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Abstract: Osteoporosis and overweight/obesity constitute major worldwide public health burdens. Aging is associated with a decrease in hormonal secretion, lean mass and bone mass, and an increase in fat accumulation. It is established that both obesity and osteoporosis are affected by genetic and environmental factors, bone remodeling and adiposity are both regulated through the hypothalamus and sympathetic nervous system. Oxytocin (OT), belongs to the pituitary hormone family and regulates the function of peripheral target organs, its circulating levels decreased with age. Nowadays, it is well established that OT plays an important role in the control of bone and fat mass and their metabolism. Of note, OT and oxytocin receptor knock out mice develop bone defects and late-onset obesity. Thus OT emerges as a promising molecule in the treatment of osteoporosis and obesity as well as associated metabolic disorders such as type 2 diabetes and cardiovascular diseases. In this review, we will discuss findings regarding the OT effects on bone and fat mass.

Keywords: adipocyte; obesity; osteoblast; osteoporosis; oxytocin.

Introduction

Human life expectancy is continuously increasing in industrialized countries. Aging is associated with immunosenescence, decrease in hormonal secretion, metabolism, lean mass and bone mass, and increase in fat accumulation. Among disorders commonly considered as being age-related, which represent a major cause of morbidity and mortality, are osteoarthritis, osteoporosis, obesity, atherosclerosis and neurodegenerative diseases. Osteoporosis and overweight/obesity constitute major worldwide public health burdens. It is well established that tight links

between osteoporosis and adiposity exist. An inverse relationship between osteogenesis and adipogenesis is well documented and thus controlling the fine balance between these two pathways is of clear therapeutic significance [1]. During the last decade, the role of a hypothalamic nonapeptide, the oxytocin (OT), has been described in the control of bone remodeling and adiposity [2–5] and thus represent an interesting strategy to treat bone and fat related disorders. Herein, we will describe the role of OT and its involvement in bone and adipose tissue homeostasis.

Oxytocin and its receptor

Generalities

OT was discovered in 1906 [6] when Sir Henry H. Dale found that an extract from the human posterior pituitary gland contracted the uterus of a pregnant cat. OT belongs to the family of pituitary hormones and is considered as an abundant neuropeptide displaying homologs all along evolution (for review see [7]). The structure of OT was determined and was the first chemically synthesized peptide in a biologically active form [8]. Like all neurohypophysial hormones, OT is a nonapeptide with a disulfide bridge between Cys residues 1 and 6. OT displays a wide spectrum of central and peripheral functions (Figure 1), from the modulation of neuroendocrine reflexes arcs including hormone secretion, to the establishment of social and relationship behaviors [9, 10]. OT is also known as the “love hormone” due to its involvement in attachments, reproduction behaviors, offspring care, as well as its ethnical connections [11, 12].

OT has long been considered to be restricted to the stimulation of uterine contractions and milk ejection. Due to this, OT is commonly used in medical obstetrics to facilitate labor in all vertebrates without significant side effects [13]. The fact that OT is found in equivalent concentrations in the neurohypophysis and plasma of both sexes suggests that OT has other physiological functions. OT is predominantly synthesized within the magnocellular neurons of the hypothalamus, but also in some peripheral tissues, including the reproductive system, heart, and bone [9, 14, 15], and its secretion is modulated by various factors, including estrogens, testosterone and leptin [9, 16, 17].

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The OT receptor (OTR) is a 389-amino acid polypeptide with seven transmembrane domains first isolated and identified in humans [18]. The *OTR* gene is expressed in a variety of peripheral tissues and its expression is regulated by various signals, e.g. by steroids in the uterus or hypothalamus [9]. OTR belongs to the class I G protein-coupled receptor (GPCR) family and is functionally coupled to the $G_{\alpha q}$ class GTP binding proteins that stimulate the activity of phospholipase C [9]. This activity leads to the generation of inositol trisphosphate which triggers Ca^{2+} release from intracellular stores, and of diacylglycerol which stimulates protein kinase C. These well-known pathways initiate a variety of cellular events. For example, in myometrial or mammary myoepithelial cells, they trigger the activation of myosin light-chain kinase activity which initiates smooth muscle contraction [19]. Due to the closely related sequences of OT and vasopressin, these pituitary hormones can act directly on each other's receptor, respectively, OTR and arginine vasopressin receptor 1A (AVPR1A) [20]. Sometimes this activation allows the induction of functions in an opposite manner [21].

