The parathyroid hormone circadian rhythm and its role in bone metabolism

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SOUHRN

Luchavová M., Zikán V.: **Cirkadiánní rytmus parathormonu a jeho role v kostním metabolizmu**

Cirkadiánní rytmus parathormonu (PTH) je dobře dokumentován u zdravých jedinců. Nicméně role tohoto rytmu v kostním metabolizmu a faktory ovlivňující fyziologii rytmu je potřeba objasnit. Základní rytmus PTH je endogenní a vnější faktory, jako např. nutriční, endokrinní nebo neurální vlivy mohou modulovat jeho amplitudu. U žen s postmenopauzální osteoporózou byl cirkadiánní rytmus PTH oploštěný a byly pozorovány další abnormality v sekreci PTH. Obnova endogenního rytmu PTH pomocí úpravy hormonálního prostředí a/nebo úpravy diety s podáváním vápníku a fosfátů v závislosti na rytmu PTH, může příznivě podporovat stimulaci kostní novotvorby. Také kalcilytika, která nabízejí nový přístup k léčbě osteoporózy, mohou pro svoji optimální účinnost vyžadovat podávání v závislosti na endogenním cirkadiánním rytmu PTH.

Klíčová slova: parathormon, cirkadiánní rytmus, osteoporóza, endokrinopatie, kalcilytika

SUMMARY

Luchavová M., Zikán V.: **The parathyroid hormone circadian rhythm and its role in bone metabolism**

The circadian rhythm of parathyroid hormone (PTH) is well established in healthy subjects; however, its role in bone metabolism and factors controlling its physiology need to be clarified. The underlying rhythm of PTH is endogenous and external factors such as nutritional, endocrine or neural factors can modulate its amplitude. In postmenopausal osteoporosis, the circadian rhythm of PTH is blunted and abnormalities in the PTH secretion pattern are observed. Restoration of endogenous PTH rhythm by modifying the hormonal environment or nutritional manipulation using timed calcium and phosphate loads may be important for stimulation of bone formation. Also calcilytics, which offer a novel approach to the treatment of osteoporosis, may require timed dosage respecting the endogenous circadian rhythm of PTH for their optimal use.

Keywords: parathyroid hormone, circadian rhythm, osteoporosis, endocrinopathies, calcilytics

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Introduction

Parathyroid hormone (PTH) is main polypeptide hormone that regulates plasma calcium and phosphate homeostasis and bone remodeling. The parathyroid gland secretes PTH in response to very small decrements in blood ionized calcium in order to maintain the normocalcaemic state. The plasma membrane of parathyroid cells contains high levels of the calcium sensing receptor (CaR), which plays a central role in the control of PTH secretion. In healthy individuals, PTH is secreted in a tonic pattern of constant secretion and in pulses which recur every 8.5 min (range, 5–12 min) [Fig. 1]. In addition to pulsatile secretion, circadian variation in PTH secretion was demonstrated as early as the 1970s [2]. Most recent studies measuring intact PTH 1–84 have confirmed biphasic rhythm with a small but significant increase between 04:00 p.m. and 07.00 p.m. and a larger broader increase in PTH between 02:00 a.m. and 06:00 a.m. and a nadir occurring at approximately 10:00–11:00 a.m. [Fig. 2]. Although PTH rhythm is in synchrony with serum calcium, phosphate and bone turnover markers [4]; the physiology of the rhythm is not fully understood. It has been demonstrated that a large component of PTH rhythm is endogenous [3] and the amplitude of the rhythm is controlled by various exogenous factors, such as dietary factors [5,6,7] and endocrine, neuroendocrine or neural factors [8,9,10]. PTH increases in advancing age; however, most studies assessing PTH in relation to bone metabolism evaluated PTH only in the morning blood collection. The blunting of the nocturnal peak of PTH levels has been observed in women with postmenopausal osteoporosis [11,12] and abnormalities in endogenous PTH rhythm were documented in some endocrine diseases such as primary or secondary hyperparathyroidism, acromegaly and adult growth hormone deficiency [13]. Once-daily PTH injections are superior to constant long-term (24 h) infusion in stimulating bone formation. Therefore, there is a possibility that restoration of endogenous PTH rhythm by modifying the hormonal environment and/or nutritional factors may have an importance for stimulation of bone formation. This review summarizes the known abnormalities of the PTH circadian rhythm and analyzes possible factors that regulate its circadian variability.

