

Special Article

The parathyroid glands — Two centuries of research at the service of clinical practice

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Abstract

The discovery of the parathyroid glands and, years later, their therapeutic potential represents an outstanding example in the history of medicine of the role of basic research in shaping clinical practice. It is an excellent example because it is a subject that has been marked by conflicting interpretations, controversies, and failed trials, until reaching the point where, in 2002, the U.S. Food and Drug Administration (FDA) approved the use of the 1-34 fragment of human parathyroid hormone (hPTH) for the treatment of osteoporosis in men and postmenopausal women at high risk of fracture. From that moment onward, its use became widespread and consolidated in routine clinical practice. However, reaching this point was far from straightforward.

Over nearly 200 years, through successive observations carried out both in the laboratory and in the clinical setting, it has been possible to achieve a comprehensive understanding of the true function of an organ that was initially poorly understood. In this paper, I aim to briefly explain and review the most significant historical milestones in the understanding of the parathyroid glands and their hormone, as well as their subsequent clinical application.

This chapter in the history of medicine deserves to be remembered, as it clearly illustrates the collective learning process and how the accumulation of observations, followed by reflection, debate, and constructive discussion, leads to deeper knowledge of phenomena and realities that were previously little known or entirely unknown. Knowledge from which—clearly demonstrated in this example and readily extrapolated to many others—society ultimately always benefits.

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The parathyroid glands are small structures approximately 4 mm in diameter, usually located on the posterior aspect of the thyroid gland. The term used to define them is not entirely precise, as they may occasionally be intrathyroidal or extrathyroidal and can even be found far from the thyroid region, such as in the mediastinum. Perhaps for this reason, they were among the last organs to be discovered. Richard Owen (Fig. 1) was the first to identify them in 1850, not in humans but in a rhinoceros during an autopsy performed at the London Zoo (1). The existence of parathyroid glands in other mammals and in humans was established 30 years later, largely thanks to the work of Rudolf Virchow and Ivar Viktor Sandström (2) (Fig. 2).



Figure 1. R. Owen 1804-1892 (Source: Wellcome Collection. Public domain).



Figure 2. R. Virchow 1821-1902 (Source: Karl Virchow. Photograph by J. C. Schaarwächter, 1891. Wellcome Library, London; CC BY 4.0).

Their true function, however, remained unknown for some time. For years, anatomists believed that these glands were merely remnants of embryonic thyroid structures without any specific function.

At the end of the 19th century, studies by the French physiologist Marcel Eugène Émile Gley (Fig. 3) helped clarify the possible role of these thyroid remnants. He observed that animals developed tetany and died after inadvertent removal of the parathyroid glands during thyroid excision (3).

Gley mistakenly attributed this phenomenon to the absence of the thyroid gland together with the presumed embryonic remnants. It would take another decade for the Austrian pathologist Jakob Erdheim (Fig. 4) to provide the missing information. Erdheim demonstrated that animals developed postoperative

tetany after thyroidectomy only when all parathyroid glands were also removed (4). Based on this evidence, he concluded that tetany was due to the absence of the parathyroid glands.

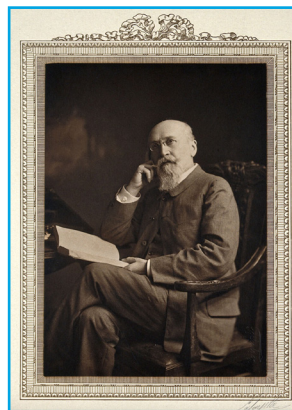


Figure 3. M. E. E. Gley 1857-1930 (Source: Wellcome Collection. Public domain).

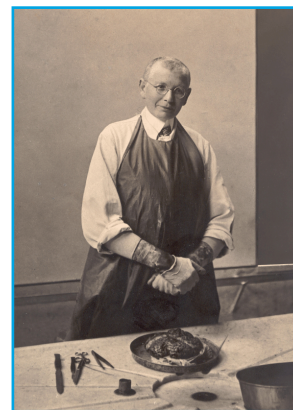


Figure 4. J. Erdheim 1874-1937 (Source: Jakob Erdheim, Wikipedia/Wikimedia Commons).