Finally, OT function can be mediated through OT production, as well as by modulation of OTR expression. Its actions are related to sexual physiological responses and behavior, but can be distinguished between central and peripheral effects.

Figure 1: Central and peripheral effects of oxytocin.

OT central action

In the central nervous system, OT is mainly expressed in magnocellular neurons within hypothalamic regions. Activation of these neurosecretory cells triggers the release of OT in the neurohypophysis [22]. The essential function of OT takes place in this brain area, as for example, it has an important role in milk ejection in response to suckling [23]. OT can be released also in the adenohypophysis and may participate in the physiological regulation of the adenohypophysial hormones such as ACTH [24]. In human, OT infusion inhibited the plasma ACTH in response to corticotropin-releasing hormone (CRH), found, for example, in the case of suckling and breast stimulation [25]. Thus, OT might control corticotropic activity of the adrenal gland via the inhibition of ACTH release under some physiological conditions.

Another central function of OT, depending on its positive behavior action, is its analgesic activity. Indeed, OT is able to increase β -endorphin and L-enkephalin release, and OT antagonists decrease the concentration of these opioids. Moreover, intrathecal injection of OT is effective in treating low back pain in humans, an effect reversed by the opiate receptor-blocker naloxone [26]. This interaction between OT and the opioid system is also involved in sexual behaviors [27].

Several studies have shown that OT action in the hypothalamus facilitates both aspects of sexual behavior (perceptive and receptive), certainly in association with other sexual hormones [28]. This is true in a large number of species, but in humans the OT role seems more related to its anxiolytic properties facilitating social interactions [29]. This anxiolytic property of OT is important in human and animal studies as stress can induce release of OT in the brain and plasma, and thus might mask the real experimental level and action of OT.

OT, the “love hormone”, exhibits a positive effect in sexual and non-sexual social behaviors [30]. This is highlighted by two interesting studies demonstrating the effect of OT on social trust and favoritism within a group [31, 32].

OT peripheral action

The uterus represents the main and classical tissue target of OT during pregnancy. During the late stages of labor, the uterine sensitivity to OT is due to an increased expression of OTR especially in the myometrium, which decreases after parturition. In rats, OT mRNA increased at term, indicating an autonomous OT pathway in the uterus, however, this observation remains to be proven

in other species including humans [9]. Nevertheless, due to this uterotonic capacity, OT is clinically used to induce labor in all mammals. However, OT has been detected in various cells of the ovary and corpus luteum, and thus may participate in early development and/or fertilization [33]. One of the other classical roles assigned to OT is milk ejection from the mammary gland. The secretion of the mammary glands is triggered by the stimulation of tactile receptors on the nipple when the infant begins to suck. This generates a signal to the secretory oxytocinergic neurons in the hypothalamus which leads to massive release of OT into the bloodstream and thus reaches the lactating breasts [9].

In males, particularly in humans, OT production and OTR are present in the testis, epididymis and prostate [34]. In addition to hypothalamic OT production, OT peripheral tissue production, might be involved in the contraction of the prostate, in the expulsion of prostatic secretions and finally in ejaculation [35].

OT is also involved in the control of blood volume and osmolality. OT is described as a natriuretic agent in the rat but its contribution to renal physiology in primates including humans has not yet been described [36]. Additionally, injection of OT decreases mean arterial pressure and leads to the stimulation of atrial natriuretic peptide (ANP) release [37]. The ANP released would also act on the kidneys to induce natriuresis, and within the brain to inhibit water and salt intake. These events lead to a gradual recovery of circulating blood volume to normal.

