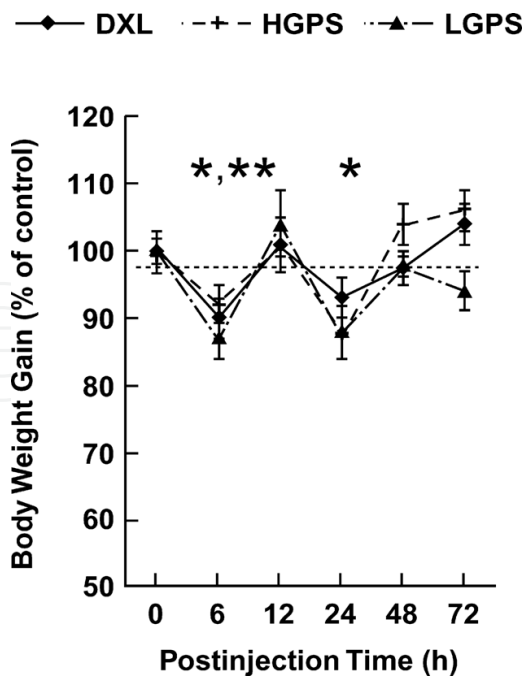


Fig. 1. Differential regulation of BW gains in different chicken lines following lipopolysaccharide (LPS) intravenous injection. The HGPS and LGPS hens were selected for high or low group productivity and survivability, respectively, and the DXL was commercial chicken line. Compared to BW from their respective controls, the BW gain was significant reduced in DXL chicks at 6 h post injection ($P<0.05$); in LGPS chicks at both 6 and 24 h post injection ($P<0.05$), and in HGPS chicks at 24 h post-injection ($P<0.01$). * = $P<0.05$ and ** = $P<0.01$ ($n=10$ /at each period in time for each line).

The interactions of genetic-LPS challenge on chicks' growth among the present chicken lines were also found in their organ development. Compared to each line's respective controls, spleen weight increased in DXL chicks at 48 h post-injection and reached a peak at 72 h post-injection ($P<0.05$ and $P<0.01$, respectively, Figure 2a), while LPS-induced increases in spleen weight were not detected in both HGPS and LGPS chicks until 72 h after injection ($P<0.05$). The LPS injection also resulted in a differential change of liver weight among the lines (Figure 2b). Compared to each line's respective controls, the LPS-induced increase in the liver weight was found only in LGPS chicks from 12 to 48 h post-injection ($P<0.01$ and $P<0.05$, respectively, Figure 2b). There were no changes in the heart weight in both DXL and HGPS chicks at any time measured ($P>0.05$) while LGPS chicks had an increased heart weight during the entire treatment period, with a peak at 72 h post-injection ($P<0.05$ and $P<0.01$, respectively, Figure 2c). The LPS-induced increase in adrenal weight was found in LGPS chicks at 6 h post-injection ($P<0.05$ and $P>0.05$, respectively, Figure 2d) while adrenal weight was not changed in HGPS and DXL chicks during the entire observed period ($P>0.05$).

The present results showed that, compared to both LGPS and DXL chicks, HGPS chicks had a delayed and transient reduction of BW gain and mild changes in organ development in response to LPS challenge (Figures 1 and 2). The data confirmed that the acute toxicity of LPS induced sickness symptoms including reduction of BW gain and changes in organ development in animals, but the effect of LPS on chickens was stain and time dependent. Similar to the present results, a genetic basis of different effects of LPS injection on BW gain was also reported by Parmentier et al. (1998). In their study, they found that although LPS injection induced an acute, transient reduction of BW weight in all of the chicken lines,

chickens selected for high antibody response to sheep red blood cells (SRBC) had a higher percentage of BW gain than chickens selected for low antibody response to SRBC and a random bred control line.