Effects of parathyroid hormone on bone remodeling

In addition to regulation of calcium homeostasis, PTH is also main hormone controlling bone remodeling [14]. Exogenous administration of PTH increases the rate of bone remodeling, but it can result in either loss or gain of bone mass depending on the balance between formation and resorption. It is well known, that pulsatility in hormone secretion can modulate target organ responsiveness. Continuously elevated concentration of PTH results in a loss of responsiveness (desensitization) of bone cells to PTH action and intermittent administration of PTH could allow resensitization of the PTH receptors. Administration of PTH intermittently produces a marked anabolic response of the skeleton. The exposure to PTH is within 2–3 hours after PTH 1–34 administration. In contrast, PTH given by continuous infusion at doses that were anabolic when given once by daily injection induced high bone resorption and hypercalcaemia. In patients with primary hyperparathyroidism continuously elevated PTH is associated with hypercalcaemia and bone loss, especially in cortical bone.

Figure 1
Ultradian rhythm of PTH. Minute- to-minute PTH concentration time profile in one subject.
Adapted according to Schmitt CP et al. [1].

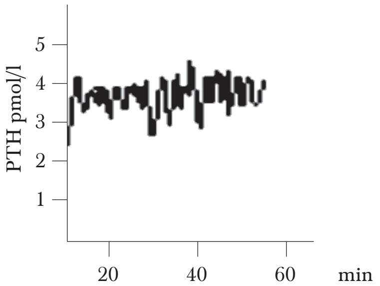
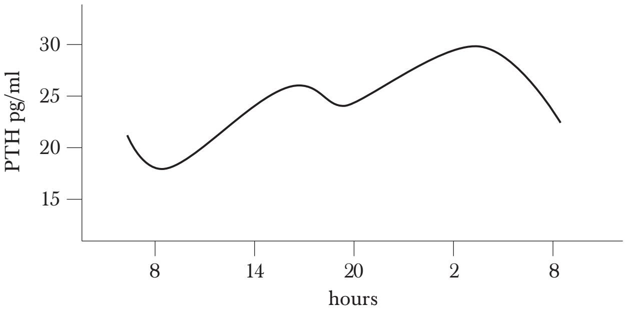


Figure 2
Circadian rhythm of PTH. Estimated population mean rhythm curve for plasma PTH. Adapted according to El-Hajj Fuleihan G. et al. [3].



At the cellular level PTH can activate the bone remodeling cycle by increasing receptor activator of nuclear factor B ligand (RANKL) from osteoblasts. RANKL increases osteoclast activity and osteoclastogenesis. OPG act as a decoy receptor for RANKL and prevents osteoclastogenesis and bone resorption by inhibiting RANKL-RANK interaction. It has been shown that subcutaneous administration of human PTH (1–38) in rats induce a transient decrease in OPG mRNA in bone. On the contrary, the continuous administration of human PTH (1–38) is associated with long-term inhibition of OPG secretion and lasting stimulation of RANKL production [15]. More recently, OPG has been shown to demonstrate a circadian rhythm in healthy subjects with a daytime increase and nocturnal decrease [4]. OPG secretion was inversely related to PTH and bone resorption marker (beta CTX) over a 24 h period. Interestingly, in postmenopausal women, the temporal relationship between PTH and OPG was altered and significantly greater nocturnal decline in serum OPG was observed when compared with healthy premenopausal women or elderly men [4]. Authors suggested that higher nocturnal increase in bone resorptive activity in postmenopausal women is related to greater decrease of OPG concentration. Circadian changes in serum OPG in subjects with osteoporosis have not been published.

