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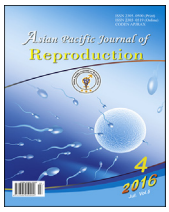

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Prenatal corticosterone exposure programs growth, behavior, reproductive function and genes in the chicken

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ABSTRACT

The aim of this review paper was to understand the role of prenatal corticosterone exposure on growth, aggressive behavior, reproductive performance and gene expression in the chicken. The phenotype, physiology, reproductive function and behavioral characteristics of an organism are not only influenced by genetic factors, but also by environmental factors that play a critical role in shaping offspring morphology. Exposure to excess glucocorticoids during embryonic development influences offspring growth, physiology and behaviors associated with alterations of hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonadal axis and serotonergic system gene expression. Another influential factor for phenotype, physiology and behavioral development is maternal derived steroid hormones that deposit in the egg. In avian species, maternal influences have aroused much attention after the discovery that avian eggs contain a variety of maternal derived steroid hormones. In addition, the environment condition during ontogeny has played a critical role in behavioral development. In avian species, for example laying chicken, high quality mother care produced chicks that were less fearful. Laying hen maternal care is found to reduce cannibalistic pecking phenomenon. Genetic selection and selection experiments will also play a critical role in animals breeding for the housing systems of the future. To optimize animal welfare and to reduce risks factors such as pecking behavior, fundamental approaches are required that merge selection of the optimal genotype with provision of a positive environment for parents and offspring, both throughout ontogeny and later life.

1. Introduction

Situation experienced during embryonic development can induce lifelong outcomes on adult phenotype and health. This phenomenon is known as “developmental programming” [1,2]. Prenatal exposure to maternal steroid hormones, including glucocorticoids (GCs) or androgens can influence multiple traits, including phenotype [3], physiology [4], and behavior [5]. The eggs of birds provide a repository for a variety of maternally growth factors and hormones [6,7] that affect development [8] in addition to the offspring phenotype [6,9]. A number of these maternally hormonal effects are seemed to be obligatory prerequisites for normal growth and development whereas; others may act as mediators of developmental plasticity [6].

GCs are known to play critical roles in embryonic development and maternal programming in mammals [10] and birds [11]. Embryonic exposure to maternal GCs is known to have both short- and long-term consequences [12,13], such as decreased birth or hatch weight, retarded growth rate, compromised immunity and even reduced survival [14–16]. Experimentally, prenatal stress or exposures to GCs can reprogram offspring physiology, resulting in a increases plasma CORT, increased

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aggressive behavior and decreases of 5-hydroxytryptamine (5-HT) system function [17]. Also, prenatal GC exposure has a negative impact on offspring phenotype quality and reproductive performance [18]. Moreover, prenatal GCs exposure reprogrammed hypothalamic-pituitary-adrenal (HPA) [19,20] and hypothalamic-pituitary-gonadal (HPG) [21] axis associated with alterations of stress and reproductive related gene expression [22–26]. Prenatal stresses also have been reported to influences on the development of offspring serotonin system and sensitize neuroendocrine systems [27]. In mammals, prenatal stress during the embryonic development offspring increased 5-HT associated with alterations of hormonal and behavioral responses to environmental stimulus, together with the HPA axis [27–29]. Moreover, prenatal stress reprogrammed HPG axis associated with alteration in reproductive performance and gene expression. However, whether all above mentioned outcomes can be transferred to the next generations is not yet studied.

