REVIEW

Actions of pituitary hormones beyond traditional targets

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Abstract

Studies over the past decade have challenged the long-held belief that pituitary hormones have singular functions in regulating specific target tissues, including master hormone secretion. Our discovery of the action of thyroid-stimulating hormone (TSH) on bone provided the first glimpse into the non-traditional functions of pituitary hormones. Here we discuss evolving experimental and clinical evidence that growth hormone (GH), follicle-stimulating hormone (FSH), adrenocorticotrophic hormone (ACTH), prolactin, oxytocin and arginine vasopressin (AVP) regulate bone and other target tissues, such as fat. Notably, genetic and pharmacologic FSH suppression increases bone mass and reduces body fat, laying the framework for targeting the FSH axis for treating obesity and osteoporosis simultaneously with a single agent. Certain 'pituitary' hormones, such as TSH and oxytocin, are also expressed in bone cells, providing local paracrine and autocrine networks for the regulation of bone mass. Overall, the continuing identification of new roles for pituitary hormones in biology provides an entirely new layer of physiologic circuitry, while unmasking new therapeutic targets.

Key Words

- ▶ follicle-stimulating hormone
- ▶ adrenocorticotrophic hormone
- ▶ growth hormone
- ▶ oxytocin
- ▶ vasopressin

Journal of Endocrinology
(2018) **237**, R83–R98

Introduction

It has become increasingly clear that pituitary hormones that have traditionally been seen as regulators of single bodily processes, including endocrine functions, have additional roles in physiology. The global deletion of these hormones or their receptors in mice has yielded unexpected skeletal and metabolic phenotypes, which have been confirmed through traditional pharmacologic approaches (Zaidi 2007). Initial reports showed that thyroid-stimulating hormone receptors (TSHRs) were expressed on bone cells and that their haploinsufficiency in *Tshr*^{+/-} mice caused osteopenia without affecting the thyroid function (Abe *et al.* 2003). Likewise, receptors for

follicle-stimulating hormone (FSHRs) are expressed in both skeletal cells and adipose tissue, where they regulate body composition (Sun *et al.* 2006, Liu *et al.* 2015, 2017, Feng *et al.* 2017). However, due to feedback circuitry, it has often been difficult to tease out specific actions of pituitary hormones on these newly described targets from known actions of the hormones they produce (Blair *et al.* 2011). With emerging evidence for such additional roles of pituitary hormones in integrative physiology, new avenues for therapy have been unmasked (Liu *et al.* 2017). In this review, we discuss these newly discovered actions of pituitary hormones and their physiologic and therapeutic relevance.

osteoclast formation *ex vivo*, while thyroid hormone levels remained unchanged. Second, the osteoporosis noted in *Tshr*-null mice could not be explained by low thyroid hormone levels, as high, rather than low levels have been implicated in bone loss. Third, and importantly, skeletal runting, but not the osteoporotic phenotype, was reversed by thyroid hormone replacement that rendered *Tshr*^{-/-} mice euthyroid (Abe *et al.* 2003).

The idea therefore emerged that TSH acted on bone independently of thyroid hormones, and that the osteoporosis of hyperthyroidism may, in part, result from low TSH (Zaidi *et al.* 2006). This latter hypothesis was studied in wild-type and *Tshr*^{-/-} mice that were rendered either euthyroid or hyperthyroid by implanting thyroxine (T4) pellets (Baliram *et al.* 2012). Hyperthyroid *Tshr*^{-/-} mice suffered greater bone loss than wild-type mice that were equally hyperthyroid (Baliram *et al.* 2012). This suggested that absent TSH signaling in *Tshr*^{-/-} mice itself contributes to hyperthyroid bone loss.

Consistent with the high-turnover osteoporosis seen in hyperthyroidism, *Tshr*^{-/-} mice and *hyt/hyt* mice, in which the TSH receptor is naturally defective, showed evidence of increased osteoclast formation (Britto *et al.* 1994, Sun *et al.* 2008). Studies further showed that recombinant TSH attenuated the genesis, function and survival of osteoclasts *in vitro* (Abe *et al.* 2003, Ma *et al.* 2009). Accordingly, osteoclastogenesis was inhibited when the constitutively activated TSHR was overexpressed in osteoclast precursors or an activating TSHR antibody was injected (Hase *et al.* 2006, Sun *et al.* 2008, Ma *et al.* 2011). Human data for a direct action of TSH on bone is equally compelling – a single subcutaneous injection of recombinant human TSH lowered serum C-terminal telopeptide (CTX) in postmenopausal women within 2 days (Mazziotti *et al.* 2005). In no instance of TSH replacement did thyroid hormones increase. We also know that these anti-osteoclastogenic actions of TSH are mediated by reduced nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Janus N-terminus kinase (JNK) activation, as well as indirectly, through diminished tumor necrosis factor α (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 the *Tnfα* gene promoter (Yamoah *et al.* 2008). Thus, TNFα production is upregulated in osteoporotic *Tshr*^{-/-} mice (Abe *et al.* 2003), and the genetic deletion of *Tnfα* in these mice reverses the osteoporosis and the bone remodeling defects, proving that the *Tshr*^{-/-} phenotype is mediated by TNFα, at least in part (Sun *et al.* 2013).

