Kidney International, Vol. 59, Suppl. 78 (2001), pp. S-186–S-189

Defects in B-cell function and metabolism in uremia: Role of parathyroid hormone

MIROSLAW SMOGORZEWSKI and SHAUL G. MASSRY

Division of Nephrology, University of Southern California, Keck School of Medicine, Los Angeles, California, USA

Defects in B-cell function and metabolism in uremia: Role of parathyroid hormone. Patients with chronic renal failure have impaired humoral immunity, inadequate B-cell proliferation and antibody production, and elevated basal levels of cytosolic calcium ($[Ca^{2+}]i$) in their B cells. Multiple mechanisms can be involved in generation of these derangements. This article reviews data suggesting that high levels of parathyroid hormone (PTH) of uremia affect the metabolism and function of B cells. We also review studies on the role of normalization of $[Ca^{2+}]i$ in these abnormalities. Small but well-documented studies suggest that treatment of dialysis patients with calcium channels blockers can reverse the elevation of $[Ca^{2+}]i$ in B cells, which was followed by improvement of B-cell function. Thus, therapy with calcium channel blockers has the potential to decrease the infectious complication of uremia.

Abnormalities in the immune system are encountered in clinical and experimental chronic renal failure (CRF), and both cellular and humoral immunity are impaired [1, 2]. The mechanisms responsible for these derangements are not fully delineated. Metabolic and toxic consequences of CRF and/or the compounding effects of malnutrition, vitamin deficiency, drug therapy, and dialysis treatment may each alone, or any combination, contribute to the genesis of the deranged immune system in CRF.

Available data indicate that lymphocytes have receptors for parathyroid hormone (PTH) [3, 4]. It is therefore reasonable to suggest that the function and/or metabolism of lymphocytes (both T and B cells) could be affected by PTH. It has been shown that PTH-(1-34) activated mononuclear leukocytes, most likely T cells, and caused them to produce a substance(s) that enhances bone resorption [5]. In addition, it was reported that PTH stimulates proliferation of thymic lymphocytes [6]. It is plausible that the state of excess PTH in patients with CRF adversely affects the function of T and B cells and, as such, contributes to the impaired cellular and humoral immunity in these patients. This communication deals with the effect of the high levels of PTH of uremia on the metabolism and function of B cells.

Key words: cytosolic calcium, calcium channel blockers, uremic toxin, dialysis, immune system.

B-CELL PROLIFERATION

Studies were conducted to examine the potential effects of PTH on B cells, since patients with CRF display variable degrees of impaired humoral immunity. Indeed, the antibody response to viral but not bacterial antigens may be reduced, and the number of total B cells has been reported to be normal or decreased. Furthermore, it was found that in dialysis patients, both the T-cell–dependent and T-cell–independent B-cell proliferation is reduced [1].

Available data indicate that *Staphylococcus aureus* Cowan I (SAC)-induced lymphocyte proliferation represents T-cell–independent B-cell proliferation [7]. SAC induced a significant increase in proliferation of B cells from both normal subjects and dialysis patients, but the increment in the dialysis patients was significantly lower than in normal subjects.

We also examined the interaction between PTH and B cells from normal subjects and dialysis patients [8]. Both PTH-(1-34) and PTH-(1-84) produced a dose-dependent inhibition of SAC-induced B-cell proliferation, but the effect of PTH-(1-84) was significantly greater than that produced by an equimolar dose of PTH-(1-34). At a dose of 4×10^{-7} mol/L, the decrement in B-cell proliferation was $-9.7 \pm 3.8\%$ with PTH-(1-34) and $55.2 \pm 6.9\%$ with PTH-(1-84) ($P < 0.01$).

Parathyroid hormone-(1-84) inhibited SAC-induced proliferation of B cells from dialysis patients, but the decrement ($47.3 \pm 3.9\%$) in the dialysis patients was significantly smaller than that in normal subjects ($58.4 \pm 2.5\%$). In 12 dialysis patients, the percentage inhibition of SAC-induced B-cell proliferation with PTH-(1-84) inversely and significantly correlated with the blood levels of PTH ($r = 0.78$, $P < 0.01$).

