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Review

Central and peripheral mechanisms of the NPY system in the regulation of bone and adipose tissue

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ABSTRACT

Skeletal research is currently undergoing a period of marked expansion. The boundaries of "bone" research are being re-evaluated and with this, a growing recognition of a more complex and interconnected biology than previously considered. One aspect that has become the focus of particular attention is the relationship between bone and fat homeostasis. Evidence from a number of avenues indicates that bone and adipose regulation are both related and interdependent.

This review examines the neuropeptide Y (NPY) system, known to exert powerful control over both bone and fat tissue. The actions of this system are characterized by signaling both within specific nuclei of the hypothalamus and also the target tissues, mediated predominantly through two G-protein coupled receptors (Y1 and Y2).

In bone tissue, elevated NPY levels act consistently to repress osteoblast activity. Moreover, both central Y2 receptor and osteoblastic Y1 receptor signaling act similarly to repress bone formation. Conversely, loss of NPY expression or receptor signaling induces increased osteoblast activity and bone mass in both cortical and cancellous envelopes.

In fat tissue, NPY action is more complex. Energy homeostasis is powerfully altered by elevations in hypothalamic NPY, resulting in increases in fat accretion and body-wide energy conservation, through the action of locally expressed Y1 receptors, while local Y2 receptors act to inhibit NPY-ergic tone. Loss of central NPY expression has a markedly reduced effect, consistent with a physiological drive to promote fat accretion. In fat tissue, NPY and Y1 receptors act to promote lipogenesis, consistent with their roles in the brain. Y2 receptors expressed in adipocytes also act in this manner, showing an opposing action to their role in the hypothalamus.

While direct investigation of these processes has yet to be completed, these responses appear to be interrelated to some degree. The starvation-based signal of elevated central NPY inducing marked inhibition of osteoblast activity, whilst promoting fat accretion, indicating skeletal tissue is a component of the energy conservation system. Moreover, when NPY expression is reduced, consistent with high calorie intake and weight gain, bone formation is stimulated, strengthening the skeleton. In conclusion, NPY acts to regulate both bone and fat tissue in a coordinated manner, and remains a strong candidate for mediating interactions between these two tissues.

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Contents

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Introduction

Osteoporosis, the long-term imbalance between bone formation and resorption, is an increasing health care problem affecting approximately one in three women and one in five men over the age of 50 years [1]. Obesity, the consequence of long-term imbalance between energy intake and energy expenditure, has reached epidemic proportions and become a major public health challenge worldwide [2]. It has been traditionally thought that bone was a structure to provide mechanical support and mineral homeostasis, and adipose tissue was an inert store for excess food intake. However, in recent years our understanding of the biology of bone and fat tissue has changed this view. In the last decade, emerging evidence has revealed previously unrecognized signaling pathways from bone and fat tissue, as well as between them [3–8]. These newly discovered pathways reflect a far more integrated physiology where bone takes on an important role in regulating energy metabolism and visa versa [9–11].

Clinical importance of the bone/fat relationship

Our emerging understanding of the interactions between skeletal and energy homeostasis has important clinical ramifications. It is clear that body weight exerts a powerful, positive effect upon bone mass [12]; the response of skeletal tissue to mechanical loading is well known. However, it has become apparent that the relationship is more complex than simple load bearing or the response of bone to muscle-induced strain. This concept is supported by studies indicating that bone mass is more closely related to fat mass ($r = 0.5$) than lean mass ($r = 0.2$) [4]. This presents the intriguing possibility that factors regulating fat mass may also regulate bone mass.