TSH inhibits osteoblastogenesis in bone marrow-derived cell cultures (Abe *et al.* 2003), but stimulates osteoblast differentiation and mineralization in murine ES cell cultures through a wntless integration 5A- (WNT5A-) dependent mechanism (Baliram *et al.* 2011). *In vivo*, intermittently administered TSH is anabolic in both rats and mice (Sampath *et al.* 2007, Sun *et al.* 2008). Thus, when injected at intervals as far apart as every two weeks into rats, TSH rescues the bone loss, 28 weeks following ovariectomy (Sun *et al.* 2008). Calcein-labeling studies are consistent with a direct bone-forming action of intermittent TSH (Sampath *et al.* 2007). Consistent with rodent data, Martini *et al.* show an increase in procollagen type I N-terminal propeptide (PINP), a marker of bone formation, validating the conclusion that a bolus dose of TSH is indeed anabolic in people (Martini *et al.* 2008). Likewise, antibody-activated TSH signaling contributes to high bone formation, independent of the actions of thyroid hormone (Cho *et al.* 2015).

Epidemiological studies in an increasing number of global cohorts document a tight relationship between low TSH levels, parameters of bone loss and even fracture risk. In fact, 4.5- and 3.2-fold increases in the risk of vertebral and non-vertebral fractures, respectively, were noted at serum TSH levels <0.1 IU/L (Bauer *et al.* 2001). There was also a strong negative correlation between low serum TSH and high CTX levels, independently of thyroid hormone levels (Zofkova & Hill 2008). Greater bone loss was also seen in patients on L-thyroxine that had suppressed TSH levels than in those without such suppression (La Vignera *et al.* 2008, Baqi *et al.* 2010, Flynn *et al.* 2010, Kim *et al.* 2015). These observations were supported by the Tromsø Study, in which participants with serum TSH <2 SD had a significantly lower bone mineral density (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). Serum levels of cathepsin K, a surrogate resorption marker, were also elevated in thyroid cancer patients on suppressive therapy (Mikosch *et al.* 2008). Concordant with this, the second Nord-Trøndelag Health Study in 1995–97 (HUNT 2) found a positive correlation between serum TSH and BMD at the distal forearm (Svare *et al.* 2009). In fact, it is now evident that in patients with elevated TSH levels, long-term fracture risk is related to the cumulative duration of periods with low TSH resulting from excessive thyroid hormone replacement (Abrahamsen *et al.* 2015). In Odense Patient data Explorative Network Thyroid Status and Register Outcomes (OPENTHYRO), fracture risk was a function of the duration of hyperthyroidism (Abrahamsen

et al. 2014). Likewise, TSH suppression increased the risk of postoperative osteoporosis in low- and intermediate-risk thyroid cancer patients (Wang *et al.* 2015c). Even hypothyroid patients requiring thyroid hormone therapy often displayed reduced BMD that correlated with low TSH levels (Christy *et al.* 2014, Karimifar *et al.* 2014).

The National Health and Nutrition Examination Survey (NHANES) has further shown that the odds ratio for correlations between TSH and bone mass ranged between 2 and 3.4 (Morris 2007). Elderly women with low-normal TSH levels (in the euthyroid range) have lower BMDs with or without weaker femoral structures (Ding *et al.* 2016, Lee *et al.* 2016). Such women also have a high vertebral fracture risk, independent of age, BMD and thyroid hormones (Mazziotti *et al.* 2010). Consistent with these data, there is a positive correlation between serum TSH and BMD in women with postmenopausal osteoporosis; in one of these studies, serum TSH was associated with osteoprotection in a regression model (van Rijn *et al.* 2014, Noh *et al.* 2015, Acar *et al.* 2016). In elderly men, lower TSH levels within the normal range were associated with an approximately 30% increase in the risk of hip fracture (Waring *et al.* 2013). Finally, genetic evidence supports the epidemiologic data for a role of TSH in human bone physiology. Patients harboring the *TSHR*^{D727E} polymorphism have high bone mass (Albagha *et al.* 2005, Heemstra *et al.* 2008, van der Deure *et al.* 2008, Liu *et al.* 2012).

FSH and mechanisms of bone loss

FSH acts on an FSHR in the osteoclasts and directly stimulates bone resorption (Sun *et al.* 2006). Supporting this conclusion, mice haploinsufficient in FSH β showed reduced bone resorption and increased bone mass, while ovarian function remained preserved (Sun *et al.* 2006). Several studies have now confirmed direct effects of FSH on the skeleton in rodents and humans. The exogenous administration of FSH to rats was found to augment ovariectomy-induced bone loss, and an FSH antagonist reduced bone loss after ovariectomy or FSH injection (Liu *et al.* 2010a,b).

