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Is primary hyperparathyroidism a pathogenic factor in some conditions mediated by B lymphocytes hyperactivity?

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ABSTRACT

Several clinical cases have shown the association of primary hyperparathyroidism and immune conditions related to B-cell hyperactivity. In some of these cases the treatment of hyperparathyroidism led to the resolution of the autoimmune phenomena. Thus, this paper hypothesizes that high levels of parathyroid hormone (PTH) may modify B lymphocytes function and induce the development of autoimmunity mediated by B-cell hyperactivity.

Introduction

Parathyroid hormone (PTH) is a pleiotropic protein that operates under endocrine, paracrine, autocrine and intracrine mechanisms. Its actions on the immune system are wide and varied, showing both stimulants and repressors effects, depending if the study is conducted either in humans or animals, or according to the type of study (*in vivo*, *ex vivo* or *in vitro*). The underlying comorbidities of patients studied are also determinant factors.

The mechanisms of action of PTH are still elusive more even when there are many possible interactions. The hormone is implicated in different processes such as epithelial-mesenchymal interactions, skeletogenesis and carcinogenesis [1,2]. In the particular case of its role on the immune system is known that PTH stimulates hematopoiesis and enhances bone marrow engraftment [3,4] acting directly on various cellular types through specific receptors or indirectly by cytokines such as interleukin-6 (IL-6). Its action in the B lymphocytes is now being investigated and it is premature to elaborate definitive conclusions. A probable pathogenic role of PTH in diverse clinical conditions mediated by B lymphocytes begins to be assumed. By instance, some patients with hyperparathyroidism and gammopathies [5–7] or autoimmune diseases [8–10] have shown total recovery of the associated condition after parathyroidectomy.

Activating action of PTH on of the hematopoietic system cells

PTH increases cells of the hematopoietic lineage, including hematopoietic progenitor cells [11]. PTH activates osteoclasts, responsible of bone resorption, through of an indirect via of upregulation of RANK-L in cells of the osteoblast lineage [12]. However the PTH receptor is also expressed by osteoclasts [13,14]. The anabolic actions of PTH in bone have been suggested to be associated with the differentiation stage of cells in the osteoclast lineage [15]. B and T lymphocytes express PTH receptors [16] and PTH induces diverse responses either activating [17,18] or inhibiting cellular function depending on diverse biological factors [19,20]. Many questions remain to be answered regarding PTH action on other cellular populations sharing the bone marrow microenvironment. PTH increases the production of interleukin-6 (IL-6) by stromal/osteoblastic cells [21] in a synergic action with fms-like tyrosine kinase 3 ligand (Flt-3L) which inhibits the cell apoptosis [22]. IL-6 is a multifunctional cytokine with effects on cell proliferation and cell survival [23], and stimulates proliferation of early hematopoietic progenitor cells [24].

Inhibitory effects of PTH on immune function

In vitro assessments to test the role of PTH as immunomodulator have shown contradictory results mainly due to methodological heterogeneity of these studies. For example, several commercial preparations of PTH have been used (rat, bovine, and human), at different concentrations and different incubating periods. In some of these studies, the lymphocytes were collected from uremic patients or animals, which render the interpretation of the results difficult due to the effect of uremic toxins. Parathyroidectomy has been found to reverse the immunologic defect in patients with high PTH levels. Nonetheless, the clinical significance of these findings is unclear.

The most relevant clinical evidence of PTH effects on the immune system is derived from patients with secondary hyperparathyroidism due to end-stage renal disease (ESRD). These patients

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are susceptible to infections due to development of an acquired immune dysfunction of multifactorial causes. The PTH is implicated in the generation of dysfunction in diverse cells of immune system [25,26] while other studies demonstrated that PTH had a stimulatory function under certain laboratory conditions [27].

Several studies have shown the abnormalities of T lymphocytes in patients with ESRD. Massry et al. [28] found a direct correlation between PTH levels in uremic patients and the degree of inhibition of lymphocyte proliferation. Ozdemir et al. [29] found that in ESRD patients the CD4/CD8 lymphocyte ratio was increased in the presence of high serum PTH levels. In contrast, Angelini et al. [30] showed a decrease in the CD4/CD8 ratio in patients with ESRD and elevated PTH levels due to a decrease in CD4, and increase of CD8 lymphocytes. Klinger et al. [18] found that PTH stimulated proliferation of T lymphocytes in a dose-dependent manner, and that the hormone did not alter the CD4/CD8 ratio. Chronic exposure to PTH may affect immune cells differently.