The biological importance of the body mass and bone mass relationship is borne out by studies identifying body mass as a strong predictor of fracture in both men and women and particularly for hip fracture [13–15]. However, the relationship with fracture is not constant across the range of body mass, with a marked increase in fracture risk at lower body weights. A recent meta-analysis showed a 2-fold increase in hip fracture risk with a decline in BMI from 25 to 20 [15]. This relationship was not independent of BMD, indicating that factors regulating BMI may also be regulating BMD/fracture. Furthermore, this relationship is dynamic with weight loss being a strong risk factor for bone loss, itself an independent predictor of fracture [13,16]. Importantly, low weight/weight loss as well as low bone density/bone loss is independent predictors of mortality in the elderly [17,18]. It is therefore clear that an ability to increase both body weight and bone mass is likely to translate into a reduction in fracture, as well as possibly mortality in the elderly and other illness groups.

The Neuropeptide Y system

Bone remodeling has long been viewed as predominantly an endocrine-and paracrine-regulated process. In recent years, however, our understanding of the importance of neuronal signals to the regulation of bone mass has expanded markedly. Moreover, adipose tissue is also known to be controlled by neural signals [19]. One such neural system of particular importance to bone and fat metabolism is the neuropeptide Y (NPY) system. NPY, a 36-amino acid peptide, is widely expressed in the central and peripheral nervous systems and plays an important role in the regulation of numerous physiological processes, including skeletal and energy homeostasis [20,21]. In the central nervous system, NPY is present in regions such as the hypothalamus, cerebral cortex, brain stem, striatum and limbic structures [22], with the highest expression in the hypothalamic arcuate nucleus [23]. In the periphery, NPY is found in the sympathetic nervous system, co-stored and co-released with noradrenaline during nerve stimulation [24]. NPY expression is increasingly being identified in peripheral tissues; interestingly, both osteoblasts and adipocytes produce NPY [25–27].

NPY mediates its effects via G protein-coupled receptors, of which five have been cloned to date: Y1, Y2, Y4, Y5 and y6 [23], each showing varying distributions across central and peripheral tissues. Y1 receptors have the widest distribution in the brain with particular expression in the PVN of the hypothalamus [28]. The Y5 receptor exhibits highest identity to the Y1 receptor [29], and is consistently co-localized with the Y1 receptor [28,30], albeit with a much less broad distribution than the Y1 receptor. The arcuate nucleus, the region with the highest NPY expression within the hypothalamus, expresses Y2 receptors. Moreover, adipocytes express both Y1 and Y2 receptors [26] and osteoblasts Y1 receptors [31,32], indicating the potential for local effects. This review will discuss central and peripheral actions of NPY in the regulation of skeletal and energy homeostasis. Much of our understanding of NPY biology has been produced through animal studies, which will form the basis of this review.

Central actions of NPY in skeletal homeostasis

Initial studies showed that intracerebroventricular infusion of NPY into the cerebral spinal fluid of wild type mice leads to a significant reduction in cancellous bone volume [33]. These were followed with targeted, hypothalamus-specific NPY over expression in the neural tissue of the arcuate nucleus [34,35]. NPY over expression within the hypothalamus decreased osteoblast activity up to 7-fold via reduction in mineral apposition rate, with changes evident on cortical and cancellous surfaces. Germline NPY knockout mice display skeleton-wide increases in bone mass, associated with enhanced osteoblast activity [36]. These changes are supported by increased expression of bone osteogenic transcription factors, RUNX2 and Osterix [31], indicating critical role of NPY in the control of bone formation. However, another study found no skeletal changes in NPY null mice [37]. A number of factors may have been involved in the lack of phenotype evident in the latter study. The most powerful being the potential for enhanced activity of the HPA axis in NPY null mice. Indeed, hypercortisolemia associated with loss of NPY is capable of reducing anabolism in these mice to wild type levels (manuscript in preparation). In addition, responses to NPY deficiency have been shown to be greater in male mice [38]. Critically, the increase in central NPY was associated with marked gain in adipose tissue (discussed below), demonstrating the ability of central NPY to control both bone and fat tissue.

