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REVIEW ARTICLE

Effect of Short-term Heat Stress on the Immune Function of Chickens: A Review

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Abstract. Previous studies indicated that exposure to heat stress for a short duration often adversely affected humoral and/or cell-mediated immunity in chickens. This effect was attributed to a rise in blood corticosteroids, although other complex mechanisms involving nervous, endocrine and immunological interactions were also implicated. It is generally conceded that the suppressive effect of heat on antibody production was more likely to occur during pre-induction and early induction phases of antibody synthesis, and that heat stress suppressed lymphocyte and phagocytic cell functions. On the other hand, short-term heat stress was sometimes shown to either exert a non-significant effect on the immune function of chickens, or, conversely, act as a stimulant, increasing both antibody production and cell-mediated responses in heat treated birds. This controversy reflects the complexity of mechanisms affecting the establishment of immune responses under different conditions of thermal stress. Studies were also reported indicating that the immune functions of heat stressed birds might be influenced by their breed and sex, while both heat stress and immunization might influence the metabolic profile of birds.

Introduction

Studies on environmental management of poultry have been traditionally directed toward production traits such as growth, feed conversion and egg production, while lesser consideration has been given to studying the impact of environmental stress on the immune function of birds. Dietert *et al.* [1] stated that an effective environmental management strategy required a balance between production traits and immune protection from disease. They classified environmental factors affecting immunity into four main categories: physical factors, infectious agents, environmental contaminants and certain nutrients. Such factors induce complex biological responses, including different forms of modulation of the immune functions of birds [1, 2].

1. Effect of heat-stress on the humoral antibody response

High environmental temperature increases the susceptibility of chickens to infectious diseases. For this reason, several experiments were carried out to determine the effect of heat stress on specific immune functions in birds. These experiments, which traditionally involved short-term heating regimens and challenge with innocuous antigens, sometimes showed that heat exerted no immunosuppressive effects [3, 4] and occasionally acted as an immunostimulant [5, 6], but in the majority of cases, acute heat stress induced detrimental effects on specific humoral and/or cellular immunological reactions. Thaxton and his colleagues [7-9] reported that chickens exposed repeatedly to acute heat stress of short duration produced significantly lower antibodies to subsequent challenge with sheep red blood cells (SRBC) than unstressed or chronically heat-stressed chickens. The results of these studies indicated that suppression of antibody synthesis occurred when the birds were stressed shortly before or after immunization with SRBC; this phenomenon was called "high environmental temperature-mediated immunosuppression" (HTS).

They also conducted experiments in which it was shown that an already established antibody response against SRBC, bovine serum albumin (BSA) or killed *Salmonella pullorum* antigen was depressed within 12 hr after exposure to acute heat stress, and this phenomenon was called "high environmental temperature-mediated immuno-depression" (HTD).

The same authors [8], investigating the effect of high environmental temperature on secondary antibody response of chickens previously primed with SRBC or BSA, reported decreased antibody production in birds on the third day following secondary immunization with SRBC, while no effect on secondary antibody production against BSA was observed at any time. In still other experiments, in which birds were exposed to heat stress 24 hr after each of primary and secondary immunization with SRBC or BSA, a transient immunosuppression was recorded only after primary immunization, suggesting that a significant depression of immunity was more likely to occur when the birds were exposed to heat stress prior to initial antibody formation. Similarly, Subba Rao and Glick [10] reported that exposure of chickens to acute, intermittent heating episodes progressively limited their humoral antibody potential, particularly during pre-induction and early induction phases, indicating that heat treatment might have reduced the ability of antigen presenting cells' to "process" the engulfed antigen, with consequently insufficient amounts of processed antigen being available to incite a strong antibody response. These authors reported that even chronically heat-stressed birds of different ages exhibited decreased capacity for antibody production against SRBC, indicating that heat might have produced adverse effects on their lymphoid organs, namely the spleen in older birds, and the bursa of Fabricious in younger birds.

More recent studies focused on the effect of heat stress on immunity in chickens selected for resistance to stress or increased capacity for antibody production. Hester *et al.* [11] compared humoral antibody response of hens selected for improved

survivability in colony cages under different conditions of stress, including thermal stress, with random-bred controls. They recorded immunodepression in both cold stressed and heat stressed birds, regardless of their genetic stock, and concluded that genetically selecting hens for survivability under conditions of social competition did not affect their humoral immune response to SRBC.