OT has been detected in other peripheral tissues including in the thymus, pancreas and adrenal gland, with different proposed potential function, demonstrating the wide spectrum of action of this hormone. Finally, OT is produced by osteoblasts [38] and adipocytes and acts on bone and fat tissues, its function on these issues will be presented in this review.

Fat and bone crosstalk

Several observations link obesity with osteoporosis: i) both diseases are affected by genetic and environmental factors, or the interaction between them, ii) normal aging is associated with both a high incidence of osteoporosis and bone marrow adiposity [39], iii) bone remodeling and adiposity are both regulated through the hypothalamus and sympathetic nervous system, iv) adipocytes and osteoblasts derive from a common progenitor, the mesenchymal stem cell [40–43], v) adipose tissue is an endocrine organ [44], and the skeleton has emerged also as

an endocrine organ, vi) pathophysiological relevance of adipose tissue in bone integrity resides in the participation of adipokines in bone remodeling, while the skeleton has effects on body weight control and glucose homeostasis through the actions of bone-derived factors such as osteocalcin and osteopontin [45–47]. Thus, there is an active cross-talk between adipose tissue and the skeleton constituting a homeostatic feedback system with adipokines and molecules secreted by osteoblasts and osteoclasts.

Osteoporosis is defined by the deterioration of bone density and microarchitecture leading to bone fragility [48]. The strength and integrity of the bone depend on the balance between resorption by osteoclasts and bone formation by osteoblasts [49, 50]. The decrease of bone mass which occurs during osteoporosis implies an acceleration of the “bone turn-over” with an imbalance between resorption and formation in favor of bone resorption [51, 52]. In addition, osteoporosis is associated with a gain in bone marrow adiposity, due to the formation of adipocytes from mesenchymal stem cells (MSC) at the expense of osteoblasts, and this adiposity is also connected to the prevalence of bone fracture in osteoporosis [43].

Associated with these bone features, post-menopausal women display body weight gain which preferentially affects the visceral (or intra-abdominal) fat depot associated with a transition of body distribution from a gynoid to an android type [53–55]. This shift in fat mass distribution favors the development of insulin resistance, which leads finally to pancreatic abnormalities, and is associated to a change in the secretion of various adipokines involved in bone turn-over. It is demonstrated that a negative correlation exists between bone and body fat mass, suggesting that obesity represents a risk for osteoporosis [40, 56, 57]. Moreover, visceral adipose tissue increase seems detrimental for bone mineral density in premenopausal obese women [58–61]. It is accepted that hypogonadism also induces adiposity in males, but the specific relation with visceral adiposity is less important [62, 63]. Finally, hormonal disturbance found in men and women can be considered at the onset of osteoporosis, adipose tissue is linked to the development of this pathology as it is a secretory organ [39].

On the one hand, evidence has shown that osteoblasts act in an endocrine fashion by the production and secretion of factors which are able to alter distant tissue function [64]. Osteocalcin, is an interesting endocrine factor produced by osteoblasts, as it seems to play an important role in energy metabolism. Mice lacking osteocalcin in the osteoblast lineage display decreased pancreatic β -cell proliferation and insulin secretion and increased adiposity. Moreover, uncarboxylated osteocalcin is able to

stimulate production of adiponectin by adipocytes, which favors insulin sensitivity [47, 65].

On the other hand, adipose tissue is known to exert endocrine function with secretion of adipokines and steroids, both of which are involved in bone homeostasis. Adipocytes from bone marrow secrete adipokines which can act in a paracrine manner. Leptin, a well-known adipokine, has been extensively studied in relation to bone. Leptin regulates osteoclast development and the production of osteoclast and osteoblast growth factors [66]. Thus its combined effects on bone formation and resorption defined leptin as a major participant in bone development, and alteration in its plasmatic and marrow level may affect bone homeostasis. Adiponectin increases osteoblasts differentiation and inhibits osteoclastogenesis and osteoclast activity, leading to an increased bone mass in mice [67]. The fact that adiponectin circulating levels are reduced in obesity can link fat mass increase to bone loss in this situation.