Parathyroid hormone-(1-84) also produced a significant ($P < 0.01$) increase in the production of cAMP by B cells from normal subjects. It is of interest that agents that increased cAMP without receptor interaction (for-

skolin and cholera toxin) also inhibited SAC-induced proliferation of B cells from normal subjects and dialysis patients, and this effect was not different between the two groups.

These observations indicate the B cells are targets for PTH. It is worthwhile to mention again that the effect of the intact hormone is greater than that of its aminoterminal fragment. This phenomenon is similar to the effects of these two moieties of PTH on T-cell function [9]. As we suggested earlier, this difference between the magnitude of the effects of PTH-(1-84) and PTH-(1-34) is consistent with the notion that the intact hormone may attach more tightly to its receptor or that other parts of PTH, in addition to its aminoterminal fragment, and may possess biologic activity. Certain data exist that support such possibilities. For example, binding sites with specificity for the middle region or the carboxy-terminal fragment of PTH have been described in canine and chicken renal membranes and in cloned rat osteosarcoma [10–12]. Also, we have found that the carboxy-terminal fragment of PTH-(19-94) exerts a biologic activity on human PMNLs in that it stimulates elastase release from these cells [13].

Several observations suggest that cAMP may inhibit B-cell function and interfere with its response to mitogens [14–16]. First, forskolin inhibited SAC-induced B-cell proliferation. Second, cAMP inhibited mouse B-cell proliferation, which is facilitated by B-cell stimulating factor 1. Third, cAMP caused a significant inhibition of immunoglobulin secretion by human lymphoblastoid B cell line. Fourth, our own data also showed that cAMP-elevating agents, such as forskolin and cholera toxin, inhibited proliferation of B cells from normal subjects and dialysis patients.

It is possible, therefore, that PTH stimulates cAMP production through its interaction with its receptors on B cells. Such an event could, at least in part, be responsible for the inhibitory effect of PTH on SAC-induced B-cell proliferation. Indeed, our studies showed that PTH-(1-84) stimulated cAMP production by B cells, and both forskolin and cholera toxin, agents known to elevate intracellular cAMP, produced inhibition of the proliferation of normal B cells compared in magnitude with that induced by PTH.

It is of interest that the effect of PTH was similar to that of forskolin and cholera toxin on B cells from normal subjects, but significantly less on B cells from normal subjects and significantly less on B cells from dialysis patients. It should be mentioned that the increase in cAMP production by forskolin and cholera toxin does not require receptor interaction, but the one induced by PTH does. It could be argued, therefore, that a down-regulation or desensitization of the PTH receptors on B cells in the dialysis patients caused by prolonged exposure to high levels of PTH in blood is associated with less production of cAMP by PTH than by forskolin and cholera toxin. Such a phenomenon may explain the differences in the action of PTH and forskolin or cholera toxin on the proliferation of B cells of the dialysis patients.