Increased susceptibility of the avian immune system to acute heat stress during pre-induction and early induction phases was attributed to increased pituitary - adrenal activity and consequently increased release of corticosteroids, which also produced lymphopenia and heteropenia in the stressed chickens [12-15]. Gross and Siegel [14] suggested that rise in the blood corticosteroid level during heat stress adversely influenced protein synthesis and caused lymphoid cell destruction thereby reducing antibody production. Others [16-19] reported that stress-induced immunosuppression was probably associated with suppression of lymphocyte proliferation factors such as interleukin (IL II) as a result of increased incorporation of endogenously released corticosteroids in lymphocyte cells. Further studies [20] showed that ACTH injections suppressed agglutinating antibodies against *S. pullorum* antigen when the antigen concentration was low. Siegel and Latimer [21] studied interactions between *S. pullorum* antigen concentration and temperature on serum antibody and corticosteroid levels in chicks subjected to acute heat stress, followed immediately by challenge with different concentrations of *S. pullorum* antigen (0.00015% - 0.15%). They reported that after one heating episode, antibody production against *S. pullorum* antigen was suppressed significantly during the induction phase in chickens immunized with lower antigen doses, as compared to those immunized with higher antigen doses. However, with two heating episodes, antibody production was suppressed in heat stressed birds receiving low antigen doses during the induction phase (4-5 days post-immunization), while the reverse occurred during the declining phase (7-14 days post-immunization). Using 2-mercaptoethanol (2-ME) to determine ME resistant (2-ME_r) antibody titres, they presented data suggesting that suppression of IgM antibodies occurred during the induction phase, while suppression of IgG antibodies occurred during the decline phase of the immune response. In other words, antigen concentration-stress interactions seemed to be due to differential responses of specific immunoglobulins. Meanwhile, significant increase in serum corticosteroids occurred in the heat-stressed birds immediately after exposure to high temperature, and continued in the form of small, yet significant, elevations for several days, indicating that sustained high level of corticosteroids induced by heating might have produced long term cytolytic effects on lymphocytes resulting in reduced IgG synthesis either directly by affecting B-cell antibody synthesis, or indirectly by inhibiting or reducing T-helper cell activities [21].

The principal effect of corticosteroids on the immune system of chickens is apparently on T-cell populations [22-24]. There is also evidence indicating that increased metabolic activity, as measured by body heat production, might occur at the onset of IgG production [25] and that immunologically active lymphocytes might

produce corticotropin-like and B-endorphin-like substances [26, 27] that stimulate synthesis of adrenal corticosteroids [28] and simultaneously modulate hypothalamic temperature control mechanisms in chickens [29]. These results, coupled with data from primates indicating the presence of a thymus-derived corticotropin-releasing factor [30], pointed to the existence of complex immunological-neuro-endocrinological interactions during the establishment of an immune response. It must be pointed out, however, that elevation of blood corticosteroid level is not a consistent finding in birds subjected to heat stress, being dependent, among other things, on their age, genetic make-up and degree of acclimation. Thus, MacFarlane and Curtis [31] reported no elevation in blood corticosterone level in 17 day old chickens exposed to high temperature; in which case the lack of adrenal response was attributed to the relative insensitivity of the adrenals of young birds to adreno-corticotrophic hormone and stressors [32]. On the other hand, Hester *et al.* [33] reported that 44 week old hens selected for survivability in colony cages also lacked a blood corticosterone response when exposed to thermal stress, indicating some form of acclimation in these birds. In this respect, it was reported that chronic or repeated exposure to heat stress might induce a decline in adrenal responsiveness [34] due to increased binding of corticosterone to hypothalamic receptors, thereby inhibiting the release of corticotropin releasing factor with consequently decreasing corticosterone output [35].