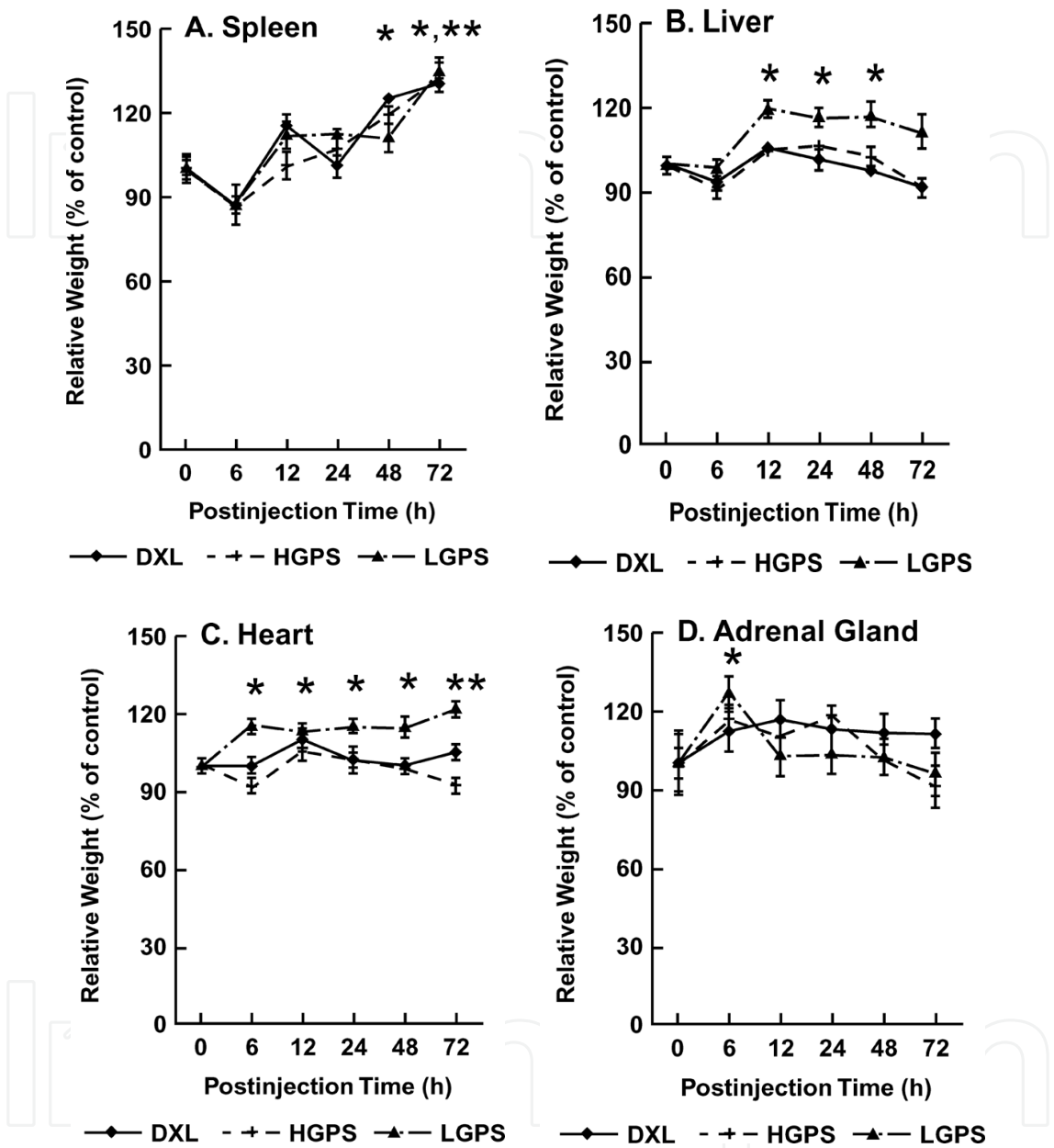


Fig. 2. Differential regulation of organ weight in different chicken lines following lipopolysaccharide (LPS) intravenous injection. The HGPS and LGPS hens were selected for high or low group productivity and survivability, respectively, and the DXL was commercial chicken line. Compared to their respective controls, spleen weight (A) was significantly increased in DXL chicks at 48 h ($P<0.05$) and 72 h ($P<0.01$) post-injection, while in both HGPS and LGPS chicks at 72 h post-injection ($P<0.05$, respectively); increased liver weight (B), heart weight (C), and adrenal gland weight (D) were found in LGPS chicks but not in both HGPS and DXL chicks from 12 to 48 h post-injection ($P<0.05$), 6 to 72 h ($P<0.05$ and $P<0.01$, respectively), and at 6 h ($P<0.05$) post injection, respectively. * = $P<0.05$ and ** = $P<0.01$ ($n=10$ /at each period in time for each line).

The reason for the differing regulation of growth performance in the present lines could be related to each line's unique characteristics in response to stress. Previous studies showed that, compared to LGPS and DXL chickens, HGPS chickens had a better fast coping response to various stressors, such as social stress, handling and transport stress, and cold and heat stimulations (Hester et al., 1996 a, b, c; Cheng et al., 2001a, b, 2002). The HGPS chickens, compared to LGPS and DXL chickens, also had a stable neuroendocrine homeostasis in response to social stress, which could be related to their higher resistance to LPS stress (Cheng et al., 2002, 2003). In agreement with this hypothesis, Quan et al. (2001) and Carobrez et al. (2002) reported that impaired coping capability to social stress increases the susceptibility to LPS challenge in rodents and caused long-term consequences on animal well-being.

3.2 LPS-induced different changes of body temperature in the different chicken lines