By that time, numerous studies had demonstrated the relationship between calcium salts and excitability of the central nervous system. William George MacCallum (Fig. 5) and Carl Voegtlin (Fig. 6) interpreted tetany as an expression of hyperexcitability and investigated the effects of calcium salts in this context. They observed that calcium infusions prevented tetany in parathyroidectomized animals. Thus, early in the 20th century, it became established that the metabolic alteration underlying tetany was hypocalcemia and that the function of the parathyroid glands was related to maintaining calcium homeostasis (5).

Nevertheless, the idea that tetany should be treated with calcium infusions had many detractors, sparking



Figure 5. W. G. MacCallum 1874-1944 (Source: Wellcome Collection. Public domain).

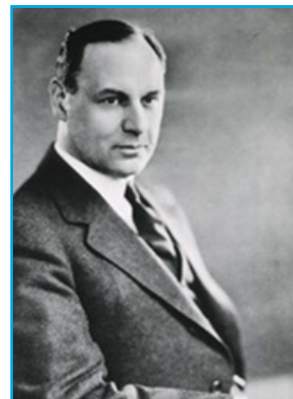


Figure 6. C. Voegtlin 1879-1960 (Source: Carl Voegtlin, Wikipedia/Wikimedia Commons).

an intense debate that lasted for decades. One reason for the controversy was that this approach conflicted with the emerging principle of organotherapy, which held that symptoms resulting from the absence of a gland should be reversed by administering extracts of that gland.

As a result, many researchers began administering infusions of parathyroid gland extracts prepared in their own laboratories. This approach was heavily criticized, partly with justification, as these preparations were not always as effective as calcium infusions. However, the controversy was resolved when the Canadian biochemist James Bertram Collip (Fig. 7) optimized extraction and purification techniques for parathyroid gland extracts (6) and demonstrated that these preparations not only prevented tetany episodes but were also capable of controlling serum calcium levels in parathyroidectomized animals. From that point onward, the role of the parathyroid glands as direct regulators of calcium homeostasis was firmly established.

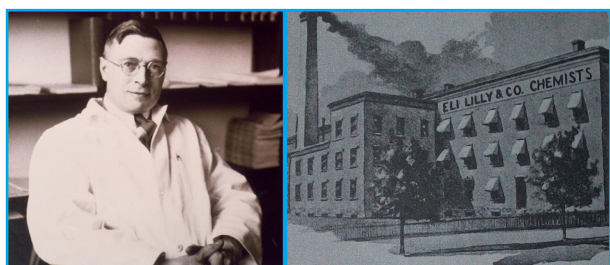


Figure 7. James Bertram Collip 1892-1965 (Source: J. B. Collip in his office at McGill University, ca. 1930, University of Toronto Library—scrapbook compiled by Barbara Collip Wyatt—Wikimedia Commons) and one of the buildings of the pharmaceutical company Eli Lilly & Co, originally opened in 1876 (Source: Eli Lilly and Company, 1886 newspaper advertisement. Public domain; Wikimedia Commons).

The relationship between the parathyroid glands and bone diseases was first documented in a commemorative volume written by thirteen of Virchow's disciples to celebrate his 70th birthday. Friedrich Daniel von Recklinghausen (7) (Fig. 8) devoted his chapter to describing autopsy findings in patients with bone disorders. He documented a case in which bone tissue had been replaced by fibrous tissue and cysts, a condition he termed *osteitis fibrosa cystica* (OFC). In the same case, he also described a reddish hypertrophic structure adjacent to the thyroid, which from today's perspective could correspond to a parathyroid adenoma. However, no hypothetical causal relationship was proposed at that time.