In women, hypergonadotropic amenorrhea (serum FSH ~35 IU/L) was found to be associated with greater bone loss than in hypogonadotropic amenorrhea (~8 IU/L) (Devleta *et al.* 2004). Likewise, women with functional hypothalamic amenorrhea, wherein both FSH and estrogen are low, showed slight-to-moderate skeletal

defects (Podfigurna-Stopa *et al.* 2012). This is contrast to luperide, which has not been shown to prevent hypogonadal hyper-resorption, wherein the acute loss of estrogen appears not to be compensated by reduced FSH levels (Drake *et al.* 2010). However, genetic evidence points to the function of FSHRs in human pathophysiology. Women harboring an activating *FSHR*^{N680S} polymorphism have been shown to display lower bone mass and high resorption markers (Rendina *et al.* 2010). Furthermore, digenic combinations between wild-type genotype of the 3'UTR marker for the aromatase (*CYP19A1*) gene, the *IVS4* marker of the same gene and the bone morphogenetic protein 15 (*BMP15*) and *FSHR* genes have been described as being osteoprotective (Mendoza *et al.* 2012). Together, these latter studies attest to a modulatory function for FSH, in addition to that of estrogen, in human skeletal physiology and a permissive role in the pathophysiology of postmenopausal osteoporosis.

The most impressive clinical correlations between bone loss and serum FSH levels are seen in Study of Women's Health across the Nations (SWAN), a longitudinal cohort of 2375 perimenopausal women. Not only was there a strong correlation between serum FSH levels and markers of bone resorption, a change in FSH levels over 4 years predicted decrements in bone mass (Sowers *et al.* 2003). Data from a cohort of Chinese women showed similar trends, notably a significant association between bone loss and high serum FSH (Xu *et al.* 2009, Wu *et al.* 2010). Furthermore, in another cohort 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). A more recent analysis of perimenopausal Chinese women aged between 45 and 50 years revealed a strong correlation between serum CTX and FSH levels (Wang *et al.* 2015a). Importantly, CTX levels were greater when serum FSH levels were >40 IU/L (Wang *et al.* 2015a). The NHANES III cohort with women between 42 and 60 years likewise showed a strong correlation between serum FSH and femoral neck BMD (Gallagher *et al.* 2010). Serum osteocalcin and CTX were also positively correlated with serum FSH, but not with estradiol in a cross-sectional study of 92 postmenopausal women (Garcia-Martin *et al.* 2012). The bone turnover range of normality (BONTURNO) study group similarly showed that women with serum FSH levels >30 IU/L had significantly higher bone turnover markers than age-matched women, despite having normal menses (Adami *et al.* 2008). Consistent with this, lower serum FSH levels and higher serum

estrogen levels have been associated with lower rates of lumbar spine bone loss during phases of the menopausal transition (Crandall *et al.* 2013).

Mechanistically, FSH increases osteoclast formation, function and survival through a distinct FSHR isoform (Sun *et al.* 2006, Wu *et al.* 2007, Robinson *et al.* 2010, Sun *et al.* 2010, Wang *et al.* 2015b). Failures to identify FSHRs on osteoclasts likely used primers targeted to the ovarian isoform (Ritter *et al.* 2008, Allan *et al.* 2010). 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, Tourkova *et al.* 2015). Cellular responsiveness to FSH also appears to be determined by the level of FSH glycosylation (Meher *et al.* 2015), with the prediction that the fully glycosylated isoform is more active on the bone FSHR. With that said, FSHR expression in bone has recently been firmly established through *in vivo* imaging of FSH binding in live mice (Feng *et al.* 2017). A small near-infrared fluorophore CH1055 conjugated to FSH was injected into live mice, followed by capture of infrared signals upon binding to its receptor in ovaries, testes and bone *in vivo* (Feng *et al.* 2017).

The osteoclastogenic response to FSH was interestingly abolished in mice lacking immunoreceptor tyrosine-based activation motif (Itam) adapter signaling molecules (Wu *et al.* 2007). This latter study suggests an interaction between FSH and immune receptor complexes, although the significance of this remains unclear. In a separate study, FSH enhanced the expression of receptor activator of nuclear factor kappa B (RANK) (Cannon *et al.* 2011). In addition, FSH indirectly stimulated osteoclast formation by releasing osteoclastogenic cytokines, namely interleukin 1 β (IL1B), TNF α and interleukin 6 (IL6) 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 years, serum FSH levels correlated with circulating cytokine concentrations (Cannon *et al.* 2010, Gertz *et al.* 2010). Gourlay *et al.* in contrast failed to show a relationship between bone mass and FSH or, indeed, estrogen (Gourlay *et al.* 2011). Interestingly, the same authors documented an independent correlation between FSH and lean mass (Gourlay *et al.* 2012).

Despite accumulating evidence for separate actions of FSH, 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 therefore 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. However, there is evidence that women with low FSH levels undergo less bone loss (Devleta *et al.* 2004) and that the effectiveness of estrogen therapy is related to the degree of FSH suppression (Kawai *et al.* 2004).

Rapid and profuse bone loss begins three years prior to the last menstrual period, when serum estrogen is relatively normal and FSH levels are rising (Randolph *et al.* 2003). This is when the rate of bone loss is maximal, and therefore cannot be attributed to changes in serum estrogen (Randolph *et al.* 2003, Sowers *et al.* 2003). To address the importance of FSH elevations in this period, Lukefahr and coworkers examined bone loss using a unique rat model of the perimenopausal transition (Lukefahr *et al.* 2012). This model, in which the ovotoxin 4-vinylcyclohexene diepoxide (VCD) is administered to rats, was characterized by a prolonged estrogen-replete period when serum FSH levels were elevated. Longitudinal measurements revealed that significant decreases in BMD (5–13%) occurred during periods of increased FSH and decreased inhibins (Lukefahr *et al.* 2012).

