Regulatory Factors of Fibroblast Growth Factor 23 and Its Research Progress in Laying Hens: A Postprint

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Abstract

Fibroblast growth factor 23 (FGF23) is a hormone that regulates phosphate homeostasis and promotes urinary phosphate excretion. This paper reviews the regulatory factors of FGF23, including vitamin D, parathyroid hormone (PTH), calcium, and phosphorus, as well as research advances on FGF23 in laying hens, providing a theoretical basis for further investigation of FGF23 function in laying hens and for reducing phosphorus content in excreta through modulation of FGF23 production.

Full Text

Regulatory Factors of Fibroblast Growth Factor 23 and Its Research Progress in Laying Hens

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Abstract: Fibroblast growth factor 23 (FGF23) is a hormone that regulates phosphate homeostasis and promotes urinary phosphate excretion. This review summarizes the regulatory factors of FGF23, including vitamin D, parathyroid hormone (PTH), calcium, and phosphate, as well as research progress on FGF23 in laying hens. The objective is to provide a theoretical basis for further studies on FGF23 function in laying hens and for reducing phosphorus excretion through regulation of FGF23 production.

Keywords: FGF23; phosphorus; regulation; laying hens
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Phosphorus plays a crucial role in maintaining normal growth and development, bone mineral metabolism, and productive performance in poultry. However, excessive phosphorus discharge from poultry excreta represents a significant source of environmental phosphorus pollution. Systemic phosphorus homeostasis depends primarily on continuous exchange among intestinal absorption, renal reabsorption and excretion, and the bone storage pool. Fibroblast growth factor 23 (FGF23) is a key hormone regulating phosphate homeostasis, while vitamin D and parathyroid hormone (PTH) also participate in phosphorus metabolism regulation. These three factors interact in complex ways [1]. Current FGF23 research has focused primarily on mammals, where FGF23 regulates phosphorus metabolism in the kidney, intestine, and bone tissue through direct and indirect mechanisms. FGF23 downregulates the expression of sodium-dependent phosphate transporters NPT2a and NPT2c in the kidney, reducing renal phosphate reabsorption [2], and also downregulates intestinal sodium-dependent phosphate transporter NPT2b expression [3], thereby decreasing intestinal phosphate absorption. Consequently, FGF23 promotes phosphate excretion and reduces blood phosphorus levels. In patients with tumor-induced osteomalacia, massive FGF23 production by tumors causes hypophosphatemia [4]. Patients with autosomal dominant hypophosphatemic rickets carry gain-of-function mutations in the FGF23 gene, leading to elevated FGF23 levels and hypophosphatemia [5-6]. Conversely, FGF23 knockout mice exhibit increased serum 1,25-dihydroxyvitamin D3 [1,25(OH) D] levels, hyperphosphatemia, and skeletal abnormalities [7]. These findings demonstrate FGF23' s critical role in mammalian phosphorus metabolism. In recent years, preliminary studies on FGF23 have been conducted in laying hens.

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This review examines the regulatory factors of FGF23—calcium, phosphorus, vitamin D, and PTH—and summarizes research progress on FGF23 in laying hens.

1 Biological Characteristics of FGF23

Human FGF23 protein consists of 251 amino acid residues, including a 24-residue signal peptide at the N-terminus, making it a secreted protein. Human FGF23 contains a proteolytic cleavage site at position 176RxxR179, where partial FGF23 is degraded into N-terminal and C-terminal fragments. Conse-

quently, both intact full-length FGF23 and its N- and C-terminal fragments circulate in blood [6]. The intact full-length FGF23 possesses physiological activity in reducing blood phosphorus, whereas the two fragments lack this activity [8].

In patients with autosomal dominant hypophosphatemic rickets/osteomalacia, FGF23 undergoes missense mutations that render it resistant to proteolysis between arginine (Arg) 179 and serine (Ser) 180. This results in elevated circulating FGF23 levels and decreased blood phosphorus [6]. FGF23 exerts its physiological functions by forming a complex with FGF receptors and heparin molecules, and requires -Klotho protein as a co-receptor to bind this complex and activate downstream Ras/mitogen-activated protein kinase (MAPK) signaling pathways [9].