At the beginning of the 20th century, the most prevalent skeletal disease in Europe was osteomalacia due to vitamin D deficiency. European pathologists and

anatomists were accustomed to performing routine autopsies on hospital patients, which explains the strong tradition of European schools of anatomical pathology. They observed that parathyroid glands were often enlarged in patients with fibrous and decalcified bone tissue. These findings led them to suspect a causal relationship, and given the contemporary perspective, they concluded that the glands were dysfunctional. They were unaware that parathyroid hypertrophy was a consequence of vitamin D deficiency rather than the cause of the disease.

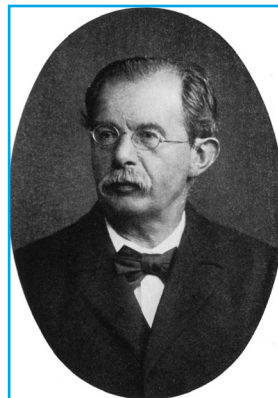


Figure 8. F. D. von Recklinghausen 1833-1910 (Source: Friedrich Daniel von Recklinghausen, Wikipedia/Wikimedia Commons).

Erdheim was perhaps the first pathologist to strongly suggest a relationship between the glands and bone disorders. He observed that some animals surviving the numerous parathyroidectomies performed in his laboratory developed dentin decalcification similar to that found in autopsies of patients with rickets (4). He therefore hypothesized that the presence of parathyroid glands was necessary for bone and dental growth. This idea raised many questions about the precise relationship between the parathyroid glands and osteomalacia, but the prevailing view at the time was that bone alterations were caused by glandular dysfunction and should therefore be treated with healthy parathyroid gland extracts.

However, the Austrian pathologist Friedrich Schlagenhauser (1866-1930), based on autopsy findings from two patients with presumed "osteomalacia" (in fact OFC) who each had a single hypertrophic gland, challenged Erdheim's interpretation and that of his contemporaries (8). He proposed that the changes observed in the gland were the cause of the bone disease and that surgical removal would therefore be the appropriate treatment. Years later, and unintentionally, the Austrian surgeon Felix Mandl (1892-1957) (Fig. 9) demonstrated that Schlagenhauser's theory was indeed correct (9).

Several more decades passed before the tireless reviews and observations of Fuller Albright (Fig. 10) established the distinction between two entities: osteomalacia in the context of secondary hyperparathy-

roidism and OFC typical of primary hyperparathyroidism (10). Indeed, at the beginning of the 20th century, OFC was considered a variant of osteomalacia.

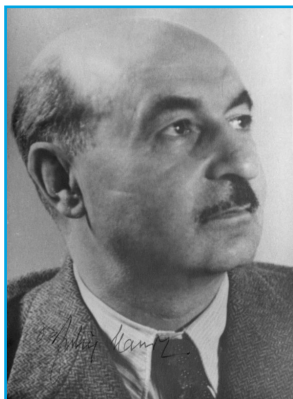


Figure 9. F. Mandl 1892-1957 (Source: Universität Wien—University of Vienna Archive, Felix Mandl (1892-1957), Surgery [Internet]).

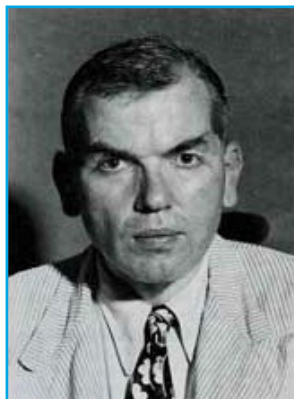


Figure 10. Fuller Albright 1900-1969. (Source: Harvard Countway Library, A photograph of Fuller Albright, Wikipedia/Wikimedia Commons).