Other tissues, peripheral or central, can act as intermediate between bone and fat, and especially the pancreas which is modulated by adipokines and secretes endocrine factors, i.e. preptin and amylin, known to modulate bone turn-over (for review see [68]).

Altogether these observations demonstrated the existence of an active crosstalk between i) adipocyte and osteoblast, and ii) adipose tissue and the skeleton and constitutes a homeostatic feedback system with adipokines and bone derived molecules, controlling the fine balance between the two pathways is of clear therapeutic significance [1, 45, 69]. In the search for pathways regulating this crosstalk, OT was discovered as a major contributor [4, 5, 15, 70]. Indeed, OT promotes the formation of osteoblasts *in vitro* at the expense of adipocytes, as well as preventing and reversing osteoporotic and obese phenotype *in vivo*.

OT regulates osteoblast/adipocyte balance

It has been shown that OT (OT^{-/-}) and OTR (OTR^{-/-}) knockout mice develop osteoporosis [3, 5, 15]. The observed defect in bone formation, associated with a decrease in osteoblast differentiation could be normalized by an intra-peritoneal injection of OT [5]. It is worth noting that haploinsufficient OT or OTR mice (OT^{+/-}, OTR^{+/-}) develop osteopenia whereas milk let-down remains normal [5]. Furthermore, OT^{-/-} mice become obese without hyperphagia and present a low sympathetic tone [71, 72].

In vitro studies

OTR is expressed by various cells including adipocytes, osteoblasts and osteoclasts. It has been shown that OT is able to induce the proliferation of human osteoblast-like cells [73] and inhibit the adipogenesis of the preadipocyte cell line 3T3-F442A [74]. Indeed, as osteoblasts and adipocytes share the same progenitor, i.e. MSC isolated from different tissues, analysis of the early step of commitment to either lineage has demonstrated that OTR expression was differentially expressed with high levels in osteoblasts [75]. Moreover, treatment of adipose-derived MSCs during differentiation with OT or a stable analog, carbetocin, enhanced osteogenesis at the expense of adipogenesis [4]. Interestingly, in the presence of a combined adipogenic/osteogenic medium, cells within a single culture dish differentiated into the two cell types. Their proportion was then altered in the expected way (adipogenesis down and osteogenesis up) when cells were chronically treated by OT or carbetocin, demonstrating a direct role of this hormone in the adipocyte/osteoblast balance [4]. Bone marrow-derived MSCs exhibit similar observations in agreement with the invasion of bone marrow by adipocytes at menopause.

The mechanisms involved in the OT pathway and governing this balance are not known yet. Nevertheless, studies on adipocyte or osteoblast showed that OT is able to induce an intracellular Ca²⁺ rise in these two type of cells. Indeed, OTR activation in osteoblast triggers increased intracellular Ca²⁺ concentration [76]. Furthermore, it is well known that OT is involved in PIP2 breakdown in adipocyte, allowing the activation of Ca²⁺-dependent pathway [77, 78]. This increased intracellular Ca²⁺ levels induces a transient phosphorylation of ERK1/2, reported also in committed mesenchymal progenitors treated with OT [4]. These data are consistent with observations showing that activation of the Ca²⁺-ERK1/2 pathway leads, on the one hand, to phosphorylation of core-binding factor subunit alpha-1 (CBFA1), the osteoblast differentiation key transcription factor also known as runt-related transcription factor 2 (RUNX2), which enhances osteogenesis [79], and on the other hand, to phosphorylation of peroxisome proliferator-activated receptor γ (PPAR γ), the adipocyte differentiation master gene, which inhibits its adipogenic activity (Figure 2) [80, 81].

Recently an original alternative pathway has been described that might explain the OT action in osteogenesis [82]. As described for some other GPCRs, OTR can be internalized after activation by OT and translocated to the nucleus. This internalization is dependent on the β -arrestin1 pathway without affecting the ERK1/2 pathway.

Figure 2: OT signaling in adipocyte/osteoblast balance. MSC, Mesenchymal stem cell.