2. Maternal hormones

Maternal steroid hormones are excreted prior to egg laying in birds or during pregnancy in mammals. Avian species have been an excellent model to investigate effects of hormones. However, egg hormones concentrations can be modulated from the beginning of the incubation as well as during the embryo development due to the hormone production of the same embryo [30]. Further, incubation and hatching conditions after egg laying can be experimentally controlled and the hormone levels can be changed by *in ovo* injection of hormones in to the egg [30]. It has been reported that avian eggs contain a variety of steroid hormones, which cause maternal effects on offspring phenotype [30,31]. Until now, thyroid hormones [32,33] insulin [34] and leptin-like immunoreactive substance [35], androgens [9,36], gestagen [37], are reported to be present in the egg of avian species. Maternal corticosterone (CORT) has also been found in avian species eggs including domestic fowl [30,38,39], Japanese quail [40], canary [9] and starlings [14]. Significant breed difference (>2 folds) in yolk CORT concentration was found between White Leghorn and Hy-Line Brown eggs [41]. Breed differences of egg yolk and albumen CORT concentrations between slow and fast growing broiler chickens also has been reported [39]. Meat-type chicks were found to demonstrate blunted HPA response to novel environment compared with layer-type chicks [42] and the remarkable difference in growth rate was found between broiler and layer chickens which was associated with hypothalamic expression of HPA axis related genes [43]. Stressed of barn swallows laid eggs contain high CORT concentration which produced low quality of offspring [16]. The elevation of egg CORT influences offspring growth rate, behavior and gene expression. Both HPA and HPG axis are related genes expression were altered by elevation of egg CORT concentrations. Breed differences in egg CORT concentrations is reported. Yolk CORT levels were higher in eggs produced by white hens, approximately twice of eggs laid by brown hens [41]. These findings imply that offspring hatching from eggs laid by White Leghorn hens are exposed to more CORT concentration. Whether, this process may permanently imprint offspring phenotype, physiology, behavior and gene expression is unknown.

In avian species, maternal influences have aroused much attention after the discovery that avian eggs contain a variety of maternal derived steroid hormones [9,30]. The CORT concentration of eggs is modified by various factors including physiological status of the hen [16], stressful environment [44], and housing condition [45], unpredictable changes in food availability [46], human disturbances [47] and social conditions.

3. Prenatal corticosterone, offspring phenotype and aggressive behavior

Offspring phenotype is a consequence of an interaction between the genotype and environment during the most sensitive periods occurring within the early embryonic or postnatal development [48]. During this period, almost all of the signals come from the mother and such influences are called maternal effects [6]. Embryos are exposed to a substantial amount of maternal derived GCs *via* yolk deposition in birds [16]. However, it is still unclear whether the amount of GCs that the embryo may be exposed can be modulated by embryonic GCs metabolic enzymes. Chronic stress modifies the HPA axis activity results in an increased exposure to GCs through an elevation of baseline levels and causes offspring phenotype shaping [15,49]. Exposure of GCs during embryonic development is known to have both short- and long-term consequences [12,13], for example decreased hatch weight [50] and compromised immunity [15]. In addition, *in ovo* administration of CORT prior to incubation increased flight performance [51] and fearful behavior [50]. Moreover, elevation of egg CORT at later stages of embryonic development improved the recall of a passive avoidance task [52], and the rate of pecking behavior at grains and pebbles in chicks [53]. The CORT-implanted seabird's chicks were more aggressive compared to the controls [54].

Avian egg yolk contains considerable amount of biologically active substances including maternal derived steroid hormones, carotenoids [55], antibodies [56,57], and antioxidants [58]. These hormones influence offspring morphology, physiology and behavior and can be transmitted to the next generation at each stage of embryonic development [30,59]. Testosterone is one of the most important androgen deposited in avian eggs [60]. Testosterone also mediates maternal effects, influences offspring phenotype [8,61], behavior [62,63] and even compromised immune system [64,65] in many wild bird species. *In ovo* injection of low dose testosterone stimulated growth of the *Fabricius bursa* whereas an inhibitory effect was seen after the high dose [66]. Furthermore, long-term consequences of yolk testosterone on immunity suggested its immuno-ornamental effects [67]. The elevation of eggs CORT prior to incubation was found to increase total yolk CORT concentration. The elevated yolk CORT slowed growth in male but not female chicks with reduced the HPA axis responsiveness of female but not male adults [40]. Thus, prenatal exposure of CORT and testosterone influence allocation and sex differences in the organizational effects of GCs [68,69]. The mechanisms and adaptive importance of such differences have yet to be determined.

Recently we have found that CORT *in ovo* increased aggressive behaviors of the chickens associated with alterations in the expression of HPA axis genes and serotonergic genes [70]. Thus, these findings suggest that prenatal exposure to access of maternal CORT may be responsible for several of the long-life neurobiological, behavioral consequences of prenatal. Our findings further suggest that early life experience or poor environments constitute a risk factor for prenatal stress disorders

later in life. Moreover, the deregulation of serotonergic system may lead to reprogramming of aggressive behavior. Future studies are required to include gender differences and monitoring environmental factors while studying the effects of prenatal CORT exposure.