Indeed, Mandl reached the same conclusion as Schlagenhauser after treating a patient who would, over time, become an emblematic clinical case in the history of the parathyroid glands. It was 1924, and Dr. Mandl had assumed responsibility for the care of Mr. Albert Jahne, a tram driver who at that time had sustained a femoral fracture. However, the symptoms of the disease had begun 3 years earlier: generalized pain, fractures, bone cysts, demineralized bones, and elevated serum calcium. As was customary at the time, the case was interpreted in the context of dysfunctional parathyroid glands and, therefore, the patient received hormone extracts. When no satisfactory clinical changes were observed, Mandl transplanted glands from a cadaver, and when clinical deterioration nevertheless continued, he decided to explore the neck, where he indeed found a single hypertrophic gland. The surprise was that after its removal the patient improved dramatically (9). Mandl went down in history as the surgeon who performed the first therapeutic parathyroidectomy, and with this, Schlagenhauser's thesis was also proven, namely that the cause of the skeletal disease resided in an adenomatous parathyroid gland.

Almost at the same time, across the Atlantic, in January 1926, a similar case arose that also became well known and symbolic in the medical literature. Dr. Eugene Floyd DuBois (1882-1959) received at Bellevue Hospital in New York City Charles Martell, a former captain of the United States Merchant Marine who had been experiencing progressive and disabling symptoms since 1919, which forced him to abandon his career four years later, in 1923. The patient also

had elevated serum calcium. DuBois was aware of the investigations on phosphocalcic metabolism (11,12) being conducted in the newly created Pavilion No. 4 of Massachusetts General Hospital (Boston, MA, United States) (13). Physicians at Massachusetts General, especially Joseph Aub, had already used Collip's bovine parathyroid gland extracts to treat patients with lead poisoning (14). Aub had observed that injections of gland extracts caused hypercalcemia and hypercalciuria, and his idea was that this would induce not only the release of calcium bound to the bone matrix but also the release of lead. The connection between the parathyroid glands and hypercalcemia thus seemed more than plausible, and DuBois' provisional diagnosis was hyperfunctioning parathyroid glands (15).

It was the 1920s, and of course the exchange of knowledge between continents was not as fluid as it is today. Thus, the successful operation in Vienna was not yet known in the United States. In any case, even if it had been known, it would not have made any difference because Martell's adenoma was located in the mediastinum, an anatomic variation still unknown at that time (16).

Additional studies by Dr. Aub, Dr. Albright, and Dr. Bauer confirmed DuBois' diagnosis (17), and in May 1927 Captain Martell underwent the first neck exploration. However, no trace of an adenoma was found. Over the following years, while Martell slowly deteriorated, up to nine interventions were performed in a futile search for a parathyroid adenoma. It was then, some years later, when news arrived from Europe about the missing anatomic detail: the finding of a parathyroid tumor in the mediastinum at autopsy in a patient with osteitis fibrosa. Thus, in 1932, after his ninth surgery, the cause of Martell's disease was identified: a small adenoma in one of the parathyroid glands located in the thoracic cavity.

Captain Martell thus became another representative clinical case in this history of clinical discoveries, and without intending it, emerged from anonymity thanks to the efforts of the physicians and researchers of the time.

Of note, the differences in how investigators on the two continents approached the understanding of the disease. While in Europe this approach arose from anatomic changes documented by pathologists, in America it was pursued starting from observation of phosphocalcic metabolism and clinical presentation (13).

In the first quarter of the 20th century, goiter due to iodine deficiency was endemic in the US region of Indiana. Many thyroidectomies were performed there, so the incidence of hypoparathyroidism and secondary hypocalcemia was frequent.

A local pharmaceutical company, Lilly, became interested in Collip's preparations (parathyroid gland

extracts) with the commercial aim of treating hypocalcemia in some patients undergoing thyroidectomy. Thus, Lilly participated in the development of PTH extract production, which facilitated availability and represented an advantage for physiologists and investigators in the field, who quickly became interested in directly analyzing the effects of these extracts on the skeleton of animals.