ANTIBODIES PRODUCTION BY B CELLS

The inhibition of B-cell proliferation by PTH may also lead to impaired antibody production by these cells. We examined the production of IgG, IgM, and IgA by B cells stimulated with SAC or with pokeweed mitogens (PWM) after eight days of culture and evaluated the effect of PTH on this process in 34 hemodialysis patients and 44 normal subjects [17]. IgG, IgM, and IgA production by B cells from patients was lower than by B cells from normal subjects. Both 1-34 and PTH-(1-84) inhibited immunoglobulin production by B cells from normal subjects and dialysis patients. However, this inhibitory effect was evident in dialysis patients only with the higher dose of PTH. The inhibition of immunoglobulin production by PTH occurred only when the hormone was added in the initiation of the B-cell culture. Inactivation of PTH abolished its inhibitory effect on immunoglobulin production. Agents that stimulate cAMP production (forskolin cholera toxin) and the cAMP analogue 8-bromoadenosine 3′,5′ cyclic monophosphate inhibited immunoglobulin production by B cells from both normal subjects and dialysis patients, and the degree of inhibition was not different between the two groups. The calcium ionophore A23187 also inhibited IgG, IgA, and IgM production by B cells from normal subjects and dialysis patients; there was no difference in the degree between the two groups. As mentioned previously in this article, the resting levels of $[Ca^{2+}]i$ of B cells from dialysis patients are significantly higher than in normal subjects. These observations show the following: (*1*) immunoglobulin production by B cells from dialysis patients is impaired; (*2*) PTH inhibits IgG, IgA, and IgM production, and this effect is at least partly mediated by PTH-induced cAMP generation and by alterations in $[Ca^{2+}]i$ of B cells; (*3*) this inhibitory effect is mediated by events that affect the initial stages of B-cell proliferation and maturation; and (*4*) the requirement for high dose of PTH for its inhibitory effect on B cells from dialysis patients is probably due to desensitization and/or down-regulation of PTH receptors on B cell. The results are consistent with the proposition that impaired immunoglobulin production by B cells from dialysis patients is at least partly due to the state of secondary hyperparathyroidism in these patients.

The observations that PTH inhibits immunoglobulin production in vitro do not provide a definite proof for a role of excess PTH in the genesis of the abnormality in the vivo immunoglobulin production. It is possible that other consequences of the uremic state and/or another as

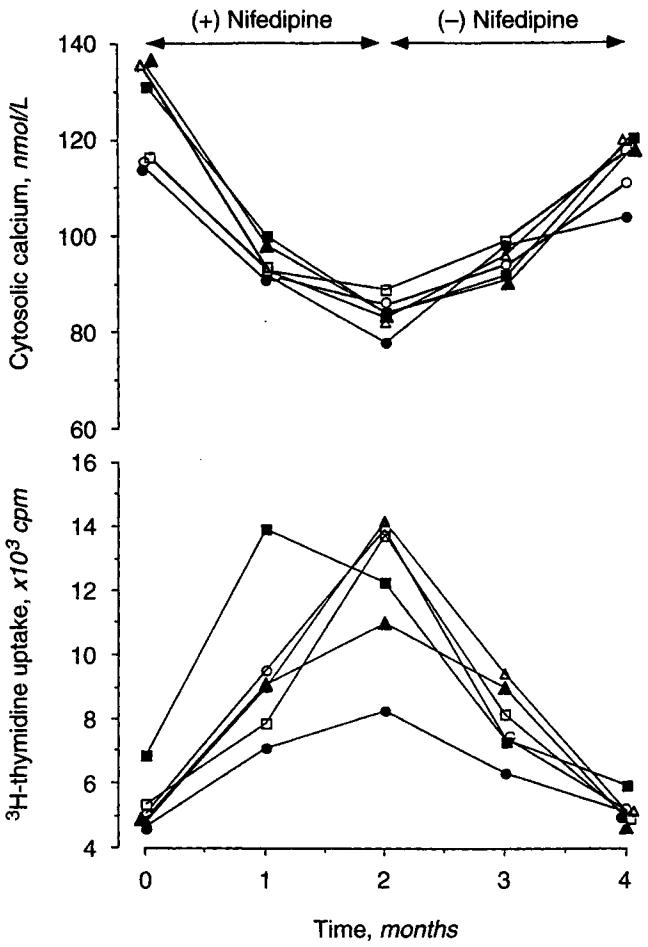

Fig. 1. Changes in [Ca^{2+}]i of B cells (upper panel) and of B-cell proliferation in response to mitogen (lower panel) of six hemodialysis patients before, during, and after cessation of nifedipine therapy. Each line represents one patient.