The involvement of this pathway in the adipocyte/osteoblast balance is not yet elucidated and further analyses are required. Of note, β -arrestin1 is a negative modulator of adipogenesis through its direct interaction with PPAR_{γ} [83] suggesting a critical role of β -arrestin1 in the adipocyte/osteoblast balance.

In vivo studies

Transcription of OT and its receptor are up-regulated by estrogens. Menopause is accompanied by decreased estrogen production and often associated with osteoporosis and very often increased fat mass. Menopause is one of the critical periods of a woman's life during which body weight gain and onset or worsening of obesity are favored [84–87]. It is at this period of hypo-estrogenism that obesity prevalence is at its highest whereas aging favors also have a positive energy balance. This body weight gain is related to adverse health effects that worsen due to changes in fat distribution observed during menopause, i.e. increased visceral adiposity [55]. This increase favors the development of insulin resistance and its clinical outcomes such as carbohydrate metabolism impairments and type 2 diabetes, hypertension and dyslipidemia, leading to increased cardiovascular risks, and cancer among other diseases [88]. The use of estrogens has been shown to normalize visceral fat mass in both animals and humans [85, 89–91]. However, the diverse effects of estrogens on non-fat organs hamper the possibility of using this

hormone therapeutically as many controversial studies have been reported, in which hormonal substitutive therapy may lead to cardiovascular diseases and breast cancer [92–95]. Whereas most of osteoporosis treatments target bone resorption by inhibiting osteoclast formation and activity, only a few promote bone formation [96–98]. Therapies developed to treat bone diseases in humans are considered to be either anti-resorptive (including estrogen, bisphosphonates, selective estrogen-receptor modulators, calcitonin, vitamin D), anabolic (parathyroid hormone) or both (strontium ranelate) [51, 99, 100]. For most of these treatments, if not all, side-effects have been reported, i.e. osteonecrosis of the jaw, atypical fractures of the femur, dysphagia, esophagitis, headache, nausea, arthralgia and dizziness among others [101–103]. Identification of such drugs would enable the development of alternative and/or complementary treatments. As mentioned above, in addition to bone loss, osteoporosis is associated with an increased bone marrow adiposity leading to the formation of adipocytes at the expense of osteoblasts leading bone to be prone to fractures [104].

Besides exercise and food restriction, there is no efficient treatment to prevent body weight gain and fat mass redistribution at the onset of menopause, whereas substitutive hormonal treatment may lead to side effects on a long-term basis, hence the need for more targeted therapies. The normalization of body weight gain and the prevention of redistribution of body fat during menopause is a major health issue that would prevent the appearance of various symptoms of the metabolic syndrome. As estrogen levels are decreased in ovariectomized (OVX) mice or rats (a situation mimicking the transition to menopause in women) and in postmenopausal women, OT levels were expected to be decreased in both cases. Indeed, plasma OT levels were lower in OVX mice and rats compared to sham-operated controls [4]. Daily subcutaneous OT injection for 8 weeks reversed bone loss in OVX mice by improving bone microarchitecture and biomechanical strength and reduced bone marrow adiposity. This effect of OT was effective in a preventive as well as in a curative manner [2]. Interestingly, body weight gain, fat mass redistribution and bone marrow adiposity were normalized upon OT treatment of OVX mice [2].

The action of OT on bone mass is primarily associated with normalization of the osteoblast/osteoclast ratio due to an increased differentiation of osteoblast and modulation of osteoclast formation and function [2, 5]. In addition to a decrease in bone marrow adiposity due to its effect on adipocyte/osteoblast balance, OT induced body weight loss and reduction of visceral adipose tissue mass in OVX mice which could be due to changes in metabolic

