

Review Article

Influence of Environmental Factors on Avian Immunity: An Overview

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Birds are the most successful animal since Mesozoic era. However, wild birds living in rapidly changing environment experience variation in resource availability, drastic change in climate and threat of infection throughout the year. Thus, in order to survive in specific environment birds have developed various strategies that help them to find food and shelter for young ones such as migration to protect themselves from the rough environments, and reproduce accordingly. We reviewed evidences supporting the hypothesis of existence of physiological trade-offs, particularly between the environmental factors leading to reproduction and immune systems of birds. Further, there is an urgent need to understand the types and physiology of avian health, as the fast-paced environmental changes noted in recent year may pose additional pressure on immunocompetence of many wild avian population. An understanding of immunity which is constantly challenged in seasonally breeding birds is equally necessary in order to develop the important strategies for their effective management in future. The purpose of this article is to provide an overview about avian immune system and stress (environmental or manmade) induced immune suppression in birds, making them a valuable model for basic immunological and environmental cross-talk studies.

Keywords: Avian; Immune system; Stress; Melatonin; Photoperiod

Introduction

Environmental changes posing additional pressure on immunocompetence and health management, which may seriously put threat on wild population of varieties of animal species. This led us the need of understanding immune physiology in the context of natural environment which further emerged the field of “Ecological Immunology” in the mid-1990s [1]. It was analysed that globally, one in eight bird species may become extinct over the next 100 years. Among those ~ 99% of the extinctions of birds are owing to human activities such as deforestation, lack of grain cultivation and hunting/gaming of birds [2]. Therefore, there is an urgent need to understand the physiology and patterns of avian health and immune status. Eco-immunologists have made many important contributions pertaining to the immune systems of wild species. Some important contribution include include (i) immune activity being expensive to animals (ii) counter balance in immune activity due to trade-offs relation with other physiological activities such as reproduction or sexual and maternal behaviours and (iii) immune status as a wealth for better performance of individual quality [3].

Features of the Avian Immune System

Birds and mammals evolved from a common reptilian ancestor more than 200 million years ago and have inherited many common immunological systems. They have developed a number of very different and, in some cases, remarkable strategies. Due to their economic importance, and the ready availability of inbred lines, most avian research immunology has involved from the domestic chicken, *Gallus gallus domesticus*. A remarkable consequence of avian research has been the understanding of fundamental immunological

concepts, especially the complete separation of developing bursa and thymus dependent lymphocyte lineages. In birds, as in mammals, the lymphoid tissue is considered to consist of two vertical compartments of differentiating lymphocytes: one responsible for the discrimination of self and non-self and the expression of cell-mediated immunity and the other responsible for the production of immunoglobulins and antibodies. The former in birds and in mammals is dependent upon the thymus (T-cell dependent system) and the latter, in birds, upon the cloacal bursa (B-cell dependent system).

Primary lymphoid organs of birds

The two major organs of avian immune system are: bursa of Fabricius (associated with B-cells) and the Thymus (associated with T-cells).

Bursa of fabricius: This structure is situated adjacent to the cloaca and predominate in young birds and gets adopted with age at the time of sexual maturity. It is the source of antigen-producing B-lymphocytes in embryonic stage. B-lymphocytes, the cells that produce antibodies, are initially produced in the embryonic liver, yolk sac and bone marrow and then move through the blood to the bursa of Fabricius where they mature. The cloacal bursa is a globular or spherical lymph epithelial organ whose inner surface is thrown into a number of folds which partly obscure the lumen. It is formed by a dorsal diverticulum of the cloacal proctodeum and its growth coincides with the period of rapid body growth after which it regresses and, in most species, is completely involuted about the time of sexual maturity. The bursa reaches its maximum size at 8-10 weeks of age then, like the thymus, it undergoes involution. By 6-7 months most bursae are heavily involuted [4].

Thymus: The thymus is located in the neck along the side of jugular vein. On each side of the neck there are 7-8 separate lobes, extending from the third cervical vertebra to the upper thoracic segments. Each lobe is encapsulated with a fine fibrous connective tissue capsule and embedded into adipose tissue. The button or bean-shaped thymic lobes reach a maximum size of 6-12 mm in diameter by 3-4 months of age of birds, before physiological involution begins with age [4].