NPY, Y2 receptors of the hypothalamus

Of the 5 known NPY receptors, Y1 and Y2 receptors have been shown to influence bone mass in mice [39]. However, the Y2 is critical to central regulatory pathways to bone. Y2 receptors are widely expressed in areas of the brain such as the hypothalamus, hippocampus and brain stem [40,41], and is the most abundant Y receptor in the central nervous system representing approximately 2/3 of the total binding capacity of NPY [42]. 80% of the NPY-expressing neurons in the arcuate co-express the Y2 receptor [43], which is thought to act as an auto-receptor that can modulate the expression and secretion of NPY and other neurotransmitters [44]. Peripherally, Y2 receptors are expressed in the white and brown adipose tissue, liver, muscle, spleen, [45], and intestine [46] and on nodose ganglion neurons innervating the large and small intestines [47]. Y2 receptors are not expressed in osteoblasts [32].

Adult-onset, hypothalamus-specific Y2 receptor deletion, corresponding to a loss of Y2 receptors from the arcuate nucleus, produces an identical bone anabolic phenotype to germline Y2 receptor deletion. This anabolic change is characterized by increased osteoblast activity with no measurable changes in parameters of osteoblast or osteoclast surface [48,49]. Importantly, this greater bone accretion was not associated with changes in the concentrations of hormones that are known to regulate bone physiology, notably leptin, thyroid hormones, insulin-like growth factor 1 (IGF-1), corticosterone, or testosterone [49], suggesting that hypothalamic Y2 receptors modulate bone formation by neural mechanisms, rather than endocrine mechanisms. Similar findings of elevated bone formation were evident in chemical lesioning studies of the arcuate using monosodium glutamate [37]. This result demonstrates that central Y2 receptor signaling, notably in the hypothalamus, plays a critical role in the regulation of bone mass.

Importantly, a recent study demonstrated that ablation of hypothalamic Y2 receptors specifically from NPY-ergic neurons produced only moderate increases in cancellous bone volume, and no effect on cortical bone mass [50]. This result indicates that within the hypothalamus the Y2 receptor-mediated regulation of bone mass is mediated through neuronal populations other than NPY neurons. Preliminary indications suggest that sympathetic neurons emanating from the paraventricular nucleus, the target region for arcuate NPY, may be responsible for the efferent pathway (unpublished observation). In addition the role of Y5 receptors, expressed in the paraventricular nucleus in addition to Y1, requires exploration, and may represent the critical pathway of arcuate NPY to bone. As outlined above, Y1 and Y5 receptors are co-expressed on NPY target neurons in the paraventricular nucleus. Thus deletion of Y1 may not be sufficient to block the NPY pathway to bone, or Y5 may be the sole receptor to transduce the signal resulting from altered NPY expression in the arcuate.

Y1 receptors of the hypothalamus

Y1 receptors are widely expressed in the central nervous system, including the hypothalamus, with a high concentration in the paraventricular nucleus (PVN), a region supplied with NPY by NPY-ergic neurons of the arcuate nucleus [41,51]. Thus changes in NPY expression in the arcuate nucleus can lead to NPY protein changes in the PVN. Similar to the phenotype resulting from Y2 receptor deletion, germline Y1 receptor deficiency produces a generalized elevation in osteoblast activity, at both axial and appendicular sites leading to greater cortical bone and cancellous accrual [25]. Importantly, In contrast to the anabolic effects in hypothalamus-specific Y2 deletion [49], loss of hypothalamic (PVN) Y1 receptors does not alter bone homeostasis [25]. Thus hypothalamic Y1 receptors are not responsible for the marked effects of germline Y1 receptor deletion on bone. In support of this possibility, Y1 receptors have recently been reported in osteoprogenitors and bone tissues [31,52] and the direct action of NPY in bone is discussed below.

