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Endocrine fibroblast growth factors in domestic animals

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ABSTRACT

Fibroblast growth factors (FGFs) are a group of structurally homologous yet functionally pleiotropic proteins. Canonical and intracellular FGFs have primarily autocrine or paracrine effects. However, the FGF19 subfamily, composed of FGF15/19, FGF21, and FGF23, act as endocrine hormones that regulate bile acid, metabolic, and phosphorus homeostasis, respectively. Current research in human and rodent models demonstrates the potential of these endocrine FGFs to target various diseases, including disorders of inherited hypophosphatemia, chronic liver disease, obesity, and insulin resistance. Many diseases targeted for therapeutic use in humans have pathophysiological overlaps in domestic animals. Despite the potential clinical and economic impact, little is known about endocrine FGFs and their signaling pathways in major domestic animal species compared with humans and laboratory animals. This review aims to describe the physiology of these endocrine FGFs, discuss their current therapeutic use, and summarize the contemporary literature regarding endocrine FGFs in domestic animals, focusing on potential future directions.

1. Introduction

Fibroblast Growth Factors (FGFs) are a group of 22 structurally similar but functionally diverse proteins comprising two main categories: 18 secreted FGFs (canonical and endocrine) and 4 intracellular FGFs. The four intracellular FGFs (FGFs11–14) are not secreted and bind to the C-terminus of voltage-gated sodium channels to regulate function. The fifteen canonical FGFs (FGFs1–10, FGFs16–18, FGF20 and FGF22) are secreted but limited to paracrine and autocrine signaling as they are tightly bound to the associated extracellular matrix. The remaining three FGFs comprise the FGF19 subfamily, known as endocrine FGFs, which includes FGF15/19, FGF21 and FGF23 [1,2]. These FGFs are unique as they bind weakly with the extracellular matrix, enter circulation, and function in an endocrine manner with broad physiological effects. FGF19 and its rodent family ortholog FGF15 regulate bile acid production and metabolism. FGF21 is a fasting hormone with autocrine, paracrine, and endocrine actions that regulate metabolic processes and crosstalk between the liver and adipose tissue. FGF23 is crucial in phosphorus homeostasis [2]. Based on their unique effects on many homeostatic mechanisms in the body, each endocrine FGF has been evaluated as a target for therapeutic interventions in humans and domestic animal species. Although studies on FGF19 in companion animals are limited, potentially translatable studies look at developing an engineered FGF19 analog with targeted effects to improve metabolic and cholestasis-related diseases. FGF21 has been studied in ruminants, dogs, and cats and has potential health and economic impacts regarding metabolic diseases. FGF23 is an emerging biomarker of phosphorus regulation in domestic animals, particularly in chronic kidney disease, and may have uses in congenital hypophosphatemias. Various approaches are underway to target endocrine FGFs and their signaling pathways in humans and domestic animal species. This article aims to review the physiology and signaling pathways of the endocrine FGFs: FGF15/19, FGF21, and FGF23, emphasizing what has been researched and potential therapeutic use of endocrine FGFs in domestic animals (Table 1).

2. Endocrine fibroblast growth factor regulation and signaling

The endocrine FGFs signal through the dimerization of an FGFR concurrently with a klotho family member receptor, most notably α-klotho binding FGF23 and β-klotho binding FGF19 and FGF21 (Fig. 1) [1,3]. A third member of the klotho family, LCTL (lactase-like protein),

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Table 1
Summary of endocrine FGF effects in domestic animals.

Endocrine FGF	Species	Effects	Refs
FGF19	Pig	Fluctuates with birth gestational age, birth modality, and enteral feeding to link to perinatal and postnatal gut development.	[8,12,48])
	Dog	Postprandial increases with gallbladder contraction.	[21]
		Inhibition associated with bile acid dysregulation.	[60]
	Chicken	Contributes to retinal development.	[23]
FGF21	Dog	Exogenous administration leads to islet cell regeneration and inhibition of hepatic gluconeogenesis.	[102,103]
	Cat	Exogenous administration leads to weight loss and a decrease in alkaline phosphatase activity but no changes in microbiome, lipids, or glucose.	[109]
	Cattle	Circulating concentrations increase during lipid mobilization and energy adaption periods driven largely by hepatic FGF21 to act on adipose and liver.	[113,114, 116,120]
		No changes in circulating metabolic parameters, total milk production, or food intake with FGF21 infusions, but hepatic triglycerides are reduced.	[115]
	Sheep	Highly expressed in the liver with adipose and liver as target tissues.	[122]
		Exogenous administration leads to decreased glucose and insulin and increased adiponectin.	[122]
FGF23	Pig	Increased colonic gene expression with increased bioavailable phosphorous.	[152]
		Dietary phosphorus increases bone receptor gene expression but not serum FGF23.	[15]
		Increased *gene* expression in piglets given a vitamin D-replete diet.	[13]
		Decreased to no effect in piglets with sows fed a vitamin D-deficient diet.	[13,153]
	Dog	Increased with inorganic dietary phosphorus.	[159]
		Biomarker of chronic kidney disease.	[160]
		Expressed by some soft tissue sarcomas.	[172]
	Cat	Biomarker of chronic kidney disease and prognosis.	[161,162]
		Decreases in cats with chronic kidney disease fed a phosphate-restricted diet.	[163]
	Sheep	Contributes to endometrium and placentome development during pregnancy.	[149]
	Chicken	Regulates growth and egg production.	[154-157]
	Horse	Increased in sick foals and prognostic indicator.	[170]

may be involved in the FGF19 signaling pathway, especially considering its high expression in mouse brown adipose tissue (BAT), but its function in the endocrine system is overall unknown [4]. The four high-affinity tyrosine kinase fibroblast growth factor receptors (FGFRs) that are part of the co-receptor complex [5], include three immunoglobulin-like (Ig-like) domains that confer ligand binding specificity. FGFRs1-3 have `a,' `b,' and `c' isoforms corresponding to an alternate exon splicing form of the third Ig-like domain [6]. The endocrine FGF19 subfamily has binding affinity for the `c' isoforms of FGFRs (e.g., FGFR1c) and FGFR4 rather than the `b' isoforms (the `a' isoform has no known signal capability) [7]. Specific studies investigating FGFR signaling pathways in domestic animal species are limited, and often, signaling mechanisms are presumed to be conserved based on shared physiological responses to pathway manipulation [8-15].

