Chapter 10
Pituitary Hormone-Driven Mechanism for Skeletal Loss

Tony Yuen, Li Sun, Wahid Abu-Amer, Peng Liu, Terry F. Davies, Harry C. Blair, Maria New, Alberta Zallone, and Mone Zaidi

Abstract A single specific function has been traditionally ascribed to each anterior and posterior pituitary glycoprotein hormone. However, it has become clear over the past decade that these hormones and their receptors have more ubiquitous functions. Organs, such as the skeleton, are regulated by and respond to pituitary hormones, particularly when circulating levels are perturbed in disease. Additionally, certain pituitary hormones are also expressed in bone cells, underscoring paracrine regulation.

The function of pituitary glycoprotein receptors in skeletal control appears evolutionarily more distant than effects on primary endocrine tissues (Blair et al. 2011). Growth hormone (GH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), prolactin, oxytocin, and vasopressin all affect bone, and in mice, the haploinsufficiency of either the ligand and/or receptor yields a skeletal phenotype with the primary target organ remaining unaffected. Recognition and in-depth analysis of the mechanism of action of each pituitary hormone has improved our understanding of bone pathophysiology and opens new avenues for therapy. Here we discuss the interaction of each pituitary hormone with bone and the potential it holds in understanding and treating osteoporosis.

Keywords Pituitary-bone axis • Pituitary hormones • GPCR's • Anti-resorptive • Anabolic

T. Yuen (✉) • L. Sun • W. Abu-Amer • P. Liu • T.F. Davies • M. New • M. Zaidi
The Mount Sinai Bone Program, Department of Medicine, and Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: tony.yuen@mssm.edu

H.C. Blair
Departments of Pathology and of Cell Biology, University of Pittsburgh School of Medicine and the Pittsburgh VA Medical Center, Pittsburgh, PA, USA

A. Zallone
Department of Histology, University of Bari, Bari, Italy

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10.1 Evolution of Pituitary Hormone Receptor Signaling

ACTH is the best example of a pituitary hormone being part of a widely distributed G protein-coupled receptor (GPCR) system, which is known to participate in local cell differentiation. However, this local function seems to pale in comparison to the pituitary-adrenal signaling axis. There are five melanocortin receptors, including the ACTH receptor MC2R, which regulate various cellular functions, such as pigment production, appetite, and sexual function. All are controlled by ligands processed from a single large prohormone, pro-opiomelanocorticin (POMC). Hormone production occurs by tissue-specific regulated proteolysis, with ACTH being the predominant product in the anterior pituitary. At other sites, pro-opiomelanocorticin, three melanotropins, and β-endorphin are synthesized from the same precursor. ACTH is produced by human macrophage/monocyte cells (Pallinger and Csaba 2008), making it possible that MC2Rs in bone may also be activated by local, instead of pituitary-derived, ACTH. This level of decentralized control is also exemplified by corticotropin-releasing factor (CRF), which stimulates pituitary ACTH production in the adult while stimulating cortisol synthesis directly in the fetus (Sirianni et al. 2005).

TSH and FSH, along with chorionic gonadotropin (hCG) and luteinizing hormone (LH), belong to the subfamily of heterodimeric protein ligands that share a common α-chain, which specificity depending on their distinct β-chains. These hormones have primitive functions. Notably, in coelenterates for example, a TSHR family gene is identifiable, widely expressed, and shows the intron-exon structure found in mammals (Vibede et al. 1998). In lower vertebrates, such as in bony fish, there is abundant TSHR expression in the thyroid, but the receptor is also detectable in the ovaries, heart, muscle, and brain (Kumar et al. 2000). In fish, the gonadal expression of LHR and FSHR is well documented. In fact, multiple differently processed forms of the FSHR occur in fish (Kobayashi and Andersen 2008); this may reflect isoforms with differing functions. Further, in fish, the FSHR binds both FSH and LH, whereas the LHR recognizes only LH (Bogerd et al. 2005). While high-level FSHR expression is restricted to gonads, low-level expression is seen in spleen (Kumar et al. 2001), quite similarly to findings in human cells.