The present study demonstrated that LPS-induced changes of core temperature (cloacal temperature) in chicks were strain and time dependent. Compared to each line's respective controls, LPS injection resulted in hypothermia in all of the treated chicks at 6 h post-injection regardless of the strain (Figure 3), but the greatest hypothermia was found in HGPS chicks (HGPS<LGPS<DXL, $P<0.001$, $P<0.01$, and $P<0.05$, respectively). At 12 h post-injection, LPS induced a significant hyperthermia in both DXL and LGPS chicks ($P<0.05$ and $P<0.01$, respectively) but not in HGPS chicks ($P=0.09$). From 12 to 72 h post-injection, compared to their respective controls, the core temperature returned to normal in both DXL and HGPS chicks ($P>0.05$), while LGPS chicks had a secondary hypothermia from 48 to 72 h post-injection ($P<0.01$ and $P<0.05$, respectively).

The present results showed that LPS injection induces changes in chickens' core temperature regardless of strain. However, each strain had a unique pattern of regulating core temperature in response to LPS immune stress (Figure 3). The HGPS chicks had transient monophasic hypothermia, the DXL chicks had a biphasic response showing an initial hypothermia followed by hyperthermia, and the LGPS chicks had a triphasic response showing an initial hypothermia, then hyperthermia, followed by a longer-lasting secondary hypothermia. Similar to the current results, previous studies found that LPS-induced different fever responses in birds, such as a monophasic hypothermia in chicks (Smith et al., 1978) and a biphasic response, i.e., an initial phase of hypothermia followed by a fever response, in chickens (Rotiroti et al., 1981), Japanese quail (Koutsos and Klasing, 2001), and pigeons (Nomoto, 1996). The LPS-induced biphasic and triphasic response were also found in rats (Derijk and Berkenbosch, 1994; Romanovsky et al., 1996) and mice (Kozak et al., 1994). The genetic bases of the different responses to the LPS immune stress between animals are likely to constitute an intrinsic characteristic of the animals' unique febrile response and could result from its capability to resist stress. The hypothesis is supported by the findings from the previous studies in which it was reported that psychological stress itself can induce an increase in core temperature, "psychogenic fever," in humans and animals (Oka et al., 2001).