3. Fibroblast growth factor 19 (FGF19)

3.1. Physiology and current therapies

FGF15/19 is a major regulator of the liver-intestinal axis that is diurnally controlled and postprandially produced as a negative feedback signal of bile acid synthesis, regulating the rate-limiting enzyme cholesterol 7α-hydroxylase (CYP7A1) (Fig. 2) [16–21]. FGF19 has distinct and separate roles during development and in maturity. In the embryo, FGF19 coordinates neural and skeletal system development, including retinal development, before it transitions to an endocrine regulator postnatally [22,23]. FGF15, the rodent family ortholog of FGF19, is an enterokine that is primarily expressed in the small intestine, with the highest expression in the ileum [4]. In adult humans, FGF19 is produced predominately in the gallbladder and common bile duct for secretion through the biliary system into the intestine, with less mRNA production in the ileum [16,24]. Although not expressed in the liver during health, hepatic FGF19 is produced in an adaptive response to cholestasis [25,26]. FGF15/19 signals through either FGFR1c or FGFR4 in heterodimerization with its co-receptor β-klotho [7] to regulate lipid and glucose metabolism, browning of white adipose tissue, and bile acid synthesis [17,27,28]. Binding to FGFR2c and FGFR3c are not well described in healthy states [29]. Additional background on FGF15/19 signaling has been reviewed elsewhere [30], with some reviews specifically focusing on the role of β-klotho signaling [31].

FGF19-β-klotho/FGFR4 binding is unique in that it only occurs in the liver [32], and activation of this pathway is heavily implicated in the pathogenesis of hepatocellular carcinoma (HCC) [33-36]. Pan-FGFR and FGFR4-specific inhibitors are under investigation in clinical trials in patients with HCC [37]. However, FGF19-β-klotho/FGFR4 targeted therapies cause dysregulation of bile acid homeostasis, resulting in gastrointestinal side effects [38] and potential bile hepatotoxicity [39]. In an attempt to reduce the side effects of bile acid dysregulation while maintaining the antitumor effects of anti-FGF19, preclinical trials of antibodies targeting the N-terminus of FGF19 have been developed [40].

Despite the tumorigenic potential of FGF19 when binding β-klotho/FGFR4 receptors, research has focused on FGF19 agonism, as the FGF19-β-klotho/FGFR1c pathway has positive clinical metabolic effects, including weight loss and improved glucose homeostasis [41]. FGF19 analogs engineered to target the β-klotho/FGFR1c co-receptors have significantly reduced hepatic fat content, improved fibrosis [42,43], and hydrophobic serum bile acid concentrations [44]. Additional β-klotho/FGFR1c-specific FGF19 analogs are being developed to retain the beneficial metabolic effects without tumorigenic potential [45].

3.2. Potential of FGF19 in domestic animals

There is a high sequence homology for human FGF19 compared to domestic animal species. The signal chain of the human FGF19 protein has the greatest sequence similarity to feline (90.7 %), with high similarity in canine (87 %), equine (87 %) and moderate to high similarity to bovine (83 %) FGF19 protein [46]. However, despite this degree of homology, few studies manipulate the FGF19 pathway in domestic animals. One study confirms that dogs have postprandial increases in FGF19 in conjunction with gallbladder contraction, similar to humans [21].

Pigs have been characterized as an important model for exploring the effects of FGF19 signaling in perinatal and postnatal development [47], and studies have focused on the changes in FGF19 during development as a potential target to improve growth and nutritional outcomes. This has implications as potential therapies for preterm infants as well as production in domestic animals [22]. Factors that may affect FGF19 in the early postnatal period in pigs include gestational age, birth modality, and postnatal enteral feeding [12,48]. FGF19 was increased in preterm piglets that were vaginally delivered compared to piglets that were born at term by cesarean delivery [48]. FGF19 serum and tissue

concentrations are lower in preterm versus newborn piglets, potentially due to lower intestinal mass compared to body weight [12]. The increases in circulating FGF19 with vaginal birth correlate with increased circulating cortisol, implicating the hypothalamic pituitary adrenal axis in FGF19 regulation and function [48]. Additionally, in neonate piglets transitioning from parenteral to enteral feeding, FGF19 dramatically and rapidly increases, followed by a gradual decrease [12].

Although they have not yet been studied in veterinary medicine, the non-tumorigenic FGF19 agonists developed for humans may have therapeutic potential to treat intrahepatic and extrahepatic cholestasis and bile acid diarrhea in domestic animals. Potential veterinary diseases include those associated with extrahepatic cholestasis like pancreatitis, hepatic fibrosis in cholangiohepatitis, small bowel diseases, cholelithiasis, or vacuolar hepatopathies with aberrant lipid or glycogen accumulation, and conditions of intrahepatic cholestasis like toxic or infectious insults [49]. Therapeutic downregulation of bile acid production in these diseases through FGF19 agonism would potentially prevent, slow, or reduce additional bile toxicity-associated consequences, like fibrosis [50], as seen in FGF19 analog clinical trials treating human liver diseases [44]. Additionally, bile acid diarrhea is an emerging condition in dogs caused by excessive bile acid retention in the intestinal tract, resulting in refractory small intestinal inflammation [51]. FGF19 analogs may provide an alternative or synergistic therapy in dogs similar to what has been reported in human clinical trials treating bile acid diarrhea [52]. The proposed application of FG19 using the translational pig model would expand our understanding of pediatric diseases, including biliary atresia and short bowel syndrome [22], which has been described in other domestic and companion animals [53-57].

Inhibition of FGF19 pathways may also ha ve therapeutic benefits for companion animals with hepatocellular carcinoma (HCC). While primary liver tumors are uncommon, HCC accounts for ~35–60 % of canine primary hepatic tumors and represents an important translational model [58,59]. However, FGFR4 inhibitors for HCC have not been explored well in veterinary medicine. In a Beagle preclinical study, the FGF19/FGFR4 inhibitor, FGF401, was associated with increased serum aminotransferase activity, particularly alanine aminotransferase activity, which was reversible with the bile acid sequestrant cholestyramine, indicating bile acid homeostasis dysregulation similar to the human phase 1/2 clinical trial [60]. Caution may be warranted when adapting FGFR4 inhibitors to treat HCC in domestic animals, as there is the potential to exacerbate bile toxicity [38,39,60].

4. Fibroblast growth factor 21 (FGF21)

4.1. Physiology and current therapies

FGF21 binds to the co-receptors, FGFR1c and β-klotho [61]. Activation of these receptors is responsible for many beneficial effects, such as weight loss and improvements in glucose, insulin, lipid homeostasis, and cardioprotection (Fig. 3) [62–64]. Downstream actions of FGF21 are primarily due to the major energy homeostasis regulator, peroxisome proliferator-activated receptor γ coactivator protein-1 (PGC-1α) [65, 66]. The biological functions of FGF21 signaling, specifically through the B-klotho receptor, have recently been reviewed [31]. Importantly, FGF21 does not activate FGFR4 or promote mitogenicity, as observed with FGF19 [36,64].

Various dietary modifications that are often associated with increased lipolysis increase endogenous circulating concentrations of FGF21, including starvation, ketogenic diets, alcohol consumption, glucocorticoid administration and catecholamines [67-69]. The liver is the primary site of circulating FGF21 production, and hepatic FGF21 is responsible for many beneficial metabolic effects, including the reduction in hepatic lipid accumulation, brown fat thermogenesis, triglyceride clearance, hepatic gluconeogenesis without glycogenolysis, tricarboxylic acid cycle flux, and ketogenesis [66,70,71].