Summary table bone: hypothalamic NPY

Gene	Expression	Effect on bone
NPY	Arcuate	Inhibits osteoblast activity
Y2 receptor	Arcuate	Inhibits osteoblast activity
Y1 receptor	PVN	No effect

Peripheral actions of NPY in skeletal homeostasis

Although hypothalamic NPY signaling has a powerful impact on peripheral activity of osteoblasts and osteoclasts, it is interesting to note that increased osteoblastic activity seen in the NPY knockout mice was not completely normalized by the replenishment of NPY into the hypothalamus of NPY knockout mice [36]. This suggests that hypothalamic NPY is not solely responsible for the bone anabolic phenotype observed in NPY knockout mice, and that non-hypothalamic NPY may play a potential role in bone formation. There are several sources of NPY in the periphery. NPY is a secretagouge of noradrenaline and is produced by sympathetic nerves [53] and by the adrenal medulla [54] as well as on peripheral tissues such as vascular smooth muscle cells and pancreatic cells [55]. Importantly, NPY is also present in osteoblasts, osteocytes [31,52] and osteoclasts (unpublished observation). Thus, given the presence of Y1 receptors in osteoblasts, peripheral NPY may act in a paracrine/autocrine manner in bone cells. Moreover, the absence of Y2 receptor in bone and NPY expression in osteoblasts and osteocytes, suggested a direct anabolic effect of the NPY system on osteoblastic cells acting through locally-expressed Y1 receptors.

Several studies have suggested a direct action of NPY within bone tissues. NPY treatment to osteoblastic cells *in vitro* inhibits the cyclic AMP response to parathyroid hormone, norepinephrine and forskolin [52,56,57]. NPY can inhibit the formation of osteoblast-like cells induced by the addition of isoprenaline to bone marrow stromal cells (BMSC) cultures [58]. Furthermore, administration of NPY to calvarial osteoblasts from wild type mice leads to a marked decrease in cell numbers, whereas, NPY treatment in osteoblast cultures from Y1 receptor knockout mice had no effect upon cell number [25]. Similarly, NPY treatment in calvarial osteoblasts reduced the expression of late stage genes (osteocalcin and DMP-1) and reduced mineral deposition, consistent with an increase in Y1 receptor expression with maturation in these cells [52].

Osteoblastic Y1 receptors

Interestingly, germline deletion of the Y1 receptor leads to an upregulation of proliferation and differentiation of mesenchymal progenitor cells isolated from bone tissues [31]. The critical role of osteoblastic Y1 receptor in bone formation has been established in a recent study in which BMSCs isolated from mice lacking the Y1 receptor solely in mature osteoblasts display enhanced mineralization *in vitro,* greater bone mass and osteoblast activity *in vivo* [31], resulting in a similar phenotype to germline Y1 knockout mice. These findings confirm the direct and functional role of Y1 receptor in inhibiting mineral deposition by mature osteoblasts, as well as reinforcing the negative effects of NPY on bone cells.

Peripheral Y2 receptors

A recent study from conditional peripheral Y2 knockdown demonstrates that peripheral Y2 receptors are not involved in the regulation of bone mass. The deletion of Y2 receptors from non-central tissues did not alter whole body bone mineral density (BMD), whole body bone mineral content (BMC), isolated femur BMD and isolated femur BMC [45]. The lack of effects on bone mass seen in this model further indicates that bone mass is primarily controlled by non-peripheral Y2 receptors, highlighting the critical role of hypothalamic

Y2 receptors on NPY-ergic neurons [50] as well as non-NPY-ergic neurons [43] in the control of bone formation.

In addition, osteoblastic Y1 receptors may be directly involved in the development of bone anabolic phenotype of germline Y2 knockout mice. Cultured BMSCs isolated from Y2 knockout mice displayed an increase in the number of osteoprogenitor cells and increased mineralization, in the absence of central neural input [32]. This increased activity was associated with a significant decrease in Y1 receptor expression in the Y2 knockout cultures [32]. Moreover, no additive skeletal changes were identified in Y1 and Y2 double knockout mice [25], indicating the possibility of Y1 and Y2 receptor sharing a common pathway from the hypothalamus to regulate peripheral bone formation.