The mechanism(s) of differential regulation of core temperature between the present lines could be related to each line's unique pattern in coping with stressors, such as the capability of behavioral and physiological plasticity including changes in the neuroendocrine and immune systems (Cheng et al., 2001a,b, 2002, 2003). A parallel study showed that LPS injection induced changes of pro-inflammatory interleukin (IL), such as IL-1 mRNA expressions, in the liver of

all of the LPS-treated chicks (Eicher and Cheng, 2003), but LGPS chicks had a heavier liver than both DXL and HGPS chicks at 12 and 48 h post-injection, during which period LGPS chicks suffered from secondary hypothermia. These results may suggest that, in response to endotoxin challenge, the liver functions of LGPS chicks were increased and might have secreted a greater amount of IL-1 protein. The hypothesis agrees with the finding that the liver is a major source of IL in endotoxemia. The LPS-induced increase in the liver's metabolic function and increase in the release of acute phase proteins and cytokines including IL-1 have been reported in experimental animals including chickens (Xie et al., 2000).

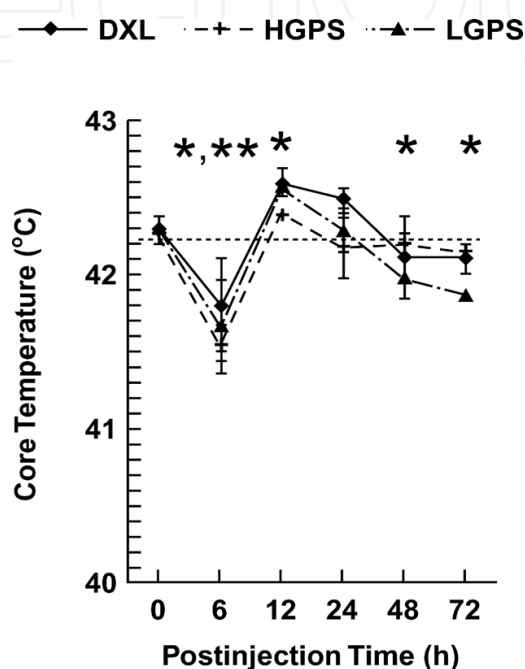


Fig. 3. Differential regulation of core temperature in different chicken lines following lipopolysaccharide (LPS) intravenous injection. The HGPS and LGPS hens were selected for high or low group productivity and survivability, respectively, and the DXL was commercial chicken line. Compared to their respective controls, LPS injection resulted in hypothermia in all of the treated chicks at 6 h post-injection, but the greatest reduction of core temperature was found in HGPS chicks ($P < 0.05$ and $P < 0.01$, respectively). By 12 h post-injection, both DXL and LGPS chicks but not HGPS chicks had hyperthermia. Core temperature returned to control levels at 24 h post injection in both DXL and HGPS chicks, while LGPS chicks had a secondary hypothermia from 48 to 72 h after injection ($P < 0.05$). * = $P < 0.05$ and ** = $P < 0.01$ ($n = 10$ /at each period in time for each line).

3.3 LPS-induced different change of behavior in the different chicken lines

The majority of significant behavioral differences between LPS and saline control groups were observed from 6 to 12 h post-injection. During this period, chicks were very inactive, as illustrated by a very large and significant increase in sitting ($P < 0.001$, Figure 4a-e). Correspondingly, standing, feeding, drinking, and moving were all significantly lower during this time compared to control chicks. By 24 h post-injection, sitting, standing, feeding, and drinking returned to control levels (Figure 4 b-e). However, the amount of time spent sitting was increased again at 48 h post-injection in all of the treated chicks, with a time length in the order LGPS > HGPS > DXL (Figure 4e). The increase in sitting in LGPS chicks could be related

