Reproduction in a majority of birds occurs at a specific time of the year that is the most favorable to the survival of young and their parents. Seasonal reproduction in birds ensures the hatching of young and dwelling in most favorable environmental conditions, like the availability of food and water. Birds have to predict the time of rich food resources. This ability is under the control of endogenous circannual rhythms (Gwinner, 2003) which is synchronized by periodically changing environmental factors. The changes in day-length are the most important signal for setting the appropriate time of year for bird reproduction. Other signals including the presence of mate, nest site, social interaction temperature or appearance of rich food supply are important for final tuning the exact moment of reproduction. The environmental components used in the timing of reproductive function include photoperiod, temperature, rainfall, humidity, food, and water in addition to other intrinsic mechanisms which may be hormonal and neural.

Environmental factors like starvation, water deprivation, radiation, pollution are associated with disturbance of homeostasis of the living being as well as a decrease in reproductive performances. Under the influence of stressors avian reproductive potential is decreased (Dickens & Bentley, 2014). Corticotrophic releasing hormone (CRH) and arginine vasotocin (AVT) mediated hormonal and neural circuitries are involved in stress modulation (Emmerson and Spencer, 2018).

The expression of AVT was observed in neurons of hypothalamus of pigeon (Berk et al., 1982), chicken (Tennyson et al., 1985; Jurkevich et al., 1997) and quail (Viglietti-Panzica, 1986) and has provided possible anatomical brain regions involved in physical and social stress in birds (Goodson et al., 2012; Nagarajan et al., 2014). We have endocrine evidence to show that stressors interfere with precise timing of reproductive hormones release within the follicular phase. The stressors delay the onset of luteinizing hormone (LH) surge. The reduction in endogenous LH/ gonadotrophin-releasing hormone (GnRH) secretion ultimately deprives the ovarian follicles of adequate gonadotrophin support leading to a decrease a level of growing follicles. Thus, there is a level of interference by stressors at ovary (Dobson & Smith, 2000). The female reproductive system of chicken comprises ovary and oviduct. The avian oviduct is a tubular organ which is composed of four distinct regions infundibulum, magnum, isthmus and shell gland (Solomon, 1991). These regions are lined by ciliated and non-ciliated epithelium (Wyburn et al., 1973). The oviduct is responsible for the egg shell formation by the secretion of their components surrounding the yolk. Infundibulum engulfs the oocyte and surrounds a primary thin albuminous layer called primary vitelline membrane around the oocyte. The largest segment of the oviduct is the magnum which is responsible for the production of several egg proteins including avidin, ovomucoid and conalbumin. Isthmus is also

Key words: Estrogen, Estrogen receptor alpha, Shell gland, Xenoestrogen
involved in egg formation. Shell gland secretes calcium ions for the formation of egg shell. The egg stays in the shell gland for a largest time around 20-22 hrs for the formation of the shell. Reproduction is such an important physiological system that animals have to ensure that they can respond to their surroundings.