4. Cross linkage of prenatal stress, corticosterone and testosterone

There are numerous evidences that CORT, testosterone and aggression are linked, they are commonly interconnected because both hormones mobilize the activity in specific brain regions, most probably associated by different however cooperative circuitries [71]. This cross linkage plays a critical role during all four stages of aggressive interaction, modifying predisposition, motivation, and active aggression [72,73]. Previous studies demonstrated various advantages of the avian model, which allows studying maternal hormones in the yolk with no interactions with neuroendocrine environment of mother and potential extrapolation of the findings from the evolutionary perspective [74]. Prenatal exposure of both CORT and testosterone can affect offspring growth, immunity, behavior [15,75] and sex allocation in birds [68,76]. Thus disclose the mechanism mediating early maternal influences whereby stress experienced by mother might negatively interpret to offspring phenotypic quality, behavior, immunity and reproductive performance.

5. The ontogeny of glucocorticoid metabolic enzymes

Glucocorticoids are crucial for development of embryo and their bioactivity is modulated by the intracellular metabolism including 11β-hydroxysteroid dehydrogenases (11β-HSDs) and 20-hydroxysteroid dehydrogenase (20-HSD) [77]. The 11β-HSD_1 activates, whereas 11β-HSD_2 inactivates GCs in mammals including man, mice and *in vitro* [78–82]. The 11β-HSD_1 is expressed predominantly in mouse liver, kidney and lung of mice [83], while $11HSD_2$ mainly exists in kidney, colon and placenta of the human [84]. In chicken, 20-HSD is an abundantly and ubiquitously expressed enzyme, which transforms GCs to inactive 20-dihydrocorticosterone in chickens [85].

The tissue distribution and ontogeny pattern of 11β-HSDs have been well established in mouse, rat and sheep [86–89], while relevant information in avian species is scarce. Partial or complete cDNA sequences encoding chicken 11β-HSD_1 [90], 11β-HSD_2 [91] and 20-HSD [92] have been cloned and the patterns of tissue-specific expression of these three genes are described for 5–7-week-old Brown Leghorn chickens. The ontogeny and tissue distribution of 11β-HSD_1, 11β-HSD_2 and 20-HSD expression during chicken embryonic development has not been reported.

In our previous publication, we reported the ontogeny and tissue distribution of GCs metabolic enzymes in slow and fast growing broiler chickens. 11β-HSD_1 and 11β-HSD_2 were found to express relatively higher in liver, kidney and intestine, following similar tissue-specific ontogenic patterns. In liver, expression of both breeds 11β-HSD_1 and 11β-HSD_2 was unregulated towards hatching, nevertheless 20-HSD displayed distinct pattern showing a significant decrease on posthatch day 1 (D1). Hepatic mRNA expression of 11β-HSD_1 and 11β-HSD_2 was higher in fast-growing chicken embryos at all the embryonic stages investigated and so was the hepatic protein content on embryonic day of 14 (E_{14}) for 11β-HSD_1 and on E_{14} and D_1 for 11β-HSD_2. The 20-HSD mRNA was higher in fast-growing chicken embryos only on E_{14} [39]. This may account to some extent for the breed disparities in embryonic development. These findings may suggest potential critical periods of 11β-HSDs sensitivity during development for numerous organ systems. 11-HSDs, the main GC activation/inactivation enzyme in the mammalian placenta, have also been expressed in the ovary of zebra finches [93] and in the oviduct and gonads of chickens [91]. This might implicated the possible low transfer rate of egg CORT deposition in birds, suggests that birds and mammals may have similar strategies to protect the embryo from overexposure to maternal CORT. Further studies are required to clarify the role of 11-HSDs in growth, behavior and reproductive function in chicken.

Several studies reported that maternal adversity during pregnancy may alter 11ß-HSDs in rat and humans [94,95]. Chronic restraint stress during pregnancy was found to decrease mRNA levels of this gene in rat [96]. Over exposure of GCs consider a common link between the prenatal environment, fetal growth and adult neuroendocrine and affective disorders in human [97]. The inhabitation of 11β-HSD_1 was found to prevent stress effects on hippocampal synaptic plasticity and impairs contextual fear behavior in mice [98]. These findings may suggest that deregulations of 11β-HSDs may affect local metabolism of GCs which is relevant for the consequences of stress influences on HPA axis plasticity and contextual aggressiveness habituation which in turn may alter reproductive performance. Moreover, selective 11β-HSD_1 inhibitors may be of interesting for the new approach to the prevention aggression in farm animals.