To leverage this selective increase in FSH early in the menopausal transition, an antibody to a 13-amino-acid-long peptide sequence within the receptor-binding domain of the FSH β -subunit was generated (Zhu *et al.* 2012a,b). The FSH antibody bound FSH specifically and blocked its action on osteoclast formation *in vitro*. When injected into ovariectomized mice, the FSH antibody attenuated bone loss not only by inhibiting bone resorption, but also by stimulating bone formation, an action we had failed to detect in the knockout models (Sun *et al.* 2006, Zhu *et al.* 2012a,b). Notably, stromal cells isolated from mice treated with the FSH antibody showed greater osteoblast precursor colony counts, similar to stromal cells isolated from *Fshr*^{-/-} mice (Zhu *et al.* 2012a). This suggested that FSH negatively regulates osteoblast differentiation via signaling-efficient FSHRs present on mesenchymal stem cells (Zhu *et al.* 2012a). There is recent direct evidence for FSH action on osteoblast precursors, *albeit* in the opposite direction (Su *et al.* 2017). Overall, the data prompt the future development of a novel FSH-blocking agent as a means of uncoupling bone formation and bone resorption to a therapeutic advantage in people. An interesting alternative strategy, for which a proof-of-principle study is available, is the use of an FSH β vaccine. It has been shown

that immunizing ovariectomized rats with the GST-FSH β antigen significantly prevents trabecular bone loss and increases bone strength (Geng *et al.* 2013).

GH in skeletal maturation

Growth hormone (GH) has for long been known to play a key role in chondrocyte and bone cell function, and thereby to modulate skeletal growth and modeling. While a GHR is expressed in osteoblasts, GH appears to exert an action via its release of insulin-like growth factors (IGFs). IGF1, the predominant growth factor, is synthesized mainly in the liver and 80% of the circulating form is bound to IGF-binding protein-3 (IGFBP3) and the acid labile subunit (ALS). Growth retardation and osteoporosis are phenotypic hallmarks in *Ghr*^{-/-} mice (De Jesus *et al.* 2009) and dwarfism in Laron syndrome, which is due to loss-of-function mutations in the *GHR* gene, is associated with osteoporosis (Laron 1999, Laron *et al.* 1999). However, the *Ghr*^{-/-} phenotype is compensated by the overexpression of IGF1 and mice lacking both liver IGF1 (LID) and ALS, with depleted serum IGF1, show reduced bone growth and bone strength in the face of high circulating GH levels (Yakar *et al.* 2002). While these results suggest that the skeletal effects of GH require IGF1, there is equally compelling evidence that GH can act independently of IGF. In ovariectomized LID mice, for example, GH reverses osteopenia (Fritton *et al.* 2010). Furthermore, GH replacement reverses the increased adiposity in hypophysectomized rats, while IGF1 replacement does not (Menagh *et al.* 2010). Together, the latter findings not only point to a direct action of GH on bone, but also extend GH actions to the control of adiposity (see below).

Pituitary hormones and intergenerational calcium transfer

A major function of the skeleton is to serve as a source for calcium ions that would mineralize the fetal skeleton during pregnancy and allow for bone growth and modeling during lactation. Both phases are characterized by excessive maternal bone resorption that has been thought to result from a combination of hypoestrogenemia and parathyroid hormone-related protein (PTHrP) production by the breast tissue (Wysolmerski 2002). Despite the loss of the maternal skeleton, with noted reductions in BMD in the region of 1–2% per month, this bone loss is

near-completely reversed upon weaning (Sowers *et al.* 1995). The mechanism of the latter effect is unclear; however, ineffective skeletal restoration, for example, over multiple pregnancies, can lead to pregnancy- and lactation-associated osteoporosis.

Plasma OXT levels peak during late pregnancy and lactation. In addition to its action on milk ejection, uterine contraction, social behavior and feeding, OXT acts on a GPCR present in abundance on osteoblasts, osteoclasts and their precursors (Argiolas *et al.* 1988, Insel & Harbaugh 1989, Nishimori *et al.* 1996, Young *et al.* 1998, Copland *et al.* 1999, Colucci *et al.* 2002, Mantella *et al.* 2003, Sclafani *et al.* 2007, Tamma *et al.* 2009). Bone marrow cells also synthesize OXT, suggesting the existence of autocrine and paracrine interactions (Tamma *et al.* 2009, Colaianni *et al.* 2011).

OXT has been shown to stimulate osteoblast differentiation and bone formation in mice (Colucci *et al.* 2002, Elabd *et al.* 2008, Tamma *et al.* 2009), and *Oxt*^{-/-} and *Oxtr*^{-/-} mice, importantly normally lactating heterozygotes, display severe osteoporosis due to a bone-forming defect (Tamma *et al.* 2009). Systemic OXT injections into wild-type rodents stimulate bone formation, increase bone mass and enhance osseointegration of titanium implants, again attesting to the skeletal anabolic action of OXT (Elabd *et al.* 2007, Tamma *et al.* 2009, Wang *et al.* 2016). These pro-osteoblastic actions are mediated, at least in part, via the nuclear localization of the OXTR following its activation by OXT and, unlike actions on social behavior and feeding, are not mediated centrally (Tamma *et al.* 2009, Di Benedetto *et al.* 2014). Thus, short-term intracerebroventricular OXT does not affect bone turnover markers.

