Dietary Manganese Regulates the Endocrine Mechanism of Reproductive Performance in Female Poultry: Postprint

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Date: 2017-10-10T00:00:00+00:00

Abstract

The reproductive performance of female poultry exerts a crucial influence on layer production and the entire broiler industry chain. As an essential component or important activator of related functional enzymes, manganese not only participates in animal growth and development, carbohydrate and lipid metabolism, but also plays a significant role in maintaining reproductive function. This review focuses on the neuroendocrine regulatory pathways of female poultry reproductive performance, summarizes the mechanisms of manganese action in the biosynthesis of sex hormones, central neuroendocrine system, and egg quality, and discusses the differences in biological activity among various manganese forms, aiming to provide theoretical support for the application of manganese in female poultry (particularly during the laying period).

Full Text

Endocrine Mechanism of Dietary Manganese on Reproduction Performance in Female Poultry

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Abstract

Reproduction performance in female poultry is critically important to egg production and the entire broiler industry chain. Manganese, as an essential constitutional component or key cofactor for functional enzymes, participates not only in animal growth and carbohydrate and lipid metabolism but also plays a

vital role in maintaining reproductive function. This review examines the neuroendocrine regulation pathways of female poultry reproduction performance, summarizes the mechanisms of manganese action in sex hormone biosynthesis, the central neuroendocrine system, and egg quality, and discusses the biological activity differences among various manganese sources to provide theoretical support for manganese application in female poultry, particularly during the laying period.

Keywords: manganese sources; female poultry; reproduction performance; neuroendocrine; egg quality

1. Neuroendocrine Regulation Mechanism of Poultry Reproduction Performance

Similar to mammals, the acquisition and maintenance of avian reproductive capacity are controlled by the reproductive axis of the neuroendocrine system (hypothalamic-pituitary-gonadal axis). Gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus synthesize and secrete GnRH, which is released into the pituitary portal system via the median eminence and binds to its receptors, thereby promoting and regulating gonadotrophs in the anterior pituitary to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The gonadotropins FSH and LH secreted by the pituitary act on the gonads through blood circulation, promoting gonadal development, maturation, and production of reproductive hormones. Therefore, the hypothalamus serves as the integration center of neuroendocrine regulation and represents the core of reproductive regulation, while the pituitary acts as the relay center for hypothalamic integration. In mammals, FSH and LH are secreted by the same anterior pituitary cells, whereas in poultry, FSH and LH are secreted by different anterior pituitary cells [**?**], suggesting that the regulatory mechanisms for FSH and LH synthesis and secretion may be more complex in birds.

Like other physiological functions, animal reproduction performance depends on both genotype and environment. Laying poultry (broiler breeders and layers) exhibit significant breed differences. Modern broilers feature rapid growth, high feed conversion efficiency, and high meat yield, but long-term selection for muscle growth has severely compromised reproductive performance in broiler breeders [**?**]. Compared with layers, broiler breeders have shorter laying sequences and are prone to superovulation, which disrupts normal oviposition behavior and results in lower total egg production [**?**], increased production of cracked and soft-shelled eggs, inadequate eggshell calcification, and significantly reduced fertility [**?**]. The primary cause of declining reproductive performance in broiler breeders is that yellow follicles (8–10 mm) in these birds are more sensitive to gonadotropins, leading to excessive recruitment and superovulation [**?**]. Further experiments revealed that superovulation may be induced by LH, while FSH can inhibit superovulation by reducing follicular sensitivity to LH [**?**], indicating that the interaction between FSH and LH plays an important role in broiler breeder reproduction, particularly in follicular recruitment.

For complex physiological functions, environmental factors play crucial roles, with nutrition being one of the most important. The environment can integrate with genotype through the neuroendocrine system (in the form of hypothalamic-pituitary-target organ axes) to regulate bodily functions. Therefore, nutritional regulation of reproductive axis activity, particularly the secretion of hypothalamic GnRH and pituitary LH and FSH, is important for improving broiler breeder reproductive performance. In broiler breeder production, altering the nutritional environment through restricted feeding significantly reduces GnRH storage in the median eminence and pituitary LH and FSH levels, delays the secretion peaks of LH and FSH and the onset of lay [**?**], markedly decreases superovulation incidence, and thereby increases laying rate [**?**].

2.1 Sex Hormone Biosynthesis

The precursor for sex hormone biosynthesis is cholesterol, which undergoes side-chain shortening and A-ring aromatization to sequentially generate 21-carbon progesterone, 19-carbon androgens, and 18-carbon estrogens. Impeded cholesterol biosynthesis leads to sex hormone deficiency [**?**]. Cholesterol biosynthesis is a multi-enzymatic process comprising four main stages: synthesis of mevalonate from acetyl-CoA, conversion of mevalonate to isopentenyl pyrophosphate, squalene synthesis, and conversion of squalene to cholesterol. Manganese serves as a cofactor for mevalonate kinase and farnesyl pyrophosphate synthase in the second and third stages of the cholesterol synthesis pathway, suggesting that influencing cholesterol synthesis may be one route through which manganese regulates sex hormone levels. Although studies in rats have shown that excessive manganese exposure significantly alters cholesterol and lipid metabolism in the liver and brain [**?**], non-excessive dietary manganese levels do not significantly affect cholesterol metabolism in animals. Dietary manganese supplementation (0–150 mg/kg) does not affect serum total cholesterol levels in geese aged 5–16 weeks [**?**], ducklings [**?**], or broilers aged 3–5 weeks [**?**], nor does it affect total cholesterol metabolism in laying hens (broiler breeders, laying hens) [**?**]. Therefore, regulating cholesterol synthesis as a precursor for sex hormones may not be the primary pathway through which manganese modulates poultry reproduction performance.