In the 1930s, Hans Selye (Fig. 11) reported that Collip's extracts did not always induce bone resorption but, under certain conditions, could also induce bone formation in the rat skeleton (18,19). However, this observation fell into oblivion for 40 years. The reasons are unclear, but one possible explanation lies in the nature of these extracts, which, although they contained many active products, still retained impurities that made them insufficiently stable.

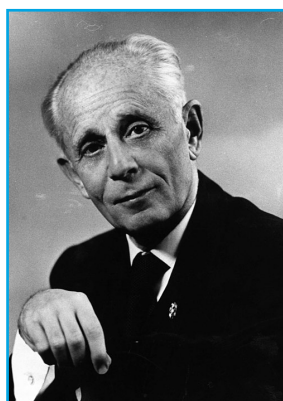


Figure 11. H. Selye (Source: Jean Paul Rioux, Portrait Hans Selye [Wikimedia Commons, CC BY-SA 4.0], 1907-1982).

Selye's idea, however, was revived by J. A. Parsons and B. Reit almost 50 years ago, in 1974 (20). While analyzing the serum calcium response in dogs treated with different doses of PTH, they observed, on the one hand, that low doses of PTH increased calcium absorption without inducing hypercalcemia and, on the other, that histologic sections of these animals' bones showed no increase in osteoclast number. Both observations led them to think that PTH might exert different actions on bone depending on the mode of administration, and that it did not always behave as an osteodestructive agent.

From that point onward, many investigators began studies on the actions of hormone fragments in the skeleton of animal models, allowing deeper understanding of these newly appreciated effects of the protein on bone. Thus, by the end of the 1960s, a preliminary clinical trial was justified to assess the reproducibility of these findings in humans (21).

Early clinical trials focused, among other aspects, on histomorphometric analysis of bone biopsies before and after receiving PTH fragments (22). In light of the

results, the authors concluded that the drug could be useful in patients with osteoporotic fractures. Subsequently, antifracture efficacy studies were conducted (23), after which the drug began to be used clinically following its approval by the European Medicines Agency in 2003.

All of these studies conducted throughout the 1980s, and up to publication of the pivotal trial (23), generated great enthusiasm within the specialized scientific community. However, some skepticism remained about their true significance, and some clinicians—familiar with the devastating skeletal consequences of primary hyperparathyroidism—found it difficult to assimilate this paradigm shift.

Parathyroid hormone stimulates bone resorption (Fig. 12) but also bone formation (Fig. 13). What happens is that, depending on the mode of administration, one set of effects may predominate over the other, so that the net result can be more destructive than formative, or vice versa. When administration is continuous, as occurs in primary hyperparathyroidism, resorptive effects predominate. The underlying mechanism is explained by the fact that PTH, through its receptors on osteoblastic lineage cells, stimulates the expression of receptor activator of nuclear factor κ B ligand (RANKL), a protein necessary and sufficient to induce osteoclast differentiation (24). However, intermittent administration of PTH attenuates RANKL expression, resulting in less striking resorption than in the continuous-administration scenario. In addition, intermittent administration increases the osteoblast pool and consequently bone formation. Through its receptor on mesenchymal cells, PTH promotes differentiation toward osteoblasts and, at the same time, decreases their capacity to differentiate into adipocytes (25,26). Furthermore, it attenuates apoptosis of osteoblasts and osteocytes (27) and activates quiescent osteoblastic lining cells on the bone surface, inducing their dedifferentiation into active osteoblasts capable of resynthesizing matrix (28).

PTH also acts on certain genes expressed specifically in osteocytes. In particular, it is a potent inhibitor of SOST expression, a gene encoding sclerostin, an antagonist of canonical WNT pathway signaling and, therefore, a strong inhibitor of bone formation. However, intermittent PTH administration does not reduce sclerostin levels as much as continuous administration, suggesting that this mechanism does not substantially contribute to the increase in osteoblast number resulting from daily PTH injections (29). What seems possible is that small transient decreases in sclerostin secretion after each PTH injection cause bursts of signaling that contribute to stimulating osteoblastogenesis, although, as noted, this is not the principal mechanism in this scenario.