In contrast to the potent osteoblastic actions of OXT, its overall effects on bone resorption *in vivo* appear minimal. OXT stimulates osteoclastogenesis, but inhibits the activity of mature osteoclasts (Tamma *et al.* 2009). While these pro-osteoclastogenic actions may contribute to intergenerational calcium transfer, the anabolic effect is likely to facilitate restoration of the maternal skeleton. Testifying to this, *Oxt*^{-/-} pups show hypomineralized skeletons, and *Oxt*^{-/-} moms display reduced bone formation markers (Liu *et al.* 2009).

Estrogen positively regulates osteoblastic OXT production and OXTR expression, and the respective actions are synergistic through a local feed-forward loop (Zallone 2006, Colaianni *et al.* 2012). In postmenopausal women, serum OXT correlates strongly with BMD, particularly at the hip, in the 6-year-long prospective Opsumit Users (OPUS) study (Breuil *et al.* 2014). Likewise,

in a cross-sectional study in women aged between 18 and 45 years, plasma OXT levels were correlated with spine and hip BMD and buckling ratio at the hip (Schorr *et al.* 2017). Low serum OXT levels, in contrast, are associated with severe osteoporosis, independently of estrogen (Breuil *et al.* 2011). In separate studies, the low nocturnal OXT secretion in amenorrheic athletes is associated with site-dependent microarchitectural deterioration (Lawson *et al.* 2013). However, in men, the Montceau les Mines Osteoporosis (MINOS) study confirms a lack of association between serum OXT and BMD, bone turnover rate or prevalent fracture (Breuil *et al.* 2015). Likewise, in mice and rabbits, OXT reverses ovariectomy-, but not orchietomy-induced bone loss (Beranger *et al.* 2014, 2015, Qiu *et al.* 2015). The findings together emphasize possible sex differences that might arise from the regulation of OXT action by estrogen (Colaanni *et al.* 2012).

Excessive secretion of prolactin (PRL) is also associated with accelerated bone turnover and osteoporosis in hyperprolactinemic states (Naylor *et al.* 2000). Antagonism of PRL by bromocriptine, a dopamine agonist, reverses the bone loss (Lotinun *et al.* 2003). It has also long been speculated that, in addition to its permissive role during lactation and suppression folliculogenesis and libido, PRL increases calcium bioavailability for both milk production and fetal skeletogenesis by promoting skeletal mobilization (Lotinun *et al.* 1998). This pro-resorptive action has traditionally been thought to arise due to the accompanying hypoenestrogenemia (Meaney *et al.* 2004). However, osteoblasts express PRL receptors (PRLRs) (Coss *et al.* 2000), suggesting that reduced osteoblastic bone formation may also play a significant role in the bone loss. The pattern of this bone loss is also distinct from that of ovariectomized rodents, where there is evidence for increased bone resorption and formation, with resorption exceeding formation. In contrast, in PRL-exposed rats there is a decoupling between the two processes with increases in bone resorption that are not accompanied by reduced bone formation (Seriwatanachai *et al.* 2008b). Consistent with this phenotype, PRL decreases osteoblast differentiation markers, in part, through the phosphoinositide 3-kinase (PI3K) signaling pathway (Seriwatanachai *et al.* 2008a,b). Osteoclasts themselves do not possess PRLRs, and PRL displays indirect pro-resorptive effects by increasing the RANK ligand/osteoprotegerin (RANKL/OPG) ratio (Coss *et al.* 2000, Seriwatanachai *et al.* 2008b).

There is also evidence that the effect of PRL on bone depends on the biological maturity of the organism. In infant rats, PRL causes net bone gain and increased

osteocalcin expression (Krishnamra & Seemoung 1996). Likewise, in fetal human osteoblasts, PRL decreases the RANKL/OPG ratio (Seriwatanachai *et al.* 2008a). These studies point to a role for PRL in bone growth and mineralization *in utero*, while accelerating bone resorption from the maternal skeleton for intergenerational calcium transfer. Further insight is needed to clarify the role of PRL in bone metabolism and determine the cellular pathways.