FGF21 is not only a hepatokine but also an adipokine, myokine, and cardiomyokine [63,65,72]. In these tissues, FGF21 remains localized and signals in an autocrine/paracrine fashion [70] where it increases cold exposure-induced browning [65,73] and promotes glucose uptake in adipose and skeletal muscle tissues [74,75], lowers plasma ceramides [76], mediates mitophagy and skeletal muscle loss [77] and protects against cardiac hypertrophy [63,78,79]. FGF21 is also produced in both the exocrine and endocrine pancreas, with around 20x higher expression

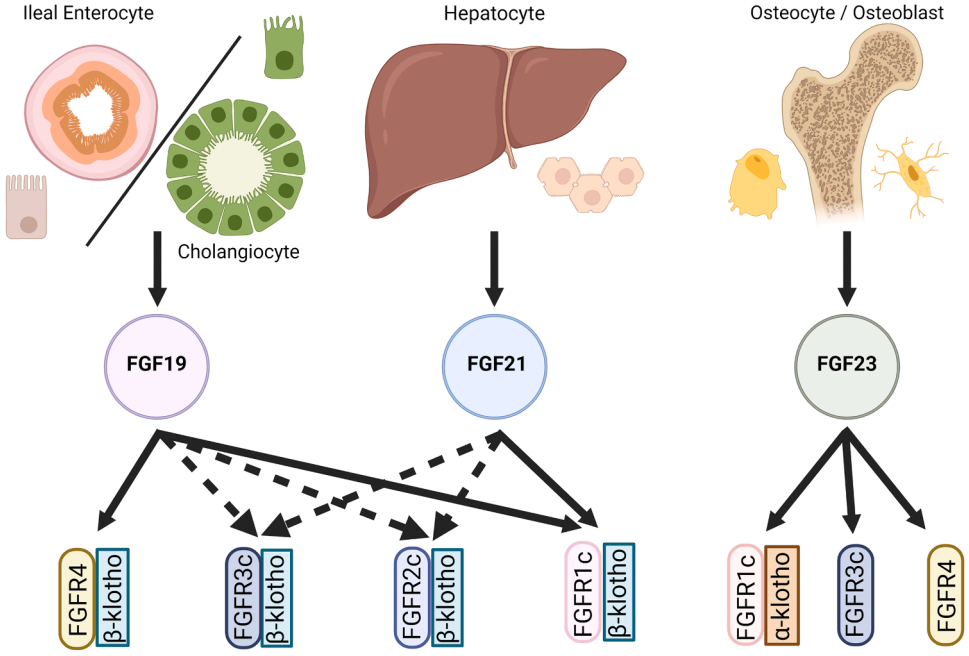

Fig. 1. Major sites of production and receptors for the endocrine FGF family members. FGF15/19 signals to all major FGFRs (FGFR1c, FGFR2c, FGFR3c, and FGFR4) in a heterodimer with its co-receptor β-klotho. FGF21 signals through FGFR1c, FGF2c, and FGF3c in a heterodimer with its co-receptor β-klotho, with its major known effects through the FGFR1c/ β-klotho complex. FGF23 signals through FGFR1c/α-klotho and klotho-independently through FGFR3c and FGFR4.

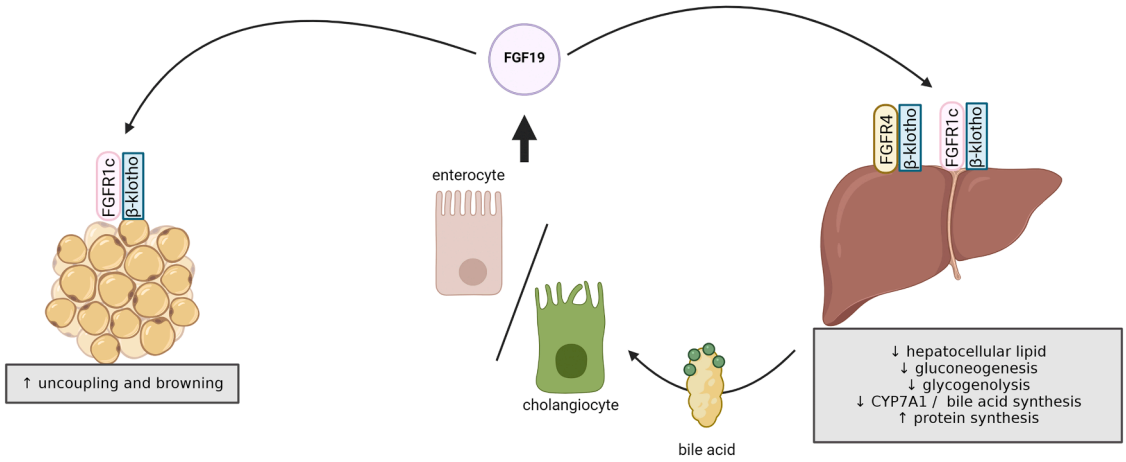

Fig. 2. Functions of FGF19. Depending on the species, FGF19 is predominantly produced either in the ileal enterocyte or the cholangiocyte. FGF19 regulates bile acid production by downregulating the rate-limiting enzyme CYP7A1 by binding FGFR4/β-klotho in the liver. FGF15/19 also has metabolic functions through FGFR1c/β-klotho binding in the adipose tissues and liver. Although FGF19 is known to bind FGFR2c and FGFR3c, the downstream mechanisms in non-neoplastic conditions are not well described.

in the acinar cells than in the islets [80]. Pancreatic FGF21 acts as a secretagogue, promoting digestive enzyme secretion from the zymogen granules [81]. Interestingly, in contrast to hepatic FGF21, which is upregulated by starvation, pancreatic FGF21 is upregulated in obesity and downregulated by fasting [80]. In the endocrine pancreas, FGF21 regulates β-cell health and insulin production [82].

Given the myriad of beneficial effects, FGF21 mimetics have been adapted for therapeutic use and have undergone preclinical trials in rodents, non-human primates, and human clinical trials [83], and FGF21 has been the subject of many recent reviews [84-88]. Several therapeutic variants have been developed with increased half-life, resistance to proteolysis, and potential for commercial manufacturing in mind while retaining the efficacy of FGF21, including LY2405319, PF-05231023, Pegbelferin (BMS-986036), Pegozafermin, BOS-580, and Efruxifermin (Fc-FGF21-RGE, AKR-001) [89-96]. These compounds allowed for less frequent dosing than recombinant human FGF21 and often resulted in decreased body weight and improved metabolic outcomes, including decreased plasma glucose and triglycerides, improved hepatic fat fraction, and decreased biomarkers of fibrosis in patients with non-alcoholic steatohepatitis [89].