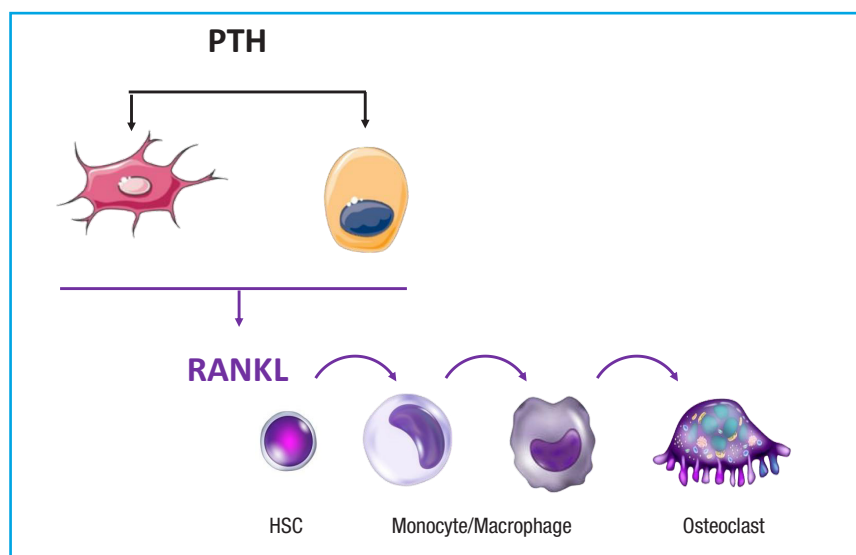


Figure 12. Effect of PTH on osteoclast differentiation: PTH stimulates RANKL expression in osteoblastic lineage cells. RANKL is a protein necessary and sufficient to stimulate osteoclast differentiation from the hematopoietic stem cell.

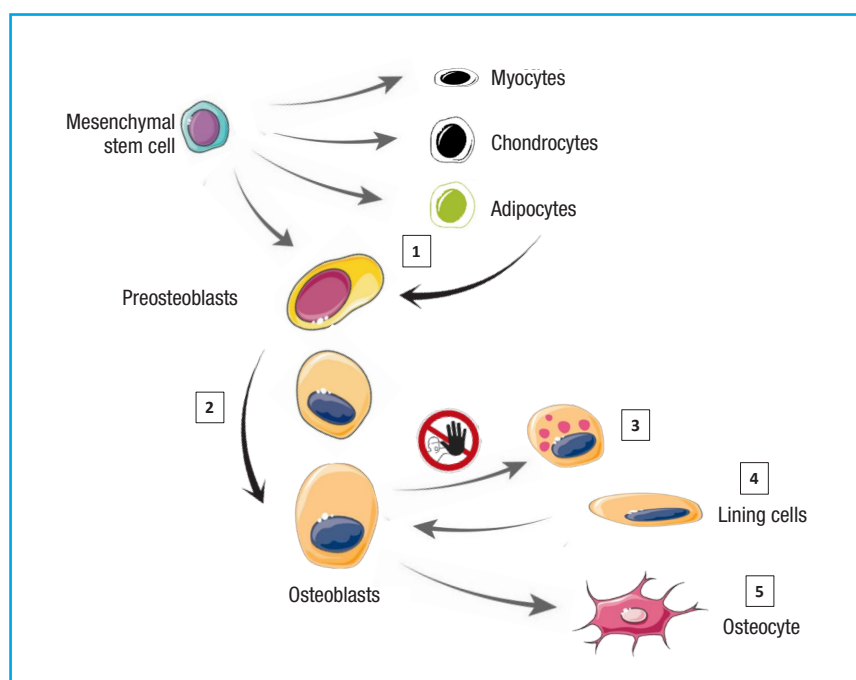


Figure 13. Effect of PTH on osteoblastic lineage cells: (1) prevents differentiation into adipocytes; (2) promotes preosteoblastic differentiation into osteoblasts; (3) inhibits osteoblast apoptosis; (4) reactivates lining cells, transforming them into osteoblasts; (5) inhibits SOST expression in osteocytes.