AVP and bone loss in hyponatremia

There are abundant receptors for arginine vasopressin (AVP), namely AVPR1 α and AVPR2, coupled to extracellular signal-regulated kinase (ERK) activation, on both osteoblasts and osteoclasts (Tamma *et al.* 2013). However, opposed to the anabolic action of OXT (Tamma *et al.* 2009), AVP reduces osteoblast differentiation and bone formation and enhances osteoclastogenesis and bone resorption (Tamma *et al.* 2013). In loss-of-function studies, the exposure of osteoblast precursors to AVPR1 α or AVPR2 antagonists, namely relcovaptan (SR49059) or (Adamantaneacetyl¹, *o*-Et-D-Tyr², Val⁴, Aminobutyryl⁶, Arg^{8,9}) vasopressin (ADAM), causes increased osteoblastogenesis, effects that are phenocopied in *Avpr1 α* ^{-/-} mice. Osteoclast formation and bone resorption are both reduced in these mice (Tamma *et al.* 2013), in sum, causing a profound increase of bone mass (Tamma *et al.* 2013). The anabolic and anti-anabolic actions, respectively, of OXT and AVP interact, so that the increased bone mass in *Avpr1 α* ^{-/-} mice is reduced in compound *Avpr1 α* ^{-/-}:*Oxtr*^{-/-} mutants (Sun *et al.* 2016). In fact, AVP and OXT can share receptors to a limited extent (Sun *et al.* 2016). While the OXTR is not indispensable for AVP action in inhibiting osteoblastogenesis, AVP-stimulated gene expression is inhibited when the OXTR is deleted in *Avpr1 α* ^{-/-} cells. In contrast, OXT does not interact with AVPRs *in vivo* in a model of lactation-induced bone loss, where OXT levels are high (Sun *et al.* 2016).

Together, the data establish a primary role for AVP signaling in bone mass regulation. They also shed light on a long-standing dogma on the mechanism(s) of the osteoporosis that accompanies chronic hyponatremic states (Renneboog *et al.* 2006, Gankam Kengne *et al.* 2008, Sandhu *et al.* 2009, Kinsella *et al.* 2010, Verbalis *et al.* 2010, Barsony *et al.* 2011, Hoorn *et al.* 2011). It is quite possible that, in a case report, the documented bone loss in a patient with syndrome of inappropriate antidiuretic hormone (SIADH) had arisen from a 30-fold elevation in serum AVP, although the accompanying high aldosterone

could be an additional culprit (Balla *et al.* 1981, Chhokar *et al.* 2004, Carbone *et al.* 2008, Sejlting *et al.* 2012). Furthermore, while AVPR2 is also expressed osteoblasts and osteoclasts, it is unlikely from our results that highly selective aquaretic AVPR2 inhibitors, such as tolvaptan, could, in fact, themselves offer osteoprotection (Hori 2013, Sun *et al.* 2016). AVPR1 α therefore appears to be the major functional skeletal receptor for AVP.

Pituitary hormones and body composition

An acute need for anti-obesity agents arises not only from the increasing population of obese individuals worldwide, currently around 600 million, but also from the relatively small armamentarium of approved anti-obesity agents that are limited by poor efficacy and unacceptable side effects. Furthermore, in women, FSH secretion begins to increase during the perimenopausal transition, preceding declines in estrogen by about 2–3 years (Sowers *et al.* 2003, Seifert-Klauss *et al.* 2012). During this period, and concurrent with the sharp decline in BMD, there is the onset of increasing visceral and bone marrow adiposity and a decrease in lean mass (Thurston *et al.* 2009, Wildman *et al.* 2012). This clinical phenotype is associated with disrupted energy metabolism and decreased physical activity (Thurston *et al.* 2009). Considering that FSHRs are present on bone and fat tissue (Sun *et al.* 2006, Cui *et al.* 2012, Liu *et al.* 2015, 2017, Feng *et al.* 2017), a question has arisen whether a single agent can be used to treat two aging-related medical conditions – osteoporosis and obesity – simultaneously.

We therefore utilized our polyclonal antibody to FSH β to examine the effect of FSH blockade in mice pair-fed on a high-fat diet, ovariectomized and sham-operated mice, and mice on a normal chow, but allowed to eat *ad libitum* (Liu *et al.* 2017). In all instances, the FSH antibody prevented the development of visceral and subcutaneous obesity and induced energy-producing ‘beige’ adipocytes. This beige phenotype was evident from immunolabeling for uncoupling protein 1 (UCP1), measuring the expression of *Ucp1* and other brown adipose tissue (BAT) genes in white adipose tissue, and examining UCP1 expression *in vivo* in live UCP1 reporter, Thermo mice (Liu *et al.* 2017). Furthermore, the FSH antibody enhanced mitochondrial density in the photo-activatable mitochondria (PhAM) mouse and enhanced basal energy expenditure and oxygen consumption, independently of increased activity. Studies with a corresponding monoclonal FSH antibody to human FSH recapitulated the data, as did mice haploinsufficient

in the *Fshr*. Importantly, the FSH antibody failed to prevent obesity in *Fshr*^{+/–} mice, testifying to its action via the FSH axis *in vivo*. Finally, there was an important, yet unexplained increase in lean mass in all groups treated with the FSH antibody. This phenotype is concordant with a strong association between reduced lean mass and high FSH levels in postmenopausal women (Gourlay *et al.* 2012).

TSHRs are also present in adipose tissue, although their precise function in physiology remains to be established. There is evidence from TSHR signaling-deficient *hyt/hyt* mice that TSHRs may be involved in inducing lipolysis in white adipose tissue, especially in mice in a hypothyroid state (Endo & Kobayashi 2012). Similar to the FSHR expression (Liu *et al.* 2017), TSHRs were induced upon differentiation of 3T3.L1 pre-adipocytes, and TSHR knockdown blocked adipocyte differentiation (Lu *et al.* 2012). *Tshr* expression was also higher in visceral adipose tissues from mice fed on a high-fat diet. In humans, TSHR expression in subcutaneous adipose tissue correlated with body mass index (BMI) (Lu *et al.* 2012).