When comparing preclinical studies and human clinical trials, it seems that there are some species-dependent effects of FGF21 analogs. For instance, although most analogs reduce body weight, whether this is due to decreased caloric intake is inconsistent, as it appears to be in monkeys but not in mice [97,98]. The full translatability between preclinical models and humans of FGF21 analogs as a treatment is still being discovered. Other inconsistent effects of various FGF21 therapies include changes in bone density [91], changes in food intake, and even the degree of impact on metabolic parameters as observed with a lack of changes with H1Ac and Pegbelferin and BOS-580 or body weight with Efruxifermin and Pegozafermin [89]. Overall, FGF21 mimetics and therapies to increase endogenous FGF21 appear to improve health and may be used as combinational therapies in various metabolic diseases, specifically, but not limited to, obesity, insulin resistance, and dyslipidemia.

4.2. Potential of FGF21 in domestic animals

FGF21 is the most studied endocrine FGF in domestic species as a potential therapeutic. However, the translational capabilities of many FGF21 analogs to veterinary medicine remain open for research with a variety of potential applications. Many companion animals are overweight and obese with associated insulin resistance [99], and hepatic lipidosis is a common cause of morbidity, mortality, and economic loss among farm and companion animals [100,101]. FGF21 has been shown to improve insulin resistance, decrease body weight, and decrease liver lipids, so it behooves veterinary scientists to examine it as a potential therapy.

A few studies use canine diabetes models to study FGF21 physiology. One study evaluated streptozotocin (STZ)-treated Beagles treated with 0.5 mg/kg canine recombinant FGF21 once a day for 12 days. Despite the high toxicity of STZ to pancreatic β-cells, this study found partially restored circulating insulin and glucose concentrations and noted inhibition of the hepatic gluconeogenic enzymes glucose 6-phosphatase and phosphoenolpyruvate carboxykinase [102], implicating FGF21 in islet function restoration post-STZ-induced damage and inhibition of hepatic gluconeogenesis. This group repeated their studies in STZ-induced diabetic dogs for an extended period (8 weeks) using PEGylated canine FGF21 (cFGF21) and compared their results to 2 U/kg porcine insulin treatment to investigate the practicality of using FGF21 treatment in the replacement of insulin in diabetic dogs [103]. They found that a single dose of recombinant cFGF21 maintained reduced blood glucose effects longer than insulin. However, dogs showed resistance to cFGF21 glucose-lowering effects at around 30 days after the initiation of the study. Remnant insulin-immunoreactive islets were histologically visible within the cFGF21-treated group, suggesting that FGF21 can prevent further STZ-induced pancreatic β-cell death by downregulating inflammation and promoting the regeneration of β-cells. Although STZ-induced models provide many benefits, such as decreased time and cost, it is not spontaneous and comes with drawbacks, such as direct STZ-induced renal and hepatic toxicity. Other canine models of type 1 diabetes mellitus (T1DM) use adjuvant therapies along with low-dose STZ to avoid the off-target toxic effects, such as in combination with partial pancreatectomy or other β-cell targeting drugs [104,105], and it would be interesting to see how studies using a combination-induced T1DM model would differ from an STZ-treated only model. Follow-up studies in canines with spontaneously occurring insulin resistance, insulin-dependent diabetes mellitus, or non-insulin-dependent diabetes mellitus are needed to better evaluate the utility of the FGF21 pathway targeting therapy in dogs.

Unlike dogs, which more commonly have insulin-dependent forms of diabetes and pancreatic islet cell destruction, cats develop an obesity-associated insulin resistance similar to human T2DM [106-108]. The FGF21 analog LY2405319 has been tested in a pilot study in overweight and obese cats at 10 mg/kg/day for two weeks, followed by an additional two-week washout period [109]. In this study, the cats treated with FGF21 lost 5.93 % of their body weight, which was regained during the washout period with no changes in food or water intake.