Taken together, these studies highlight a system whereby central modulation of NPY, primarily in the arcuate nucleus, induces marked changes in osteoblast activity. These efferent, sympathetic signals are modulated however, by local processes involving Y1 receptors expressed upon osteoblast and osteoprogenitor populations. In this manner, while hypothalamic NPY is ideally placed to modulate bone mass in a generalized manner throughout the skeleton, NPY locally produced in bone and acting on osteoblastic Y1 receptors enables local fine tuning of efferent neural NPY signaling.

Summary table bone: peripheral NPY

Gene	Expression	Effect on bone
NPY	Sympathetic nerves, osteoblasts	Inhibits osteoblast activity
Y1 receptor	Osteoblasts, osteoprogenitors	Inhibits osteoblast activity
Y2 receptor	Not expressed in osteoblasts	No effect

Central actions of NPY in adiposity

Central control of energy balance is predominantly a function of hypothalamic pathways including key connections with the arcuate nucleus, where NPY expression is highest. The arcuate is located at the base of hypothalamus, and has direct access to circulating hormones due to a semi-permeable blood brain barrier [59]. Therefore, NPY-ergic neurons within the arcuate are able to respond rapidly to peripheral signals such as insulin [60], ghrelin [61] and leptin [62], and then project broadly to other brain regions to modulate energy homeostasis [63], demonstrating a pivotal role of hypothalamic NPY in coordinating this complicate process.

NPY expression increases under conditions of food deprivation, which contributes to an increase in food intake and contributes subsequently to positive energy balance [64–67]. NPY-mediated changes can be marked, with body weight increased by around 75% in the three weeks following NPY over expression in the hypothalamus; this increase being the result of a 4-fold increase in white adipose tissue mass [68]. Intracerebroventricular or hypothalamus-specific administration of NPY to normal rodents leads to multiple defects characteristic of obesity, including hyperphagia, but it also induces many neuroendocrine and metabolic changes that favor energy storage [69–72]. These changes include, hyperleptinemia, hypercorticosteronemia, hyperinsulinemia, increased de novo lipogenesis in white adipose tissue, activation of the hypothalamo–pituitary–adrenal axis [73–75], and decreased activity of the hypothalamo–pituitary-thyrotropic [76], -somatotropic, and -gonadotropic axes [77,78]. More importantly, all of these neuroendocrine and metabolic effects of central NPY administration, notably the increased adiposity, persist even when NPY-induced hyperphagia is prevented by pair-feeding [69,71]. This indicates that hyperphagia is not the only mechanism by which central NPY increases adiposity, moreover, the metabolic and hormonal changes and decreased energy expenditure contribute to central NPY induced adiposity [69,79–81].

Unexpectedly, body weight and adiposity were normal in the first-reported NPY-deficient mice fed with a normal chow [82]. However, a recent study has demonstrated a moderate increase in fat mass in NPY null mice, however, no effect on body weight, or lean mass [36]. These findings indicate that the effect of NPY on fat mass is predominantly in response to calorie deprivation and involves responses to increased NPY production. Consistent with this notion, metabolic responses to NPY deficiency are best demonstrated in conditions where NPY levels are normally elevated. In particular, NPY deficiency has modified responses to fasting, and it also attenuates hyperphagia and the obesity syndrome of leptin deficient *ob*/*ob* mice, known to express high levels of NPY in the hypothalamus [82,83]. These data illustrate the prominent role played by elevated NPY production in the protection against negative energy balance and starvation. Moreover, consistent with this role of promoting positive energy balance, reduced NPY production does not appear to play a role in inhibiting the excessive accrual and storage of energy.