We and others have recently reported the production of a TSHβ variant by bone marrow macrophages (Vincent et al. 2009; Baliram et al. 2013); this splice variant activates the TSHR and may do so locally in bone. Lymphocytes also express TSH (Smith et al. 1983; Harbour et al. 1989), but such production is unlikely to affect circulating levels. There is no evidence, however, for bone or marrow cell production of FSH, although coproduction of TSHβ and FSH is noted in CD11β cells from mouse thyroid (Klein and Wang 2004). Overall, therefore, the presence of GPCRs in tissues other than traditional endocrine targets, such as the skeleton, and in cases, coexistence of their ligands, comes as no surprise. What does come as a surprise, however, is that the skeleton appears to be more sensitive to GPCR stimulation than the primary target organs, at least in mouse genetic and limited human studies.

10.2 Growth Hormone and IGF-1 Action on Bone

Growth hormone (GH), a single-chain polypeptide, plays a vital role in bone growth, modeling, and remodeling. It directly acts through a GPCR, but its primary action occurs via the release of insulin-like growth factors (IGFs). IGF-1 is synthesized mainly in the liver, and ~80 % circulates bound to IGF-binding protein-3 (IGFBP3) and the acid labile subunit (ALS). In GHR-deficient mice, both growth retardation and osteoporosis are rescued by IGF-1 overexpression (De Jesus et al. 2009), attesting to the relative importance of IGF-1 over GH. Furthermore, despite elevated GH levels, mice lacking both liver IGF-1 (LID) and ALS, with depleted serum IGF-1, show reduced bone growth and bone strength (Yakar et al. 2002). These results suggest that the skeletal effects of GH require IGF-1. In addition, GH-induced osteoclastic activity appears to require IGF-1 released from bone, which then activates bone resorption by acting on osteoclastic receptors, as well as by altering RANKL expression (Guicheux et al. 1998; Hou et al. 1997; Rubin et al. 2002).

Nonetheless, evidence to suggest that GH can act independently of IGF is somewhat limited and, in some instances, contradictory. GH replacement reverses the increased adiposity in hypophysectomized rats, while IGF-1 replacement does not (Menagh et al. 2010). Furthermore, GH reverses osteopenia in ovariectomized LID mice (Fritton et al. 2010). These results suggest that GH also directly acts on bone.

10.3 FSH Facilitates Bone Loss Along with Estrogen Deprivation

We discovered that FSH directly stimulates bone resorption by osteoclasts (Sun et al. 2006; Iqbal et al. 2006). Several studies have confirmed direct effects of FSH on the skeleton in rodents and humans. For example, amenorrheic women with a higher mean serum FSH (~35 IU/L) have greater bone loss than those with lower levels (~8 IU/L) in the face of near-equal estrogen levels (Devleta et al. 2004). Patients with functional hypothalamic amenorrhea, in whom both FSH and estrogen were low, show slight to moderate skeletal defects (Podfigurna-Stopa et al. 2012). Women harboring an activating FSHR-N680S polymorphism, rs6166, have lower bone mass and high resorption markers (Rendina et al. 2010); this attests to a role for FSHRs in human physiology. The exogenous administration of FSH to rats augments ovariectomy-induced bone loss, and a FSH antagonist reduces bone loss after ovariectomy or FSH injection (Liu et al. 2010a, b).

FSH increases osteoclast formation, function, and survival through a distinct FSHR isoform (Sun et al. 2006, 2010, Robinson et al. 2010; Wu et al. 2007). Two groups have, however, failed to identify FSHRs on osteoclasts, having likely used primers targeted to the ovarian isoform (Allan et al. 2010; Ritter et al. 2008). We very consistently find FSHR in human $CD14^{+}$ cells and osteoclasts using nested primers and sequencing to verify the specificity of the reaction and amplifying

regions that contain an intron to avoid the pitfall of genomic DNA contamination (Robinson et al. 2010).

Wu et al. show that the osteoclastogenic response to FSH was abolished in mice lacking ITAM adapter signaling molecules (Wu et al. 2007). This suggests an interaction between FSH and immune receptor complexes, although the significance of such an interaction remains unclear. In a separate study, FSHR activation was shown to enhance RANK receptor expression (Cannon et al. 2011). In addition, FSH indirectly stimulates osteoclast formation by releasing osteoclastogenic cytokines, namely, IL-1β, TNF-α, and IL-6, in proportion to the surface expression of FSHRs (Iqbal et al. 2006; Cannon et al. 2010). In a study of 36 women between the ages of 20 and 50, serum FSH concentrations correlated with circulating cytokine concentrations (Cannon et al. 2010; Gertz et al. 2010).

