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Dysfunction of polymorphonuclear leukocytes in uremia: Role of parathyroid hormone

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Dysfunction of polymorphonuclear leukocytes in uremia: Role of parathyroid hormone. Polymorphonuclear leukocytes (PMNLs) from uremic patients have elevated basal levels of cytosolic calcium ($[Ca^{2+}]i$), reduced calcium signal after activation of Fcγ RIII receptor, and impaired phagocytosis. Chronic excess of parathyroid hormone (PTH) in uremia mediates its effect on PMNL's metabolism and function through the sustained elevation of their $[Ca^{2+}]i$. Because calcium channel blockers interfere with this effect of PTH on PMNLs, treatment of patients on hemodialysis with verapamil, nifedipine, or amlodipine was associated with an improvement in metabolism and phagocytosis of PMNLs in humans. The therapy with calcium channel blockers should be continued in order to maintain its beneficial effects.

Uremic patients have an increased susceptibility to infection [1]. This may be partly caused by defective leukocyte function. Indeed, polymorphonuclear leukocytes (PMNLs) from uremic patients display impaired migration [2] and defective phagocytic [3] and bactericidal activities [4]. The pathogenesis of these derangements is not evident. Certain clinical observations suggest that parathyroid hormone (PTH) affects leukocyte function. It has been reported that random migration and chemotaxis of PMNLs were impaired in patients with primary hyperparathyroidism and normal renal function, and these defects disappeared after removal of the adenoma [5]. Others found that sera from uremic patients with high blood PTH levels stimulated chemiluminescence of PMNLs, and the decrease in blood levels of PTH after parathyroidectomy was associated with a reduction in this stimulatory effect [6].

Studies from our laboratory have demonstrated that PMNLs are a target for PTH action. Indeed, acute exposure of leukocytes to PTH-(1-84) increased elastase release from these cells [7] and impaired their random migration [2]. The aminoterminal fragment of the hormone was inert in regard to PMNLs function, and the 19-84 amino-sequence fragment of PTH increased elastase release from PMNLs as the PTH-(1-84) did [2, 7].

A large body of evidence exists that implicates the state of secondary hyperparathyroidism in the genesis of PMNLs dysfunction in uremic patients. Random migration of PMNLs is impaired in chronic renal failure (CRF) patients, and an inverse relationship exists between random migration of PMNLs and blood levels of PTH in these patients [2]. PMNLs of CRF patients and those treated with hemodialysis have elevated basal levels of cytosolic calcium ($[Ca^{2+}]i$), reduced adenosine 5′-triphosphate (ATP) content, and impaired phagocytosis [3]. These derangements are due to the state of secondary hyperparathyroidism of CRF. Studies in CRF rats support this conclusion and further demonstrate that these derangements are prevented by prior parathyroidectomy of CRF animals or by their treatment with verapamil [8]. Also, glucose uptake by and glycogen content of PMNLs are reduced, and the activity of their glycogen synthase is impaired in patients with CRF [9]. The treatment of these patients with verapamil or $1,25(OH)_2D_3$ (which suppresses the activity of the parathyroid glands) reversed these abnormalities [9]. Finally, oxygen consumption by PMNLs from rats and humans with CRF is decreased [10]; this abnormality is prevented by prior parathyroidectomy of the CRF animals or by their treatment with verapamil [10]. The treatment of rats with preexisting CRF with verapamil reversed the derangement in the oxygen consumption by these cells as well [10].

Since chronic excess of PTH mediates its effect on PMNLs metabolism and function through the sustained elevation of their $[Ca^{2+}]i$ and since calcium channel blockers interfere with this effect of PTH on $[Ca^{2+}]i$ of PMNLs, these drugs could be useful in preventing and/or reversing the adverse effects of PTH on PMNLs. Such a beneficial effect of calcium channel blockers on PMNL function and metabolism was confirmed in a study of two groups of hemodialysis patients [11]. Indeed, the PMNLs of hemodialysis patients without therapy with a calcium channel blocker displayed elevated basal levels of $[Ca^{2+}]i$, reduced ATP content, and impaired phagocyto-

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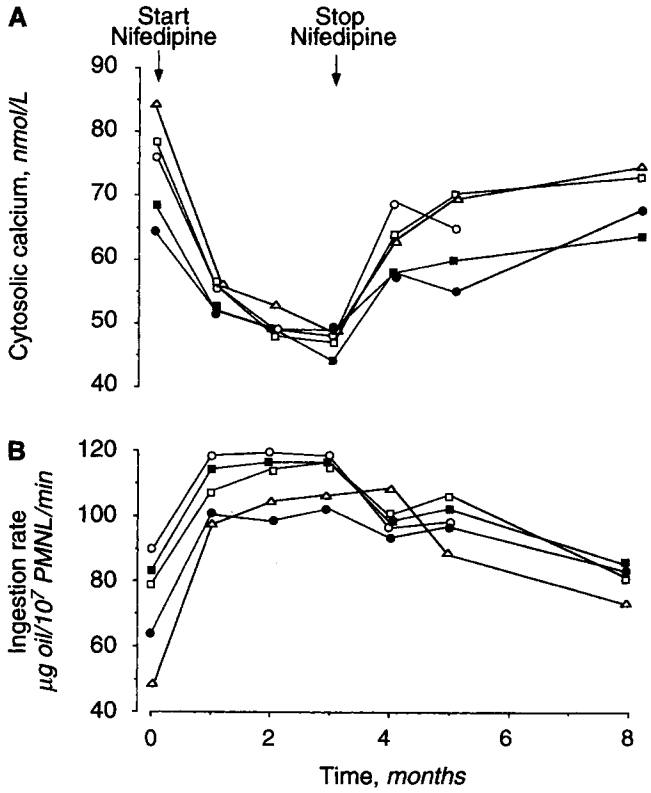

Fig. 1. Changes in cytosolic calcium ([Ca^{2+}]i) of polymorphonuclear leukocytes (PMNLs; *A*) and phagocytosis (*B*) observed in the five hemodialysis patients before, during, and after cessation of nifedipine therapy. Each line represents one patient.

sis. In contrast, the PMNLs of hemodialysis patients who were receiving nifedipine had normal levels of [Ca^{2+}]i, ATP content, and phagocytosis.

In a prospective study of hemodialysis patients, the basal levels of [Ca^{2+}]i and phagocytosis of PMNLs were examined before, monthly for two months during treatment with nifedipine (30 mg/day), and monthly for additional two months after discontinuation of the drug. Therapy with amlodipine reversed the derangements in the PMNL's [Ca^{2+}]i and phagocytosis, with the values being normal during the treatment period. However, the abnormalities in [Ca^{2+}]i and phagocytosis of the PMNLs re-emerged after discontinuation of the treatment with the calcium channel blocker (Fig. 1) [12].

These observations and others cited earlier demonstrate that calcium channel blockers are effective in reversing the effects of uremia on the metabolism, [Ca^{2+}]i, ATP content, glucose uptake, glycogen content, glycogen synthase, and function (phagocytosis) of PMNLs in humans. The therapy with the calcium channel blocker should be continued in order to maintain their beneficial effects.

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