This is in contrast to the effects of NPY on bone mass, which are evident in both reduced and increased NPY states. The requirement for a skeletal response to calorie deprivation is consistent with the need to conserve energy through the body. Thus as NPY expression increases in the hypothalamus during starvation, bone formation is reduced to conserve energy. However, a skeletal response is also required during calorie excess, when NPY levels are reduced. Thus with diet-induced obesity or genetic NPY ablation, osteoblast activity is increased; a response consistent with a greater need to weight bearing [52]. Interestingly, osteocytes when loaded *in vitro* also displayed a reduction in NPY expression, suggesting the possibility of local, load-induced coordination of bone mass and body weight by NPY, acting within the hypothalamus and the osteoblast lineage.

Hypothalamic Y1 and Y5 receptors in adiposity

Y1 receptors have been considered important regulators of energy homeostasis. Several studies have reported the generation of Y1 receptor knockout mice using different gene deletion strategies [84–87]. But, despite the hypothesized role as a “feeding receptor” to mediate the orexigenic action of NPY, germline Y1 receptor-deficient mice, similar to first NPY knockout mice, did not display any major abnormalities in regard to food intake [84,86]. And conditional hypothalamus-specific Y1 receptor deletion does not alter body weight, food intake, fat mass or glucose metabolism compared to controls [25]. However, consistent with NPY's primary action in energy homeostasis being responses to elevated NPY production, the hyperphagia induced by intracerebroventricular NPY was diminished in germline Y1 knockout mice [85,88]. While, deletion of Y1 receptors in genetically obese *ob*/*ob* mice, in which hypothalamic NPY-ergic activity is chronically increased, significantly reduced food intake and body weight [89]. This indicates that hypothalamic Y1 receptors mediate anabolic effects of NPY only under conditions of elevated hypothalamic NPY levels. In addition to initial role as a feeding receptor, a growing evidence has revealed that Y1 receptors play important roles in mediating many other aspects of energy homeostasis, including energy expenditure, oxidative fuel selection, physical activity and pancreatic insulin secretion [25,84,85,90].

Paradoxically, in the absence of hyperphagia, germline Y1 receptor knockout mice develop late-onset obesity that is associated with hyperinsulinemia and increased glucose uptake and glycogen synthesis in adipose tissue [84,85,91,92]. These metabolic changes may relate to decreased physical activity [85] or decreased basal metabolic rate [25,84,90]. This apparent discrepancy may be reconciled by differential effects of hypothalamic and non-hypothalamic Y1 receptors, as discussed below.

Similar to hypothalamic Y1 receptors, hypothalamic Y5 receptors have also been identified as a feeding receptor implicated in mediating the obesogenic effects of NPY [93,94]. Unlike Y1 receptor deficient mice, germline Y5 receptor knockout mice are hyperphagic and are not protected against leptin-deficiency-induced obesity [93]. Germline Y5 receptor knockout mice display exacerbated fasting-induced increases

in hypothalamic expression of the orexigenic NPY and agouti related peptide (AgRP), and exacerbated decreases in the anorexigenic peptides proopiomelanocortin (POMC), and cocaine and amphetamine-related transcript (CART) [95]. In keeping with the findings that Y1 and Y5 genes are coordinately regulated by the same promoter region [96] and are co-expressed in the same neurons [30,97], there also appears to be redundancy between Y1 and Y5 receptors in the control of energy homeostasis [93]. Taken together, these findings provide important insights into the role of Y5 receptor in energy homeostasis and indicate the need of dual blockade of Y1 and Y5 receptors.