The knowledge about how the B lymphocytes are dysfunctional on ESDR patients are based in studies that evaluate the response to vaccination. PTH was found to affect several aspects of the B-cell function (proliferation, antibodies production, and metabolism). Gaciong et al. [31] reported that the defect in antibody production in uremic patients was due to the direct action of PTH on B lymphocytes, and that B lymphocytes from ESRD patients produce very low amounts of IgG following T-cell stimulation *in vitro*. Clinically, the plasma levels of IgG, IgM, and IgA are usually in the normal range in uremic patients, while specific antibody responses are significantly depressed [32,33].

The hypothesis

According to the known functions of PTH over B lymphocytes, and IL-6 production, and based on clinical cases showing the association of primary hyperparathyroidism and immune conditions related to B cells hyperactivity, we hypothesize that high levels of PTH may lead to B-cell mediated autoimmunity through direct and indirect mechanisms.

Evaluation of the hypothesis

Case reports show the association between autoimmunity and hyperparathyroidism

Several conditions showing hyperparathyroidism and B-cell hyperactivity have been reported. Diverse hematological diseases as chronic lymphocytic leukemia [34], gammapathy of undetermined significance [7,35,36], multiple myeloma [37–39], and autoimmune diseases such as systemic lupus erythematosus [40], antiphospholipid syndrome [41], rheumatoid arthritis [42], celiac disease [43], Sjögreńs syndrome [8], Graves disease [44,45], myasthenia gravis [46], polymyositis [47,48] vasculitis [49,50], the association of autoimmune pancreatitis, sclerosing cholangitis and possible autoimmune hypoglycemia [9], anemia and thrombocytopenia are some of the examples found in the literature [11]. Most cases reported refer only to the clinical association without showing the response to hyperparathyroidism treatment. However, the total recovery of the hematological or autoimmune condition has been reported in some cases [5–10] after the treatment of hyperparathyroidism. These reports are clinically relevant, and an additional pathogenic factor may be implicated in some patients in whom a parathyroidectomy or its medical treatment may reverse the phenomena.

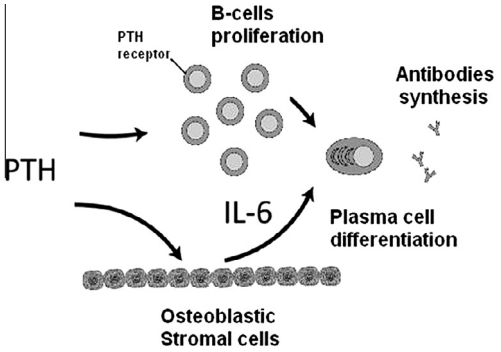

Fig. 1. Hypothetical mechanisms of autoimmune phenomena associated with hyperparathyroidism. PTH may stimulate directly B lymphocytes through its actions with its receptor. In an indirect way, PTH may activate B lymphocytes through the induction of IL-6 on stroma/osteoblast cells. IL-6 stimulates activation and differentiation of B cells into plasmocytes.

Hypothesized mechanism for B-cell hyperactivity induced by PTH

PTH may contribute in some cases to the development of autoimmune phenomena in a direct form stimulating T and B lymphocytes through its action with its receptor. In an indirect way the PTH could activate B cells through the induction of IL-6 on stromal/osteoblast cells. This cytokine stimulates B lymphocytes for activation and differentiation into plasmocytes and the subsequent production of antibodies [51,52]. Additionally, IL-6 is produced and secreted by human parathyroid gland and it is probable that this production and secretion contribute directly to the elevation of serum levels of IL-6 in patients with primary hyperparathyroidism [53]. Surely other associated factors must be acting in synergism with PTH in patients with primary hyperparathyroidism to trigger the development of hyperactivity of B lymphocytes. Fig. 1 presents a summary of these hypothesized mechanisms.

Consequences of the hypothesis and conclusion

A novel pathogenical factor in autoimmune phenomena is described. The action of PTH on the immune cell may contribute to development of autoimmunity. The observation of cases with both primary hyperparathyroidism and autoimmune diseases are noteworthy. The reverse of autoimmune phenomena after parathyroidectomy should alert us to this event.

In all patients with *de novo* autoimmune phenomenon, levels of calcium and PTH should be studied because, at least theoretically, a reversible form of autoimmunity could be present.

Conflict of interest

None.

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