2.1 Vitamin D

Vitamin D is converted to its active form 1,25(OH) D through the actions of 25-hydroxylase and 1 -hydroxylase. 1,25(OH) D binds to the vitamin D receptor (VDR) and retinoid X receptor (RXR) to form a heterodimeric complex 1,25(OH) D -VDR-RXR, which then binds to vitamin D response elements (VDREs) to regulate gene transcription. Numerous studies have reported VDREs in the promoter region of the FGF23 gene [10-11]. VDR knockout mice exhibit significantly lower serum FGF23 levels than wild-type mice [10,12], and FGF23 expression in these deficient mice is not regulated by 1,25(OH) D [12]. In vivo treatment with 1,25(OH) D increases serum FGF23 levels in both wild-type and hyp mice [10]. Administration of 1,25(OH) D to mice causes a dramatic increase in serum FGF23 within 24 hours, with FGF23 mRNA expression increasing 57-fold in calvarial bone and 8-fold in tibial bone, while no elevation is observed in non-osseous tissues such as kidney, liver, brain, jejunum, or spleen [13]. These in vivo studies demonstrate that 1,25(OH) D upregulates circulating FGF23 expression, likely through the VDR pathway, and that this regulation exhibits tissue specificity.

In vitro cell and tissue culture studies similarly demonstrate that 1,25(OH) D upregulates FGF23 expression. 1,25(OH) D increases FGF23 mRNA expression in osteoblasts and upregulates FGF23 promoter activity in both osteoblastic and non-osteoblastic cells [10]. 1,25(OH) D stimulates FGF23 secretion from primary mature osteoblasts/osteocytes, particularly under high phosphate conditions where it dramatically upregulates FGF23 expression [14]. 1,25(OH) D also upregulates FGF23 mRNA expression in UMR106 cells [13], an effect further enhanced by leptin but attenuated by interleukin-6 (IL-6) [15]. Additionally, 1,25(OH) D upregulates both FGF23 mRNA and protein expression in cultured calvarial bones from uremic and normal mice [16]. These findings indicate that 1,25(OH) D upregulates FGF23 mRNA and protein expression in osteocytes, osteoblasts, osteoblast-like cells, and cultured bone tissue, with the regulatory process potentially modulated by phosphate, leptin, IL-6, and cellular differentiation status.

2.2 PTH

Most studies in humans, animals, and cells indicate that PTH upregulates FGF23 expression. Patients with primary hyperparathyroidism exhibit increased PTH secretion and significantly elevated plasma FGF23 levels compared to controls, with both plasma PTH and FGF23 decreasing significantly after parathyroidectomy [17]. In chronic kidney disease (CKD) patients with advanced secondary hyperparathyroidism, serum FGF23 levels correlate positively with phosphate levels, the calcium-phosphate product, and PTH levels, and decrease following total parathyroidectomy [18]. Intermittent PTH (1-34) treatment for 18 months in postmenopausal osteoporotic women increases serum FGF23 levels [19]. These human studies demonstrate a positive correlation between serum PTH and FGF23 levels, indicating that PTH upregulates FGF23 expression. In patients with chronic hypoparathyroidism and hyperphosphatemia, elevated serum FGF23 levels likely result from negative feedback due to increased blood phosphate [20]. In uremic rats, both bone FGF23 mRNA expression and plasma FGF23 levels are elevated, decreasing after parathyroidectomy [21]. In mouse models of primary hyperparathyroidism and wild-type mice injected with PTH, plasma FGF23 levels and calvarial FGF23 mRNA expression are increased [22-23], and PTH treatment of osteoblast-like UMR106 cells also enhances FGF23 mRNA expression [23]. Meir et al. [24] further demonstrated through in vivo and in vitro studies that PTH increases FGF23 transcription through orphan nuclear receptor-mediated mechanisms. These animal and cell studies consistently show that PTH upregulates FGF23 expression, although conflicting reports exist. Short-term PTH infusion for 6 hours in humans decreased FGF23 secretion [25], and PTH treatment of cultured rat calvarial bones did not alter FGF23 protein in culture medium or calvarial FGF23 mRNA expression [16]. The reasons and mechanisms underlying these discrepancies require further investigation.