Hypothalamic Y2 receptors in adiposity

The Y2 receptor, most markedly expressed in the arcuate, has been defined as an inhibitory auto-receptor; acting to reduce the expression of NPY in NPY-ergic neurons [44]. Thus hypothalamic Y2 receptor action should reduce NPY production and thereby attenuate the obesogenic actions of NPY. Consistent with this notion, loss of hypothalamic Y2 receptors leads to increased body weight gain associated with hyperphagia [50]. Confirming a negative feedback mechanism between NPY expression and Y2 receptors on NPY-ergic neurons, a hypothalamus-specific deletion of Y2 receptors, confined to NPY-ergic neurons, lead to increased NPY and decreased proopiomelanocortin (POMC) mRNA expression in the arcuate nucleus, and also demonstrated a marked increase in adiposity [50]. These data demonstrate the anti-obesogenic role of Y2 receptors in the brain, which modulate the critical NPY: POMC ratio, a fundamental determinant of global energy homeostasis.

Summary table adipose: hypothalamic NPY

Gene	Expression	Effect on adipose
NPY	Arcuate	Increase fat accretion
Y1 receptor	PVN	Increase fat accretion
Y2 receptor	Arcuate	Decrease fat accretion
Y5 receptor	PVN	Increase fat accretion

Peripheral actions of NPY in adiposity

Y1 receptor actions

Similar to effects on osteoblasts, the NPY system can have direct effects on white adipose tissue in the periphery through Y1 receptors. NPY is locally secreted by visceral adipose tissue and promotes proliferation of adipocyte precursors via Y1 receptors expressed on the adipocytes and pre-adipocytes [27]. Blocking Y1 receptors on rodent and human adipocytes *in vitro* enhances lipolysis [98,99]. In keeping with a direct action of peripheral Y1 receptor signaling in adipogenesis, peripheral Y1 receptor signaling has recently been shown to be a critical regulator of fat mass and lipid oxidation [90]. More importantly, in contrast to the exacerbated diet-induced obesity in germline Y1-deficient mice [90], conditional peripheral Y1 receptor knockdown leads to resistance to diet-induced obesity, as evidenced by a marked reduction in weight gain and fat accretion accompanied with increased energy expenditure and lipid oxidation compared to controls [90]. Thus Y1 receptors of the hypothalamus and periphery act in opposition, with central Y1 acting to reduce adiposity, while peripheral, adipocytic Y1 acts to stimulate fat accretion.

Y2 receptor actions

Interestingly, the effects of germline Y2 receptor deletion are the opposite of that for central Y2 knockout. Central deletion of Y2 receptors leads to greater NPY expression and with it weight gain [50], whereas germline deletion of Y2 receptor leads to significant reductions in adiposity and body weight [43,100]. In contrast to osteoblasts, adipocytes also express Y2 receptors, which also mediate NPY signals to regulate adipose tissue biology, acting in opposition to hypothalamic Y2 receptors, by stimulating adipose tissue accretion. Conditional knockdown of peripheral Y2 receptors leads to marked reduction in adiposity and weight gain, and improvements in glucose tolerance and protection against diet-induced obesity. Interestingly, this occurred without adverse effects on lean tissue or change in bone mass [45]. Another study reported that chronic stress combined with a high calorie diet produces a marked upregulation of plasma and adipose tissue NPY expression, promotes adipogenesis [26]. This increase in adipose tissue production was blocked by pharmacological or local genetic Y2 receptor antagonism. This finding suggests that obesogenic action of peripheral Y2 receptor in the white adipose tissue is opposite to well-known anti-obesity action of hypothalamic Y2 receptors.