The effect of environmental temperature on the immune responsiveness of an animal also depends on the demand put on the animal's capacity to maintain a normal state of homeothermia. To cope with a particular thermal environment, animals use specific as well as non-specific regulatory mechanisms [13, 29, 36]. However, at temperatures deviating from thermoneutrality, heat production by the animal's body must be changed. This in turn, might entail changing the feed intake or increasing thermoregulatory heat production, or both [36]. The latter authors investigated the effect of constant *versus* fluctuating environmental temperatures on humoral immune responses induced by SRBC injections in *ad libitum* and restricted-fed, heat acclimated and non-acclimated pullets. Two constant temperatures (15°C and 35°C), and two fluctuating temperatures (10 - 20°C and 30 - 40°C), were used in these studies, while control pullets were kept constantly at 25°C. The results showed a significant increase in antibody titres of the SRBC-immunized pullets at all temperatures by days 5 and 10 post-immunization. However, by day 5 post-immunization, total anti-SRBC antibody titre was significantly higher in birds kept at 10-20°C, 35°C and 30-40°C, than those kept constantly at 25°C. Meanwhile, 2-ME_T antibody titres increased significantly at 35°C and 30-40°C. These results indicated that restricted feeding both at low and high temperatures increased total antibody production within 5 days post immunization. On the other hand, exchange of the birds to low or high temperature immediately before immunization decreased total antibody production at day 5 post-immunization. Although the low fluctuating temperature (10-20°C) increased the total titre by about 7%, constant low temperature of 15°C did not significantly influence antibody level, nor the spleen and bursa weights. These results indicated that if depression of antibody production was

to be expected, a change in temperature at the time of immunization was probably more important than the absolute temperature itself [36].

2. Effect of heat-stress on cell mediated immunity (CMI)

Morgan *et al.* [37] studied the effect of high environmental temperature on immediate hypersensitivity reaction (IHR) in chickens and showed that an anaphylactic reaction induced by *i.v.* challenge with BSA in previously sensitized birds, was significantly reduced by exposing the birds to 43°C for 30 min. This effect was noted when the birds were heated repeatedly within 24 hr prior to challenge. On the other hand, Pitkin [38] reported a reduction in delayed type hypersensitivity (DTH) and impairment of lymphocyte functions in heat-stressed mice, while Lee and Reid [39] reported significantly decreased lymphocyte transformation induced by phytohaemagglutinin (PHA) in avian lymphocytes cultured at 37°C as compared to those cultured at 41°C. However, Maheswaran and Thies [40] obtained the reverse effect with concanavalin A (Con A). Regnier and Kelly [41] investigated *in vivo* and *in vitro* effects of heat stress on CMI and antibody production in chickens. Using dinitrofluorobenzene (DNFB) and PHA for skin tests, and PHA for whole blood lymphocyte transformation assays, they reported a significant reduction of wattle swelling in birds exposed to an air temperature of 36°C for 5 days *versus* those maintained constantly at 26°C. PHA-induced lymphocyte transformation, as measured by ^{3}H-thymidine uptake, was also significantly suppressed in the former birds. Similar changes were observed in chickens subjected to cold stress at 1°C for 5 days. The overall results of these studies suggested that thermal stress might adversely affect T effector cell or regulatory amplifier cell responses of chicken lymphocytes. However, these changes could also be attributed to reduction in circulating lymphocytes which occurred on day 5 in thermally stressed birds. The authors [41] also speculated on the possible role of corticosterone and other serum factors, such as thymic hormone, lymphokines and other immunoregulatory substances, in suppressing CMI. On the other hand, they reported non-significant decrease in antibody production against SRBC in either heat stressed or cold stressed chickens.

3. Heat-induced immunomodulation as related to breed

Although many workers previously showed that acute, intermittent heat stress adversely affected antibody production in chickens, considerable variation was found between different genetic lines of chickens undergoing similar levels of heat-stress [42]. It was suggested that selection for antibody production might alter stress susceptibility, and this, in turn, might influence the effect of stress on immune responsiveness [4]. Thaxton and Siegel [8, 43, 44] reported a significant heat-induced decrease in antibody production in an inbred line of chickens selected for high susceptibility to heat from a randombred Athens flock, and a similarly significant heat-induced immunosuppression was reported in a New Hampshire line selected for high bursa weight [7, 10, 44]. According to Siegel [45], more corticosteroids released during heat stress were bound to the thymus cells of a line selected for high stress response than one selected for low