2.2 Central Neuroendocrine System

Manganese deficiency in laying hens reduces laying rate and downregulates blood levels of progesterone, estrogen, LH, and FSH [**?**]. Dietary manganese supplementation (200 mg/kg) significantly increases FSH expression in the pituitary of broiler breeders at peak lay but has no significant effect on LH [**?**]. Thus, pituitary LH and FSH synthesis and secretion, particularly FSH, are likely important targets for manganese regulation of poultry reproduction performance. Three main pathways may influence pituitary gonadotropin secretion.

The first pathway involves direct action of manganese on anterior pituitary cells

to regulate gonadotroph activity. The anterior pituitary exhibits considerable affinity for manganese [**?**], and ingested manganese is rapidly absorbed and deposited in the cerebellum, hypothalamus, and pituitary [**?**], enabling direct action on cells in these tissues. Currently, only limited studies have shown that manganese ions (Mn2+) can act as calcium ion (Ca2+) antagonists to regulate prolactin (PRL) secretion [**?**], and whether Mn2+ can directly affect LH and FSH secretion requires further experimental verification.

The second pathway involves altering GnRH synthesis and secretion to modify its stimulatory effect on pituitary gonadotrophs. Studies have shown that dietary supplementation with 200 mg/kg manganese increases hypothalamic GnRH-1 expression levels to twice those of the control group in broiler breeders at peak lay [**?**]. Using SD rats as an animal model, intracerebroventricular injection of manganese chloride (MnCl2) dose-dependently induced LH secretion, an effect that could be completely blocked by GnRH receptor inhibitors, suggesting that manganese-induced LH secretion is mediated through GnRH [**?**]. In vitro experiments have confirmed that manganese promotes GnRH secretion by activating the guanylate cyclase (GC)/protein kinase G (PKG) pathway [**?**].

The third pathway involves regulating dopamine and PRL synthesis and secretion to alter their effects on pituitary gonadotrophs. Dopamine is an important regulator of PRL secretion from the anterior pituitary [**?**] and also works synergistically with PRL to regulate gonadotropin secretion [**?**]. Numerous studies have shown that excessive manganese accumulation in the brain through the blood-brain barrier can cause degenerative changes in dopaminergic neurons and significantly reduce dopamine synthesis and secretion [**?**]. Follow-up surveys of manganese miners have found that excessive manganese disrupts endocrine system activity and alters blood levels of PRL, FSH, and LH [**?**]. However, our research results indicate that dietary manganese (0–240 mg/kg) does not significantly affect PRL synthesis or dopamine synthesis enzymes in broiler breeder pituitaries. Therefore, under non-toxic conditions, the effects of manganese on dopamine and PRL are very limited, and whether manganese can influence avian reproduction performance through dopamine and PRL is closely related to dietary manganese levels.

2.3 Eggshell Quality

Egg quality is an important manifestation of female poultry reproduction performance, and eggshell quality significantly affects hatchability. In broiler breeder eggs, for example, thick-shelled eggs (>1.080 mm) exhibit significantly higher hatchability and fertility rates and lower mid-to-late embryonic mortality than thin-shelled eggs [**?**]. Sun et al. [**?**] reported that haugh unit, albumen height, and egg weight are positively correlated with fertility and hatchability, while eggshell strength is negatively correlated with fertile egg hatchability. Studies have shown that long-term feeding of manganese-deficient diets significantly reduces eggshell strength and increases cracked, soft-shelled, and misshapen eggs [**?**, **?**], negatively affecting both fertility and hatchability [**?**, **?**].

Changes in eggshell quality may result from altered microstructure. In manganese-deficient diets, eggshell mammillary knobs are large and irregular, and levels of hexosamine and hexuronic acid in the eggshell decrease significantly [**?**]. Dietary manganese supplementation reduces mammillary cone size, increases eggshell mucopolysaccharide and uronic acid levels, and upregulates Gal $ $1-3 glucosyltransferase expression in the eggshell gland [**?**]. As manganese is a specific cofactor for glycosyltransferases, dietary manganese can affect eggshell quality and the fertility and hatchability of hatching eggs by regulating mucopolysaccharide glycosylation in the eggshell.