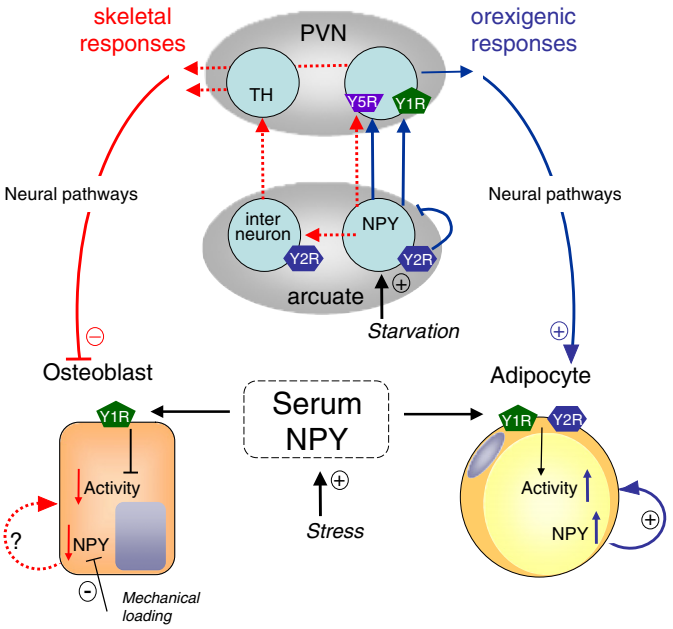

Fig. 1. Central and peripheral regulation of bone and fat mass by NPY and its receptors. Central pathways originate with increased NPY expression in NPY-ergic neurons in the arcuate nucleus. These neurons propagate orexigenic signals (blue arrows) via synapses with efferent neurons in the paraventricular nucleus through signaling via Y1 and Y5 receptors. These neurons are also known to induce skeletal responses (red arrows), however the exact mechanism is yet to be elucidated (dotted lines). Direct Y5 receptor signaling and indirect signaling via Y2 on non-NPY-ergic neurons are currently investigated hypotheses. NPY is also produced by peripheral sources, most notably during stress (sympathetic neurons/adrenals) and can signal directly to Y1 receptors in bone cells and Y1 and Y2 receptors in fat cells. In addition NPY is expressed in adipocytes and can stimulate lipid accrual, while the role of osteoblastic NPY is yet to be determined, but is know to reduce in response to mechanical load.

These studies indicate that novel drugs that target peripheral rather than central Y1 and/or Y2 receptors could provide benefits for the treatment of obesity and glucose intolerance without adverse effects on lean and bone mass, with the additional benefit of avoiding side effects often associated with pharmaceuticals that act on the central nervous system.

Summary table adipose: peripheral NPY

Gene	Expression	Effect on adipose
NPY	Sympathetic nerves, adipocytes	Increase fat accretion
Y1 receptor	Adipocytes, pre-adipocytes	Increase fat accretion
Y2 receptor	Adipocytes	Increase fat accretion

Interaction between bone and fat

NPY, acting via Y1 and Y2 receptors, is clearly involved in skeletal and adipose homeostasis (Fig. 1). However, the degree to which these

processes are interrelated remains to be elucidated. At present evidence suggest that there may be a degree of connection between the NPY-mediated changes in energy and skeletal homeostasis. Elevation of central NPY levels, as seen in a negative energy balance state, triggers energy conservation and an inhibition in the formation of bone [68,101]. Intriguingly, when NPY is exogenously elevated, the bone loss persists, despite being accompanied by marked weight gain and an increased in white adipose tissue mass, *i.e.* if the brain perceives the body is starving, then bone formation is altered accordingly, despite greater loading. Thus although there is strong and positive link between body weight and bone mass due to mechanical loading, this result also indicates that the central perception of energy status, and with it body weight, may have an important impact on peripheral activity of osteoblasts and osteocytes, through NPY-mediated processes.

Conversely, hypothalamic NPY level is decreased during times of energy excess or after short term overfeeding with increased serum leptin levels [101,102]. This reduction of NPY significantly increases bone mass in association with enhanced osteoblast activity as evident in the mice model lacking NPY [36]. High calorie intake-induced reduction of NPY ensures that sufficient bone is formed to guarantee mechanical competence of the skeleton during the times of increased weight bearing. Therefore, in addition to the well-defined actions of mechanical loading from body weight on bone mass, the central NPY, an indication of energy status, could be also placed to coordinate bone mass to body weight [36,103]. It remains to be determined whether the NPY system also plays a role in the direct signaling between bone and fat.

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