**ESTROGEN AND SEX DIFFERENTIATION**

Sex steroid participates in the regulation of female reproductive physiology of chickens. Estradiol is involved in the development of female secondary sexual characteristics, follicle maturation and differentiation, vitellogenesis (Hrabia et al., 2008; Gonzalez-Moran et al., 2013). In female reproduction, estradiol elevates the concentration of plasma vitellogenin by two processes in which includes increase production of vitellogenin and VLDL (Very low-density lipoprotein) and decreases their uptake by the ovary. Vitellogenin (VTG) and very low-density apolipoprotein (apo-VLDL) are estrogen-inducible egg yolk precursor proteins and egg yolk proteins, respectively, produced in the liver of female birds during periods of egg-laying (Mattsson et al., 2011). During embryo development of reproductive system, estradiol play a crucial role in sex differentiation of the brain. In avian reproduction, estradiol play important role in development of female reproductive organs (Scheib, 1983). It is also involved to demasculinize brain under the control of adult reproductive behaviours (Balthazart and Ball, 1995). In sex differentiation required genomic actions are mediated by both kinds of estrogen receptors of the nuclear receptor family, these are ERα and ERβ. There are many studies in rodents species which state that both kinds of ERs shows opposite roles (Lindberg et al., 2003; Hillisch et al., 2004; Harris, 2007; Hili et al., 2007). In avian species like quail, it was found that ERα is expressed during the early development of brain while ERβ was expressed in adult brain (Axelsson et al., 2007). It has been previously reported that ER mRNA is expressed in embryonic oviduct that is also known as mullerian ducts during the differentiation of both male and female quail embryo (Mattsson et al., 2008a). The treatment of ER antagonist propyl pyrazole triol (PPT), stimulates retention of mullerian duct followed by the development of ovotestis like structure in the embryo of male quail (Mattsson et al., 2008a). Thus ERα has a crucial role in the differentiation of reproductive tract of female (Mattsson et al., 2008b). In female chicken exogenous estrogen causes ERα mediated development of female characteristics in male embryo by inhibiting mullerian duct and also cause male reproductive malformations (Brunstrom et al., 2009; Mattsson et al., 2011). In case of male chicken (Rooster) ER beta and ER alpha are expressed in principal and basal cells of epididymis region of the testis, ER-beta is predominantly expressed in somatic cells and some germ cells. ER-alpha is distributed in the distal part of efferent ductle of the epididymis (Bahr et al., 2006). Estrogen is also known to be involved in the proliferation of primordial germ cells in embryonic condition through the GPR-30 mediated EGFR/Akt/β catenin signaling pathway (Ge et al., 2012). Various studies of early exposure of estrogen suggest that it causes uterine abnormalities, production of shell-less eggs as well as impaired egg laying birds (Greenwood and Bhly 1938; Rissman et al, 1984; Gildersleeve et al., 1985). Estrogen modulates Na+/K+ ATPase, carbonic anhydrase, Na+/H+ exchanger (NHE3) and aquaporin2. Therefore, it is believable to derive that the estrogen-responsive system may also have a regulatory role in reabsorption through avian efferent ductules (Bahr et al., 2006).