Correlations between bone mineral density (BMD) declines and serum FSH levels have been documented extensively. The Study of Women's Health Across The Nations (SWAN), a longitudinal cohort of 2,375 perimenopausal women, showed a strong correlation between serum FSH levels and markers of bone resorption, as well as an equally strong correlation between changes in FSH levels over 4 years and decrements in BMD (Sowers et al. 2003). Analyses of data from Chinese women showed similar trends: a significant association between bone loss and high serum FSH (Xu et al. 2009; Wu et al. 2010). In a group of southern Chinese women aged between 45 and 55 years, those in the highest quartile of serum FSH lost bone at a 1.3- to 2.3-fold higher rate than those in the lowest quartile (Cheung et al. 2011). Furthermore, analysis of a National Health and Nutrition Examination Survey (NHANES) III cohort of women between the ages of 42 and 60 years showed a strong correlation between serum FSH and femoral neck BMD (Gallagher et al. 2010). Likewise, a cross-sectional analysis of 92 postmenopausal women found that serum osteocalcin and C-telopeptide levels were both positively correlated with FSH, but not with estradiol (Garcia-Martin et al. 2012).

The BONTURNO Study group showed that women with serum FSH levels of >30 IU/mL had significantly higher bone turnover markers than age-matched women, despite having normal menses (Adami et al. 2008). In contrast, Gourlay et al. fail to show a strong relationship between bone mass and FSH or indeed estrogen (Gourlay et al. 2011). Interestingly, however, the same authors show an independent correlation between FSH and lean mass (Gourlay et al. 2012). This latter association makes biological sense inasmuch as FSHRs are present on mesenchymal stem cells (Sun et al. 2006), known to have the propensity for adipocyte and myocyte differentiation. Notwithstanding whether there is a cause-effect relationship between a rising FSH and BMD changes, there is clear evidence favoring the use of FSH as a serum marker for identifying "fast bone losers" during the early phases of the menopausal transition, most notably the late perimenopause (Zaidi et al. 2009).

It has been difficult to tease out the action of FSH from that of estrogen in vivo as FSH releases estrogen and the actions of FSH and estrogen on the osteoclast are opposed. The injection of FSH into mice with intact ovaries (Ritter et al. 2008) or its transgenic overexpression (Allan et al. 2010), even in *hpg* mice, is unlikely to

reveal pro-resorptive actions of FSH. This is because direct effects of FSH on the osteoclast will invariably be masked by the anti-resorptive and anabolic actions of the ovarian estrogen so released in response to FSH.

Clinically, there is evidence that women with low FSH levels undergo less bone loss than women with higher FSH levels, estrogen levels being nearly equal (Devleta et al. 2004), and importantly, that the effectiveness of estrogen therapy is related to the degree of FSH suppression (Kawai et al. 2004). With that said, patients with pituitary hypogonadism do lose bone. Luperide treatment, and hence the lowering of FSH, has not been shown to prevent hypogonadal hyper-resorption (Drake et al. 2010). While this proves that low estrogen is a *cause of* acute hypogonadal bone loss, it does not exclude a role for FSH in human skeletal homeostasis (Drake et al. 2010). Rather than blocking FSH in acute hypogonadism, where the effect of low estrogen is likely to be overwhelming, FSH inhibition during the late perimenopause, particularly when estrogen levels are normal and FSH is high, could potentially be of therapeutic significance.

We have recently developed a polyclonal antibody against a 13-amino acid long conserved peptide sequence of the computationally defined FSHR-binding domain of FSHβ (Zhu et al. 2012a, b). We found that this antibody not only attenuated osteoclastogenesis induced by FSH in vitro, but also prevented the loss of bone post-ovariectomy (Zhu et al. 2012a, b). Most importantly, we noted through a detailed histomorphometric analysis that while bone resorption was reduced, bone formation was surprisingly elevated significantly (Zhu et al. 2012a). This decoupling likely underscored the osteoprotective action of the antibody. Further studies documented FSHRs on mesenchymal stem cells. Additionally, bone marrow stromal cells from $FSHR^{-/-}$ mice showed significantly greater colony-forming (Cfu-f) potential, suggesting a profound increase in osteoblastogenesis in the absence of the FSHR. Importantly, antibody injections did not affect serum estrogen levels in wild-type mice (Zhu et al. 2012a). Collectively, our studies provide clear evidence that lowering FSH in a hypogonadal state prevents bone loss.