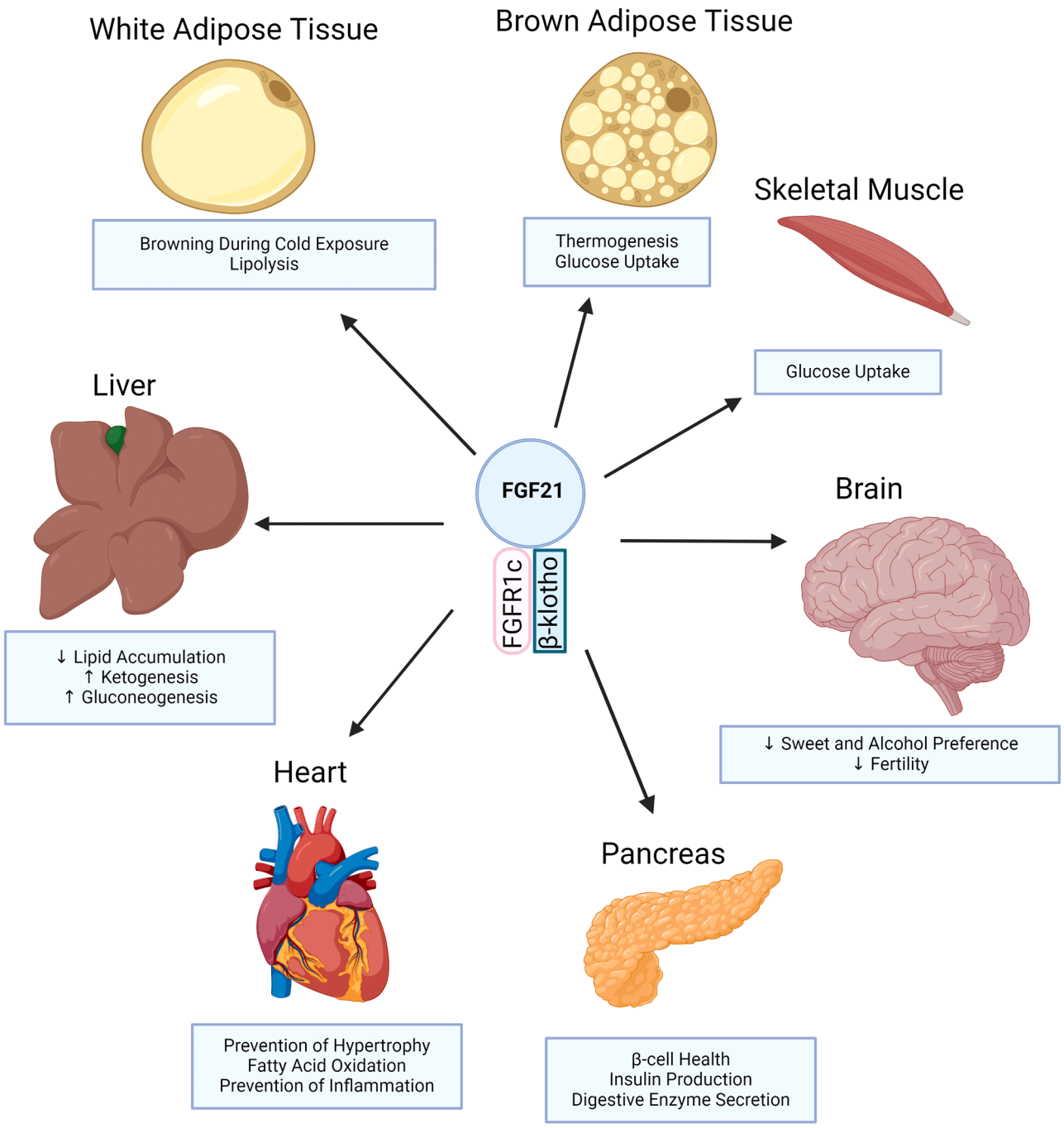

Fig. 3. Functions of FGF21. FGF21 has endocrine, paracrine, and autocrine effects in the liver, white and brown adipose tissues, skeletal muscle, brain, pancreas, and heart. FGF21's metabolic actions are through FGFR1c/β-klotho binding. Overall, FGF21 decreases the effects of lipotoxicity by increasing glucose uptake, promoting thermogenesis and β-oxidation, and inducing ketogenesis, among other starvation-adaption responses. Although FGF21 is known to bind FGFR2c and FGFR3c, the downstream mechanisms in non-neoplastic conditions are not well described.

Interestingly, the cats lacked notable alterations in their circulating lipids, glucose, insulin, or indirect measures of insulin resistance, the more commonly described metabolic effects for FGF21. There were also no measurable effects on the feline microbiome, with no changes in fecal microbial alpha or beta diversity or abundance compared to the control cats using whole genome shotgun metagenomic sequencing. Despite the rapid and marked weight loss, FGF21-treated cats in this study tended to have a decrease in liver lipid content compared to saline-treated cats. In addition, serum alkaline phosphatase activity, an inducible enzyme associated with hepatocellular lipid content, was reduced by 27 % compared to saline-treated cats. More work is needed to explore the FGF21 signaling pathways and FGF21 therapeutic potential in domestic cats, particularly in cats with more severe hepatic lipid disturbances, such as in clinical hepatic lipidosis. In cases of congenital portosystemic shunts (CPSS), cats with CPSS have increased mRNA expression of FGF21 compared to control cats without CPSS, potentially because FGF21 is upregulated by mitochondrial and endoplasmic reticulum stress [110,111].

Probably the most well-described domestic animal regarding FGF21 physiology is the dairy cow, where the potential relevance of FGF21 has been recently reviewed [112]. Early lactating dairy cattle undergo massive lipid mobilization with concurrent FGF21, glucagon, and

non-esterified fatty acid increases while producing high-fat, calorically dense milk in a negative energy balance [113]. In a study evaluating this metabolically stressful time of a cow, plasma FGF21 concentration in cattle dramatically increased during parturition and early lactation from nearly 0 pg/ml to ~1600 pg/mL and had similar circulating levels in feed-restricted late-lactating dairy cows. As fluxes in circulating FGF21 correlated with hepatic *FGF21* mRNA expression, FGF21 production in cows seemed to be driven by the liver with marginal contribution, if any, by the tail head (subcutaneous) white adipose tissue and no contribution by the skeletal muscle [114], similar to what is reported for other species [70]. In the same study, this group also determined that *β-klotho* mRNA expression is highest in the adipose tissues (perirenal, omental, mammary, and subcutaneous—in decreasing order) and liver in prepubertal 6-month-old heifers [114]. In early lactating dairy cattle treated with 3 mg/kg LY2405319 intra-jugular infusions followed by nine consecutive days of an LY2405319 continuous rate infusion (CRI) of 6.3 mg/kg, there were no changes in the circulating metabolic parameters plasma glucose, insulin, adiponectin concentrations or other parameters like total milk production or food intake [11,115]. Despite the lack of adiponectin secretion or changes in circulating metabolic parameters, FGF21 activity on the white adipose tissue was confirmed by increased phosphorylation of the downstream target, ERK1/2, suggesting that the FGF21 signaling pathway is different in dairy cattle in comparison to the more studied laboratory animal rodents, non-human primates, and humans [11]. This lack of metabolic changes parallels the effects of exogenous FGF21 administration in cats with no changes in circulating glucose or insulin [109]. Adiponectin concentrations were not measured in the FGF21-treated cats; however, the potential lack of FGF21 effect on adiponectin leading to a lack of changes in glucose, insulin, and lipid homeostasis in cats and cattle provides an interesting mechanism for future investigations.

Other groups have recognized FGF21 as a key metabolic regulator and indicator of energy balance in dairy cattle and evaluated changes in FGF21 and its signaling pathway under various states of disease and nutrition. In the prepartum period, serum FGF21 concentrations in dairy cattle gradually increased, peaking at parturition, followed by a rapid decline [116], suggesting that FGF21 is critical in the adaption of energy metabolism. Several groups have also demonstrated increased hepatic gene expression [9] and serum concentrations of FGF21 in cows with ketosis [116]. There are a few studies evaluating the effects of diet on FGF21 with mixed results in serum concentration and hepatic gene expression that vary based on the degree of overfeeding as well as the current reproductive and lactational status of the cow [9,10,117-119]. Supplementation with L-carnitine reduced hepatic *FGF21, β-Klotho* and *PPARα* gene expression [9].

Additional studies in dairy cattle evaluated lipid parameters, including measuring serum lipid metabolites and hepatic lipid accumulation through biopsies. The cows had decreased circulating free fatty acids following an LY2405319 intra-jugular infusion, but this decrease was not sustained over a 9-day CRI period [113]. While treatment with LY2405319 only tended to decrease hepatic triglyceride content in cats, FGF21 pathway activation significantly affected hepatic triglyceride concentration in cattle. Cows treated with LY2405319 had decreased hepatic triglycerides despite being in the early lactating, negative energy balance phase when liver lipid storage is typically in excess [100,115], demonstrating that there is an effect of FGF21 on lipid homeostasis in cattle. Human FGF21, of which LY2405319 is a recombinant version, has 91.7 % protein similarity with bovine FGF21 [46], so utilization of this human protein in a cow is likely to have appropriate effects. It would be worthwhile to see if FGF21 can be therapeutic in cattle with hepatic lipidosis, as this disease most commonly occurs in early lactating cattle.

In studies looking at cultured calf hepatocytes, high concentrations of non-esterified fatty acids resulted in a dose-dependent increase in FGF21 secretion from cultured cells, suggesting a physiological response of the hepatocytes to conditions of increased lipolysis and a potential positive feedback loop between lipids and FGF21 [120]. The positive correlation between serum NEFAs and serum FGF21 was also observed in peripartum dairy cattle [116] and serum FGF21 concentrations had a strong positive predictive value for triacylglycerol levels in the livers of early lactating cows, further supporting a physiologic response of FGF21 in hepatic lipid disorders and leading the authors to suggest that serum FGF21 could be used as a biomarker for fatty liver disease in lactating dairy cows. Evaluation of the treatment with FGF21 in the late postnatal period and early lactational period to reduce the risk of ketosis or displaced abomasum would be interesting as this could provide a significant economic benefit. However, additional studies would also be needed to determine the effects on milk production.