6. Serotonin system and aggression

In mammals, prenatal stressors re-program the 5-hydrodxytryptamine (serotonin) (5-HT) system in rat [99,100]. Previous studies have shown that central 5-HT system plays a crucial role in modulating aggression in animals [101]. Elevated serotonergic activity usually predisposes reduced aggression both animals and humans [102]. Deregulations of both systems are associated with mental health in general and with mood disorders in particular in humans [103]. Low levels of blood 5-HT are associated with changed physiological functions, including the HPA axis and aggressive behavior in primates and rodents [104,105]. In chickens, the frequency of aggressive behaviors increased in the hens of Dekalb XL (DXL) and high group productivity and survivability (LGPS) treated with 5-hydroxytryptamine (serotonin) receptor 1A (5-HT1A) antagonist indicating that serotonin plays a major role in aggressive behaviors [106]. However, in avian species, the majority of studies investigating the effects of artificial elevations of egg yolk CORT focused on growth and behavior [107]. Our recent publication suggests that CORT *in ovo* during the embryonic development increased platelet 5-HT uptake, decreased whole blood 5-HT concentration associated with down-regulation of hypothalamic tryptophan hydroxylase 1 (TPH1) mRNA, up-regulation of 5-HT receptor 1A (5-HTR1A) and monoamine oxidase A (MAO-A) mRNA, but not monoamine oxidase B (MAO-B) [70]. It is well known that the GCs including CORT and cortisol are responsive to stress and affect aggression. However, whilst 5-HT and GCs can both have an excitatory

effect on aggression [102], the relationship between 5-HT and GCs is need to be more elucidated, and much of the characteristics in function depend upon timing. 5-HT modulates a four-stage functional pattern of influences: (1) predisposed (positively or negatively) toward aggression, (2) motivated toward behavior, (3) responsive to stress (including aggression) and passively allowing aggression, and lastly (4) chronically applied 5-HT and glucocorticoids inhibit aggression. The deregulations of 5-HT can increase the aggressiveness which in turn can affect reproductive performance in chicken.

7. Impact of stress on reproductive function

Reproductive functions in mammals can be programmed by prenatal GCs exposure [108]. In avian species, maternal stress modulates reproductive hormones concentrations in their eggs [109] and thereby influences offspring phenotype [110] and behavior [111] and reproductive capacity [25]. Prenatal stress is reported to has a negative impact on reproductive function in quail which was transmitted to next generations [112]. The negative effects of stress are thought to be regulated by the interactions of the HPA axis and the hypothalamic-pituitary-gonadal (HPG) axis [113]. For example, corticotropin releasing hormone (CRH), a key hypothalamic neuropeptide that activates the HPA signaling cascade, has been also reported to suppress gonadotropin releasing hormone ($GnRH_1$) release from hypothalamus in birds [114]. Although GCs are crucial in helping animals to recover from exposure to a stressor, GCs also influence the HPG axis function in male and female song sparrows [21]. CORT exposure inhibited follicle stimulating hormone (FSH) and luteinizing hormone (LH) secretion from the pituitary *in vitro* [115,116]. In addition, the treatment of CORT suppressed the development of follicles which was energy status dependent in laying hens associated with decreased availability of circulating yolk precursor [117]. Early life stress induced permanent modification in HPG axis in later life in chickens [118]. Recently, we have investigated the effects of prenatal CORT exposure on reproductive performance. Egg elevated CORT reduced egg production and egg quality, associated with the decreased ovary and oviduct weight. In addition, *in ovo* CORT exposure decreased LH receptor and FSH receptor mRNA abundance in theca cells of ovarian follicle 1 (F1), F2 and F3. Moreover, yolk CORT concentrations were significantly greater in eggs laid by hens prenatally exposed to high dose CORT [25]. It is possible that these effects could be transmitted across multiple generations [119]. Thus, it presents new ways for research on the transgenerational epigenetic effects of aggression and stress in avian species is meaningful.

