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REVIEW

# Atypical pituitary hormone–target tissue axis

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**Abstract** **A long-held belief is that pituitary hormones bind to their cognate receptors in classical target glands to actuate their manifold functions. However, a number of studies have shown that multiple types of pituitary hormone receptors are widely expressed in non-classical target organs. Each pituitary gland-derived hormone exhibits a wide range of nonconventional biological effects in these non-classical target organs. Herein, the extra biological functions of pituitary hormones, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, adrenocorticotrophic hormone, and prolactin when they act on non-classical organs were summarized, defined by the novel concept of an "atypical pituitary hormone–target tissue axis." This novel proposal explains the pathomechanisms of abnormal glucose and lipid metabolism, obesity, hypertension, fatty liver, and atherosclerosis while offering a more comprehensive and systematic insights into the coordinated regulation of environmental factors, genetic factors, and neuroendocrine hormones on human biological functions. The continued exploration of the physiology of the "atypical pituitary hormone–target tissue axis" could enable the identification of novel therapeutic targets for metabolic diseases.**

**Keywords** thyroid-stimulating hormone; follicle-stimulating hormone; luteinizing hormone; adrenocorticotrophic hormone; prolactin

## Introduction

The hypothalamus–pituitary–target gland axis has been recognized as a fundamental functional framework of the mammalian endocrine system. The anterior pituitary gland synthesizes and secretes multiple hormones, including thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), prolactin (PRL), and growth hormone (GH). Each hormone binds to its cognate receptor in its classical target gland (such as the thyroid for TSH, the gonads for FSH and LH, and the adrenal gland for ACTH) to regulate critical physiological pathways that play a role in growth, development, energy metabolism, immune function, and reproduction among other functions. In past decades, a number of reports have shown that multiple types of pituitary hormone receptors are widely expressed in non-classical target organs. Thus, each pituitary gland-derived hormone exhibits a wide range of unconventional biological effects in these non-classical target organs. Herein, the physiological functions of pituitary hormones in these non-classical organs were summarized, a process referred to as an "atypical pituitary hormone–target tissue axis" (Fig. 1). The findings provide new insights into the biological function of pituitary hormones and expand the current knowledge of their targets and the functions they regulate.

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## Overview of the typical hypothalamus–pituitary–target tissue axis

Classical endocrinology holds that endocrine regulation in the human body is realized through many functional regulatory "axes." Gaining an understanding of the regulatory function of these "classical axes" is clearly essential to identify the pathomechanisms of endocrine and metabolic disorders, which is critical for guilding diagonosis and effective treatment in clinical practice.

Control of pituitary hormone synthesis is achieved via a homeostatic feedback loop involving the hypothalamic–pituitary–target tissue axis (Fig. 2). Notably, cells in the

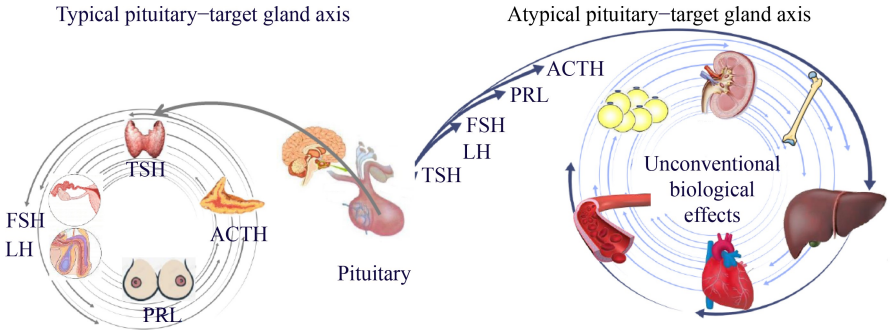


**Fig. 1** General schematic of "atypical pituitary hormone–target tissue axis."

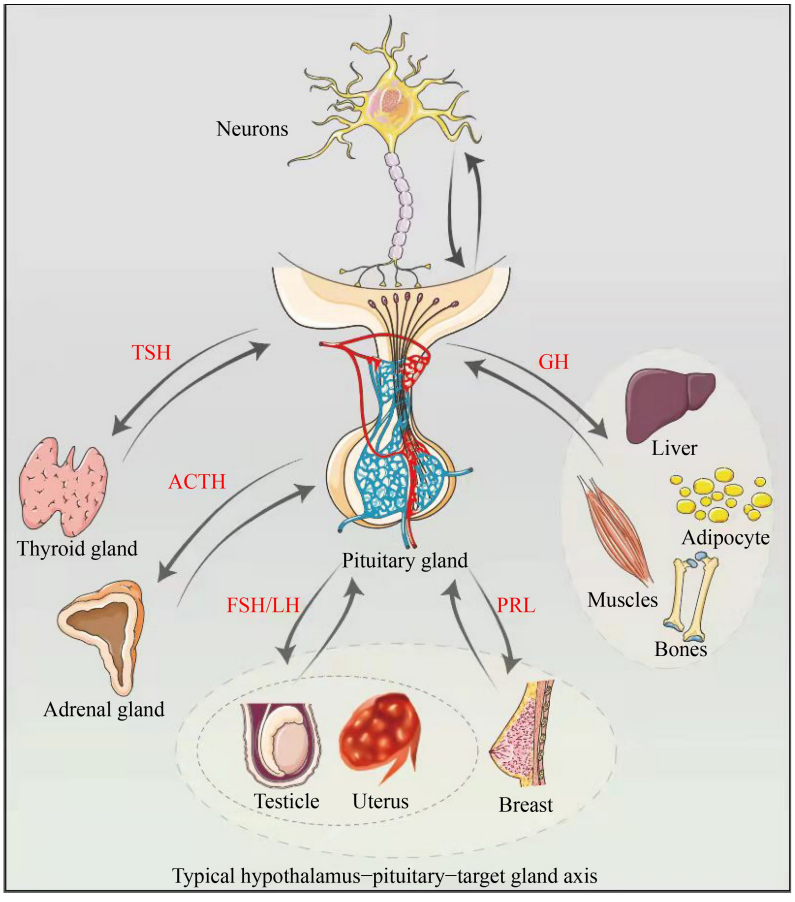


**Fig. 2** Schematic of the typical hypothalamus–pituitary–target tissue axis.

hypothalamus and pituitary gland monitor circulating hormone concentrations and secrete trophic hormones to activate specific pathways for hormone synthesis and release. Target hormones, in turn, serve as powerful negative feedback regulators of their respective trophic hormone, often also suppressing the secretion of hypothalamic-releasing hormones. Typical examples are TSH, FSH, LH, ACTH, and GH.

Hormones determine cellular target actions by binding with high specificity to receptor proteins. Whether a peripheral cell is hormonally responsive depends, to a large extent, on the presence and function of specific and selective hormone receptors and the downstream signaling pathway molecules. Thus, receptor expression and intracellular effector pathways activated by the hormone signal are key determinants for which cells will respond and how to respond.