pathways. Analysis of different parameters of energy balance showed that OT treatment induced a switch favoring a preferential use of lipids rather than carbohydrates [2]. Promoting the utilization of fatty acids within the fat cells is a way to limit their release into the bloodstream and thereby to alleviate their systemic side effects. Furthermore, it has recently been shown that a novel pathway by which cardiac natriuretic peptides, through its receptor NPRA, cGMP and PKG can activate p38 α MAPK to increase mitochondrial biogenesis and uncoupled respiration [105]. Importantly, it has been shown that ANP and β -adrenergic agonists can act together in an additive manner to more robustly promote brown adipocyte features and functions. These observations might support the concept of cardiac natriuretic peptides as cardiometabolic hormones that are able to turn on the machinery characteristic of brown fat thermogenesis in human and mouse adipocytes. Thus cardiac natriuretic peptides together with catecholamine may modulate energy expenditure to regulate the distribution of body fat and lean mass with a relevant role in controlling cardiovascular risk and potentially inducing beneficial metabolic effects in the cardiometabolic patients [105]. Of note, perfusion of female rat hearts with OT resulted in a significantly stimulated ANP release [37]. As chronic BNP perfusion in mice has an enhancing effect on oxygen consumption and the expression of brown adipocyte markers in adipose tissue, it is tempting to postulate that ANP might be involved in the effects of OT. Thus, the hypothesis that OT treatment, through ANP secretion, participate to an increased lipolysis or in the conversion of mature white adipocytes into fat-burning cells cannot be excluded.

Anti-obesity effects of OT given either centrally or peripherally have been reported using diet induced obese rats. Indeed, high fat diet induced obese rats that received OT loose body weight and fat mass through the activation of PPAR α pathway, increased lipid utilization and decreased food intake [70, 106, 107]. OT treatment, intraperitoneal injection, induced a decreased food intake and body weight in diet induced obese rats [108]. Interestingly, OT beneficial effects on body weight reduction can be observed in mice and rat but also in other animal models such as rabbits as OT treatment was sufficient to eliminate glucocorticoid-induced marrow adiposity [109].

In orchidectomized mice (animal model of hypogonadism in male) OT treatment normalized fat mass and its redistribution as it did in female mice; however, OT treatment did not normalize bone defects. Altogether, these observations indicate that OT affects bone physiology only in females and fat physiology in both genders [110].

OT circulating levels

Several reports analyzed circulating levels of OT, it appears that the levels are not in agreement with OTR affinity and that an extraction step is mandatory before measurements [111]. Circulating levels of OT are reported to be associated with the development of bone and fat mass defects.

Indeed, OT plasma levels were correlated with the development of osteopenia or osteoporosis in a small and confirmed in a large postmenopausal women cohort [4, 112, 113] where higher OT levels were associated with higher bone mineral density. These data are in agreement with previous observations reported in mice and rats [4]. It has been suggested that the decreased OT levels associated with overweight and obesity can be associated with an increased rate of OT degradation due to oxytocinase activity [114].

However, for men, in agreement with the lack of effects of OT on osteoporotic male mice, OT levels were not linked to bone mineral density, bone turnover rate, or prevalent fractures [115].

Conclusion

It is now well established that OT plays an important role in the control of energy metabolism [116]. Moreover, reports are in favor of a crucial role of OT in humans as OT treatments allow a decreased food intake and lower OT levels in obese and diabetic patients [117–120]. Given the relationship between adipocyte and osteoblast, OT is clearly controlling the fine balance between these two types of cells. Collectively, these observations indicate that OT plasma levels represent a novel diagnostic marker for bone and fat related disease and that OT administration holds promise as a potential therapy to combat

Figure 3: Schematic representation of the effects of OT on adipose and bone tissues leading to reduction of osteoporosis, obesity and associated metabolic disorders.

osteoporosis, overweight, obesity and associated diseases such as diabetes and cardiovascular disorders (Figure 3). Further studies, including large human cohorts, are required and will shed some light on the clinical efficiency of OT. As it is well known that OT half-life is very short, characterization of stable OT analogs, harboring extended half-life, such as carbetocin [121] or conjugated OT [122] is of high importance for an efficient treatment. Alternatively, it is well established that oxytocinases are very active; an approach consisting in the development of oxytocinase inhibitors represents a potential therapeutic option.

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