FGF21 also has a role in the energy balance and reproductive physiology of beef cattle, where, like dairy cows, FGF21 plays an important role in pubertal onset, adaption to nutritional transition, rate of body weight gain, circulating markers of metabolism and rate of milk production. The authors conclude that FGF21 may serve as an important biomarker for evaluating important financial parameters in beef cattle production [121]. Further work is needed to prospectively evaluate FGF21 in this capacity.

The same group that studied FGF21 in dairy cattle did a study that surveyed FGF21 signaling machinery and administered LY2405319 for 13 days to non-lactating Finn x Dorset ewes with adequate body condition [122]. Out of the liver, subcutaneous adipose, omental adipose, retroperitoneal adipose, kidney, gracilis muscle, and lung, the group found *FGF21* mRNA was most highly expressed in the sheep's liver at 17-fold higher than any other expressing tissue. Other tissues with lower expression were the subcutaneous and retroperitoneal adipose tissue and kidney. There was no expression in the omental fat and skeletal muscle. *β-klotho* mRNA was expressed in the subcutaneous, omental, and retroperitoneal adipose tissues and liver, and *FGFR1c* was expressed in the subcutaneous adipose tissue (other adipose stores were not examined), indicating that the adipose tissues and liver are FGF21 targets. FGF21 targeting of the adipose tissue was confirmed by increased pERK1/2 and EGR1 protein in the subcutaneous adipose tissue following a 5 mg/kg bolus. In contrast to the lack of insulin and glucose homeostasis changes in cattle with LY2405319 administration, sheep had decreased circulating glucose concentration, a transient decrease in insulin concentration, and increased adiponectin concentration with a 15 mg/kg/day dose over 13 days. The conflicting actions of FGF21 in early lactating cattle and non-lactating sheep raise the question of whether early lactation is an FGF21-resistant state in ruminants.

The potential effects of FGF21 pathway activation in cardiovascular disease and pancreatitis have yet to be explored in domestic animals. It would be interesting to see if FGF21 concentrations are altered in dogs and cats with various cardiomyopathies or if FGF21 pathway activation could augment current cardioprotective therapies. Studies show that chronic pancreatitis is frequently underdiagnosed, and currently, there are no effective treatments for acute or chronic pancreatitis beyond supportive care for domestic cats or dogs [123,124]. Most cases of diabetes mellitus in dogs are insulin-dependent, and diabetes mellitus occurs in around 28–30 % of dogs with pancreatitis [125], suggesting that these inflammatory processes destroy islets. FGF21 pathway-targeting therapy can potentially be utilized to restore islet health in diabetic dogs. Based on the effects of FGF21 in STZ-treated Beagles [103], there is potential that activation of the FGF21 pathway may provide anti-inflammatory and β-cell protective effects in clinical pancreatitis as well. While FGF21 was initially hailed as a potential therapy for human obesity and insulin resistance and potentially as a therapy for diabetes mellitus in veterinary patients [88] the benefits extend beyond metabolic diseases. Additional studies investigating FGF21 in these diseases are warranted, and should FGF21 be shown to have protective effects, the impact on current treatments for dogs and cats could be profound. In ruminants, manipulation of the FGF21 pathway or monitoring of serum FGF21 could improve economic outcomes and heard management.

5. Fibroblast growth factor 23 (FGF23)

5.1. Physiology and current therapies

The primary function of Fibroblast Growth Factor 23 (FGF23) is regulating phosphorus homeostasis along with vitamin D and parathyroid hormone (PTH) in the body, creating cross-talk with the kidney, bone, and parathyroid gland [126] (Fig. 4). FGF23 is produced predominantly by osteocytes in bone [127-129] and secreted in a bioactive, physiologically intact form, with proteolysis as an important regulatory mechanism to inactivate FGF23. The post-transcriptional regulatory mechanisms of FGF23 have been previously described [130].

Once in circulation, FGF23 signals via the dimerization of co-receptors α-klotho and an FGFR, primarily FGFR1c [127,131,132]. The initial effects of FGF23 occur in the epithelial cells of the distal renal convoluted tubule, where FGF23 promotes the retention of Na^+ and Ca^{2+} from the urine by activating the sodium-chloride cotransporter (NCC) and Transient Receptor Potential Cation Channel Subfamily V Member 5 (TRPV5) channels, respectively, via activation of with-no-lysine kinase 4 (WNK4) [127,133,134]. The cells of the renal proximal convoluted tubule downregulate 1α-hydroxylase (CYP27A1) to reduce 1,25-dihydroxyvitamin D_3 (active form of vitamin D) synthesis and to reduce circulating levels of phosphorus and calcium. Additionally, FGF23 downregulates the membranous expression of NPT2A/C via the Erk1/2-SGK pathway through phosphorylation of the scaffolding protein, Na^+/H^+ exchange regulatory factor-1 (NHERF-1). With the phosphorylation of NHERF-1, NPT2A/C is degraded, preventing phosphate reabsorption and promoting phosphate excretion in the urine [128,135].

In the bone, FGF23 suppresses tissue nonspecific alkaline phosphatase (TNAP) via klotho-independent autocrine/paracrine signaling through the FGFR3-ERK pathway [136]. This results in decreased inorganic pyrophosphatase degradation and, subsequently, decreased phosphate available for bone mineralization [127,136]. FGF23 also acts on osteopontin, another inhibitor of mineralization. However, experiments have shown contradictory effects of FGF23 on mineralization, suggesting its role in mineralization is likely to be complicated [137]. FGF23 suppresses osteopontin, an inhibitor of mineralization, partly indirectly via its actions on TNAP, as inorganic phosphate stimulates osteopontin secretion [136].

In the parathyroid gland, the effect of FGF23 on PTH levels is unclear, with conflicting results found in different studies [138-140]. For example, in rats, short-term administration of FGF23 results in decreased FGF23 mRNA expression and decreased serum PTH concentration; similarly, primary culture of bovine parathyroid gland cells incubated with FGF23 had a decrease in *PTH* mRNA [140]. FGF23 is thought to suppress PTH production via MAPK and calcineurin/NFAT pathways [141,142]. In contrast, long-term administration of FGF23 to rats resulted in upregulation of PTH secretion and parathyroid cell hyperplasia [139]. Many studies use different species models and cell cultures over variable lengths of time and doses, which likely contribute to the inconsistent findings.