TSH is produced by the pituitary thyrotrophs and stimulates thyroid functions by using specific membrane TSH receptor (TSHR), which belongs to the superfamily of G protein-coupled receptors (GPCRs), on thyroid cells. The physiological roles of TSH include stimulation of differentiated thyroid functions, such as iodine uptake and organification; production and release of iodothyronines

from the gland; and promotion of thyroid growth [1].

FSH and LH are synthesized by the pituitary gonadotropes, and they are the two pituitary gonadotrophins involved in the regulation of gonadal function. By binding to its receptor (FSHR), FSH regulates granulosa cell function in the ovary, including the development and selection of ovarian follicles, oocyte maturation, and, in concert with LH, the ovulatory process [2]. In testes, FSH regulates the function of sertoli cells, and thereby the proper development and maturation of germ cells. The LH receptor (LHR) is mainly present on testicular Leydig cells and ovarian theca, luteal, and mature granulosa cells. By binding to LHR, LH stimulates the production of androstenedione in theca cells and androgens in Leydig cells [3]. LH also plays a pivotal role in the ovulation and the formation and function of the corpus luteum.

TSH, FSH, and LH are glycoprotein-based hormones composed of α and β subunits. Their α subunits are identical peptides, whereas the β subunit is a unique peptide that endows each hormone with the ability to bind to its own cognate receptor.

Proopiomelanocortin is a precursor of several peptides, including adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH), γ-melanocyte-stimulating hormone (γ-MSH), and β-endorphin, which are synthesized and secreted from the corticotroph cells of the anterior pituitary [4]. The physiological receptor of ACTH is the melanocortin 2 receptor (MC2R), which belongs to the melanocortin-receptor family. To date, five melanocortin receptors have been identified: MC1R, MC2R, MC3R, MC4R, and MC5R. MC2R, which is principally expressed in cells of the adrenal cortex, responds only to ACTH; the other MCRs respond to α-MSH, β-MSH, ACTH, and γ-MSH, in roughly that order of sensitivity [5]. Physiologically, ACTH stimulates the adrenal glands to produce glucocorticoids, and it is required for fetal and neonatal adrenal gland development [6].

PRL is mainly synthesized and secreted by lactotroph cells of the anterior pituitary gland. The actions of PRL are mediated by the dimeric transmembrane receptor, PRL receptor (PRLR), which is a member of the hematopoietic cytokine receptor superfamily. The effects of PRL on the mammary gland include growth and development of the mammary gland (mammogenesis), synthesis of milk (lactogenesis), and maintenance of milk secretion (galactopoiesis) [7].

## Atypical hypothalamus–pituitary–target tissue axis

In addition to traditional target tissues, multiple other organs and tissues express the cognate pituitary hormone receptors to transduce the signals of these hormones in those tissues. Zaidi *et al.* [8] have reviewed the actions of pituitary hormones beyond traditional targets. However, that review was much more focused on TSH and FSH and mostly on the bone, with minimal focus on body composition. Therefore, in the present review, the discovered non-classical biological function of pituitary hormones was summarized in detail and comprehensively.

### TSH

Under physiological conditions, TSH regulates the synthesis and secretion of thyroid-derived hormones via TSH receptor (TSHR) signaling. TSHR mainly localizes to the thyroid follicular cell membrane. Extra-thyroid sources of TSHR have long been known [9]. In parallel with the pituitary–thyroid endocrine axis, an additional TSH-related circuitry functions beyond the thyroid (Fig. 3). Studies have found that TSHR is also expressed in multiple organs and tissues besides the thyroid, such as the liver, adipose tissue, myocardium, bones, thymus, kidney, and brain [10–23].

#### *Liver*

Previous studies have demonstrated that TSHR is expressed in the hepatocyte cell membrane [24–28]. Such expression suggests that TSH potentially plays important pathophysiological roles in hepatocytes via TSHR signaling, in addition to its classical effect on the regulation of thyroid hormone synthesis and secretion [29–31].

In the liver, TSHR signaling plays an important role in the regulation of lipid synthesis and lipid metabolism. TSH increases the biosynthesis of cholesterol and inhibits the conversion of cholesterol to bile acids (BAs), leading to hypercholesterolemia [32–34]. TSH promotes the expression of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCR), a rate-limiting enzyme in cholesterol synthesis, thereby stimulating the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate–responsive element binding protein (cAMP/PKA/CREB) signaling system [35,36]. Other studies have demonstrated the effect of TSH on hepatic HMGCR phosphorylation and the elevation of cholesterol levels [37,38]. In addition, TSH could suppress the synthesis of hepatic BAs via the SREBP-2/HNF-4α/CYP7A1 pathway [39]. These results unveiled a novel mechanism of hypercholesterolemia that involves a direct action of TSH in the liver and presented a potential therapeutic target for hypercholesteremia [40].

Apart from focusing on the association between TSH and hepatic cholesterol metabolism, a study has identified a direct effect of TSH on triglyceride synthesis in liver