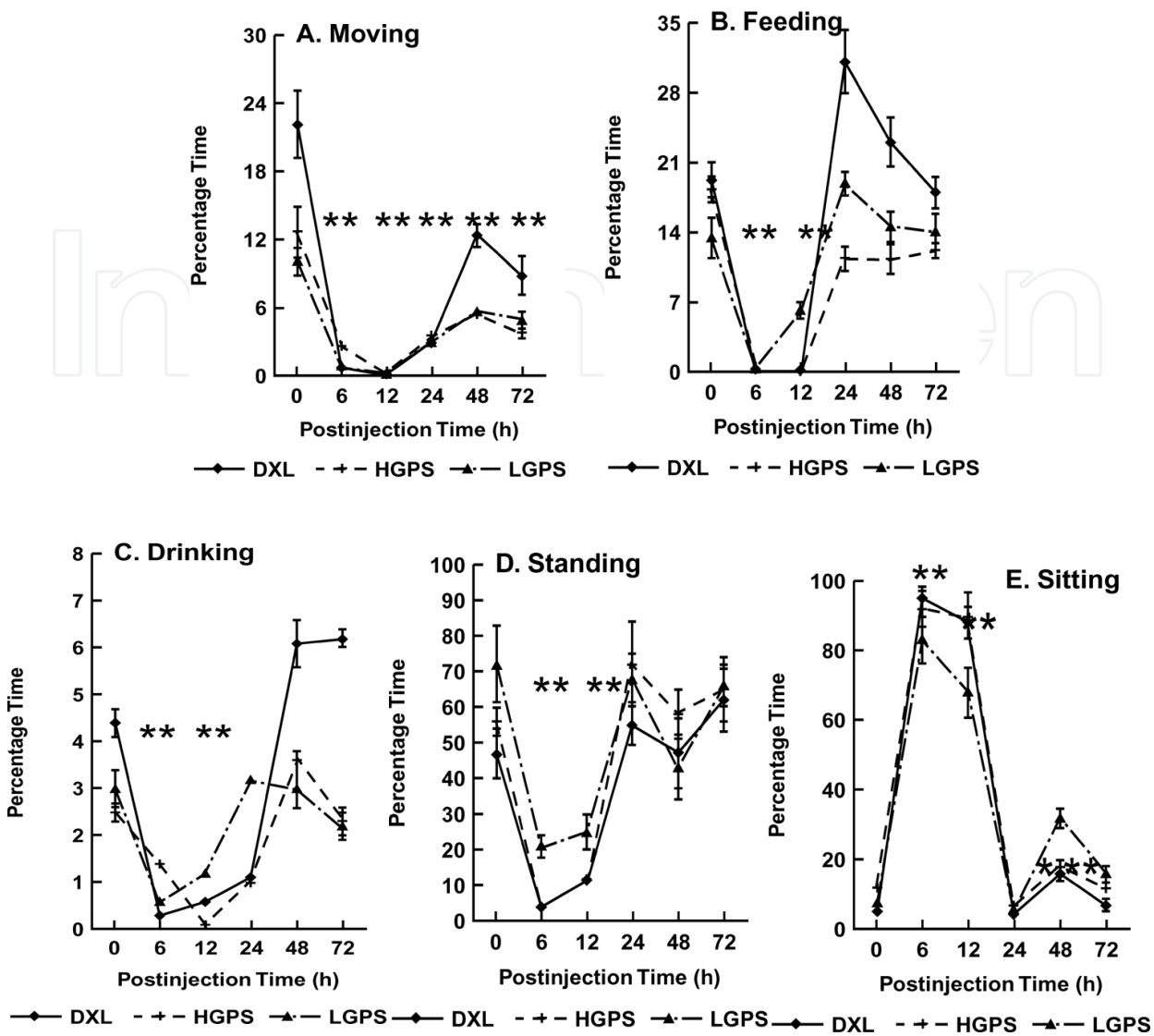


Fig. 4. Differential regulation of behavioral plasticity in different chicken lines following lipopolysaccharide (LPS) intravenous injection; A) movement, B) feeding, C) drinking, D) standing, and E) sitting. The HGPS and LGPS hens were selected for high or low group productivity and survivability, respectively, and the DXL was commercial chicken line. Compared to their respective controls, all of the treated chicks were very inactive at 6 to 12 h post injection, as illustrated by a very large and significant increase in sitting ($P<0.01$, Figure 4a-e). Correspondingly, standing, feeding, drinking, and moving were all significantly lower during this time. By 24 h post injection, setting, standing, feeding, and drinking returned to the control levels (Figure 4 b-e). However, the amount of time spent sitting was increased again at 48 h post injection in all of the treated chicks in the order LGPS > HGPS > DXL ($P<0.05$ and $P<0.01$, respectively, Figure 4e). * = $P<0.05$ and ** = $P<0.01$ ($n=10$ /at each period in time for each line).

to their secondary peak of hypothermia, which started at 48 h post-injection (Figure 2). Interestingly, the amount of time that chicks spent moving was suppressed in all LPS-injected groups and had not returned to control levels even after 72 h post-injection, suggesting that there may still have been some mild effect from the LPS injection (Figure 4a).

4. Conclusion

The LPS injection induced a series of sickness symptoms in the infected individuals at both behavioral and clinical levels, but the reactions were in a genotypic- and phenotypic-specific manner. Compared to both LGPS and DXL chicks, HGPS chicks had acute, transient behavioral and physical changes with less effect on BW gain and organ development. These results suggested that genetic selection for productivity and survivability may also have altered the mechanisms controlling the animals' immunity and stress response including LPS challenge. This hypothesis is in agreement with the previous findings that the genetic selection for one indicator could result in changes in other characteristics in animals including chickens. For instance, chickens selected for their high level of plasma corticosterone, compared to a reversely selected line, greatly resisted *E. coli* challenge (Gross and Siegel, 1975). Bayyari et al. (1997) also reported that genetic selection from increased body weight and egg production in turkeys affected their immune and physiological responses.