Secondary lymphoid organs of birds

The secondary lymphatic organs are the spleen, bone marrow, mural lymph nodules and lymph nodes along with the lymphatic circulatory system of vessels and capillaries that transport lymph fluid throughout the body. The spleen is divided into red and white pulp. The white pulp is where the T-lymphocytes reside.

The spleen is surrounded by a thin capsule of collagen and reticular fibres; poorly developed connective tissue trabeculae enter the splenic tissue from the capsula. Branches of the splenic artery travel in these trabeculae then enter in the splenic pulp. The central artery divides into smaller central arterioles, which also possess a single muscle layer and from this several penicillar capillaries arise [5].

Avian lung associated immune system

The prevention of entry of foreign material to the tissues of the lung is crucial, as such entry is likely to lead to the induction of acquired immune responses which in turn may result in damaging inflammatory reactions and subsequently compromise the physiological capacity of this vital organ [6]. Alveolar and airway macrophages, the mucociliary escalator and the release of surfactant are mechanisms of non-specific defence which is unique to this organ [7].

The lung is a major target organ for numerous viral and bacterial diseases of birds. To control this constant threat birds have developed a highly organized lung-associated immune system (LAIS). Most prominent in the avian lung is the bronchus-associated lymphoid tissue (BALT) which is located at the junctions between the primary bronchus and the caudal secondary bronchi and at the ostia to the air sacs. BALT nodules are absent in newly hatched birds, but gradually developed into the mature structures found from 6-8 weeks onwards. They are organized into distinct B and T cell areas, frequently comprise germinal centres and are covered by a characteristic follicle-associated epithelium. A striking feature of the avian lung is the low number of macrophages on the respiratory surface under non-inflammatory conditions [8]. In addition to the cellular components humoral defence mechanisms are found on the lung surface including secretory IgA. The compartmentalization of the immune system in the avian lung into BALT and non BALT regions need to be taken into account in studies on the host-pathogen interaction since these structures may have distinct functional properties during an immune response.

Lymphocytes

Lymphocytes enter the lung from the vascular pool and then populate the various compartments of the lung, eventually draining through lymphatics to the bronchial nodes and then returning to the blood stream. It is recognized that a common pathway of lymphocyte

traffic exists between the gut and the lung, suggesting a mechanism of mucosa associated adhesion and homing molecules [9]. Recruitment or compartmentalization of lymphocytes to the lung from the systemic pool is also a well recognized phenomenon. Chronic inflammation in the lung interstitium is often associated with a lymphopaenia in the circulation. It is now also clear that the air spaces of the lung are not a sump where cells from the lung parenchyma are dumped, but rather are full of macrophages and lymphocytes that can traffic through the epithelial lining back into the tissues. In pathologic situations; however, this normal traffic may be significantly altered.

Heterophils

The counterparts of mammalian neutrophils are the avian heterophils. Like neutrophils, heterophils form the first line of cellular defence against invading microbial pathogens. They have phagocytic capability but, in contrast to mammalian neutrophils, they lack myeloperoxidase, they do not produce significant amounts of bacterial activity by oxidative burst and their granule components seem to differ from those in mammalian neutrophils. The activation of heterophils by pathogens or by cytokines induces the expression of various pro-inflammatory cytokines such as IL-1, IL-6 and IL-8 [10].

Avian immune cytokines

Inflammations on cytokines expression pattern mostly come from chicken. In general chicken cytokines have only 25-30% amino acid identity with their mammalian orthologues. As a result, there are few, if any, cross reactive monoclonal antibodies (mAbs) or bioassays. Moreover, cross-hybridization or degenerative RT-PCR/PCR approaches also have been unsuccessful. Prior to the release of the chicken genome sequence has radically altered our ability to understand both the repertoire [11]. Although there are only a few reliable ELISAs or bioassays developed for avian cytokines, the use of molecular techniques, and in particular quantitative RT-PCR (Taqman) has allowed investigation of cytokine responses in a number of diseases including salmonellosis, coccidiosis and thyroiditis. In addition the use of recombinant cytokines as therapeutic agents or as vaccine adjuvant is being explored. However, in recent years advances in avian immunology and genetics have led to the discovery of few recombinant cytokines or monoclonal antibodies against avian cytokines. The availability of new technologies (such as real-time quantitative; RT qPCR) now allows the quantification of expression of messenger RNA from cytokine genes without the need for protein and antibody [12].