The discovery of the actions of FGF23 has expanded our understanding of the bone-heart link in cases of chronic kidney disease. In humans with chronic kidney disease, increased serum FGF23 concentration is independently associated with a higher risk of developing new-onset left ventricular hypertrophy [143]. In humans with chronic kidney disease, serum aldosterone concentrations are increased, leading to volume overload, hypertension, and progression of kidney disease. FGF23 has also been shown to stimulate the renin-angiotensin-aldosterone system in the heart, contributing to cardiac hypertrophy and fibrosis [144,145]. This deleterious effect of left

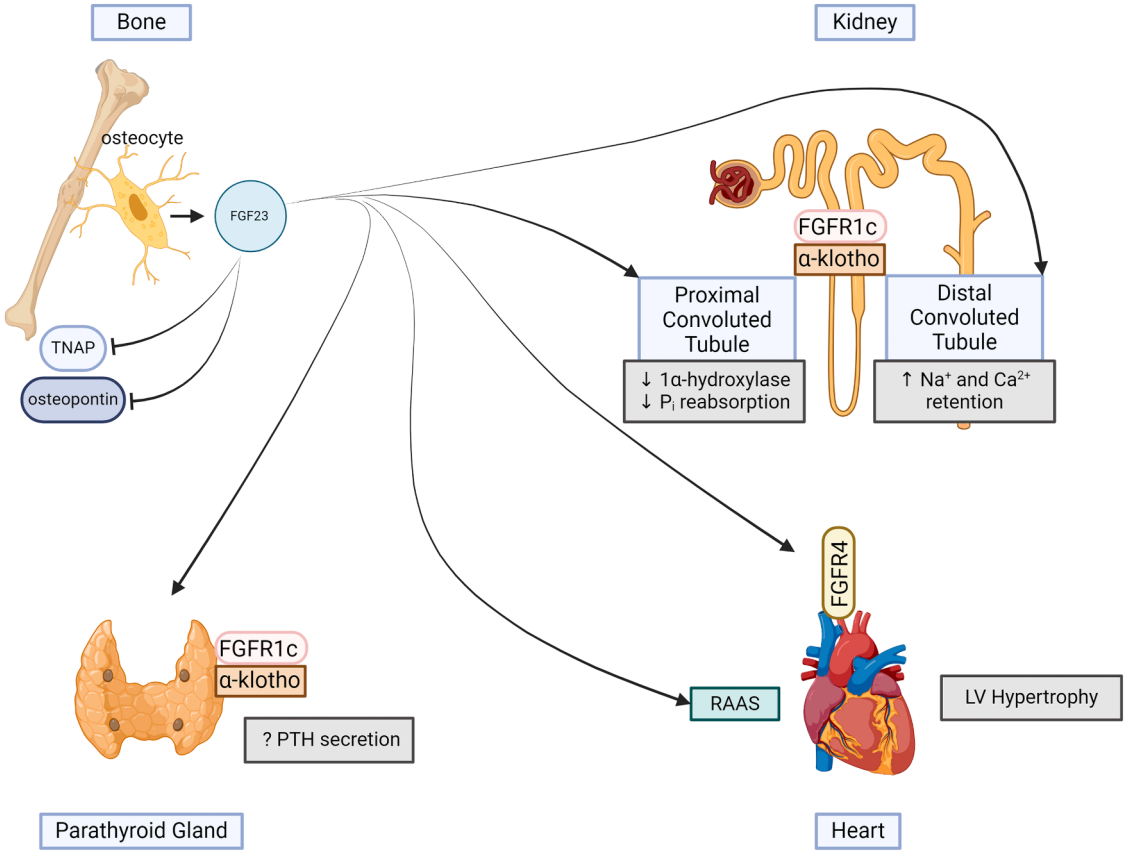

Fig. 4. Functions of FGF23. FGF23 is produced primarily by osteocytes with autocrine/paracrine signaling to the osteoblast and endocrine signaling to the kidney, heart, and parathyroid glands. Post-translational glycosylation activates FGF23 and prevents proteolytic cleavage.

ventricular hypertrophy with increased FGF23 has precluded potential uses of FGF23 analog therapy. Instead, potential and current clinical therapeutics target FGF23 to prevent it from binding with FGFRs.

One significant application of FGF23 targeting therapy is for the syndrome of X-linked hypophosphatemia (XLH). XLH results from a mutation in the PHEX gene, leading to a lack of FGF23 regulation. Subsequent increased levels of FGF23 lead to hypophosphatemia, decreased 1α-hydroxylase activity, and rickets [146]. In a phase 2 clinical trial of children with XLH, burosamab, an anti-FGF23 monoclonal antibody, led to overall clinical improvement with an increase in physical function, reduced pain, and improved renal tubular phosphate reabsorption and serum phosphorus [147]. In a phase 3 clinical trial of adults with XLH treated with burosamab, most treated patients had a serum phosphate concentration above the lower reference interval, along with an improvement in stiffness but not a significant improvement in physical function or pain [148]. Burosamab is currently an FDA-approved drug to treat X-linked hypophosphatemia.

5.2. Potential in domestic animals

FGF23 is the most studied in domestic animals regarding its role in phosphorus and phosphatonin system pathophysiology and disease biomarker potential. One study compared the expression of phosphatonin-related genes in horse, sheep, and dog kidneys [14]. There was little variability in FGFR1c expression between the different species, but sodium-phosphate cotransporter SLC34A1 mRNA was highly expressed in dog kidneys compared with sheep and horse kidneys. In this study, klotho mRNA expression was positively correlated with SLC34A1 and A3 mRNA expression.

Expression of FGFRs1-4, FGF23, klotho and sodium-phosphate cotransporters SLC20A1 and SLCA2 has been detected in the endometrium and placentome of the ewe throughout pregnancy, with *FGF23* mRNA expression at the highest on day 17 and lowest on day 70 of gestation [149]. *FGF23, FGFRs1-2*, and *klotho* mRNA expression has also been detected in the endometrium of the cycling ewe, with expression of *FGFRs1-2* and *FGF23* peaking at day 9 of the estrus cycle. In contrast, *klotho* expression was highest on day 1 and declined over the estrus cycle [150]. The authors suggested the change in expression was due to progesterone and progesterone receptor signaling. This hypothesis may be backed up by another study that found administration of exogenous progesterone prior to implantation of the conceptus resulted in increased expression of *FGFR2* mRNA in the endometrium but decreased expression of *klotho* mRNA in placentomes at day 125 of pregnancy [151]. However, no change in *FGF23* mRNA expression in either endometrium or placentomes was detected.

In pigs, adding phytase to the diet (thought to increase phytate-bound phosphorus availability) increased colonic *FGF23* mRNA expression [152]. However, while there was increased colonic and duodenal mRNA expression of calcium channels (*TPRV5, 6, PMCA1b, calbindin D28K*), there was no difference in phosphorus channel (*SLC34A1, SLC34A2* and *SLC34A3*) expression in the duodenum, colon, and kidney. Conversely, another study found no expression of *FGF23* mRNA in intestinal samples and that dietary phosphorus in pigs did not alter bone *FGF23* mRNA expression but did increase *FGFR4* and *klotho* mRNA expression [15]. In pigs whose mothers were fed a vitamin D-deficient diet during gestation, there was marked variability in *FGF23* mRNA expression in the femur and vertebra at different ages; nonetheless, significantly decreased *FGF23* mRNA expression was detected in 3-week-old piglets (at weaning) from mothers fed a vitamin D deficient diet [153]. However, another study found no response in metatarsal bone *FGF23* mRNA expression at different ages in piglets from mothers fed a vitamin D deficient diet but did find increased *FGF23* expression if piglets themselves were fed a vitamin D replete diet, regardless of the maternal diet [13].