Factors controlling the circadian variability of PTH

Nutritional factors

Acute fasting abolished the PTH circadian variability [7] as well as circadian rhythm of bone resorption marker [16]. In humans, studies measuring biochemical markers of bone resorption and PTH showed that evening calcium (Ca) supplementation (1000 mg at 23 h for 14 days) blunted the nocturnal increase in PTH as well as nocturnal increase in bone resorption marker (urine deoxypyridinoline and NTX). In contrast, morning Ca supplementation had no significant effect on overall daily excretion of bone resorption marker [5]. These data showed that timing of Ca ingestion may be important to influence PTH rhythm and its effects on bone resorption. Bed-time calcium load can be useful to decrease nocturnal calcium wasting. But these results do not mean that each pattern of nocturnal increase in PTH is deleterious for the bone, because the nocturnal PTH peak seems to be useful to decline night-time urinary calcium excretion and inefficient renal calcium conservation at night may contribute to the osteoporotic process. Fraser et al. showed that the circadian rhythms for serum phosphate and PTH are very similar to the acrophase for serum phosphate which precedes that for PTH [7]. Postmenopausal osteoporotic women showed a blunting of their nocturnal serum phosphate and PTH increases. However, the cause of the blunted phosphate and PTH response to nocturnal fasting is unknown. It has been hypothesized that the administration of phosphate load at night-time to stimulate PTH increase and calcium given in the morning may restore the endogenous PTH circadian rhythm [13]. However, no long-term study proving this approach has been published yet. Silverberg et al. studied oral phosphate administration for 5 days in healthy postmenopausal women and in osteoporotic women and young healthy individuals [17]. In osteoporotic women, the age-appropriate rise in PTH was not observed when compared to healthy postmenopausal women and 1,25 $(OH)_2$ D_3 production decreased. The cause of this blunted PTH response after oral phosphate administration in osteoporotic women is unknown. The results support the hypothesis of abnormal PTH responsiveness in osteoporosis [18]. On the other hand, there is a possibility of suppression of parathyroid gland activity due to a non-parathyroid mechanism [18].

Endocrine factors

The abnormalities in the PTH circadian rhythm or its pulsatile secretion abnormalities in endocrinopathies are reviewed in Table 1.

Hyperparathyroidism

The alteration in PTH variability is caused by changes in hormone secretion and in hormone synthesis. The rhythm is altered in atrophic or hypertrophic gland. Changes in secretion, e.g. ectopic secretion, cause changes in frequency, shift in secretion peak, lost of the rhythmicity. Patients with primary hyperparathyroidism lose the circadian rhythm for PTH, which is restored after adenoma removal [19]. In addition, the lost of circadian rhythm of PTH was documented in patients with pseudohypoparathyroidism [20]. Secondary hyperparathyroidism is characterized by proportional increases in both the pulsatile and tonic secretion components and glomerular filtration rate dependent decrease of metabolic hormone clearance, which accounts for a two- to threefold increase of mean plasma PTH [21]. Age-related increases in serum PTH concentrations, which are observed both in men and in women, may contribute to the increase of bone resorption [22] and cortical bone loss. It is assumed that vitamin D deficiency, impaired renal 1α hydroxylase activity and low calcium absorption may contribute to the secondary hyperparathyroidism of aging. Ledger et al. showed that elderly women had an exaggerated response to EDTA induced hypocalcaemia and also had a higher non- suppressible component of PTH secretion [23]. Interestingly, these abnormalities disappeared after 1 week of 1.25-dihydroxyvitamin D_3 therapy. Changes in PTH circadian rhythm or its pulsatile secretion has not been studied in vitamin D deficiency.

Sex hormone deficiency

Estrogen deficiency in menopause is a major cause of osteoporosis in women. Estrogen acts to maintain the appropriate ratio between bone-forming osteoblasts and bone-resorbing osteoclasts. In addition, estrogen improves calcium balance through effects on intestinal and renal calcium handling. It has been postulated that estrogen deficiency along with vitamin D deficiency, impaired renal 1α hydroxylase activity and low calcium intake may contribute to the secondary hyperparathyroidism in elderly. No age-related increases in serum PTH was observed in postmenopausal women who had been on long-term estrogen therapy [24].

Table 1

Changes in PTH circadian rhythm or its secretory dynamics and skeletal sensitivity to the effects of PTH in endocrine abnormalities

Hormone	Bone sensitivity to PTH	PTH secretory dynamics	PTH circadian rhythm
Growth hormone/IGF-1	Decreased in deficiency [34] Increased in excess [33]	Altered in excess [32]	Altered in deficiency [34] Altered in excess [33]
Estradiol	Increased in deficiency [25]	E2 – reduces pulsatility [46]	Altered in women with postmenopausal osteoporosis [12,11]
Testosterone	Increased in deficiency [25]	Not tested	Not tested
Cortisol	Decreased in excess [36]	Increases pulsatility [35]	Not tested
Trijodthyronine	Decreased in deficiency [42]	Not tested Lower PTH in excess, higher in deficiency [42]	Not tested
Prolactin	Not tested	Not tested Higher PTH in excess [48]	Not tested
$1,25(OH)_2D_3$	Decreased in deficiency	Not tested; Altered response to acute changes in serum calcium in deficiency [23]	Not tested
PTH	Not tested	Altered in PHPT [28]	Lost in PHPT [19]
Calcitonin	Increased in deficiency (*)	Not tested	Not tested