10.4 TSH Exerts Osteoprotection Through a Dual Action

TSH directly inhibits osteoclasts (Abe et al. 2003). TSHR haploinsufficiency in heterozygotic $TSHR^{+/-}$ mice results in osteoporosis, while thyroid hormone levels remain unaffected (Abe et al. 2003). Moreover, $TSHR^{-/-}$ mice are osteoporotic, a phenotype that cannot be explained by the known pro-osteoclastic action of thyroid hormones, particularly as $TSHR^{-/-}$ mice are hypothyroid (Novack 2003). Furthermore, thyroid hormone replacement that renders $TSHR^{-/-}$ mice euthyroid reverses skeletal runting but not the osteoporotic phenotype (Abe et al. 2003). Thus, TSH acts on bone independently of thyroid hormones. These findings also suggest that the osteoporosis of hyperthyroidism may, in part, be due to low TSH (Zaidi et al. 2006; Baliram et al. 2012). At least 20 clinical studies have since documented tight and highly reproducible correlations between low TSH levels, bone loss, bone

geometry, and fracture risk in patient cohorts across the globe [e.g., (Mazziotti et al. 2010; Moon et al. 2015; Morris 2007; Grimnes et al. 2008; Frohlich and Wahl 2015; Kim et al. 2015; Blum et al. 2015; Noh et al. 2015; Tournis et al. 2015; Leader et al. 2014; Abrahamsen et al. 2014; Christy et al. 2014; Taylor et al. 2013; Chin et al. 2013; Kim et al. 2006, 2010; Baqi et al. 2010a, b; Svare et al. 2009; Heemstra et al. 2008; Mikosch et al. 2008)]. Evidence also shows that TSH protects the skeleton by exerting anti-resorptive and anabolic actions in rodent models and in people (Abe et al. 2003; Ma et al. 2011; Dumic-Cule et al. 2014; Hase et al. 2006; Zhang et al. 2014; Bagriacik et al. 2012; Baliram et al. 2011; Boutin et al. 2014; Sampath et al. 2007; Martini et al. 2008; Mazziotti et al. 2005).

The osteoporosis of TSHR deficiency is of the high-turnover variety. Osteoclastic activity is increased in $TSHR^{-/-}$ mice, similar to *hyt*/*hyt* mice in which TSHR signaling is defective (Britto et al. 1994; Sun et al. 2008). Recombinant TSH has been shown to attenuate the genesis, function, and survival of osteoclasts in ex vivo murine bone marrow (Abe et al. 2003) and in vitro ES cell cultures (Ma et al. 2009). The latter suggested a role early in bone development (Ma et al. 2009). In contrast, the overexpression of constitutively activated TSHR in osteoclast precursor cells (Hase et al. 2006) or transgenically, in mouse precursors (Sun et al. 2008), inhibited osteoclastogenesis. In postmenopausal women, a single subcutaneous injection of TSH drastically lowered serum C-telopeptide to premenopausal levels within 2 days, with recovery at day 7 (Mazziotti et al. 2005). In none of the studies with TSH replacement did thyroid hormones increase, exemplifying again that the pituitary-bone axis is more primitive than the pituitary-thyroid axis.

This anti-osteoclastogenic action of TSH is mediated by reduced NF-κB and JNK signaling and TNFα production (Abe et al. 2003; Hase et al. 2006). The effect of TSH on TNFα synthesis is mediated transcriptionally by binding of two high mobility group box proteins, HMGB1 and HMGB2, to TNFα gene promoter (Yamoah et al. 2008). TNFα production is expectedly upregulated in osteoporotic $TSHR^{-/-}$ mice (Abe et al. 2003), and the genetic deletion of TNFα in these mice reverses the osteoporosis, as well as the bone formation and resorption defects, proving that the $TSHR^{-/-}$ phenotype is mediated by TNFα, at least in part (Hase et al. 2006; Sun et al. 2013). The osteoporosis, low bone formation, and hyper-resorption that accompany TSH deficiency were fully rescued in compound mouse mutants in which TNFα is genetically deleted on a homozygote $TSHR^{-/-}$ or heterozygote $TSHR^{+/-}$ background (Sun et al. 2013). Studies using ex vivo bone marrow cell cultures show that TSH inhibits and stimulates TNFα production from macrophages and osteoblasts, respectively (Sun et al. 2013). TNFα, in turn, stimulates osteoclastogenesis but also enhances the production of a variant TSHβ in bone marrow (Baliram et al. 2013; Sun et al. 2013). This locally produced TSH suppresses osteoclast formation in a negative feedback loop.