response. Regnier *et al.* [3] and Gross and Colmano [46] also reported genetically based differences in stress-induced alterations of the immune responses of these birds with significantly increased antibody titres being observed in New Hampshire as compared to Hubbard breed, and it was postulated that this difference might be associated with protracted immunoglobulin catabolism in the former breed [46]. The studies of Regnier and Kelley [41] on CMI of thermally stressed chickens of the New Hampshire and Hubbreeds also indicated that significant differences existed between the two breeds in their magnitudes of PHA and DNFB skin responses, PHA-induced lymphocyte transformation and total blood lymphocyte counts. Following thermal stress, the reduction in wattle swelling and DNFB skin sensitivity, as well suppression of lymphocyte transformation and total circulating lymphocyte counts of the New Hampshire chickens surpassed those recorded in the Hubbard breed. It was also shown that during cold stress, significantly lower packed cell volume (PCV) occurred in New Hampshire than Hubbard chickens. Leitner *et al.* [47] demonstrated significant differences in antibody response to SRBC between chickens selected for high antibody response and those selected for low antibody response. Further, Parmentier *et al.* [48] reported that selection of chickens for increased antibody response to SRBC resulted in increased antibody production following vaccination against Newcastle, infectious bronchitis and infectious bursal disease, and similar results were reported by Pevzener *et al.* [49] and Heller *et al.* [50]. Comparing the development of the immune system in early (k^+) *versus* late (K) feathering egg-type chickens, Hartmann and Merat [51] suggested that the late feathering allele (K) might be associated with retardation of the immune system's development. However, Bacon *et al.* [52] found no difference in antibody response to SRBC between early and late feathering lines of white leghorns, and similar results were reported in broilers [53]. Gross [54] also found non-significant interactions between chickens' genotype and the environment. Similarly, Donker *et al.* [4], studying the effect of heat stress on antibody production in chicken lines selected over six generations for high and low antibody response to SRBC, reported little variation among the selected lines. On the other hand, Al-Bisher *et al.* [6] reported that primary immunization with SRBC induced higher antibody production in Leghorn than a native Saudi chicken.

Selective breeding for resistance was investigated in some detail in mice in which it was shown that differences in antibody production against SRBC between lines selected for high and low antibody responses were associated with variations between these animal lines in terms of antigen handling by macrophages and the multiplication rate of B-lymphocytes [55-57]. According to the latter authors, low responding mice exhibited higher macrophage catabolic rate than high responding mice, and this could have reduced the effectiveness of B-cell triggering to produce antibodies against SRBC in the low responders. These variations were most pronounced at low SRBC dose levels and a larger dose of sheep erythrocytes was therefore necessary to produce a detectable antibody response in low responding mice. In chickens, it was shown that differences between genetic lines selected for high and low antibody production against SRBC were

largest when the birds were immunized with the same dose levels originally used for their selection [54, 58].

4. Heat-induced immunomodulation as related to sex

The effect of sex on immune functions was studied mainly in mammals in which it was observed that the immune capabilities of females often superseded those of males [59-65]. In this respect, it was reported that gonadal hormones could modulate the immune response [62, 63] by either directly exerting an immunoregulatory effect on effector lymphocytes [63, 64] or indirectly by altering the endocrine activities of the hypothalamus, pituitary gland, thymus and gonads [66, 67]. Studies dealing with sex-related differences in the immune response of chickens are few [68], but there are indications from a number of studies that female chickens mounted a significantly higher antibody response to SRBC in comparison to males subjected to the same antigen dose under the same conditions [6, 68, 69]. Others [4, 53], however, either found no sex related or inconsistent differences in antibody production between male and female chickens. Further studies to verify the existence, magnitude and underlying causes of sex-related differences in the immune functions of these birds are needed.

5. Metabolic, physiological and blood chemical studies in thermally-induced immunomodulation

To understand the disorders associated with stress, it is imperative to understand the metabolic and physiological implications that serve as a route for these disorders [70]. The chicken's capacity for thermoregulation develops shortly after hatching and becomes relatively mature by the age of 2-3 weeks [71,72]; thereafter, birds can deal with a wide range of external temperatures [71]. Within a small range of temperature variation, birds, like other homeothermic animals, usually succeed in maintaining a constant body temperature by regulating heat loss through physical processes. However, at non-thermoneutral temperatures, additional chemical energy is needed for thermoregulation. Acclimation to non-thermoneutral conditions is mainly accomplished by changing feed intake or by extra heat production. However, if feed intake remains unchanged, the expenditure of energy for thermoregulation reduces the amount of energy available for production [35, 73]. In such cases, the amount of retained energy as well as the composition of gained energy will be affected [74].