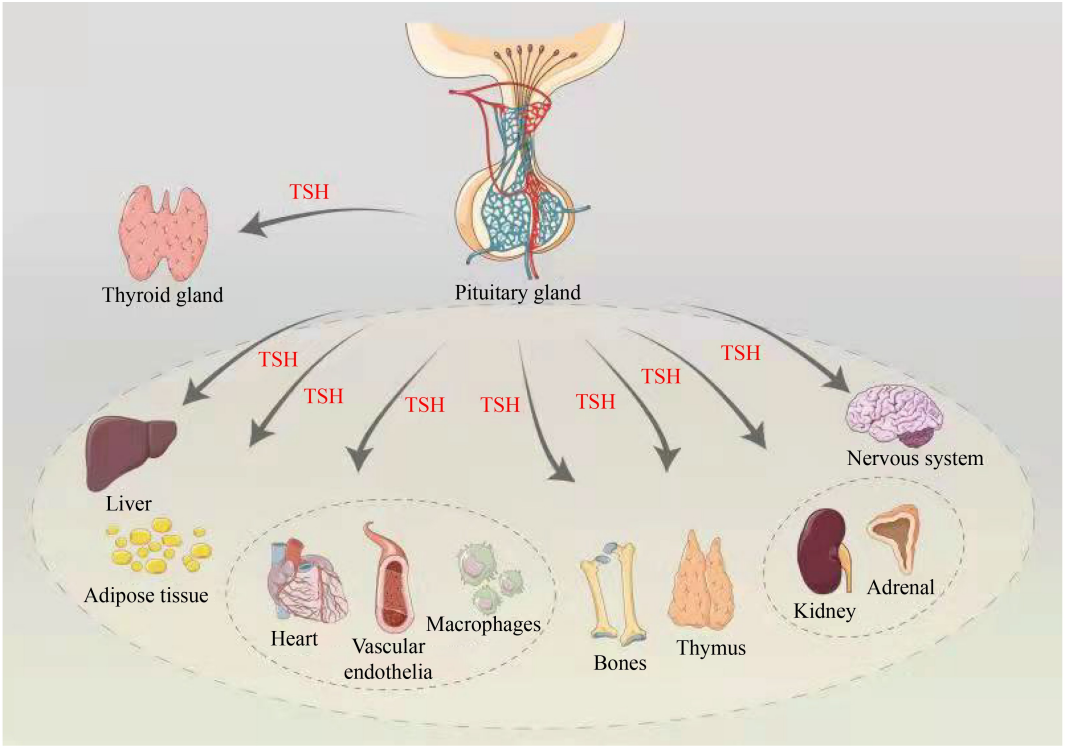


**Fig. 3** Pituitary TSH–target tissue axis.

[41]. TSH binds to TSHR in the hepatocytes, increases hepatic SREBP-1c activity via the cAMP/PKA/PPARα pathway, and decreases AMPK activity, eventually leading to hepatic triglyceride accumulation [42,43]. These findings revealed a novel regulatory action of TSH in the metabolism of hepatic triglycerides, suggesting an important role of TSH in the pathogenesis of nonalcoholic fatty liver disease (NAFLD) [42,44,45].

In addition, TSH could regulate glucose metabolism. It enhances hepatic CRTC2 expression via the TSHR/cAMP/PKA pathway and then increases the amount of the CRTC2:CREB complex to increase PEPCK and G6P expression, eventually leading to an increase in hepatic gluconeogenesis [46]. Furthermore, TSH could increase liver gluconeogenesis via inducing endoplasmic reticulum stress and thus affect the secretion of adipokines, such as leptin, leading to defects in pancreatic β-cell function and contributing to insulin resistance.

Further, TSH downregulates the expression of lncRNA-AK044604 and the deacetylase activity of SIRT1/SIRT3, resulting in increased CypD acetylation and hepatic mitochondrial stress, thereby suggesting a potential role of TSH in oxidative stress-related liver disease [47].

A liver-specific TSHR-knockout (LT-KO) mouse exhibited not only lower hepatic triglyceride and cholesterol content due to modified synthesis and catabolism of lipids in the liver but also decreased serum lipids, especially serum LDL-C levels [41]. The abnormalities of TSHR in the thyroid affects whole-body energy balance; however, measurements taken in metabolic chambers showed that LT-KO had no effect on systemic energy metabolism. Shih *et al*. [48] have reported that TSHR expression was elevated in hepatocellular carcinoma (HCC) samples, and this finding was associated with adverse postoperative outcomes in patients with early-stage HCC. Moreover, the elevated TSHR was found to be functional receptor via *in-vitro* experiments, and the activation of TSHR via TSH resulted in increased cellular cAMP levels and resistance of cells to an anticancer agent [48].

*Adipose tissue*

Studies have demonstrated that TSHR was expressed in cultured rat preadipocytes, and the expression and function of TSHR are closely related to preadipocyte differentiation [49,50]. The expression of TSHR was also found to occur in differentiated 3T3-L1 cells and be induced by insulin, dexamethasone, and isobutylmethy-lxanthine treatment [51]. TSH activates p70, S6K, and PKB/Akt in a PI3K-dependent manner, which, in turn, activates caspase 3 levels, decreases apoptosis, and eventually regulates the cell survival in 3T3-L1 preadipocytes [52,53]. Knockdown of TSHR blocked the adipocyte differentiation of 3T3-L1 preadipocytes.

A previous study has explored the expression and function of TSHR in brown adipose tissue. TSH stimulates the activity of type II iodothyronine deiodinase

and the expression of uncoupling protein 1 (UCP1) in brown adipocytes [54]. Further, TSH was found to be associated with thermogenic regulation in mouse brown adipose tissue and protect hypothyroid mice from a further drop in temperature upon cold challenge [55]. In adipose tissue-specific TSHR knockout (KO) mice, the adipocyte size and, in turn, the basal lipolysis increased [56].

In addition to these thermogenic effects, TSH plays an important role in adipocyte differentiation and triglyceride (TG) synthesis and interferes the conversion of white fat to beige fat, which may promote obesity development in some cases [57,58]. TSHR protein expression in subcutaneous adipose tissue is correlated with body mass index (BMI) [57]. In mice, TSHR protein expression is higher in visceral adipose tissues in obese mice than in lean controls. *Tshr* KO mice, which have normal thyroid hormone levels after thyroid hormone supplementation, resisted high-fat diet-induced obesity. TSH could directly induce the activity of glycerol-3-phosphate-acyltransferase 3 (GPAT3), the rate-limiting enzyme in TG synthesis, via the AMPK/PPARγ pathway [59]. Knockout of *Tshr* decreases adiposity, increases energy expenditure, and markedly promotes the development of beige adipocytes in epididymal and inguinal subcutaneous white fat via a mechanism that likely involves the AMPK/PRDM16/PGC1α pathway [60].

*Cardiomyocytes, vascular endothelial cells, and macrophages*

Functional TSHR is also present in cardiomyocytes at the mRNA and protein levels, indicating a possible role in cardiac function of hyperthyroidism [61]. The TSHR mRNA levels in porcine heart varies regionally, with the highest expression in the coronary artery, adipose tissue, and right atrium, suggesting a functional or pathological role of TSHR in these parts [62]. Functional TSHR is expressed in ventricular myocytes to induce BNP secretion and HMGCR upregulation via the cAMP/PKA/pCREB signaling pathway, thereby defining the pathophysiological role of TSH in heart failure-associated hypothyroidism [63].

The binding of TSH and its receptor in cardiomyocytes was demonstrated to induce the systolic and diastolic dysfunction of the heart, leading to heart failure [64]. TSH lengthens the action potential, which causes a reduction in the amplitude of Ito and IK1 currents, providing evidence that hypothyroidism-induced disturbances of cardiac electrical function could be caused by the elevation of circulating TSH [10]. TSH inhibits the activity of sarcoplasmic reticulum calcium ATPase (SERCA2a) by binding to TSH receptors to inhibit the protein kinase A/phospholamban (PKA/PLN) signaling pathway, resulting in cardiac systolic and diastolic dysfunction [64]. TSH inhibits repolarizing $K^+$ currents via a TSHR/PKA pathway to remodel cardiac electrical activity and affect cardiac rhythm in states of hypothyroidism [65].