The role of TSH in osteoblast regulation is less defined. While it inhibits osteoblastogenesis in bone marrow-derived cell cultures, TSH stimulates differentiation and mineralization in murine cell cultures through a Wnt5a-dependent mechanism

(Baliram et al. 2011). Likewise, in vivo, intermittently administered TSH is anabolic in both rats and mice (Sampath et al. 2007; Sun et al. 2008). Thus, the effect of TSH may be differentiation stage dependent. However, in vivo, in rats, TSH, injected up to once every 2 weeks, inhibits ovariectomy-induced bone loss 28 weeks following ovariectomy (Sun et al. 2008). Calcein labeling provides evidence for a direct anabolic action of intermittent TSH (Sampath et al. 2007). In humans, Martini et al. (2008) show an increase in PINP, a marker of bone formation, validating the conclusion that bolus doses of TSH are indeed anabolic.

Consistent with our work and that of other labs, epidemiologic studies show 4.5-fold increase in the risk of vertebral fractures, and 3.2-fold increase in the risk of non-vertebral fractures is seen at TSH levels <0.1 IU/L (Bauer et al. 2001). There is also a strong negative correlation between low serum TSH and high C-telopeptide levels, without an association with thyroid hormone (Zofkova and Hill 2008). In patients on L-thyroxine, greater bone loss has been noted in those with a suppressed TSH than in those without suppression (Baqi et al. 2010b; La Vignera et al. 2008; Flynn et al. 2010). The Tromso study supports this: participants with serum TSH below 2 SD had a significantly lower BMD, those with TSH above 2 SD had a significantly increased BMD, whereas there was no association between TSH and BMD at normal TSH levels (Grimnes et al. 2008). In patients taking suppressive doses of thyroxine for thyroid cancer, the serum level of cathepsin K, a surrogate resorption marker, was elevated (Mikosch et al. 2008), and the HUNT 2 study found a positive correlation between TSH and BMD at the distal forearm (Svare et al. 2009). Furthermore, evaluation of the NHANES data has shown that the odds ratio for correlations between TSH and bone mass ranged between 2 and 3.4 (Morris 2007). Euthyroid women with serum TSH in the lower tertile of normal displayed a higher incidence of vertebral fractures, independent of age, BMD, and thyroid hormones (Mazziotti et al. 2010). Finally, patients harboring the TSHR-D727E polymorphism had high bone mass (Heemstra et al. 2008); similar allelic associations have been reported from the United Kingdom and in the Rotterdam study (van der Deure et al. 2008; Albagha et al. 2005).

Physiologically, therefore, TSH uncouples bone remodeling by inhibiting osteoclastic bone resorption and stimulating osteoblastic bone formation, particularly when given intermittently. Furthermore, absent TSH signaling stimulates bone remodeling directly and through TNFα production, causing net bone loss. We compared the effect of inducing hyperthyroidism through the implantation of T_4 pellets in wild-type and $TSHR^{-/-}$ mice to determine whether mice with absent TSHR signaling lost more bone (Baliram et al. 2012). Whereas wild-type hyperthyroid mice lost bone, expectedly from the pro-resorptive actions of thyroid hormones, the loss was greater in hyperthyroid $TSHR^{-/-}$ mice – clearly demonstrating a direct action of TSH signaling on bone that was independent of thyroid hormone levels (Baliram et al. 2012). Low TSH levels may thus contribute to the pathophysiology of osteoporosis of hyperthyroidism, which has traditionally been attributed to high thyroid hormone levels alone.

10.5 ACTH Directly Affects VEGF Expression in Bone

Glucocorticoids, under natural regulation mainly by ACTH, are important co-regulators of many processes including vascular tone, central metabolism, and immune response. At higher, pharmacological levels, they exert anti-inflammatory and immunosuppressant effects, with incident complications including diabetes, osteoporosis, and osteonecrosis. Osteonecrosis, in particular, is a painful debilitating condition that affects metabolically active bone, typically the femoral head (Mankin 1992), and invariably requires surgical treatment. The underlying mechanisms of glucocorticoid-induced osteonecrosis are poorly understood, although a key finding is that osteonecrosis occurs prior to macroscopic vascular changes (Eberhardt et al. 2001).