Histologic studies indicate that during the first 10 months after initiating intermittent PTH there is an increase in osteoblast number and bone formation rate without an increase in osteoclast number, clearly providing a therapeutic window in which the desired anabolic effects are achieved (30). The molecular and cellular mechanisms by which PTH increases osteoblast number, as well as those contributing to the anabolic effect of intermittent administration, have thus been partially clarified over the last 20 years.

PTH exerts its effects through binding to the type 1 PTH receptor (PTH1R), located on the cell membrane. PTH1R is a member of the class B family of G protein-coupled receptors. It is expressed mainly in the skeleton and kidneys, where it regulates skeletal development, bone turnover, and calcium and phosphate homeostasis, but it is also expressed in the mammary gland and vascular wall smooth muscle (31). PTH is not the only endogenous ligand capable of triggering its activation. The other ligand is PTH-related protein (PTHrP), a polypeptide with three isoforms of 139, 141,

and 173 amino acids. Unlike PTH, which is secreted by the parathyroid glands and has endocrine actions on distant organs, PTHrP is secreted by a wide variety of tissues and acts in a paracrine manner to regulate cellular differentiation and proliferation within the tissues from which it is secreted, mainly the chondral growth plate and the mammary gland (32–34). A synthetic ligand analogous to PTHrP also exists, consisting of 34 amino acids, of which ten at the carboxy-terminal end differ from the original endogenous molecule. This ligand is abaloparatide (ABL), which was approved by the FDA in 2017 as an osteoanabolic agent for the treatment of osteoporosis (35).

All ligands share similarities in the first 34 residues of the amino-terminal domain through which they bind to PTH1R. Ligand binding to PTH1R at the cell surface induces receptor changes that initiate coupling and activation of heterotrimeric G proteins (G_α , G_β , and G_γ), followed by activation of multiple intracellular signaling cascades (32). The interaction of PTH1R with G_s stimulates activation of adenylyl cyclase, the enzyme that generates the second messenger cyclic adenosine monophosphate (cAMP). cAMP activates protein kinase A (PKA), which in turn activates several transcription factors, including cAMP response element-binding protein (CREB). This enables its nuclear translocation and binding to response elements in its target genes (36,37). PKA also phosphorylates and thereby inhibits a type of salt-inducible kinases (SIKs),

which leads, on the one hand, to dephosphorylation of their substrates—class IIa histone deacetylases (HDACs) and cAMP-regulated transcriptional coactivators (CRTC2) (38)—and, on the other hand, facilitates their nuclear translocation (Fig. 14).

Activation of PKA and inhibition of SIK activity by PTH have been shown to be essential for the regulation of genes expressed in osteoblastic lineage cells. Class IIa HDAC4 and HDAC5 block expression of the osteocyte-specific *SOST* gene by inhibiting myocyte enhancer factor 2C (MEF2C). On the other hand, CRTC2 stimulates CREB-driven expression of receptor activator of nuclear factor κ B ligand (RANKL).

Several studies have shown that PTH1R has 2 distinct high-affinity conformations: the R0 conformation, which is G protein-independent, and the RG conformation, which is G protein-dependent. Thus, ligand affinity for receptor conformations triggers cAMP signaling responses that differ in intracellular duration (39,40).

All ligands stimulate a transient increase in cAMP production from the cell surface. However, those that preferentially associate with the R0 receptor conformation induce a more sustained production derived from a second phase of cAMP generation. This occurs when the ligand–receptor– β -arrestin complex is internalized through endosomes and remains in the cytoplasm (41,42).