3.1 Biological Utilization

Dietary manganese supplements can be broadly divided into two forms: inorganic and organic manganese. Organic manganese is produced through specific chemical reaction systems that complex or chelate organic compounds (amino acids, small peptides, proteins) with manganese elements. Using the slope-ratio method with manganese sulfate (MnSO4) biological utilization set at 100%, the relative biological utilization of organic manganese can be calculated. Yang et al. [**?**] reported that the relative biological utilization of two amino acid-chelated manganese sources in broilers was 136% and 143% (using tibia fat-free dry weight manganese content as the indicator) or 114% and 144% (using tibia ash manganese content as the indicator), demonstrating that relative biological utilization calculations for organic manganese are closely related to the sensitivity of the indicator. Since dietary manganese can affect manganese-containing superoxide dismutase (MnSOD) expression at both transcriptional and translational levels [**?**], Luo et al. [**?**] proposed that cardiac MnSOD gene expression could more sensitively reflect the biological utilization of manganese from different sources and is superior to using tibia strength and ash as biological indicators for estimating organic manganese bioavailability.

The relative biological utilization of organic manganese is closely related to its chelation strength. Polarography can be used to estimate organic manganese chelation strength and classify different organic manganese sources into high, medium, and low chelation strength categories [**?**]. Chelation strength can effectively reflect broiler utilization of organic manganese, with medium chelation strength organic manganese showing the highest relative biological utilization, followed by high chelation strength organic manganese, while low chelation strength organic manganese is similar to inorganic manganese [**?**]. The different biological utilization rates of organic manganese with varying chelation strengths may be closely related to manganese transport in the intestine and release in target tissues [**?**]. The relative biological utilization of different manganese sources is also affected by the rearing environment. In thermoneutral and high-temperature environments, Smith et al. [**?**] found that the biological utilization of manganese proteinate in broilers was 125% and 145%, respectively. Biological utilization studies of different manganese sources have focused primarily on broilers, with research on laying hens still limited. However, relevant

studies have shown that the relative biological utilization of organic manganese in Lohmann laying hens is also higher than that of MnSO4 [?]. Medium chelation strength organic manganese can significantly alleviate the adverse effects of high-temperature heat stress on broiler breeder laying performance, while the effect of inorganic manganese is not significant [?].

3.2 Reproductive Axis

Although the relative biological utilization of organic manganese is higher than that of inorganic manganese, dietary supplementation with organic versus inorganic manganese shows no significant differences in improving female poultry reproduction performance, such as laying rate, hatchability, and fertility [?, ?, ?, ?]. Xie et al. [?] fed broiler breeders different forms of manganese and found that medium-strength organic manganese tended to increase blood manganese levels, but organic manganese groups showed significantly lower GnRH-1 expression in the thalamus than inorganic manganese groups. This finding conflicts with the high biological utilization of organic manganese, particularly medium chelation strength organic manganese. The central nervous system differs from other tissues in that it is protected by the blood-brain barrier, so manganese regulation of central GnRH-1 requires passage through this barrier. Although chelated/complexed organic manganese can facilitate manganese absorption and transport in the digestive tract [?], the chelated/complexed state alters the physicochemical properties of manganese (molecular weight, polarity, etc.) [?], making organic manganese less able to cross the blood-brain barrier. Therefore, the utilization of organic manganese in central target tissues may differ substantially from that in other target organs.

3.3 Egg Quality

Manganese is crucial for eggshell microstructure and quality. Using an exponential model, Xiao et al. [?] determined that the relative biological utilization of manganese amino acid complex in laying hens was as high as 357% for eggshell thickness, 406% for eggshell strength, and 458% for elastic modulus, demonstrating that manganese amino acid complex can significantly improve eggshell quality. However, findings on the effects of organic versus inorganic manganese on eggshell quality formation are inconsistent. Feeding broiler breeders organic and inorganic manganese for 16 weeks revealed no significant differences in eggshell thickness or strength [?]. Studies on supplementation with mixed organic trace minerals (manganese, copper, zinc) also show inconsistent results regarding egg quality improvement. Gheisari et al. [?] suggested that adding 50%–75% organic trace minerals is sufficient to maintain egg quality, while Mabe et al. [?] and Stefanello et al. [?] found no significant differences between organic and inorganic trace mineral supplementation on egg quality. These inconsistent results are closely related to factors including animal model, experimental duration, and properties of organic trace minerals (chelation strength).

Conclusion

Manganese is an important essential trace mineral in poultry nutrition. Extensive research has been conducted on broilers, covering manganese requirements, absorption mechanisms, and biological utilization evaluation of different manganese sources, providing scientific basis for manganese nutrition in broiler health, growth, bone development, and trace mineral emission reduction. Although early studies and research on humans and model animals have demonstrated that manganese is crucial for maintaining animal reproduction performance, systematic research on manganese regulation of poultry reproduction performance is lacking compared with broiler studies. Laying hens represent a unique physiological period, where dietary manganese must meet metabolic demands for bone and other tissues while also affecting eggshell formation and reproductive hormone synthesis and secretion. Whether NRC-recommended nutrient requirements can meet the manganese nutritional needs of laying hens requires support from scientific experimental data. Furthermore, due to significant physiological differences between poultry and mammals, and because most human and model animal studies involve manganese toxicity models, the endocrine mechanisms through which dietary manganese supplementation regulates poultry reproduction performance require further investigation.

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