Functional TSHR also occurs in vascular endothelial cells and macrophages, where it promotes an inflammatory response and induces oxidative stress, leading to atherosclerosis and increased risk of cardiovascular events [66]. TSH contributes to atherogenesis through the activation of MAPKs (ERK1/2, p38α, and JNK) and IκB/p65 pathways in macrophages and thus increases inflammatory cytokine production and the recruitment of monocytes, suggesting that elevated TSH is an independent risk factor for atherosclerosis [67–69].

*Bone*

TSHR is mainly expressed in the early and middle stages of osteoclast and osteoblast formation [70]. TSHR-deficient mice displayed loss of bone mineral density, high-turnover osteoporosis, and focal osteosclerosis. In euthyroid mice, even a 50% reduction in TSHR resulted in significant osteoporosis and focal osteosclerosis, even though dietary supplementation with thyroid hormone normalized the serum thyroid hormone levels. These results suggested that these effects of TSH/TSHR signaling in the bone are likely independent of the effects on TH production by the throide.

TSH/TSHR signaling acts to inhibit osteoclast and osteoblast formation through different mechanisms [71]. TSH impairs osteoclast formation and promotes osteoclast apoptosis by inhibiting the JNK/c-Jun and NF-κB pathway. TSH, through the independent mechanism of Runx-2 and Osterix, downregulates the expression of differentiation factors LRP-5 and Flk-1 and thus inhibits the differentiation of osteoblasts and decreases the expression of collagen type 1, bone sialoprotein, and osteocalcin.

The osteoporosis that occurred in TSHR null mice was the result of the enhancement of osteoclast differentiation. The mRNA and protein levels of TNFα, an osteoclast cytokine, increased in the bone marrow of TSHR-KO mice, and an TNFα antibody inhibited this increase [72]. TSH also inhibits the proliferation of osteoclast precursors by inhibiting TNFα in $CD11b^+$ osteoclast progenitor cells. TSH/TSHR interferes with downstream AP-1 and NF-κB signal transduction, leading to a decrease in TNFα expression and osteoclast formation. These results suggested that TNFα is a key cytokine for mediating the anti-bone resorption effects of TSH [73].

As mentioned above, the TSHR-KO mice showed high-turnover osteoporosis and focal osteosclerosis. Indeed, low TSH levels are correlated with increased fracture risk in humans, and a single administration of recombinant human TSH could inhibit bone resorption. This evidence

suggested that low TSH levels increase the risk factor for osteoporosis in individuals with hyperthyroidism [74]. Systemic administration of low TSH levels prevented bone loss and restored bone mass in aged ovariectomy (OVX) rats by inhibiting RANKL-induced osteoclast formation and stimulating osteoblast differentiation. Intermittently administered TSH restored OVX-induced bone loss and improved bone strength in rodents [75]. Moreover, intermittent and continuous TSHR activation induced antiresorptive actions *ex vivo*. By contrast, TSHR inactivation in congenital hypothyroid mice stimulated osteoclast differentiation, suggesting that TSHR has a critical role in regulating bone remodeling [76].

*Thymus*

As early as the 1990s, researchers have demonstrated that TSHR mRNA and protein expression occurs in the thymus, along with other thyroid-related genes, such as sodium iodide symporter (NIS), thyroid peroxidase (TPO), and thyroglobulin (Tg) [77]. These expression patterns indicate a potential role of TSH within the thymus, independent of its function in the thyroid gland [78].

TSH could act as a growth factor for the regulation of T cell development. TSH is able to bind and activate TSHR that is present on thymocytes, thereby activating calcium signaling and cyclic adenosine monophosphate signaling pathways, which lead to enhanced T cell development [79]. In addition, utilizing a subclinical hypothyroidism mouse model, which was characterized by elevated serum TSH with unchanged thyroid hormone levels, showed that TSH promoted thymus development by increasing the number of thymocytes and inhibiting thymocyte apoptosis, which may be related to ERK signaling pathway [80].

Using thyroiditis-prone NOD.H2h4 mice and two transgenic BALB/c lines showed that low intrathymic expression of TSHR is associated with susceptibility to developing pathogenic TSHR autoantibodies in Graves' disease, whereas high intrathymic TSHR mRNA levels are protective [81].

*Kidney and adrenal gland*

TSHR mRNA and protein expression has also been detected in various human extrathyroidal tissues by using liquid hybridization analysis and immunohistochemical studies, including in the kidney and adrenal gland. Human kidney tissues and cell lines expressed TSHR and Tg, and the intracellular cAMP level significantly increased after TSH stimulation of these cell lines, strongly suggesting that the TSHR expressed in the kidney is functional [77,82]. However, a kidney-specific KO of TSHR or transplant of kidneys from whole-body KO mice into wild-type mice is required to determine the physiological function of this signaling pathway in this organ.

Finally, TSH regulates blood pressure via changing renal hemodynamics and peripheral vascular resistance.

*Nervous system*

Elevated TSH levels during pregnancy cause a decreased expression of thyroid hormone-responsive genes in fetal brain tissue, including an abnormal expression of brain development-related genes *Egr1*, *Arc*, *p-ERK*, *BDNF*, *and Rap1*; a reduced activity of cAMP response element binding protein (CREB) signal pathway; a disordered neuronal arrangement; and abnormal migration of cerebral cortex and hippocampus [83]. Together, these affects lead to a decline in the offspring's intelligence.

**FSH**

FSH is a heterodimeric glycoprotein hormone secreted by gonadotrope cells in the anterior pituitary. The FSH receptor (FSHR) is a glycosylated transmembrane protein that belongs to the family of GPCRs [84]. FSHRs are mainly observed in gonadal tissues. FSH, via binding to FSHRs, stimulates the development of the Graafian follicle in females and promotes the differentiation of sperm in males.

Analysis of tissue expression demonstrated that the FSHR in the Chinese alligator was expressed not only in the ovary but also in the liver, stomach, intestine, pancreas, and oviduct at similar levels (Fig. 4) [85]. A study in females has found that the highest expression of FSHR was observed in the kidney, followed by the cerebellum and lung. This finding proved that the main location of FSHR is in the tubules of kidney, Purkinje cells, medulla of cerebellum, and alveolar cells of lung [86]. Transcripts and protein for FSHR have also been found in the abdominal adipose tissue of female chickens [85].

*Liver*

FSHR is expressed in human and mouse liver. FSH, via binding to hepatic FSHR, activates the Gi2α/β-arrestin-2/Akt pathway and upregulates SREBP-2, which drives HMGCR transcription and *de-novo* cholesterol biosynthesis, resulting in an increase of cholesterol accumulation. Furthermore, blocking FSH signaling could significantly reduce cholesterol biosynthesis in the liver [87].