Isales et al. (2010) discovered that bone-forming units strongly express MC2Rs. We showed that as with the adrenal cortex, ACTH induces VEGF production in osteoblasts through its action on MC2Rs (Zaidi et al. 2010). This likely translates into the protection by ACTH of glucocorticoid-induced osteonecrosis in a rabbit model (Zaidi et al. 2010). An independent report with consistent findings was recently published (Wang et al. 2010). We speculate that VEGF suppression secondary to ACTH suppression may contribute to the bone damage with long-term glucocorticoid therapy. Much needs to be done to validate this idea toward a therapeutic advantage, considering that ACTH analogs are already approved for human use.

10.6 Effects of Prolactin on Bone

Prolactin (PRL), a peptide hormone secreted by the anterior pituitary, acts to induce and maintain lactation, as well as to suppress folliculogenesis and libido. During pregnancy, it increases the calcium bioavailability for milk production and fetal skeletalogenesis by promoting intestinal calcium absorption and skeletal mobilization (Lotinun et al. 1998). Accelerated bone turnover and bone loss is noted in hyperprolactinemic adults (Naylor et al. 2000). Antagonism of PRL by bromocriptine, a dopamine agonist, reverses the bone loss (Lotinun et al. 2003).

This osteoclastic action of PRL is traditionally thought to arise from the accompanying hypoestrogenemia (Meaney et al. 2004). However, it has been shown that osteoblasts express PRLRs (Coss et al. 2000), suggesting a direct interaction between PRL and the osteoblast. In fact, the pattern of bone loss is distinct in PRL-exposed and ovariectomized rats (Seriwatanachai et al. 2008a). Ex vivo, PRL decreases osteoblast differentiation markers (Seriwatanachai et al. 2008a), in part, through the PI3K signaling pathway (Seriwatanachai et al. 2008b). PRL injected into adult mice accelerates bone resorption (Seriwatanachai et al. 2008a), notably by increasing the RANK/OPG ratio (Seriwatanachai et al. 2008a). Osteoclasts themselves do not possess PRLRs (Coss et al. 2000). In contrast, in infant rats, PRL

causes net bone gain (Krishnamra and Seemoung 1996), increasing osteocalcin expression. Likewise, in human fetal osteoblast cells, PRL decreases the RANKL/OPG ratio (Seriwatanachai et al. 2008b). It appears therefore that the net effect of PLR on bone depends on the stage of development. In the fetus, it promotes bone growth and mineralization while accelerating bone resorption in the mother to make nutrients available.

10.7 Opposing Actions of Oxytocin and Vasopressin on Bone

Oxytocin (OXT) is a nonapeptide synthesized in the hypothalamus and released into circulation via the posterior pituitary. Its primary function is to mediate the milk ejection reflex in nursing mammals. It also stimulates uterine contraction during parturition; however OXT is not a requirement for this function. Thus, OXT null mice can deliver normally but are unable to nurse. Subcutaneous OXT injection completely rescues the milk ejection phenotype, attesting to this being a peripheral, as opposed to a central action (Nishimori et al. 1996). Central actions of OXT include the regulation of social behavior, including sexual and maternal behavior, affiliation, social memory, as well as penile erection and ejaculation (Young et al. 1998; Insel and Harbaugh 1989; Mantella et al. 2003; Argiolas et al. 1988). It also controls food, predominantly carbohydrate, intake centrally (Sclafani et al. 2007). Thus, the social amnesia, aggressive behavior, and overfeeding observed in $OXT^{-/-}$ and $OXTR^{-/-}$ mice are reversed on intracerebroventricular OXT injection (Ferguson et al. 2000).

OXT acts on a GPCR, present in abundance on osteoblasts (Copland et al. 1999), osteoclasts, and their precursors (Colucci et al. 2002). In line with the ubiquitous distribution of OXTRs, cells of bone marrow also synthesize OXT, suggesting the existence of autocrine and paracrine interactions (Colaianni et al. 2011). In vitro, OXT stimulates osteoblast differentiation and bone formation. Thus, $OXT^{-/-}$ and $OXTR^{-/-}$ mice, including the haploinsufficient heterozygotes with normal lactation, display severe osteoporosis due to a bone-forming defect (Tamma et al. 2009). This not only indicates that the osteoblast is the target for OXT but also that bone is more sensitive to OXT than the breast, hitherto considered its primary target. Once again, the finding emphasizes a relatively primitive pituitary-bone axis. Effects of OXT on bone resorption in vivo appear minimal, as OXT stimulates osteoclastogenesis but inhibits the activity of mature osteoclasts, with a net zero effect on resorption.