**ESTROGEN AND SHELL GLAND**

The oviduct of the hen is the studied for steroid action of estrogen (Dougherty & Sanders, 2005). The egg shell formation is regulated by the action of estradiol. Egg shell quality is determined by the availability of calcium. Dietary calcium is the main source of calcium, used in shell formation while bones are a secondary source of calcium. It was reported that intestinal calcium absorption decrease in mammals like rat with an increase in age (Horst et al., 1978). It was also reported in human (Schachater et al., 1960; Avioli et al., 1965, Bullamore et al., 1970) as well as in chickens (Al-Batshan et al., 1994; Hansen, 2002). Estrogen increase synthesis of calcium-binding protein, calbindin D28K (CaBP D28K) (Berry & Brake, 1991) as well as also stimulates calcium transport in intestinal tissue. Thus estrogens have a strong relationship in the absorption of calcium followed by a crucial role in shell formation (Al-Batshan et al., 1994). Estrogen not only involved in the regulation of reproductive behaviour but it also promotes epithelial cells to further transformation into the tubular glands due to the process of cyto differentiation. In this process oviduct-specific genes like obalbumins are transactivated (Palmiter & Wrenn, 1971; Socher & Ormalley, 1973). During egg laying the calcification of egg and calcium metabolism takes place by...
Calcium carbonate and other ions that are supplied by blood vascular system through trans-epithelial layer are involved in egg shell formation. In this process carbonate ions are formed due to the association of metabolic carbon dioxide (CO₂) with water molecule (H₂O) in the presence of carbonic anhydrase enzyme (CA). There is alleviation in egg production associated with poor quality of egg shell (egg thinning) which is the main problem in egg industries (Wolfenson et al., 1982). It has been previously reported that synthetic estrogen-like ethynylestradiol inhibits the expression of CA and also modulate shell gland activity by anatomical or histological changes in quail (Berg et al., 2001, Holm et al.,2001). This egg shell thinning is a threat to the wild species of birds (Berg et al., 2004). The role of CA activity has been well documented in egg shell formation in the last seven decades ago (Benesch et al., 1944). The inhibition of CA in laying chickens causes the production of eggs without their shells. Although the transport of both carbonate and calcium ions are tightly coupled with each other in the shell gland mucosa (Eastin & Spaziani, 1978). The role of estrogen in mammals like pig and mice is in the regulation of endometrial function (Pincus & Bialy, 1963; Hodgen & Falk, 1971). The chicken Lohmann Brown hybrids, exhibit an increase in CA containing capillaries when they were administered by phytoestrogen like daidzein (Wistedt et al., 2012). The duodenal calcium absorption is needed for shell formation as a main source of calcium. Duodenal calcium increases about six-fold when shell is being formed (Holm et al., 2006; Jonchere et al., 2012) while skeletal elements are used as a secondary store of calcium which leads to alleviates ion of bone strength and bone fractures (Webster, 2004). The mRNA study of calbindin (a calcium-binding protein) suggests that the estrogen modulates shell formation indirectly via up regulation the expression of calbindin followed by increase concentration of calcium in plasma (Bar et al., 1996). It has been reported that the estradiol upregulates the expression of the ATP dependent plasma membrane calcium pump (PMCA) at dose-dependent manner and it also plays crucial role calcium reabsorption as well as at cellular level in shell gland (Dick et al., 2003; Yang et al., 2011). What kinds of direct effects of estradiol take place on shell gland is still not clear a dose of 10 μ g/Kg estradiol causes thickness in egg-shell of Tegel pullets (Saki et al., 2002). Food supplement of daidzein also shows an increase in thickness of egg shell of ISA layers (Ni et al., 2007). Daidzein has estrogenic activity and plays important role in the development of shell gland (Wistedt et al., 2012). The genistein is an isoflavonoid which also has an estrogenic effect and protects chickens from heat stress (Kamboh et al., 2013). The hesperidin which is a type of flavonoids also mimics the roles of estrogen (Chiba et al., 2003). Several factors that modulate the function of estrogen-like xenoestrogens. Xenoestrogens are synthetic chemical compounds that are associated with impaired function of the female reproductive tract. Polychlorinated biphenyls (PCBs) and dioxins act as an endocrine disruptor. They induce the expression of estrogen receptors and also modulate their function in shell gland (Hrabia et al., 2013). Bis-phenol-A like xenoestrogens also has cell proliferative role in chicken shell gland (Yigit & Daglioglu, 2010). Expression of egg yolk proteins is therefore widely used as an indicator of xenoestrogen exposure in egg-laying vertebrates (Mattsson et al., 2011). It is also known to modulate heat stress in chickens (Kamboh et al., 2013).

The activity of gonadal steroids like estrogen is governed through the estrogen receptors. In poultry farming egg production and egg shell quality, both are decreased with the increase of chicken's age. Large size but less number of eggs were laid by old chickens while small and more eggs were laid by young chickens. Egg shell thinning is the main problem which is associated with an increase in age of egg industries (Izat et al., 1985; Joyner et al., 1987; Al-Batshan et al., 1994; Hansen et al., 2003). In this problem includes softening of egg shell followed broken shells. It problem arise due to alleviation in hormonal sensitivity associated with respective tissues like egg laying and shell quality shows the close relationship in response to hormonal milieu (Williams and Sharp, 1978; Hansen et al., 2003). In the decrease of hormonal sensitivity towards the steroid, response tissue causes declined intestinal absorption of duodenal calcium which is involved in shell formation (Al-Batshan et al., 1994; Hansen, 1998, 2002; Hansen et al., 2003).
Since hormones, mediated actions are required hormones specific receptor-related mechanisms. In hen, these actions are mediated by estrogen receptor alpha. Thus in chicken, the estrogen receptor alpha distribution decreased with increase in age of chicken (Hansen et al., 2003). It was earlier reported that in shell gland, estrogen have a crucial role in cell proliferation under the influence of estrogen. (Mattsson et al., 2008b; Mattsson & Brunstrom, 2017).