In chickens where calcium and phosphorus are tightly regulated, FGF23 likely plays a role in growth and egg production. A recent review and meta-analysis of FGF23 reports similar plasma FGF23 concentrations in broilers and laying hens with a positive correlation between FGF23 and plasma phosphorus and vitamin D [154]. While there were no sex-specific differences in FGF23 plasma concentrations, as observed in other species, plasma FGF23 concentrations increased with age, likely associated with developmental changes [154]. A few studies evaluate FGF23 in laying hens and provide evidence to suggest that FGF23 is a driver of Vitamin D metabolism across ovulation [155-157], with increased medullary bone *FGF23* gene expression at the start of eggshell formation and maximal gene expression during the active phase of mineralization [156]. Increases in medullary bone expression are also observed relatively rapidly following ovulation at 18–19 h post ovulation and coincide with high inorganic phosphate and low $1,25(OH)_2D_3$ plasma concentrations, further supporting the role of FGF23 across the egg-laying cycle. This tight balance between FGF23 and phosphorus in laying hens is further supported by studies where hens vaccinated with a peptide to induce neutralizing FGF23 antibodies had reduced phosphorus excretion [158]. Alternatively, *FGF23* gene expression was controlled by phosphorus intake, with phosphorus restriction resulting in decreased *FGF23* mRNA expression. Given the role of FGF23 in phosphate excretion, these findings led to the suggestion that dietary non-phytate phosphate could be safely restricted in laying hens and that over-supplementation of dietary phosphorus was nutritionally inconsequential [157], impacting important poultry management decisions. While FGF23 is not routinely evaluated in poultry production, it can potentially be used as a marker of production or dietary management.

Finally, in dogs, it has been shown that the type of phosphate being fed impacts phosphorus metabolism, with inorganic dietary phosphate resulting in higher serum FGF23 and phosphorus concentrations [159].

In disease states, much of the research on FGF23 in domestic animals has focused on chronic kidney disease, particularly in cats, but also in dogs. The phosphatonin system, particularly FGF23, is important in the pathogenesis and progression of chronic kidney disease—metabolic bone disease in humans. As in humans, it is well established in cats and dogs that plasma FGF23 concentrations increase with increasing severity of kidney disease [160,161]. This increase in plasma FGF23 concentrations is positively correlated with plasma PTH and phosphorus concentrations. In cats with chronic kidney disease, survival was negatively correlated with plasma FGF23 concentration [162]. Feeding a phosphate-restricted diet to treat chronic kidney disease in cats with hyperphosphatemia was associated with decreased plasma phosphate, PTH and FGF23 concentrations [163]. However, feeding a phosphate-restricted diet to cats with chronic kidney disease that are normophosphatemic or have lower plasma phosphate concentrations is associated with increased plasma total calcium concentration. The impact of the increase in total calcium concentrations is not completely clear but may be associated with the progression of chronic kidney disease in these feline patients [164-166]. Cats with “uptrends” in calcium but normophosphatemia can have increased FGF23; as such, International Renal Interest Society (IRIS) 2023 guidelines for the treatment of chronic kidney disease in cats suggest assessing plasma FGF23 concentrations as a useful guide for whether a phosphate-restricted diet would be beneficial even if plasma phosphate concentration is within the target range [167].

Interestingly, plasma total magnesium concentrations are inversely correlated with plasma FGF23 concentration in cats with chronic kidney disease [168], despite low magnesium being associated with increased mortality in humans with chronic kidney disease. A tight positive correlation between plasma intact FGF23 concentration and serum aldosterone concentration (a hormone that promotes sodium reabsorption in the kidney) has also been found in cats and dogs [169]. However, no association was found between high salt intake, serum phosphate, and FGF23 concentrations in cats.

In sick foals, serum FGF23 and aldosterone concentrations were greater than in healthy foals, while serum klotho concentrations were lower [170]. In the sick foals, the increased FGF23 and aldosterone

concentrations were associated with higher phosphorus and PTH, and high FGF23 and low klotho were associated with an increased likelihood of death.

Tumor-induced osteomalacia is a rare paraneoplastic disease of humans whereby some mesenchymal tumors (phosphaturic mesenchymal tumor-mixed connective tissue type) may express phosphatonin system genes, particularly FGF23, resulting in urinary phosphate loss and osteomalacia [171]. This syndrome may occur in dogs; one study detected high *FGF23* mRNA expression and histologic features of phosphaturic mesenchymal tumors in 3 out of 49 soft tissue sarcomas of dogs [172].

6. Summary and conclusions

The endocrine Fibroblast Growth Factor family members, FGF15/19, FGF21, and FGF23, are vital to many homeostatic mechanisms in the body. The members of this family generally exert actions through a Fibroblast Growth Factor Receptor (FGFR) and a klotho family member. FGFR-targeting drugs under investigation for human cancer treatment may one day be utilized in veterinary medicine, particularly as veterinary oncology moves to an individualized omics-based approach for patient treatment [166]. The FGF19 pathway is poorly studied in domestic animals, with only a pre-clinical study on an FGF4 receptor inhibitor in dogs. FGF21, via the co-receptors FGFR1c and β-klotho, potently regulates lipid homeostasis and insulin sensitivity. FGF21 pathway-targeting therapies generally improve global metabolic health by decreasing body weight, insulin resistance, liver lipid concentration and fibrosis. However, despite similar metabolic diseases in domestic animals of obesity, insulin resistance, and increased liver lipid, FGF21 requires further study in veterinary medicine. Given preliminary studies in domestic animals, FGF21 may prove helpful in some common diseases, such as pancreatitis and diabetes mellitus. FGF21 therapy may also be beneficial as an adjunct therapy in ruminants with hepatic lipidosis, as it can alleviate some lipotoxicity within the hepatocyte and help restore hepatic function. This may also translate to companion animals with fatty liver diseases, such as cats. Hepatic lipidosis is a deadly, acute condition in domestic cats. Using FGF21 therapeutics to acutely alleviate hepatic lipotoxicity and at least partially restore liver function, allowing the veterinarian to deal with the underlying condition, could be revolutionary for veterinary medicine. Research exploring the physiology and pathophysiology of FGF23 in domestic animals already bears fruit in managing feline chronic kidney disease. It may be that future study of FG23 control and signaling allows for manipulating calcium and phosphorus metabolism in production animals and for discovering congenital or tumor-induced phosphate wasting disorders in animals. The endocrine FGFs are a family of important proteins with potential diagnostic and therapeutic benefits in veterinary medicine and deserve further study.

CRediT authorship contribution statement

Emily J. Brinker: Writing – review & editing, Writing – original draft. **Michael R. Hardcastle:** Writing – review & editing. **Keren E. Dittmer:** Writing – review & editing. **Emily C. Graff:** Writing – review & editing, Conceptualization.

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