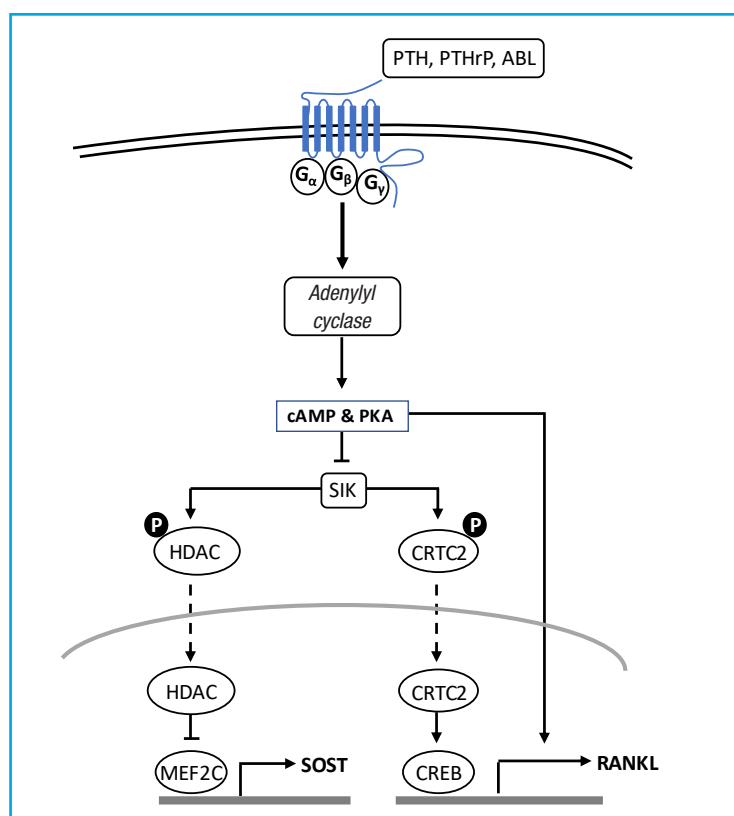


Figure 14. Model of intracellular signaling of PTH1R and activation of gene expression. Scheme based on a figure published at <https://doi.org/10.1038/s41574-024-01014-7>.

All PTH1R ligands (PTH, PTHrP, and ABL) show similar binding affinity for the RG conformation, whereas affinity for the R0 conformation differs: it is greatest for PTH, followed by PTHrP, and then ABL. Despite the fact that ABL and PTH have similar affinity for the RG conformation and that ABL has the lowest affinity for the R0 conformation, ABL is the ligand that induces the most transient intracellular cAMP response compared with the other ligands (41-43).

This difference in ligand binding preference for one or the other PTH1R conformation, and the duration of cytoplasmic cAMP activity, could explain the differences observed between ABL and teriparatide (TPTD) in clinical models. In this regard, in the pivotal ACTIVE trial (Abaloparatide Comparator Trial in Vertebral Endpoints), which compared the effects of ABL and TPTD, the resorption marker C-terminal telopeptide of type I collagen (CTX) remained elevated throughout the 18 months of the study in the TPTD arm, whereas its increase was much more modest in the ABL arm (44).

It seems that the fleeting cAMP signaling induced by activation of the RG conformation of PTH1R is sufficient to ensure osteoforming effects and that, in this situation, RANKL expression is more limited, translating into a more modest resorptive action than when the R0 receptor conformation is activated. Therefore, this difference in binding preference for one or the other receptor conformation may explain why the overall anabolic action of ABL appears to be somewhat more pronounced than that of the other ligands.

In any case, what is fascinating about this history of discoveries—especially from a biological standpoint—is the realization that the same substance can have opposing effects depending on the mode of administration. We can conclude by noting that a long time has passed since Owen discovered the parathyroid glands in a rhinoceros. Since then, many scholars in their respective fields—anatomists, pathologists, physiologists, clinicians, and laboratory investigators—have contributed their effort and curiosity so that today we can use fragments of the hormone for therapeutic purposes. The road has been long, but it has been worth it.

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