Inflammatory reactions

Inflammatory stimuli applied to the respiratory system efficiently elicit macrophages and heterophils to the respiratory surface. This was clearly shown by the high number of macrophages recovered from the lung and air sacs of turkeys after inoculation of incomplete Freund's adjuvant (IFA) into the abdominal air sacs. These macrophages showed rapid adhesion to glass surfaces, phagocytosis of zymosan particles and killing of *Escherichia coli* by *in vitro* assays. There is limited knowledge about adhesions mechanisms of micro organisms to avian respiratory macrophages. Mechanisms of leukocyte recruitment serving immune defences could be designed in a way that (under normal circumstances) avoided accumulating these cells in the capillary bed of the alveoli and compromising the gaseous

exchange system. To unravel these complex problems, detailed knowledge of the specific cells, molecules and mechanisms involved in lung immunology is required [13].

Melatonin, Seasonal Immunity and Reproduction

Immunomodulatory property of melatonin is well documented in seasonally breeding animals. Previous studies elucidated the interaction of peripheral melatonin with seasonal pattern of immunity and reproduction in various tropical birds including Indian tropical male bird, *Perdicula asiatica* [14]. Tropical changes in the environmental factors are significantly different than temperate zones. Indian tropical bird, *P. asiatica* is a summer breeder, where pineal gland activity showed opposite relationship with gonadal activity [15]. The seasonal change in the development, regression and regeneration has been reported in thymus and spleen of and bursa of Fabricius of birds [14]. The annual changes in spleen weight present an inverse relationship with gonadal function and a direct relation with peripheral melatonin level. Further, circulating total leukocyte and lymphocyte count, which accounts for general immune status showed changes parallel to each other and directly proportional to blastogenic response in lymphoid organs i.e. spleen. On the hand the environmental factors i.e. photoperiod, temperature, relative humidity varies throughout the year also profound impact on the immune status of this bird. Several studies also supported that photoperiod and temperature play an important role in the regulation of the lymphoid organs such as thymus, spleen and other parameters of immune system i.e. total leukocyte count, lymphocyte count and blastogenic response of the splenocytes in mammals [16,17,18]. Our data on spleen weight, total leukocyte count and splenocytes proliferative response to the mitogen Con A suggests that slight changes in photoperiod of tropical zone as noted during dawn and dusk can affect immune status of this bird. Our study of splenocytes proliferative response to the mitogen Con A in the different month throughout the year showed lowest splenocytes proliferation as well as % stimulation ratio (%SR) in the month of April when days were long (13L:11D). In other words increasing trend of melatonin concentration in serum during the winter suppressed the strong effect of winter stressors, enhanced the immune parameters and helped the bird to remain healthy and fit in order to combat with winter born diseases (sudden death syndrome, chick flue, conjunctivitis etc.). Seasonal changes in photoperiod and temperature influences the interior milieu i.e. hormonal concentration, which required for the various seasonal adjustments of metabolic activities. This alteration could be due to internal level of melatonin and gonadal/adrenal steroids. During summer days i.e. long photoperiod, higher gonadal steroids in circulation is responsible for reproductive activity in this birds and thereby decreases the immune status as steroid suppresses immunity in general [19,20].

Photoperoid and Lung Associated Immune System (LAIS)

Recent studies on lung associated LAIS in birds had helped us in understanding the problems related with respiratory diseases in bird epidemics and its related respiratory tract diseases (influenza or avian flu) [21,22]. Photoperiod had influenced the LAIS in different photoperiodic conditions given to birds during reproductive inactive

