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TOXICITY OF PARATHYROID HORMONE IN UREMIA

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Abstract

The most significant complication of elevated parathyroid hormone (PTH) levels in uremia is the development of osteitis fibrosa cystica. The hormone also appears to play a role in soft-tissue and organ calcification, metabolic abnormalities (glucose, lipids), and electroencephalographic changes seen in uremic patients. Its role in the hematological abnormalities of uremia (anemia, bleeding) is controversial. A role for PTH in heart and skeletal muscle dysfunction in uremia has not been clearly established. Further studies are required to establish PTH as a "universal" toxin in uremia.

INTRODUCTION

The pathogenesis of the uremic syndrome has been variously attributed to (*a*) retention of nitrogenous waste products, (*b*) excessive accumulation of several peptide hormones, including parathyroid hormone (PTH), and (*c*) deficiencies of essential compounds that may not be produced in adequate amounts in uremia.

Numerous attempts to identify substances that accumulate in renal failure and ultimately reach levels that are toxic to vital functions have yielded disappointing results. In recent years a role for PTH as a "uremic toxin" has been proposed (1–4). This manuscript reviews the evidence of PTH as a uremic toxin.

Parathyroid hormone is an 84-amino-acid peptide secreted by the parathyroid glands in response to changes in ionized serum calcium (5). Circulating PTH is present as the intact hormone, carboxy (C), and amino (N) terminal fragments (5). Its levels are markedly elevated in uremic patients as a result of both increased secretion of the hormone and

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decreased renal degradation, particularly of C-terminal fragments. The hormone exerts its major physiologic effects on kidney and bone (5). In the kidney it increases calcium reabsorption, decreases phosphate reabsorption, and increases the synthesis of 1,25-dihydroxy D_3 from 25-hydroxy vitamin D_3 (6). PTH mobilizes both calcium and phosphorus from the skeleton. In both organs the effects of the hormone are mediated by increases in cyclic AMP, and this nucleotide or its analogues mimic the action of PTH on kidney and bone (6). It was proposed, therefore, that cyclic AMP is a "second messenger" responsible for the effects of PTH on its target tissues.

The hormone also affects the concentrations of phosphatidic acid and phosphoinositides (phosphatidylinositol, diphosphoinositide, and triphosphoinositide) in renal plasma membranes (6). It also increases the levels of cytosolic calcium in renal cells in culture (7). Such effects may represent another mechanism through which PTH exerts its biological action on target tissues. The ability of PTH to activate adenylate cyclase and increase cyclic AMP levels in bone and kidney resides in the first 30 amino acids of the N-terminal portion of the molecule. Carboxy terminal fragments are "biologically inactive" when tested for their ability to increase cyclic AMP. Whether or not C-terminal fragments, the main immunoreactive form of PTH in the serum of uremic subjects, can affect the metabolism of phosphoinositides and the levels of cytosolic calcium is not known. If these fragments are indeed devoid of any effect on phospholipid metabolism and on the levels of cytosolic calcium, one would have to postulate that the "toxicity" of the hormone in uremia is related to circulating intact hormone and its N-terminal fragments, the levels of which may be elevated 2- to 10-fold in uremia, as compared to elevations of 50- to 200-fold for C-terminal fragments.

SKELETAL DISEASE IN UREMIA

There is universal agreement that PTH plays a primary role in the development of osteitis fibrosa cystica, one of the forms of osteodystrophy seen in uremic patients (8). There is a strong correlation between the degree and duration of hyperparathyroidism and the severity of osteitis fibrosa cystica in patients with end-stage renal disease (8). Preventing the development of secondary hyperparathyroidism will ameliorate the changes of osteitis fibrosa cystica that occur both in uremic man and in animals with experimental renal disease (8).

Controversy exists, however, as to whether or not high levels of PTH (which occur in uremia) affect the function of other organs besides the skeleton, such as red blood cells, brain, heart, liver, or muscle. Although the

known biological actions of PTH (hypercalcemia, phosphaturia, and increased excretion of cyclic AMP in the urine) reside in the N-terminal portion of the PTH molecule, it is not known if very high concentrations of immunoreactive C-terminal fragments have other biological effects that may result in some of the biochemical alterations observed in uremia. Several investigators suggest that secondary hyperparathyroidism in uremia results in increased calcium content of several tissues such as skin, blood vessels, and brain, but other potentially "toxic" effects of PTH are less widely accepted and remain at best controversial.