Epidemiologic studies support the notion that TSH is associated with an obesity phenotype. In a cross-sectional study of 194 healthy euthyroid postmenopausal women, BMI had a positive independent association with serum TSH levels (Lambrinoudaki *et al.* 2015). Serum TSH also correlated with BMI in a cohort of 800 hospitalized patients with BMIs of ≥ 30 kg/m² (Betry *et al.* 2015). Furthermore, in 60 euthyroid subjects, TSH correlated with BMI and visceral and subcutaneous adipose tissue volumes (Muscogiuri *et al.* 2013). Serum TSH has also been noted as being a predictor for obesity in euthyroid females. Notably, body weight, BMI, waist circumference and body fat were all found to be increased in women with serum TSH >2.5 IU/L compared to those with TSH ≤ 2.5 IU/L (Zhang *et al.* 2012). Moreover, in patients with subclinical hypothyroidism who had high pretreatment serum TSH levels, but normal thyroid hormones, a significant decrease in visceral adipose tissue volume was noted following levothyroxine treatment (Akbaba *et al.* 2016).

With that said, several studies have failed to document correlations or shown negative correlations between serum TSH and obesity indices. Notably, a population-based German cohort consisting of over 2000 adults aged between 20 and 79 years showed no association between serum TSH levels and visceral adipose tissue (Witte *et al.* 2017). In a different cohort of over 4800 patients, BMI was inversely related to higher TSH levels in patients who were classified as BAT positive upon F-18-fluorodesoxyglucose

positron emission tomography-computer tomography (FDG-PET/CT) (Brendle *et al.* 2018).

In addition to FSH and TSH, there is also a strong and well-documented relationship between OXT and body composition. Injection of OXT reduced body weight in mice fed both on high-fat diet or normal chow, body fat in ovariectomized mice and bone marrow fat in glucocorticoid-treated rabbits (Beranger *et al.* 2014, Qiu *et al.* 2015, Li *et al.* 2016, Maejima *et al.* 2017). Reduced OXT expression, in contrast, underscores hyperphagic obesity of single-minded 1 (Sim1) haploinsufficient mice, which are also cured upon OXT injection (Tolson *et al.* 2010). A cross-sectional study of women aged between 18 and 45 years further documented highest plasma OXT levels in those who were overweight or obese, with strong correlations between OXT levels and BMI and total, visceral and subcutaneous fat (Schorr *et al.* 2017).

However, in contrast to the peripheral action of FSH and TSH through adipose tissue GPCRs, OXT appears to act on the central nervous system to regulate body composition via a primary action on feeding. Several lines of evidence attest to this. First, unlike bone cells, there are no OXTRs yet identified in fat tissue. Second, chronic central OXT infusion in high-fat-diet-induced obese rats resulted in decreased body weight, increased adipose tissue lipolysis, increased fatty acid β -oxidation and reduced glucose intolerance and insulin resistance (Deblon *et al.* 2011). Third, feeding stimulated and starvation reduced OXT secretion from the pituitary (Kublaoui *et al.* 2008, Zhang & Cai 2011). Fourth, patients affected by *SIM1* gene mutation and by Prader–Willi syndrome, in whom hyperphagia and obesity are characteristic clinical features, displayed reduced numbers and size of OXT-ergic neurons in paraventricular nuclei (Swaab *et al.* 1995, Holder *et al.* 2000). These findings suggest that the prominent effects of OXT on body composition are mediated centrally through an effect on feeding, although there is some evidence for a peripheral action. For example, the late-onset obesity in *Oxtr*^{−/−} mice is independently of daily intake of chow (Takayanagi *et al.* 2008). However, OXT infusion by subcutaneously implanted osmotic minipumps in diet-induced obese mice reduced food intake (Maejima *et al.* 2011, Morton *et al.* 2012). Intraperitoneal OXT injection likewise induced c-Fos expression in the hypothalamus (Maejima *et al.* 2011). These findings together suggest that peripherally administered OXT could cross the blood–brain barrier and *vice versa*. Cell-specific conditional deletion of OXTRs in the periphery vs centrally in OXT-ergic neurons should provide firm conclusions regarding the primary site of action of OXT.

Ubiquity of ‘pituitary’ hormone expression

Not only have receptors been identified on tissues other than what are considered primary endocrine targets, ‘pituitary’ hormones themselves are produced in non-pituitary locations. Among the most exciting revelations has been the clear documentation of GH production in various compartments of the eye, particularly in retinal ganglion cells (Baudet *et al.* 2003, Harvey *et al.* 2004, Harvey & Aramburo 2017, Martinez-Moreno *et al.* 2018). Here, they act on GHRs to regulate retinal development, and specifically, the processes of neurite outgrowth, retinal vascularization and neuronal cell proliferation and apoptosis (Harvey & Aramburo 2017, Martinez-Moreno *et al.* 2018). Transgenic GH overexpression has been associated with increased axial length of the eye, whereas siRNA knockdown reduces axonal growth (Grimbley *et al.* 2009, Martin *et al.* 2011). Additionally, GH is expressed in lymphoid tissues, including thymus and spleen, as well as in both the male and female reproductive tracts (Hull & Harvey 2014). However, apart from effects on steroidogenesis and ovarian cell proliferation, the mechanism of these extra-pituitary actions is relatively unclear.