The present study provided evidence that genetic differences in chickens' productivity and behavioral styles were associated with hereditary plasticity of the behavioral and physiological homeostasis in response to LPS challenge. The LPS-induced alterations in behavioral and physical measurements were found in all of the three chicken lines, but the most pronounced changes were found in the LGPS line. The results demonstrated that, in chickens as in mammals, the cellular mechanisms regulating the response to LPS challenge are genotypic and phenotypic dependent. The differential responses between the present lines are consistent with the hypothesis that, in poultry, population differences exist in response to various stressors, and LPS challenge can be a useful indicator to evaluate the efficacy of immunity and capability to adapt infection in poultry. The present chicken lines may also provide a new animal model for biomedical investigation on the effects of genetics, epigenetics, and gene-environmental interactions on inflammatory disorders and infectious diseases.

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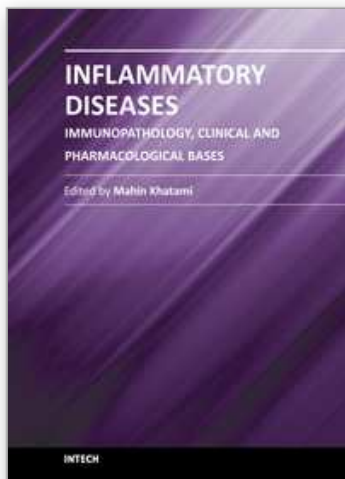
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This book is a collection of comprehensive reviews contributed by experts in the diverse fields of acute and chronic inflammatory diseases, with emphasis on current pharmacological and diagnostic options. Interested professionals are also encouraged to review the contributions made by experts in a second related book entitled "Inflammation, Chronic Diseases and Cancer"; it deals with immunobiology, clinical reviews, and perspectives of the mechanisms of immune inflammatory responses that are involved in alterations of immune dynamics during the genesis, progression and manifestation of a number of inflammatory diseases and cancers, as well as perspectives for diagnosis, and treatment or prevention of these disabling and potentially preventable diseases, particularly for the growing population of older adults around the globe.

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