phase (RIP) and reproductive active phase (RAP). The tropical bird *P. asiatica* is photoperiodic; hence, there was a significant difference in relative testes weight following 8 weeks exposure to different photoperiodic regimes during both the reproductive phases. Testes weight significantly decreased under short photoperiod (SP) while it increased under long photoperiod (LP) as it was reported earlier also [23]. Further it has been reported that short photoperiodic induction of circulatory melatonin level helps the birds in improving the general immunity and lung associated immunity. This was supported with increase in size of BALT and non-BALT nodules in the lungs of birds under SP and decreased nodular size under LP reflecting that photoperiod does affect the lymphatic nodules size of lungs as it does to the general immunity. BALT and non-BALT nodules which consist of lymphocyte (T-cells and B-cells) aggregates are the major component of avian LAIS. These nodules play a crucial role in the development of local immune response to inhaled antigens [24,25,26]. The level of circulatory gonadal steroid is equally influenced by different photoperiodic regimes; hence, SP decreased testosterone and increased circulatory melatonin level as well as lung lymphocyte proliferation when compared with other photoperiodic group birds. This indicates that due to increased level and duration of circulatory melatonin the general immunity was enhanced during RIP than RAP. It has been reported that lymphatic tissues (spleen, thymus and bone marrow) and immunocompetent cells of birds and mammals possess melatonin receptor and being influenced by circulatory level of melatonin [27,28,29]. Thus, the expressions of Mel_{1a} and Mel_{1b} receptor types changed significantly during both the reproductive phases depending on the duration of light (under different photoperiodic regimes). Further, combined interplay of the gonadal steroid and melatonin appears to be responsible for regulating seasonal variation in LAIS for the fitness of the respiratory system of a seasonally breeding bird. Due to increased duration of darkness under SP and RIP a general as well as lung-associated fitness was more in birds. Many studies show that melatonin and photoperiod are involved in pathophysiology of avian and mammalian species in various ways [30-35]. Respiratory diseases play an important role in poultry and result in substantial economic losses to the poultry industry. In addition, several important poultry pathogens enter the host through the lung surface and subsequently disseminate to their target organs in the body. There is very limited knowledge about the lung-associated immune system in the chicken and in poultry in general which might be a consequence of the unique and complex anatomy and function of the avian lung. For the first time described organized lymphoid structures in the bronchial mucosa of the chicken lung [14]. BALT development was shown to follow the same time course in specific pathogen free (SPF) and conventional chickens [22] but seems to be influenced by environmental stimuli. However, the presence of inflammatory substances such as endotoxins in the inhaled air cannot be excluded and may play a role in BALT formation. It is therefore, conceivable that antigenic stimulation is required for the induction of BALT formation and for the development into fully mature structures in the first few weeks after hatch. The demonstration of a highly developed and constitutively present BALT structure in the chicken and turkey stimulated some investigators to suggest that these mucosa-associated lymphoid structures may functionally compensate for the lack of lymph nodes in birds [22].

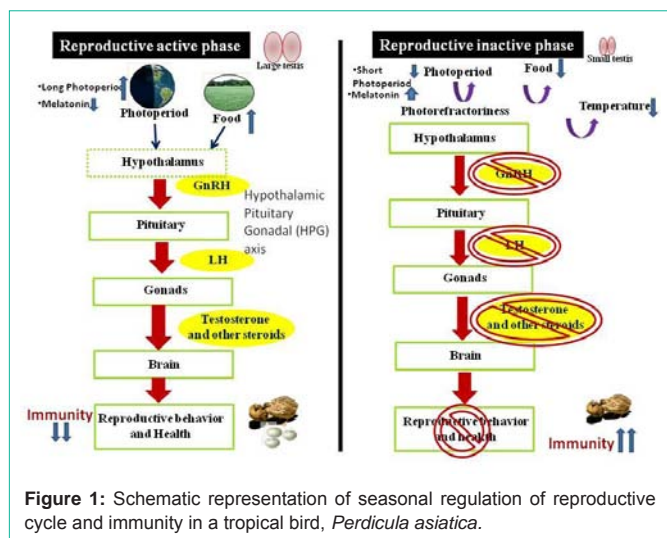


Figure 1: Schematic representation of seasonal regulation of reproductive cycle and immunity in a tropical bird, *Perdicula asiatica*.

Environmental Factors and Immunity

Previous studies have shown that low ambient temperatures, reduced food availability, and other energetically demanding winter conditions compromise immune function, and these factors can be manipulated and controlled in the laboratory [37]. Because many stressors are seasonally recurrent in nature, individuals of some species may have evolved mechanisms to anticipate and counteract these recurring threats to maximize immunity. Short photoperiods have been hypothesized to serve as a cue used by animals to enhance immune function in advance of energy-compromising conditions [38]. This enhancement appears to be mediated by the pineal hormone, melatonin. Increased duration of melatonin treatment (mimicking long nights) enhances immune function, either directly or indirectly by affecting the secretion of steroid hormones and prolactin (Figure 1) [39].

In a nocturnal birds the Indian spotted owl, *Athene brama* is predated on the field rodents, mice, lizards and other small pests of agricultural crops is victim of the frequent use of herbicides and pesticides that directly or indirectly influences immunity via the food chain [40]. Therefore nature of the food may challenge the immunity, and this could be the reason behind the decreasing number of some predatory birds like owls, vultures and kites. Several studies on spotted owl have inferred that habitat quality, prey abundance and weather are having drastic influence on reproduction and immunity [41-42]. However, only few studies dealing with reproduction of birds in relation to immune capacity under natural condition have been carried out [43-44]. In addition, owlets have to endure many stressors in their natural environments, for e.g., they experience food shortage, predator pressure, high parasite densities with season, and social pressure that strongly influence immunity [45].