In vivo gain-of-function studies document a direct effect of OXT on bone. Intraperitoneal OXT injections result in increased BMD and ex vivo osteoblast formation (Tamma et al. 2009). In contrast, short-term intracerebroventricular OXT does not affect bone turnover markers. OXT injections in wild-type rats alter the RANKL/OPG ratio in favor on bone formation, again attesting to an anabolic action (Elabd et al. 2007).

Although unproven, OXT may have a critical role in bone anabolism during pregnancy and lactation. Both are characterized by excessive bone resorption in favor of fetal and postpartum bone growth, respectively (Wysolmerski 2002). This bone loss is, however, completely reversed upon weaning by a yet unidentified mechanism (Sowers et al. 1995). OXT peaks in blood during late pregnancy and lactation, and while its proosteoclastogenic action may contribute to intergenerational calcium transfer, its anabolic action could enable the restoration of the maternal skeleton. That $OXT^{-/-}$ pups show hypomineralized skeletons, and $OXT^{-/-}$ moms display reduced bone formation markers are suggestive of such actions. The question whether estrogen, via its positive regulation of osteoblastic OXT production, can synergize this action through a local feed-forward loop remains to be determined. These studies nonetheless pave the way for a greater understanding of pregnancy and lactation-associated osteoporosis, as well as new potential therapeutic options.

Arginine-vasopressin (AVP), another posterior pituitary hormone, is a nonapeptide that differs from OXT only by two amino acids. Its primary functions are to retain water in the body by increasing water reabsorption in the kidney and to constrict blood vessels, thereby increasing arterial blood pressure. AVP exerts its actions through G protein-coupled receptors. AVPR1A is present in the kidney, liver, peripheral vasculature, and brain. AVPR2 is expressed predominantly in the kidney. Expression of AVPR1A and AVPR2 is also found in osteoblasts and osteoclasts (Tamma et al. 2013). AVPR1B, also known as vasopressin 3 receptor, is expressed in the anterior pituitary and the brain, but not in the skeleton.

AVP can affect the skeleton directly and is yet another component of the pituitary-bone axis. For example, mice injected with AVP display reduced osteoblast formation and increased osteoclast formation (Tamma et al. 2013). Conversely, mice injected with the AVPR1A antagonist SR49059 had enhanced bone mass due to increased osteoblastogenesis and reduced osteoclast formation and bone resorption (Tamma et al. 2013). This high bone mass phenotype was also observed in AVPR1A-deficient mice (Tamma et al. 2013). In contrast, AVPR2 does not have a significant role in bone remodeling, since the specific AVPR2 inhibitor tolvaptan does not affect bone formation or bone mass (Sun et al. 2016). Collectively, the data establish a primary role for AVP signaling in bone mass regulation. Of note is that hyponatremic patients have elevated circulating AVP levels and a high fracture risk, prompting for further studies on the skeletal actions of AVPR inhibitors used commonly in these patients.

The highly homologous AVP and OXT can share their receptors in the regulation of bone formation by osteoblasts. AVPR1A and OXTR have opposing effects on bone mass. Notably, the deletion of OXTR in $OXTR^{-/-}$:$AVPR1A^{-/-}$ double-mutant mice reversed the high bone mass phenotype in $AVPR1A^{-/-}$ mice (Sun et al. 2016). While AVP-stimulated gene expression is inhibited when the OXTR is deleted in $AVPR1A^{-/-}$ cells, OXTR is dispensable for AVP action in inhibiting osteoblastogenesis and gene expression (Sun et al. 2016). Furthermore, OXT does not interact with AVPRs in vivo in a model of lactation-induced bone loss in which OXT levels are high (Sun et al. 2016).

10.8 Conclusion

The direct regulation of bone by glycoprotein hormones, since their discovery, helps explain some of the inconsistencies of older models that assumed that pituitary signaling was mediated entirely via endocrine organs through steroid-family signals. Important direct responses include actions of TSH, FSH, ACTH, oxytocin, and vasopressin in bone. It is important, in evaluating these new signaling mechanisms, to consider that the skeletal responses may or may not have similar mechanisms to the responses of the traditional endocrine targets and that the signals may vary in importance due to secondary endocrine and paracrine control. Nevertheless, the discovery of direct skeletal responses of pituitary hormones offers a new set of therapeutic opportunities.

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