8. Stress, 5-hydroxytryptamine and aggressive behavior

Previous studies have shown that central serotonin (5-HT) system plays a crucial role in modulating aggression in chicken [120]. Elevated serotonergic activity usually predisposes reduced aggression in humans [102]. In the brain the biosynthesis of 5-HT is controlled by the rate-limiting enzyme tryptophan hydroxylase (TPH) in mammals [121]. TPH_1 is the predominant isoform responsible for 5-HT synthesis in both central and periphery mice tissues [122,123], while TPH_2 was found only in humans and mice brain [124]. Serotonergic activity is determined by the extracellular 5-HT levels that are regulated by 5-HT release, reuptake and metabolism. Activation of 5-HT1A autoreceptor (5-HTR1A) located on the presynaptic membranes inhibits the release of serotonin, while the 5-HT released to the synaptic spaces is either taken up by the serotonin transporter back to the presynaptic neurons, or inactivated by monoamine oxidase (MAO) in mice [125]. In rat, dexamethasone during the pregnancy elevated plasma CORT levels, increased aggressive behavior and altered monoamine metabolism adult offspring brain [126]. In chicken, maternal CORT exposure influences offspring's physiology *via* increasing plasma CORT concentrations [107], decreasing blood 5-HT concentration whilst increased platelets 5-HT uptake [70]. The above mentioned data suggested that the modification of the 5-HT system during early embryonic development may alter its functions in mediating aggressive or fearful behaviors [127]. Furthermore, prenatal alterations of the 5-HT system have long-life implications on both physiology and behavior, particularly aggressive and fearful behaviors. Whether these modifications can be transmitted to next generation or not is of an interest area of research particularly in chickens.

9. Stress and epigenetic programming of aggressive behavior

Epigenetic modifications are reversible and mitotically heritable alterations in genomic expression that occur independently of changes in the gene sequence (Annu Rev) [128]. Chronic stress can induce heritable changes in gene expression patterns through DNA methylation or through histone modifications in birds and mammals [129–131]. Prenatal exposure to synthetic GCs increased global DNA methylation in many organs of guinea pigs [132,133]. In avian species, only one study reported the effects of social isolation and restraint in early life on corticotropin releasing hormone receptor-1 and early growth response gene expression in the chicken hypothalamus [119].

Maternal stress increases the CpG (The regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide) methylation of the GR promoter in the mononuclear cells in the cord blood of human infants [134,135] and rodents [136]. Early life stress increases the methylation of the GR promoter in human leukocytes [137] and the methylation of the CRH promoter in different brain areas in rats [138]. DNA methylation is one mechanism through which prenatal stress can be translated into changes in gene expression and can lead to phenotypes changes in mice [139]. Methylation changes at GR promoter were found to be associated with alterations in GR expression and the birth weight in humans subjected to prenatal stress [140]. Our recent finding suggests that embryonic exposure to CORT increased the CpG methylation of GR and CRH gene promoters in the chicken hypothalamus [70]. In addition, CORT *in ovo* retarded growth and increased aggressive behavioral associated with increased GR and CRH promoter methylation. To understand the relationship between epigenetic modification of GR and CRH genes, growth, and aggressive behavior in chickens, it is crucial to deconstruct early life trials and study each one in its own right and then look together how they interacts with each other. Finally, it seems intuitive that prenatal CORT exposure and context-dependent epigenetic modifications cooperate, consequential in

the offspring variation observed in behaviors; nevertheless until now this hypothesis has never been studied experimentally.

10. Conclusion

This review aimed to discuss the role of prenatal corticosterone exposure on growth, behavior development, reproductive function and genes in the chicken. In addition, it shows some of the relationships between these aspects in shaping the individual behavioral characteristics and reproductive capacity of chicken. From our studies on prenatal corticosterone exposure on programming, it became obvious that CORT *in ovo* affects offspring phenotype, behavior and reproductive performance. More attention should be taken for the environment in which we keep the parent stock of our farm animals. We have to think about incorporating elements from such successful early life environments in commercial rearing systems, for example heat stress, food restriction, housing condition and so on should be considered. However, whether the early stress experiences will be passed on by affecting next generation phenotype, aggressive behaviors, and reproductive capacity is of interest research question and need to be answered. Also it is still unclear if the epigenetic modification of stress related genes will pass to the next generation. Additional studies are required in commercial systems, where data on behavior and technical performance are collected both in parent stock, young animals and adults, to be able to evaluate the importance of the different life phases for behavioral development and reproductive performance of farm animals.

Conflict of interest statement

We declare that we have no conflict of interest.

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