Abbreviations: *in animal models [48], not tested in human; PTH: parathyroid hormone; PHPT: primary hyperparathyroidism; E2: estradiole; IGF-1: insulin-like growth factor

Both estrogen and testosterone deficiency have been shown to increase skeletal sensitivity to PTH [25]. Ledger et al. showed that in elderly women suppression of PTH secretion (by 24 h calcium infusion) resulted in a greater decrease in bone resorption markers than that found in young premenopausal women [22]. By contrast, bone resorption decreased to a greater extent in the younger men (age 40–50 years) as compared to the elderly men (age 70–78 years) [26]. Authors indicated that elderly men have only partial sex steroid deficiency and therefore, in contrast to elderly postmenopausal women, appear to be relatively protected against the bone resorbing effects of the age-related increase in serum PTH. The circadian rhythm of serum intact PTH differed between the sexes, with an earlier and greater increase at night in men [27]. In postmenopausal osteoporotic women, the further blunting of nocturnal increase in PTH levels was observed [11,12]. In fact, in postmenopausal osteoporotic women PTH levels decreased during the period between 10:00 p.m. and 7:00 a.m. [12]. It has been reported that the blunting of nocturnal PTH peak resulting in the inefficient renal calcium conservation during the night could contribute to the bone loss [11]. Whether sex steroid replacement can restore the circadian rhythm of PTH in osteoporotic men and women has not been investigated. In another study, Harms et al. reported that estrogen replacement therapy decreases PTH pulsatility in postmenopausal women [46].

GH-IGF-1 axis

Growth hormone (GH) production peaks during the first two hours of sleep. The production drops by sleep deprivation. GH is known to play an important role in bone metabolism. There is an evidence, that GH may have a regulatory role in PTH secretion and full anabolic effect of PTH on bone may require the action of GH/ insulin like growth factor – 1 (IGF-1) system [29,30]. Acromegaly is associated with skeletal changes characterized by appositional bone growth, increased bone dimensions and increased bone turnover [31]. A correlation between PTH concentration and bone turnover markers in active and treated acromegaly has led to the suggestion that the effect of GH/IGF-1 system on bone turnover may be mediated by PTH. Active acromegaly enhances spontaneous PTH pulsatility by increasing the PTH puls half-duration and increasing the PTH puls mass [32]. Biochemical cure of acromegaly resulted in increased levels of PTH and decreased levels of nephrogenous cAMP (a marker of PTH renal activity), serum calcium and bone turnover markers concentrations [33]. These results suggest reduced PTH target-organ sensitivity. Adult growth hormone deficiency (AGHD) is associated with bone insensitivity to PTH and abnormal PTH circadian rhythm. Typical is the reduction of bone turnover and increased prevalence of osteoporosis. GH replacement therapy restores bone sensitivity to PTH and enhances PTH circadian rhythm with subsequent changes in bone turnover, Ca, and PO_4 metabolism resulting in BMD increase in AGHD patients [34]. Recently, Joseph et al. showed that decrease in GH/IGF-1 with aging may contribute to the PTH rhythm abnormalities and to the decreased effects of PTH on bone and renal cells in postmenopausal women with osteoporosis [8]. Moreover, the study of Joseph et al. showed that GH treatment decreased PTH circulating levels, restored the circadian rhythm of PTH and resulted in increased sensitivity to the effects of PTH with the increases in bone remodeling markers as well as urinary cAMP excretion [8]. However, whether changes in PTH rhythm are causative or create a response to the pathology needs to be investigated.

Hypercortisolism

The central mechanism of bone loss in glucocorticoid induced osteoporosis is reduced bone formation, due to actions that affect cells of the osteoblastic lineage. Glucocorticoids (GCs) have also indirect actions on bone. The hypothalamic-pituitary – gonadal axis and growth hormone – IGF-1 axis are decreased by GCs. Moreover, GCs may affect spontaneous PTH secretory dynamic, with a reducing the tonic release of PTH and an increase in its pulsatile secretion [35]. The abnormalities in PTH secretory dynamic may reflect either direct or indirect effects of GCs on the parathyroid glands or effects at the level of bone cells activity. The exogenous intermittent PTH treatment in patients treated with low dose GCs treatment resulted in a partial inhibition of the PTH-induced increase in bone formation [36]. The decrease in bone responsiveness to PTH may be partially explained by the alteration of GH-IGF-1 axis by GCs. Indeed, GH administration can reverse some of the negative effects of chronic GCs treatment on the bone metabolism [37]. In addition, abnormalities in endogenous GH secretion may change PTH rhythm [38]. It has been hypothesized that secretory dynamics of PTH could reflect effects at the level of bone metabolism with signals generated from bone to the parathyroid [35]. Signals generated from bone to parathyroids are not well known. Recently, FGF-23 which is synthesized in osteocytes was able to suppress PTH secretion and PTH gene expression in rats [19]. More recently, Samadfam et al. showed that osteoblastic bone formation is a potent modulator of FGF-23 production and release into the circulation [40]. As GCs have pro-apoptotic effects on osteoblasts and osteocytes, it is tempting to speculate that GCs could change FGF-23 production and abnormalities in FGF-23 secretion can influence the PTH secretory dynamic; however, further investigation is necessary to test this hypothesis.