Physiological studies on birds subjected to thermal stress focused mainly on the bird's hormonal and behavioral responses, and on certain other physiological measurements, such as body temperature, respiration, oxygen consumption, electrolyte status, blood pressure and heart rate [75-79]. A few studies were also carried out on the effect of temperature on white blood cells counts of chickens. Chancellor and Glick [80] reported that exposure of birds to relatively high environmental temperatures for 30 min induced a marked decrease in total white blood cells and heterophil percentage, with an increase in lymphocytes percentage in birds bled within 30 min after exposure to heat

stress, whereas birds bled 2 hours after heat exposure exhibited a significant increase in heterophils and a significant decrease in lymphocytes. On the other hand, Maxwell [81] reported increased blood basophil counts in chickens undergoing stress and proposed that basophilia could serve as an indicator in stressed birds.

Genetic variations were implicated in determining the birds' physiological responses to heat-stress [82, 83]. Pech-Waffenschmidt *et al.* [82] showed that different feathering types of chickens subjected to short or long-term heat stress exhibited different effects on their body surface temperature, heat loss mechanisms, core temperature, blood CO_2 levels, and, to a lesser extent, blood pH. Hester *et al.* [33] reported that hens selected for resistance to colony cages and subjected to heat stress experienced heterophilia and increased heterophil:lymphocyte ratio which could be regarded as an indication of their better adaptability to social stress. According to Harrison and Biellier [77], when a bird is exposed to a stressful temperature, or an abrupt temperature change, there was an initial period of rapid disturbance characterized either by an overshoot or an undershoot of metabolic levels; however, a plateau is eventually reached, which represented a state of acclimation, at which various physiological measurements stabilize at new levels, different from the pre-stress values.

Henken *et al.* [35, 36, 84, 85] associated various metabolic changes with the effect of environmental temperature on the immune response of chickens. Studying the effect of *i.m.* injection of SRBC on heat production in *ad libitum* and restricted fed pullets reared at 10°C *versus* control pullets reared at normal (21°C) temperature, these workers [35] reported that the injection itself decreased body heat production for 2-4 hr post-injection in restricted-fed birds held at 10°C. On the other hand, a significant decrease in heat production in response to *i.m.* injection occurred in *ad libitum* fed groups whether held at 21°C or at 10°C. These authors suggested that the"injection effect" was probably due to reduced physical activities of the birds for a short time after injection, and should be taken into consideration as a confounding factor when measuring the effect of the immune response on energy metabolism, especially during the first few hours following parentral immunization. Stress effects on protein and energy metabolism due to handling and blood sampling of birds were also reported by other workers [86-88]. Henken and Brandsma [89] also studied the effect of the immune response on energy balance characteristics and protein and fat gains in pullets immunized *i.m.* with SRBC versus controls injected with PBS. In those studies, feed intake, body weight gain and metabolizable energy (ME) were not affected significantly, whereas the magnitude and composition of energy gains were significantly influenced by SRBC immunization.

During 1-5 days post-immunization, anti-SRBC antibody titres increased progressively, and the immunized birds exhibited significantly higher energy retention, coupled with significantly increased fat deposition and reduced maintenance requirements for ME than sham-immunized controls. These results indicated that SRBC-