Extra-pituitary sources of TSH have long been known (Smith *et al.* 1983a, Blalock 2005). In parallel with the pituitary–thyroid endocrine axis, there is additional TSH-related circuitry that functions beyond the thyroid to involve, for example, the immune system. Immune cells, mainly macrophages, produce a novel TSH- β_v (Vincent *et al.* 2009, Baliram *et al.* 2013, 2016). In the mouse, the TSH- β -coding region is located in segments of exons 4 and 5, while exon 4 is missing in mouse TSH- β_v . In contrast, the human TSH gene contains three exonic sequences, but exon 2 is missing in the human TSH- β_v . Molecular docking and cell-based assays show that TSH- β and TSH- β_v bind to and signal through the TSHR with similar binding affinities (Baliram *et al.* 2013, 2016). However, while thyroid hormones suppress the production of pituitary TSH, macrophage-derived TSH- β_v is enhanced. Locally produced TSH- β_v in response to hyperthyroidism may, in fact, offer some limited protection to the skeleton (Baliram *et al.* 2012), but this assumption is speculative. However, interestingly, TSH- β_v is also synthesized by mouse and human pituitary (Schaefer & Klein 2009, Vincent *et al.* 2009). Lymphocytes are also known to express TSH (Smith *et al.* 1983b, Harbour *et al.* 1989), but there is no evidence yet for bone or marrow cell production of FSH, although co-production of TSH- β and FSH is noted in CD11b⁺ cells from mouse thyroid (Klein & Wang 2004).

We have shown that Oxt, apart from its neurohypophyseal origin, is produced in abundance by both human and murine osteoblasts (Colaïanni *et al.* 2011). Production of osteoblast Oxt is under the control of estrogen, which acts by activating the MAP kinase Erk (Colaïanni *et al.* 2011, 2012). This non-genomic mechanism of estrogen action is in contrast to its genomic control of *Oxtr* expression (Tamma *et al.* 2009). We surmise that there is a local feed-forward loop in bone marrow through which the Oxt so produced from osteoblasts in response to estrogen acts upon its receptor to exert a potent anabolic action. We also show that the absence of Oxtrs in osteoblasts derived from *Oxtr*^{-/-} mice or the attenuation of *Oxtr* expression in silenced cells inhibits estrogen-induced osteoblast differentiation, transcription factor upregulation and/or Oxt production *in vitro*. *In vivo*, *Oxtr*^{-/-} and *Col2.3-Cre+;Oxtr^{fl/fl}* mice display a bone formation defect and fail to display increases in trabecular bone volume, cortical thickness and bone formation in response to estrogen (Colaïanni *et al.* 2012). Physiologically, therefore, feed-forward Oxt release in bone marrow by a rising estrogen concentration may facilitate rapid skeletal recovery during the latter phases of lactation.

Conclusion

The direct regulation of body composition, importantly bone mass and adipose tissue, by hormones from pituitary gland helps explain some of the inconsistencies of older models that assumed monogamous pituitary signaling through single targets. However, this latter assumption of singularity cannot be explained by highly distributed functions of primitive pituitary hormones in lower organisms. Nontraditional and important direct actions have thus emerged, which relate to effects of both anterior and posterior pituitary hormones on bone mass, body fat and energy homeostasis. Interestingly, these newly described signaling pathways appear not to have identical mechanisms to traditional endocrine targets, so that, for example, the FSHR in bone and fat tissue couples with a G_i protein as opposed to traditional FSHR-G_s coupling in the ovarian follicular cell. There is also increasing evidence for ligands, receptors and their splice variants to be co-expressed in the same tissue, in essence, highlighting yet uncharacterized paracrine and autocrine control mechanisms. Newly discovered targets of these otherwise 'old' hormones also provide unique opportunities for the therapy of diseases that we can now attribute to changes

in the levels of circulating pituitary hormones. Thus, we posit that there is a pituitary–bone and pituitary–adipose axis that, when perturbed, causes diseases, such as obesity and osteoporosis, but can be potentially utilized to target novel therapeutics for use in people.

Declaration of interest

Mone Zaidi is a named inventor of an issued US patent related to osteoclastic bone resorption filed by the Icahn School of Medicine at Mount Sinai (ISMMMS). In the event the issued patent is licensed, he would be entitled to a share of any proceeds ISMMMS receives from the licensee. All other authors have nothing to disclose.

Funding

Mone Zaidi, Li Sun, Terry F Davies, Harry C Blair and Clifford J Rosen are supported by grants from the National Institutes of Health. Alberta Zallone is supported by the Ministry of Education, Italy. Maria I New is supported by the Children's Hormone Research Foundation, New York, USA.

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Received in final form 5 March 2018

Accepted 19 March 2018

Accepted Preprint published online 19 March 2018