TSH-thyroid hormone axis

Thyroid hormone increases bone remodeling, both osteoblast and osteoclasts activity are increased, by elevated levels of thyroid hormone. The osteoporosis associated with hyperthyroidism is traditionally viewed as secondary consequence of altered thyroid function. However, there is the evidence, that TSH has direct effect via the TSH receptor found on osteoblast and osteoclast precursors and low levels of TSH causes decrease of BMD. A mild hypercalcaemia with lowered PTH secretion was observed in hyperthyroidism [41]. In addition the circadian rhythm of bone resorption markers has been lost in some patients with thyrotoxicosis [13]. In contrast, primary hypothyreosis results in decrease in bone remodeling. Bone sensitivity to hypocalcemia is lowered and basal PTH secretion is increased [42]. The changes in pulsatile or circadian PTH variability have not been studied in patients with hypothyreosis.

Neuroendocrine and neural regulation

Although dietary and endocrine factors are most relevant candidates for the regulation of PTH rhythm, neural and/or neurohumoral regulation cannot be dismissed. In this regard the relationship between prolactin and PTH secretion has been studied. Prolactin secretion provides a significant circadian variability and prolactin can directly stimulate PTH secretion in vitro [43]. Logue et al. found a strong correlation between endogenous PTH secretion and prolactin levels, with changes in PTH preceding prolactin peak by 2 hours [19]. However, this relationship was abolished by an acute sleep shift [9]. No other clinical studies, such as the PTH variability in patients with prolactinomas have been conducted.

Schmitt et al. showed that sympathetic nervous system has a modulating effect on pulsatile PTH secretion as selective –1 adrenergic blockade acutely increased plasma PTH by augmenting the mass of hormone secreted per burst, but it did not alter the rhythmicity of pulsatile PTH release [44]. In uremic patients after total parathyroidectomy and heterotopic auto transplantation of parathyroid tissue, oscillatory PTH secretion is transiently lost but recovers within months, compatible with functional re-innervations of the auto transplanted tissue [40]. Therefore, there is a possibility that neural regulation can play a role in the regulation of PTH secretory pattern. It has been shown that sympathetic stimulation provides a circadian rhythmicity to bone mass by interacting with the clock genes Per and Cry in osteoblast [45]; however whether neural regulation also regulates the clock genes in parathyroids needs to be clarified.

Conclusion

The circadian rhythm of PTH in healthy human subjects is clearly established; however, factors controlling the physiology of the rhythm and its effects on bone metabolism need to be investigated. Alterations in endogenous PTH circadian rhythm and its secretory dynamics have been observed in women with postmenopausal osteoporosis and in patients with some endocrine abnormalities. Hormones may influence the bone sensitivity to the effects of PTH and/or PTH secretory pattern. The blunting of the circadian rhythm of PTH may results in a loss of responsiveness (desensitization) of bone cells to PTH and that this, in turn, results in stimulation of bone resorption and cortical bone loss. However, whether changes in PTH rhythm are causative or create a response to the pathology needs to be clarified. Intermittent PTH administration is a powerful osteoanabolic therapy. In contrast continuous PTH administration or endogenous PTH excess results in a bone loss. Therefore, there is a possibility that also endogenous PTH circadian variability or its pulsatile secretory pattern might be important for stimulation of bone formation. Restoration of bone sensitivity to the effects of PTH by modifying the hormonal environment and/or nutritional manipulation by using timed calcium and phosphate loads may be another approach to the treatment of osteoporosis. Calcilytic compounds, new pharmacological agents, offers a novel approach to the treatment of osteoporosis and their optimal use may require timed dosing respecting the endogenous circadian rhythm of PTH.

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