2.3 Calcium and Phosphate

Dietary phosphate is a key regulator of FGF23 secretion, with numerous studies demonstrating that high phosphate upregulates FGF23 production in humans and animals. In healthy individuals subjected to dietary phosphate interventions for more than two days, the high-phosphate group exhibits significantly higher serum FGF23 levels than the low-phosphate group [26-29], though serum FGF23 shows no correlation with calcium levels [26]. In hypoparathyroid patients with chronic hyperphosphatemia, serum FGF23 levels correlate positively with phosphate levels, indicating that serum phosphate directly or indirectly increases FGF23 levels [20]. Reducing dietary phosphate content in mice from 1.65% to 0.02% for five days causes serum FGF23 levels to fluctuate over a sevenfold range in a dose-dependent manner, with FGF23 mRNA expression in calvarial bone suppressed by 85% in wild-type mice fed 0.02% low-phosphate diet compared to those fed 1.00% high-phosphate diet [30]. These human and animal studies demonstrate that high-phosphate diets/feed elevate serum phos-

phate and FGF23 levels, with serum phosphate levels correlating positively with FGF23 mRNA expression, though the specific mechanisms underlying phosphate regulation of FGF23 expression remain unclear. Some studies suggest that FGF23 levels are not regulated by phosphate levels, as acute changes in serum phosphate within six hours do not affect intact FGF23 levels [31]. Rendenbach et al. [32] found that treating mouse primary osteoblasts with culture media containing 1 and 4 mmol/L sodium phosphate for six hours did not alter FGF23 mRNA expression, possibly because the high-phosphate treatment duration was too short to induce significant changes in FGF23 expression.

Research on calcium regulation of FGF23 remains controversial. In rats with 5/6 nephrectomy, serum FGF23 levels correlate positively with phosphate levels and weakly negatively with serum calcium levels [12], while intravenous calcium injection for 60 minutes increases serum calcium without significantly changing serum FGF23 levels [33]. Conversely, studies in primary hyperparathyroidism patients found positive correlations between serum FGF23 and calcium levels, with little relationship to serum phosphate [17,34], though other research reported no significant change in serum FGF23 levels after parathyroidectomy despite decreased serum calcium to normal levels [34]. Studies in knockout and wild-type mice also revealed positive correlations between serum FGF23 and calcium levels. In Gcm / and Cyp27b1 / mice, serum FGF23 levels correlate positively with calcium and 1,25(OH) D levels but not with serum phosphate [35]. Additionally, feeding wild-type rats a low-calcium diet revealed positive correlations between serum FGF23 and calcium levels, and increasing dietary calcium for 10 days elevated both serum calcium and FGF23 levels without changing serum phosphate [36]. However, in wild-type, PTH knockout, and PTH-calcium-sensing receptor (CaSR) double-knockout mice, serum FGF23 levels showed exponential correlations with phosphate, calcium, and calcium-phosphate product, with correlation coefficient (r) values of 0.58, 0.65, and 0.70, respectively [37]. These controversial results likely stem from differences in experimental models and the complex interactions among calcium, phosphate, PTH, FGF23, and 1,25(OH) D in vivo. Whether calcium regulates FGF23 directly or indirectly through phosphate, PTH, or 1,25(OH) D requires more comprehensive and in-depth studies for confirmation.

3 Research Progress of FGF23 in Laying Hens

As a macroelement, phosphorus serves essential physiological functions in poultry, but excessive phosphorus discharge from the poultry industry contributes to environmental phosphorus pollution. Since FGF23 has been identified as an important hormone regulating phosphate homeostasis in mammals, relevant research has recently been initiated in laying hens.

3.1 Molecular Characteristics of FGF23 Protein in Laying Hens

Gene sequencing and bioinformatic analysis of laying hen FGF23 reveal that it comprises 254 amino acid residues, with amino acid sequence identities of 57%,

58%, and 37% to human, mouse, and zebrafish, respectively. Laying hen FGF23 contains a 25-residue signal peptide at the N-terminus and a proteolytic cleavage site at position 180RxxR183 [38], suggesting that laying hen FGF23 is also a secreted protein that is enzymatically cleaved into N-terminal and C-terminal fragments in vivo.