*Bile duct*

The biliary epithelia express FSHR and FSH, the latter

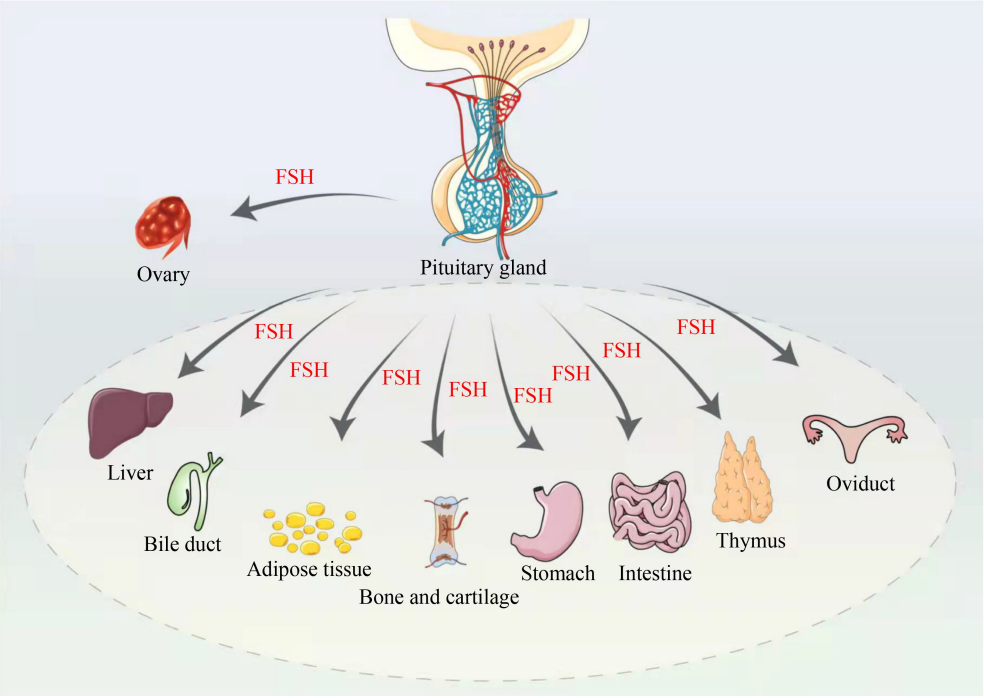


**Fig. 4** Pituitary FSH–target tissue axis.

being a trophic factor for cholangiocyte proliferation. Immunohistochemistry in liver sections and real-time PCR of RNA from purified cholangiocytes showed that this cell type expresses the protein and the message for FSHR.

Chronic administration of FSH to rats increased cholangiocyte proliferation and intrahepatic ductal mass by cAMP-dependent phosphorylation of FSH, resulting in an increase in the levels of two FSH receptor mRNA transcripts. FSH increases cholangiocyte proliferation by an autocrine mechanism via cAMP-dependent phosphorylation of ERK1/2 and Elk-1. Administration *in vivo* of a neutralizing anti-FSH antibody to female and male BDL rats for 1 week reduced cholangiocyte mitosis and intrahepatic ductal mass, concomitant with increased biliary apoptosis [88].

*Adipose tissue*

Transcripts and protein for FSHR have been demonstrated in the abdominal adipose tissue of female chickens. FSH stimulates lipid biosynthesis by upregulating FSHR mRNA expression in abdominal fat, which is involved in retinol, PPAR signaling, and lipid metabolism pathways [89]. Blocking the action of FSH genetically or pharmacologically in mice is known to lower serum cholesterol and increase bone mass. Zidi and Rosen have further investigated the association between FSH antibody and visceral adiposity and energy homeostasis. A polyclonal FSH antibody caused profound beiging, increased cellular mitochondrial density, activated brown adipose tissue, and enhanced thermogenesis, making an anti-FSH agent a potential therapeutic for obesity [90,91]. Zaidi and Ye have recently reported on a possible causal role for rising serum FSH levels in exaggerated Alzheimer's disease (AD) pathophysiology that occurs during menopause and that FSH does so by promoting a C/EBPβ–AEP/δ-secretase pathway [92]. Zaidi and Ye have also recently revealed that blocking FSH reduced bone loss, serum cholesterol, body fat, and AD pathology. Moreover, the anti-FSH antibody could become a potent agent in the future for co-therapy of osteoporosis, obesity, dyslipidemia, and AD.

*Bone and cartilage*

FSHRs are expressed on the surface of murine and human osteoclasts and their precursors. They are also present on mesenchymal stem cells, which are progenitor cells for osteoblasts, but not on mature osteoblasts.

FSH has a direct role in the bone loss that occurred in hypogonadal mice. A complete loss of FSH signaling in $FSHR^{-/-}$ and $FSH\beta^{-/-}$ mice protected the animals from bone loss despite severe hypogonadism. In adult hypogonadal mice or mice lacking either FSHβ or FSHR, the absence of FSH signaling prevented the increase in bone resorption otherwise seen in hypogonadal states, such as after OVX. Bone mass increased and osteoclastic resorption decreased in haploinsufficient $FSH\beta^{+/-}$ mice

with normal ovarian function, suggesting that the skeletal action of FSH is independent of estrogen [93]. FSH stimulates osteoclastogenesis and bone resorption by acting on a $G_{i2\alpha}$-coupled FSHR and then activates Erk1/2, Akt, and NF-κB to result in enhanced osteoclast formation and function. FSH-β null mice exhibited lower TNF-α levels, and those lacking TNF-α were found to be resistant to hypogonadal-related bone loss in the presence of high FSH levels compared with controls. Thus, TNF-α is likely critical for the effect of FSH on bone mass.

## LH

The gene expression levels of LHR in tissues are similar to those of FSHR. A study in female yaks showed that FSHR and LHR are located in the pineal gland, hypothalamus, pituitary, and gonad [64]. LHR was also expressed in the renal tubules of the kidney, Purkinje cells, and medulla of the cerebellum, and alveolar cells of the lung, similar to FSHR. Another study has demonstrated that LHR was expressed in canine lymphatic tissue [94]. Immunohistochemical analysis of lymph node tissue specimens revealed that LHR was expressed in lymphocytes from neoplastic and non-neoplastic lymph nodes [94]. However, LHR was expressed by a significantly higher percentage of lymphocytes from neoplastic lymph nodes than from non-neoplastic lymph nodes (Fig. 5) [95].

*Hippocampus*

LH acts directly on the dorsal hippocampus to reduce spatial memory [96]. Infusion of human chorionic gonadotropin (hCG) into the dorsal hippocampus of ovariectomized female rats was sufficient to cause impaired spatial memory, even in the presence of estradiol [96]. Infusion of the LHR antagonist dg-hCG into the dorsal hippocampus reversed the spatial memory deficits induced by OVX in female rats. The gonadotropin-releasing hormone (GnRH) antagonist antide did not affect memory positively or negatively when it was applied directly to the dorsal hippocampus of female rats nor did it restore spatial memory performance in female rats.