immunized pullets ate more and gained less than the controls, suggesting that immunization induced a shift in metabolism in favor of fat deposition at the time when antibody production was increasing. Similar effects are induced by increased corticosteroid production. Several studies previously indicated that during the establishment of an immune response, blood corticosteroid levels were elevated as a result of the activity of lymphokines released by immunoreactive lymphocytes, which, in turn, raised the respiratory exchange ratio with a shift toward increased fat synthesis, even though heat production might not be necessarily affected [90-92]. Antibody synthesis could also raise heat production since antibodies are proteins whose synthesis requires energy expenditure [25, 93]. On the other hand, the study of Henken and Brandsma [89] showed that between 6-10 days post immunization, antibody titre was decreasing, and, during that period, SRBC-immunized birds deposited significantly less fat and significantly more protein than controls. These two groups of birds also showed significant differences in body heat production, with lower heat production being recorded in SRBC-immunized pullets during the period of escalating antibody synthesis (1-5 days post-immunization). Siegel *et al.* [25] also recorded a significant increase in heat production in chickens immunized with SRBC, as compared to PBS injected chickens, on the 4th day post-immunization, i.e., during the period of antibody induction. Similar effects on metabolic rate and performance traits might also occur in birds as a result of vaccination against infectious diseases [89]. For instance, vaccination against Marek's disease in day old chicks was shown to reduce feed intake by the birds until the age of 12 weeks [39] and this was associated with increased corticosterone and thyroxine blood levels, and, hence, changes in the metabolic rate, due to the vaccination process itself. Henken *et al.* [84] also conducted immunological and physiological studies designed to investigate the effect of environmental temperature on some aspects of protein and energy metabolism in pullets immunized with SRBC. Using different levels of constant and fluctuating temperatures, they reported significant differences within each heat treatment, depending on the type of immunization (SRBC *versus* PBS), nutrition (*ad libitum versus* restricted feeding) and length of the heat-treatment period.

The results indicated that feed conversion was significantly higher in birds kept at low temperatures of 15°C and 10-20°C, than controls kept constantly at 25°C. Feed intake also increased, whereas growth rate and protein gain were unaffected, by low temperature (15°C). By contrast, high temperature exposures (35°C and 30-40°C) induced significant reductions both in feed intake and growth rate of the chickens, whereas neither protein gain nor feed conversion were affected. On the other hand, restricted feeding reduced the growth rate and feed conversion significantly, while differences due to immunization and degree of acclimation were non-significant. In another study dealing with the effect of low environmental temperature on humoral antibody response of SRBC-immunized pullets [94], they reported a significant increase in feed intake in birds reared at temperatures that were either fixed at 10°C or fluctuated

between 5-15°C. In the latter instance, the birds also exhibited a significantly reduced growth rate. On the other hand, at low temperature, fat gain increased significantly during the period extending from the day of immunization with SRBC to the peak of antibody production, while non-significant effect was observed on protein gain, although pullets subjected to low temperatures tended to deposit less protein than controls. These studies generally indicate that complex interactions exist between environment, metabolism and immune capabilities of birds, and further studies are needed to elucidate these various interactions.

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(مقالة استعراضية)

تأثير الإجهاد الحراري قصير الأمد على وظائف الجهاز المناعي في الدجاج

سعود بن إبراهيم المفرج، عبد العزيز احمد البشر، منصور فارس حسين
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ملخص البحث. تشير الدراسات المنشورة إلى أن تعريض الدواجن للإجهاد الحراري لفترة زمنية قصيرة يؤثر تأثيرا سلبيا على كفاءة النظام المناعي بشقيه الخلطي والخلوي. ويعتقد أن السبب في ذلك هو ارتفاع مستويات الهرمونات الاسترويدية القشرية في الدم، بالإضافة إلى بعض العوامل العصبية والهرمونية والمناعية الأخرى. وتتفق أغلب الدراسات السابقة علي أن تأثير الحرارة السلبي علي إنتاج الأجسام المضادة يبلغ ذروته إذا ما تعرض الطائر للحرارة قبل البدء في تشييد الأجسام المضادة او بعد البدء في تشييدها بوقت قليل. وتؤثر الحرارة كذلك علي أعداد الخلايا العائية ووظائفها.

من ناحية ثانية، فان بعض التجارب تدل على أن تعريض الطيور للإجهاد الحراري لفترة وجيزة لا يؤثر بدرجة كبيرة على كفاءة الجهاز المناعي، وقد يكون للإجهاد الحراري قصير الأمد أحيانا تأثير تنشيطي يزيد من قدرة الطائر علي إنتاج الأجسام المضادة وعلى الاستجابة المناعية الخلوية. ويعكس هذا التباين في النتائج الآليات المعقدة التي ترافق نشوء المناعة في الطيور أثناء تعرضها للإجهاد الحراري. وتدل الدراسات المنشورة علي أن كلا من التعرض للإجهاد الحراري ونشوء الاستجابة المناعية يؤثران على عمليات التمثيل الغذائي.

وتتناول هذه المقالة الاستعراضية أيضا الفروقات بين السلالات وبين الجنسين فيما يتعلق بمستوى الاستجابة المناعية للطيور المتعرضة للإجهاد الحراري.