3.2 Tissue-Specific Expression of FGF23 in Laying Hens

In mammals, FGF23 mRNA expression in bone tissue is dozens of times higher than in other tissues, with extremely low expression in liver [39-41]. Real-time quantitative PCR detection reveals that laying hen FGF23 mRNA is widely distributed across various tissues, with the highest expression in liver, followed by calvarial bone, tibial bone, femur, brain, spleen, duodenum, jejunum, and ileum, while expression levels are relatively low in heart and kidney [38]. This tissue expression pattern in laying hens differs substantially from that in mammals. The expression pattern of the FGF23 co-receptor -Klotho in laying hens is similar to that in mammals [38], with high expression in kidney, suggesting that kidney is also a target organ for FGF23 action in laying hens.

3.3 Regulatory Factors of FGF23 Expression in Laying Hens

Feeding laying hens high-phosphate diet (0.80% available phosphorus) and low-phosphate diet (0.15% available phosphorus) for 11 days revealed that the high-phosphate diet significantly increased serum phosphate levels without affecting serum calcium levels. The high-phosphate diet also significantly upregulated FGF23 mRNA expression in tibial bone, femur, and calvarial bone but did not significantly affect FGF23 mRNA expression in liver [38]. These findings indicate that dietary and serum phosphate levels may regulate FGF23 mRNA expression in bone tissue of laying hens, consistent with mammalian research results, while serum calcium levels may not participate in regulating FGF23 mRNA expression in bone tissue. Additionally, since high-phosphate diet did not alter FGF23 mRNA expression in laying hen liver, the regulatory factors and functions of highly expressed FGF23 in laying hen liver require further investigation.

Studies utilizing FGF23 neutralizing antibodies in laying hens demonstrate that FGF23 functions similarly to mammalian FGF23 in promoting phosphorus excretion. Immunizing laying hens with an FGF23 antigenic peptide produces FGF23 neutralizing antibodies in both the hens and their eggs. Chicks that acquire maternal FGF23 neutralizing antibodies do not show reduced serum phosphate or bone ash content when fed phosphorus-deficient diets [43], indicating that FGF23 neutralizing antibodies can reduce phosphorus requirements. Moreover, FGF23 neutralizing antibodies and dietary phytase exhibit additive effects in chicks fed low-phosphate diets [44], increasing serum phosphate and 1,25(OH) D levels and tibiotarsal bone ash content [45]. FGF23 neutralizing antibodies can also reduce serum FGF23 levels, increase serum phosphate levels, and decrease phosphorus excretion in laying hens [46]. Remarkably, FGF23 neu-

tralizing antibodies can improve eggshell quality without affecting egg quality [47], though the specific mechanisms require further investigation.

4 Summary and Outlook

As a major poultry producer, China cannot ignore the environmental pollution caused by phosphorus in poultry waste. FGF23 is an important hormone regulating phosphorus metabolism. FGF23 neutralizing antibodies in laying hens not only increase phosphorus utilization and reduce phosphorus excretion but also improve eggshell quality, demonstrating practical application value. Calcium, phosphorus, vitamin D, and PTH regulate FGF23 production to varying degrees in mammals, while dietary phosphorus can regulate FGF23 expression in bone tissue of laying hens. Adjusting dietary calcium, phosphorus, and vitamin D levels to reduce FGF23 production in laying hens without compromising productive performance could significantly reduce phosphorus pollution from chicken manure. Furthermore, while FGF23 is produced primarily by bone tissue in mammals, liver shows the highest FGF23 mRNA expression in laying hens and is not regulated by dietary phosphorus, indicating species- and tissue-specific expression patterns that differ markedly from mammals. Therefore, determining the regulatory patterns of FGF23 expression in different tissues and their respective functions in laying hens requires further investigation, which is crucial for systematically and comprehensively elucidating the physiological roles of FGF23 in laying hens.

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Note: Figure translations are in progress. See original paper for figures.