*Oviducts*

The porcine oviduct possesses immunoreactive and functional LH receptors, similar to human oviduct. The level of LHR protein in oviduct homogenates of sows treated with estradiol significantly increased. LH could cause relaxation of the oviduct, and the inhibitory effect of LH on spontaneous contraction in isthmus and ampulla depended on the presence of estradiol and progesterone [97].

*Urinary tract*

LHR and FSHR were found to be expressed in the lower urinary tract (LUT) of dogs [98]. A reduction in the overall LHR and FSHR expression in the urinary bladder and urethra at mRNA and protein levels was also found in gonadectomised dogs. More obvious and more uniform changes in the expression of LHR and FSHR in different regions and tissue layers of the LUT was found in female spayed dogs than in male castrated dogs.

*Eye*

LH is present in the living human eye. It potentially plays

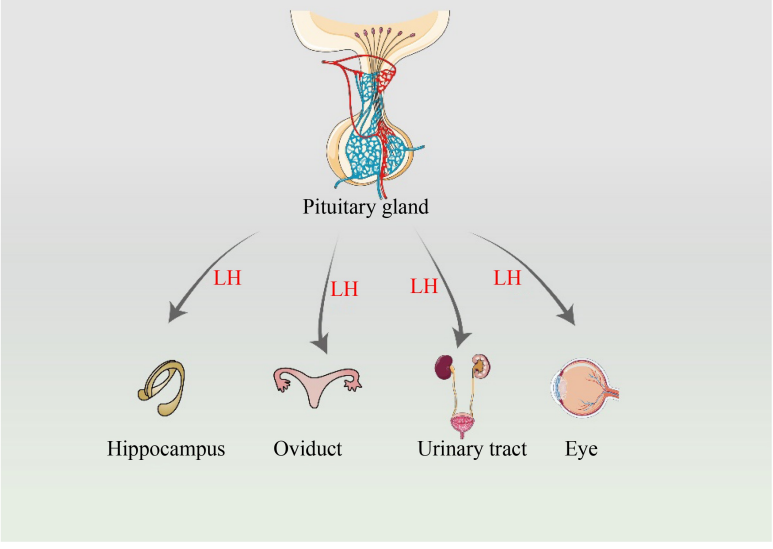


**Fig. 5** Pituitary LH–target tissue axis.

a role in ocular physiology, possibly via enhancement of the phototransduction cascade in cone photoreceptors [99]. Proliferative diabetic retinopathy is significantly associated with increased intraocular LH concentration.

## ACTH

Similarly to the expression of other thyroid hormone receptors outside their typical target tissues, ACTH receptors have been identified outside the adrenal gland. In a previous study, the expression of MC2R and MC5R proteins was evaluated in fetal mouse tissues and organs by immunohistochemical analysis. On the basis of the differential stage- and tissue-specific expression patterns of these receptors, the data suggested that ACTH may affect the histogenesis and/or functions of these tissues and organs during fetal development in mice via MC2R and/or MC5R (Fig. 6) [100].

*Reproductive system (including ovaries, uterus, and testes)*

The receptor for ACTH, melanocortin type 2 receptor (MC2R), was detectable by immunohistochemistry within luteal cells of the corpora lutea [101,102]. ACTH directly upregulates the *in-vitro* progesterone production in corpora lutea via MC2R but indirectly hampers luteal function via a cortisol-glucocorticoid-receptor-associated mechanism.

Robust expression of MC5R in human endometrium at the protein level was shown, along with the modulation of strong expression of MC2R and MC3R in this tissue. By contrast, MC1R is only very weakly expressed in endometrial glandular epithelium, and negligible expression of MC4R could be found in any endometrial cell type [103]. The content of vascular smooth muscle cells in the decidua tissue decreases after exposure to high concentrations of ACTH, and ACTH appears to promote involution of vascular structures in cultured decidua. ACTH may bind to stromal MCRs and elicit alterations in the expression of angiogenic growth factors or proteases that, in turn, act on the vasculature.

MC2R was shown to be expressed within fetal Leydig cells [104], as confirmed by subsequent real-time PCR studies. Real-time PCR studies also confirmed that MC2R was expressed in fetal testes at 100-fold higher levels than in adult testes. LH and ACTH could regulate testicular steroidogenesis during fetal development in the mouse, suggesting that fetal Leydig cells, but not adult Leydig cells, are sensitive to ACTH stimulation.

The expression of MC2R in newborn testes is limited to interstitial tissue, as determined by immunohistochemistry. ACTH induces rapid stimulation of cAMP production within 3 min, before testosterone production become apparent. LH and ACTH, acting through their respective receptors, stimulate steroidogenesis by fetal-type Leydig cells via arachidonic acid, protein kinase A, and ERK1/2 activation of StAR.

*Bone*

High concentrations of ACTH have an anabolic effect on

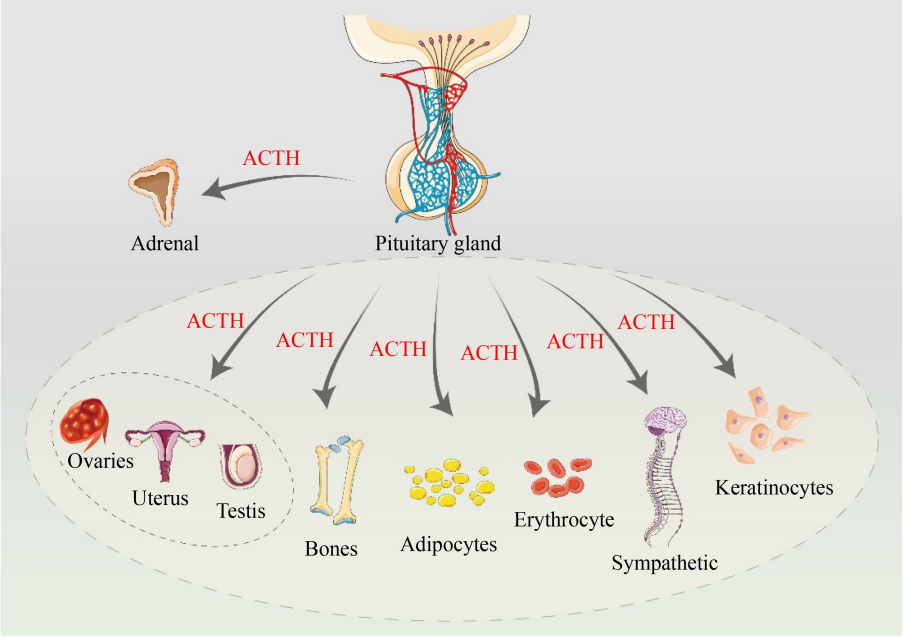


**Fig. 6** Pituitary ACTH–target tissue axis.

osteoblasts [105]. Mechanistically, ACTH receptors in bone cells binds directly to ACTH, which, in turn, stimulates osteoblast proliferation. In addition, ACTH may act synergistically with glucocorticoids (locally or systemic) to promote osteoblast differentiation, as cortisol does not appear to have an adverse effect on bone proliferation or differentiation at physiological levels.