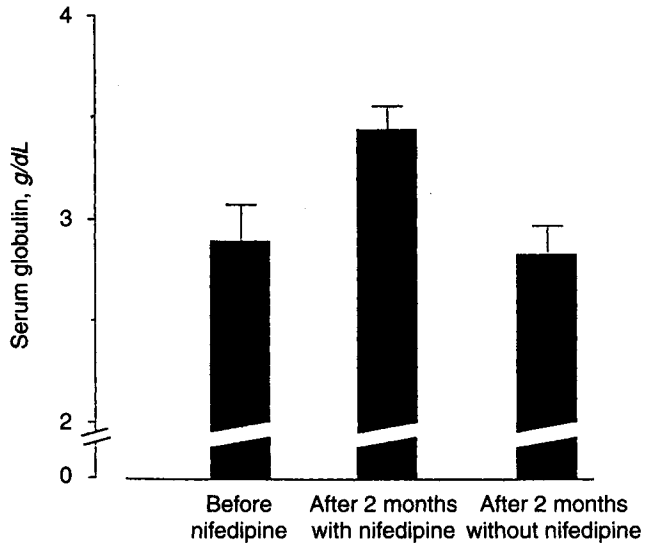

Fig. 2. Changes in the serum levels of globulin in six dialysis patients before, during, and after cessation of nifedipine therapy. Each column represents the mean of data from six hemodialysis patients, and brackets denote one SE.

yet unidentified factor accumulate in the blood of uremic patients and underlie the impaired humoral immunity. To definitely incriminate the excess PTH in the genesis of impaired humoral immunity in CRF, one must document that reduced antibody production in response to antigens is normal in a CRF state without excess PTH.

We examined in vivo antibody production in response to sheep red blood cells (SRBCs), bovine serum albumin (BSA), and influenza vaccine in normal rats, CRF rats, and parathyroidectomized (PTX) CRF rats maintained normocalcemic [18]. The antibody response to all three antigens in CRF rats was significantly and markedly lower than in normal or CRF-PTX rats. The response to SRBCs, the IgG anti-BSA, and the IgG and IgM anti-influenza vaccine in CRF-PTX rats was not different from normal, whereas the IgM anti-BSA was lower than in normal rats but higher than in CRF rats. These observations demonstrate that the state of secondary hyperparathyroidism of CRF plays a paramount role in the genesis of impaired humoral immunity of CRF.

Treatment of hemodialysis patients with the calcium channel blocker nifedipine produced marked and significant improvement in the basal levels of [Ca^{2+}]i and ATP content of B cells and in their proliferation in response to SAC as compared with hemodialysis patients who were not receiving treatment with nifedipine. The values of all of these parameters of B-cell metabolism and function in the group of patients treated with nifedipine approached the normal values. Furthermore, the blood levels of IgG were significantly higher in patients receiving nifedipine than those without treatment with this calcium channel blocker [19].

A prospective study further demonstrated that the treatment of hemodialysis patients with nifedipine reversed the abnormalities in [Ca^{2+}]i and proliferation of B cells (Fig. 1) and in blood levels of immunoglobulin (Fig. 2) within two months, and that these derangements re-emerged after discontinuation of therapy with the drug [20]. It appears, therefore, that the treatment of hemodialysis patients with a calcium channel blocker is beneficial in combating the adverse effects of uremia on the function of B cells. The treatment must be maintained in order to maintain the benefit of the treatment.

Reprint requests to Miroslaw Smogorzewski, M.D., Division of Nephrology, LAC/USC Medical Center, 1200 North State Street, RM #4250, Los Angeles, California 90033, USA.

REFERENCES

1. Massry SG, Alexiewicz JM, Gaciong Z, Klinger M: Secondary hyperparathyroidism and the immune system in chronic renal failure. *Semin Nephrol* 11:186–201, 1991
2. Descamps-Latscha B, Chatenoud L: T cells and B cells in chronic renal failure. *Semin Nephrol* 16:182–191, 1996