ESTROGEN AND STRESS

Hypothalamic-pituitary-adrenal (HPA) axis responds immediately to stress and irrespective of its origin alters the output of stress hormones (CRH/AVP-ACTH-Corticoids). It has been reported that CRH is the principal regulator of the HPA axis (Gillies & Lowry, 1982). AVT is another hormone of hypothalamic-pituitary-adrenal (HPA) axis (Kuenzel & Jurkevich, 2010). In addition to classic CRH, AVT also comprises the neural components of the classical hypothalamic-pituitary-adrenal (HPA) axis (Kuenzel & Jurkevich, 2010). Central administration of CRH or AVT increases plasma corticosterone (CORT) secretion in birds, plasma adrenocorticotropic hormone (ACTH) and CORT in rodents (Pryce et al., 2011) and plasma cortisol in sheep and cattle (Yayou et al., 2008). In rodents, neurons containing CRH and AVP (Sawchenko et al., 1984) have been extensively studied and their anatomical regions in the brain have been well characterized following different types of stressors such as immobilization, water deprivation, or social interaction (Ho et al., 2010). Temperature is another environmental factor which modulates gonadal growth. This is visible in females since they put more effort into reproduction than males. Low temperature can inhibit reproductive system via elevated corticosterone levels (Siegels, 1980). Acute heat stress causes elevation of the level of estradiol but a decrease in non-heat-acclimated domestic fowl (Wang et al., 1989).

Estrogen regulates the reproductive function through the feedback mechanisms. These hormones perform their function at their optimum physiological level but when their level rise from their optimum range, the suppression occurs by the feedback control mechanism. The administration of estrogen and progesterone in mammal-like rat model causes suppression of corticosterone level (Viau & Meaney, 1991). In male rats, testosterone decreases glucocorticoids and ACTH in the influence of stress (Viau & Meaney, 1991; Viau, 2002). Thus gonadal steroids reduce the stress level.

In non-laying hens, fasting changed estrogen production by stroma, white and yellow follicles reflecting the alterations observed in the activity of P450 arom. It is interesting that during a pause in egg laying estrogen production by stroma and white follicles significantly increased (Proszkowiec-Weglarz et al., 2005). During food deprivation, overall ovarian estrogen synthesis is decreased. Since last three decades, some studies have been done on the neuroendocrine system including adrenal-gonad/thyroid-gonad relationship and role of external and internal factors in reproductive regulation of birds and mammals (Singh & Chaturvedi, 1993; Singh & Chaturvedi, 2006). Gonadectomy increases both corticosterone and ACTH in the male rat which can be normalized by the exogenous administration of testosterone (Seale et al., 2004). These studies indicate that steroid hormones (estrogen and testosterone) have anti-stress property via functional modulation of the adrenal gland in both sexes (Toufexis et al., 2014).

Estrogen receptor can be activated by endogenous components and there have been concerns regarding the adverse effect of dietary phytoestrogens. Activation of the estrogen receptor is determined by the interaction of three principal components; ligands, receptors, and effectors, which together determine the magnitude and character of transcriptional activity of ER in target tissues. The estrogenic activity of estrogens, antiestrogen, xenoestrogens is also cell-context-dependent. Thus the activity of estrogen, anti-estrogen varies in different tissues and sex. Simultaneously activation of both receptors and treatment with higher doses may be required to fully activate sexual behavior and associated neuro-chemical events.

CONCLUDING REMARKS

Altogether, these studies first describe the role of estrogen in shell gland and its physiology. This study suggesting that estrogen play a crucial role in stress modulation in the physiology of shell gland. It regulates the function of shell gland through the estrogen receptors alpha (α). This review also states the co-relation between HPA and HPG axis in stress in which female sex steroids regulate the corticosteroids through the feed-back control and play their stress modulatory effects. We hope that the present review will stimulate further research for estrogen action on shell glands.

ACKNOWLEDGEMENT

This research work was supported by the Start-up grant of University grants commission, New Delhi to RS (grant number F.30-12/2014[BSR]).
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