*Adipocytes*

Adipocytes express functional MC2R and MC5R [106]. ACTH could stimulate lipolysis in rodent adipose tissues and mouse adipocytes via MC2R-dependant cAMP/PKA activation [107,108]. Moreover, ACTH increases intracellular cAMP levels and inhibits leptin secretion and production by activating MC2R and MC5R, respectively [106]. The inhibitory effects could be reversed by the antagonists of MCR.

ACTH increases the activity of brown adipose tissues and the browning of white adipose tissues [109,110]. An *in-vivo* study has shown that cold exposure could double serum ACTH concentrations and fecal corticosterone excretion, whereas an *in-vitro* study has shown that ACTH increases UCP1 expression, induces glycerol release, and uncouples respiration [110,111].

*Erythrocytes*

ACTH promotes erythroblast differentiation, and melanocortin receptors promote the differentiation of red blood cells [112]. EPO plays an important role in the process of erythrocyte differentiation, EPO signal transduction requires MC2R and MC1R signal transduction, and MC5R-mediated enucleation is required in the process of erythrocyte differentiation.

*Sympathetic ganglia*

Rat sympathetic ganglia, which are the stomatogastric ganglion (StG) and the superior cervical ganglion (SCG), expressed *MC2R* mRNA and thus appeared to be a target tissue for the peripheral actions of ACTH [113]. The levels of *MC2R* mRNA in SCG increased in stressed rats. The presence of MC2R mRNA in sympathetic ganglia suggested that ACTH may trigger cAMP-mediated changes in the expression of different target genes through its cognate receptor.

*Keratinocytes*

Keratinocytes express enzymes involved in cortisol biosynthesis at the transcriptional level. Immunohistochemistry confirmed that HSD11B1 and HSD11B2 are also present in the epidermis [114]. This finding strongly suggested that HSD11B2 is associated with keratinocyte differentiation. Keratinocytes could convert cortisone to cortisol and modulate cortisol degradation. HSD11 isoenzymes could modulate the local concentration of cortisol in keratinocytes. Keratinocytes are not only able to metabolize cortisone to cortisol but also respond to stimulation with ACTH by initiating *de-novo* cortisol production.

**PRL**

The actions of PRL are mediated by PRLR, which is a dimeric transmembrane protein that is expressed in most organs in mammals. PRLRs are found in the mammary gland and the ovary, two of the best-characterized sites of PRL actions in mammals. They are also found in numerous parts of the CNS, such as the hypothalamus, cerebral cortex, choroid plexus, thalamus, and olfactory bulb. In addition, PRLRs are present in a wide range of peripheral organs, such as the pituitary gland, heart, lung, thymus, spleen, liver, pancreas, kidney, adrenal gland, uterus, skeletal muscle, and skin (Fig. 7).

*Liver*

The presence of functional PRLR in hepatocytes has been reported [115]. In human studies, lower PRL levels were found in individuals with NAFLD and in patients with more severe hepatic steatosis, suggesting a possible involvement of PRL in the development, progression, and severity of NAFLD. Furthermore, a new association between the central nervous system and the liver has been uncovered, in which PRL-PRLR signaling protects the liver against lipid accumulation via the inhibition of the CD36 pathway [116]. CD36 is a key transporter of liver free fatty-acid uptake, and thus, PRL-mediated suppression of this pathway ameliorates hepatic steatosis [116]. *In-vitro* and *in-vivo* studies have suggested that PRL reduces the accumulation of hepatic TGs through PRLR signaling, thereby improving hepatic steatosis. PRL decreases the expression of stearoyl-coenzyme A desaturase 1 (SCD1), the rate-limiting enzyme in the biosynthesis of monounsaturated fatty acids [117]. Therefore, downregulation of PRLR expression could significantly induce hepatic steatosis, and modification of PRL by PRLR may be a potential therapeutic target for NAFLD.

Although PRL is thought to reduce liver fat content, chronic hyperprolactinemia is plausibly involved in the development of NAFLD. PRL may be directly involved in changes in the signaling pathways of *de-novo* lipogenesis, which leads to fatty liver [118]. In diabetic murine models, the TG content in the liver increased with the administration of high doses of PRL [119]. PRL is also thought to be involved in the regulation of liver insulin sensitivity in rodents [120].

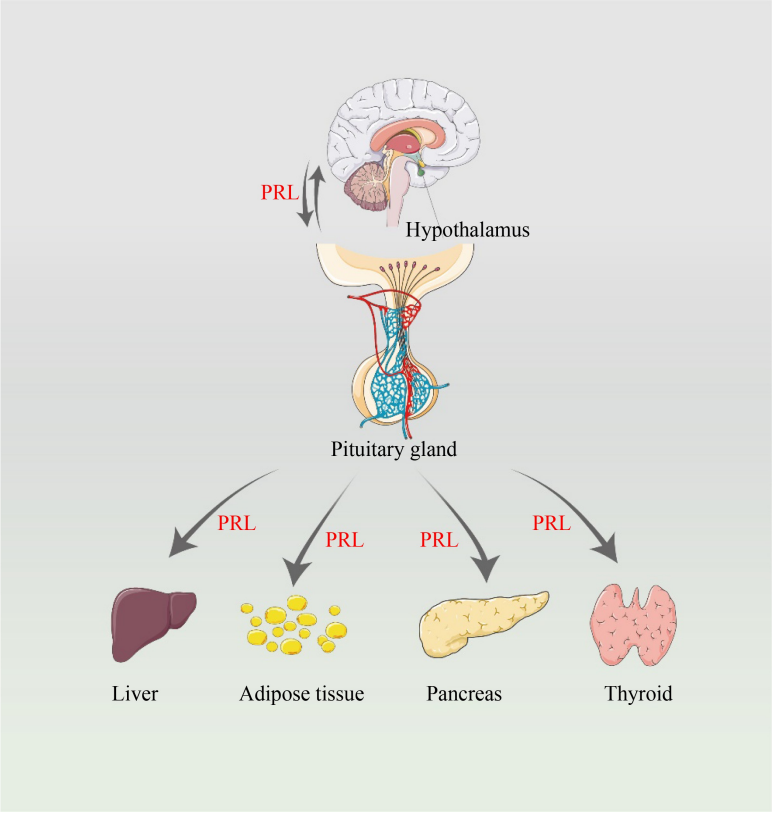


**Fig. 7** Pituitary PRL–target tissue axis.

*The adipose tissue*

Ling *et al.* [121] have identified mRNA and protein expression of PRLR in mouse adipose tissue and shown it to be upregulated during lactation. PRLR was also reported to be present in human adipose tissue, and PRL was shown to inhibit basal- and cortisol-induced lipoprotein lipase activity [122,123].