3. YAMAMOTO I, POTTS JT JR, SEGRE GV: Circulating bovine lymphocytes contain receptors for parathyroid hormone. *J Clin Invest* 71:404–407, 1983
4. PERRY HM III, CHAPPEL JC, BELLORIN-FONT E, TAMAO J, MARTIN KJ, TEITELBAUM SL: Parathyroid hormone receptors in circulating human mononuclear leukocytes. *J Biol Chem* 259:5531–5535, 1984
5. PERRY HM: Parathyroid hormone-lymphocyte interactions modulate bone resorption. *Endocrinology* 119:2333–2339, 1986
6. ATKINSON MJ, HESCH RD, CADA C, WADWACH M, PERRIS AD: Parathyroid hormone stimulation of mitosis in rat thymic lymphocyte is independent of cyclic AMP. *J Bone Miner Res* 4:303–309, 1987
7. FALKOFF RJM, ZHU LPO, FAUCI AS: Separate signals for human B-cell proliferation and differentiation in response to *Staphylococcus aureus*: Evidence for a two-signal model of B-cell activation. *J Immunol* 129:97–102, 1982
8. ALEXIEWICZ JM, KLINGER M, PITTS TO, GACIONG Z, LINKER-ISRAELI M, MASSRY SG: Parathyroid hormone inhibits B cell proliferation: Implications in chronic renal failure. *J Am Soc Nephrol* 1:236–244, 1990
9. KLINGER M, ALEXIEWICZ JM, LINKER-ISRAELI M, PITTS TO, GACIONG Z, FADDA GZ, MASSRY SG: Effect of parathyroid hormone on human T cell activation. *Kidney Int* 37:1543–1551, 1990
10. RIZZOLI RE, MURRAY TM, MARX SJ, AURBACH GD: Binding of radioiodinated bovine parathyroid hormone (1-84) to canine renal cortical membrane. *Endocrinology* 112:1302–1312, 1983
11. RAO LG, MURRAY TM: Binding of intact parathyroid hormone into rat osteosarcoma cells: Major contribution of binding sites for the carboxyterminal region of the hormone. *Endocrinology* 117:1632–1638, 1985
12. MCKEE MD, MURRAY TM: Binding of intact parathyroid hormone to chicken renal plasma membranes: Evidence for a second binding site with carboxyl-terminal specificity. *Endocrinology* 117:1930–1939, 1985
13. MASSRY SG, SCHAEFER RM, TESCHNER M, ROEDER M, ZULL JF, HEIDLAND A: Effect of parathyroid hormone on elastase release from human polymorphonuclear leukocytes. *Kidney Int* 36:883–890, 1989
14. SHENKER BJ, MATT WC: Suppression of human lymphocyte responsiveness by forskolin: Reversal by 12-O-tetradecanoylphorbol-13-acetate, diacylglycerol and ionomycin. *Immunopharmacology* 13: 73–86, 1987
15. HOFFMANN MK: The requirement for high intracellular cyclic adenosine monophosphate concentrations distinguishes two pathways of B-cell activation induced with lymphokines and antibody to immunoglobulin. *J Immunol* 140:580–582, 1988
16. SHEARER WT, PATKE CL, GILLIAM EB, ROSENBLATT HM, BARRON KS, ORSON FM: Modulation of a human lymphoblastoid B-cell line by cyclic AMP. *J Immunol* 141:1678–1686, 1988
17. GACIONG Z, ALEXIEWICZ JM, LINKER-ISRAELI M, SHULMAN IA, PITTS TO, MASSRY SG: Inhibition of immunolgobulin production by parathyroid hormone: Implications in chronic renal failure. *Kidney Int* 40:96–106, 1991
18. GACIONG Z, ALEXIEWICZ JM, MASSRY SG: Impaired in vivo antibody production in CRF rats: Role of secondary hyperparathyroidism. *Kidney Int* 40:862–867, 1991
19. ALEXIEWICZ JM, SMOGORZEWSKI M, AKMAL M, KLIN M, MASSRY SG: Nifedipine reverses the abnormalities in $[Ca^{2+}]i$ and proliferation of B cells from dialysis patients. *Kidney Int* 50:1249–1254, 1996
20. ALEXIEWICZ JM, SMOGORZEWSKI M, AKMAL M, MASSRY SG: A longitudinal study of the effect of nifedipine therapy and its discontinuation on $[Ca^{2+}]i$ and proliferation of B lymphocytes of dialysis patients. *Am J Kidney Dis* 29:233–238, 1997