Stress-immune Interactions in Birds

Birds encounter maximally the drastic changes in environment whether manmade or from nature. In nature generally they face shortage of food due to natural calamities, less or no water condition in summer and a restricted movement during heavy rainfall in monsoon of tropics. Several reports suggested that hormones like

corticosterone and melatonin whose seasonal changes in circulatory level are known does influence reproduction, immunity and stress. But what pathway these hormone utilizes during or under stress for physiological homeostasis to survive under extreme environmental condition is not clean. Experimental stress given to *P. asiatica* that it generally encounters in nature helped to explore the possible immune regulation following stress. The oxidative load increased following stress. A significant restoration in free radicals was observed in immobilised birds following melatonin pre-treatment suggesting that in immobilised birds, melatonin restored the oxidative damage significantly. It appears that melatonin might have stimulated the antioxidative enzymes like (SOD and catalase) which were responsible for scavenging the increased free radicals in lymphatic tissue of birds under induced stress. In other vertebrates negative correlation between several enzymatic and non-enzymatic antioxidants and damages due to generation of free radicals in different types of immune cells or tissues were noted [46,47]. Further, studies on birds have shown the effects of the immune response on the redox balance, but had inconsistent results [48]. Our measured immune status of birds under experimental stress by challenging the isolated splenocytes *in vitro* with mitogen Con A, blastogenic response in terms of % stimulation ratio (%SR) and the total leukocyte count (TLC) showed drastic variation. Our result showed that %SR was significantly high in melatonin pre-treated experimentally stressed birds and being highest in immobilised birds as compared to the birds without treatment. In addition we also measured H/L ratio or leukocyte profile, a useful parameter, in the field of conservation physiology as they are altered by stress and that numbers of neutrophils and lymphocytes presented an opposite manner. Our study showed significant changes and highest value of H/L ratio in immobilised birds. However, when we compared H/L ratio of melatonin pre-treated experimentally stressed birds and compared with the birds without treatment, H/L ratio was significantly low [49]. Cumulative we proposed a link between melatonin and immune activities in this bird.

Melatonin, Glucocorticoid and Immunity

A variety of natural factors may influence immunity in wild birds. Group-living species experience different sorts of stressors than individual or pair-living bird species. Experiments showed increase in compromised humoral immunity in house finches (*Carpodacus mexicanus*), although these effects were not mediated directly by glucocorticoids (GCs) [50]. In zebra finches, pair-housing induces subordinate but not dominant individuals to reduce immune function [51]. In cooperative-breeders, alleviation of reproductive responsibilities can have positive effects, but when environmental conditions are demanding, help during breeding may not offset stress-induced immune suppression [52]. Environmental conditions generally may have broad effects on stress-immune interactions. Incidence of *Mycoplasma gallisepticum* infections and GC responses to stressors in house finches vary among populations and years, but not in an obviously intelligible way [45,53]. GC release by birds varies along urbanization gradients, and songbird populations in urban areas tend to have higher disease prevalence than rural ones [54].

More study in these contexts is needed as different species harbour different pathogens depending on habitat. Evidence from wild species supports the generalizations above based on domesticated or poultry

ones [55]. Moreover, GC responses to stressors tend to be repeatable within individuals irrespective of the stressor on immunity are likewise unstudied [49,56].

Conclusion

Present review summarize that in rapidly changing environment is imposing additional pressure on immunocompetence and health maintenance of wild birds. Thus it will become increasingly important to identify how human activities alter the immune defences of birds and do our best to prevent these physiological changes in birds. The photoperiod via melatonin does improve the suppressed immune status and oxidative damage in wild birds as noted various species of birds including, *Perdica asiatica*. These observations suggest that melatonin treatment may be used as a therapy to enhance the immunity and thereby survival of birds under stressful environmental conditions. In addition, photoperiodic length might be used as a mode of therapy to enhance the immunity in poultry industry by increasing level of endogenous melatonin noninvasively to save the population of birds. Future studies will provide comprehensive examination of deleterious effects of changing environment on avian immunity.

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