PRL could decrease brown adipose tissue metabolism and induce obesity. In pituitary-grafted female rats, the mass of the white fat depots was significantly greater than that in the sham controls, whereas the mass of the brown fat depots was significantly (24%) reduced [124].

PRL enhances adipocyte differentiation in NIH-3T3 fibroblasts. Nanbu-Wakao *et al.* [125] have demonstrated that PRL increases the expression of C/EBPβ and PPARγ mRNA and augments adipogenic differentiation of NIH-3T3 cells. Moreover, expression of the PRLR receptor in NIH-3T3 cells effectively transforms the cells into fat-rich adipocytes [125]. In addition, by using female gene KO mice, Flint *et al.* [126] have shown that the absence of PRLR impaired the development of internal and subcutaneous adipose tissue due to reduced numbers of adipocytes.

PRL regulates adiponectin secretion and its receptor expression in adipose tissues. In female mice expressing PRL, the serum levels of adiponectin decreased, but in PRLR-deficient mice, the adiponectin levels were unaffected [127]. In cultured human adipocytes, PRL increased the expression of adiponectin receptor 1 mRNA but reduced the secretion of adiponectin. As decreased adiponectin levels have been associated with insulin resistance, PRL may induce insulin resistance by suppressing adiponectin levels [127].

Leptin is an adipocyte-derived satiety factor that is involved in the regulation of food intake and body weight. PRL acts on the adipose tissue to increase leptin synthesis and secretion. A significant increase in serum leptin concentrations occurred in hyperprolactinemic animals in comparison to controls. This stimulatory effect of PRL on serum leptin levels was significantly reduced by food deprivation, suggesting an important role for PRL in the regulation of food intake [128].

*Hypothalamus and pituitary gland*

Female rats with hyperprolactinemia resulting from ectopic pituitary grafts consumed significantly more food and gained more weight than sham-operated controls [124,129]. Intracerebroventricular administration of PRL also increased food intake. Paraventricular nucleus (PVN), ventromedial nucleus (VMH), and medial preoptic nucleus (MPOA) expressed PRLR, but injection of PRL at different sites demonstrated different effects on

virgin female rats. PVN is the most sensitive to the orexigenic properties of PRL, many injections of PRL into VMH were necessary before an increase in feeding was observed, and no dose of PRL stimulated feeding when infused in MPOA [129].

*Pancreas*

The effects of PRLR deletion on islet development, insulin production, and glucose tolerance have also been studied. Compared with wild-type litters, mice lacking PRLR showed reduced islet density and β cell mass [130]. This finding was accompanied by a decrease in pancreatic insulin mRNA levels and glucose-dependent insulin secretion *in vivo* and *in vitro*. The decrease in the number of islets partly explains the decrease in insulin mRNA and glucose-dependent insulin secretion *in vivo*. Two other possibilities could not be ignored: individual islets may produce less insulin and the reduction in glucose-stimulated insulin secretion may be, in part, due to reduced expression of glucose transporter 2 and/or glucokinase. PRLR deficiency was found to be associated with islet and β cell dysplasia. It also reduced pancreatic insulin mRNA levels and decreased insulin response to glucose secretion and mild glucose intolerance.

One newly described function for PRL is in the proliferation of pancreatic β cells; in mice, PRLR was required for β-cell proliferation and maintenance of normal glucose homeostasis during pregnancy [131]. Heterozygous $PRLR^{+/-}$ mice are glucose intolerant during pregnancy and their wild-type offspring are at increased risk of developing glucose intolerance during their own pregnancies. Thus, PRL activity during pregnancy is important not only for normal glucose homeostasis in the pregnancy of the dam but also in future pregnancies of the offspring. In pregnant wild-type mice, PRL repressed the islet levels of menin, which controls the growth of pancreatic β cells and stimulates β cell proliferation [132,133]. These results expanded the understanding of the mechanisms that underlie diabetes mellitus pathogenesis and revealed potential targets for therapy in this disease.

*Thyroid gland*

PRLR null mice were significantly more likely to develop medullary thyroid carcinoma [134]. $PRLR^{-/-}$ mice exhibited mild hypothyroidism. PRLR mRNA was expressed in two compartments: thyroid follicles and C cells, which are sites of calcitonin production. In the absence of PRL signaling, the apparent morphology of the follicle did not change, and the C cell compartment did not seem to be affected.

The thyroid nodule frequency and thyroid volume increase in patients with prolactinoma [135]. PRL promotes tumorigenesis by promoting cell proliferation, increasing cell motility, and supporting tumor vascularization. Increasing evidence has shown that locally produced PRL acts in autocrine manner rather than pituitary-secreted PRL acting in a paracrine manner and promotes tumor growth, as dopamine analogs could not suppress PRL production in extrapituitary areas.

## Significance and prospective of the "atypical pituitary hormone–target tissue axis"

The novel concept of "atypical pituitary hormone–target tissue axis" is a breakthrough and expansion of the traditional biological functions of pituitary hormones. It provides a new view for studying the mutual regulation of hypothalamic–pituitary hormones and peripheral tissue metabolism and opens up a new field exploring the biological function of pituitary hormones. The new perspective of an "atypical pituitary hormone–target tissue axis" explains the pathomechanisms of abnormal glucose and lipid metabolism, obesity, hypertension, fatty liver, and atherosclerosis while offering a more comprehensive and systematic insight into the coordinated regulation of environmental factors, genetic factors, and neuroendocrine hormones on human biological functions. In this manner, the concept of an "atypical pituitary hormone–target tissue axis" could further enrich and improve the understanding of endocrinology.

Although a substantial amount of findings on the actions of pituitary hormones beyond traditional targets has emerged during the last several decades, many issues remain unresolved, including elucidation of the physiological function and signaling pathway of pituitary hormones in their non-classical targets organs, identification of new biological roles and novel target tissues for pituitary hormones, and demonstration of the pathophysiological and therapeutic implications of "atypical pituitary hormone–target tissue axis." Tissue-specific ablation of pituitary hormones receptor mouse lines is a vital tool for uncovering the various *in-vivo* activities of a given hormone in specific tissues. Continuous exploration of the physiology of "atypical pituitary hormone–target tissue axis" is highly important as it could enable the manipulation of the system with greater precision and sophistication than is currently possible and perhaps the discovery of novel therapeutic targets for metabolic disease in human.

## Compliance with ethics guidelines

Chao Xu, Zhao He, Yongfeng Song, Shanshan Shao, Guang Yang , and Jiajun Zhao declare no competing financial interests. This

manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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