ROLE IN ANEMIA

Anemia is common in patients with uremia. Its pathogenesis includes both decreased erythropoiesis and increased red blood cell destruction. It was suggested that PTH at high concentrations, as seen in uremia, may inhibit erythropoiesis (1). Caro et al (9) found that levels of N-terminal PTH correlated with plasma concentrations of erythropoietin in uremic patients, and they suggested that PTH may decrease the responsiveness to erythropoietin in such individuals. Patients with primary hyperparathyroidism may have anemia, and a rise in hemoglobin after parathyroidectomy has been reported in patients with uremia (3). High levels of PTH may induce moderate to marked bone marrow fibrosis, which would thus decrease the number of red blood cell forming units. A relation between the degree of bone marrow fibrosis and the anemia of uremia has been reported (3).

Intact PTH, but not its amino or carboxy terminal fragments, added to mouse (10) or to human peripheral blood cultures inhibited erythroid colony growth (11). These observations suggest a role for PTH as an inhibitor of erythropoiesis. However, Podjarny et al (12) found no correlation between hematocrit and PTH levels measured by a carboxy-terminal radioimmunoassay. It is possible that C-terminal fragments are inactive and only intact PTH is inhibitory.

The improvement in hemoglobin levels reported in some patients after parathyroidectomy may not be due to decreased PTH levels but rather to changes in the oxygen dissociation curve as a function of phosphate levels (13). Other researchers found inhibition of heme synthesis only at very high PTH levels that in general exceeded those seen in patients with uremia (10). Delwiche et al (14), using PTH preparations of different purities, demonstrated that inhibition of erythroid colony growth was not related to the intact hormone but rather to an unknown contaminant in the partially purified gland extract. Addition of increasing concentrations of crude PTH produced a dose-dependent inhibition of early erythroid (BFU-E) and

granulocyte macrophage progenitor (CFU-GM) growth in human marrow cell cultures. However, the biologically active N-terminal fragment, 1-34 PTH, and pure intact PTH 1-84 failed to inhibit significantly hematopoietic colony growth.

Bogin et al (15) suggested that PTH decreases the life span of red blood cells in uremia. Addition of 1-34 PTH or intact PTH, but not the C-terminal 53-84 PTH, increased the osmotic fragility of human red blood cells, an effect that required calcium and was partially blocked by verapamil. PTH and/or calcium may affect the phospholipid composition of red blood cell membranes, and thereby increase the rigidity of the cells and enhance their osmotic fragility.

The bleeding tendency of uremic patients, which may be due in part to defective platelet aggregation, has also been attributed to PTH. Intact PTH 1-84, but not its N-terminal fragment 1-34, inhibited platelet aggregation induced by ADP, fibrin, collagen, or calcium ionophore (3, 16). However, Leithner et al (17) found no effect of synthetic PTH in vitro on platelet aggregation. Furthermore, platelet aggregation studies were normal before and after parathyroidectomy in six patients with primary hyperparathyroidism. They found that parathyroid gland extracts affected platelet aggregation, which may mean that other factors or contaminants of the PTH extracts were responsible for the effects reported. In summary, conflicting results have appeared regarding an effect of PTH per se on erythroid production. Contaminants in some of the preparations of PTH used may have been responsible for the results obtained. Thus, the in vitro inhibitory effects on erythropoiesis described with parathyroid gland extracts are not specific and may not be related to the circulating form of PTH.

EFFECTS ON THE NERVOUS SYSTEM

Abnormalities in behavior and/or mentation, changes in the electroencephalogram (EEG), disturbances of the autonomic nervous system, and peripheral neuropathy occur in uremic patients. PTH appears to play a role in these abnormalities (3). Uremia of three days duration in dogs increased the calcium content of brain and peripheral nerves. There was slowing of the EEG pattern and decreased conduction velocity in peripheral nerves. Parathyroidectomy prevented these changes, which could be reproduced by administration of PTH to normal dogs. These studies suggest that EEG changes observed in dogs with acute renal failure require the presence of PTH and correlate with increases in brain calcium. In patients with both primary or secondary hyperparathyroidism, abnormalities of the EEG have improved after parathyroidectomy (4).

By contrast, Cooper et al (18) found no changes in nerve conduction velocity in 10 patients with acute renal failure. In dogs with chronic uremia, despite increases in brain calcium, the prevention of secondary hyperparathyroidism forestalled the development of EEG abnormalities. These observations suggest that the effect of PTH on the EEG may be independent of changes in brain calcium. However, to the best of our knowledge, no specific receptors for PTH have been described in the brain.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

Myocardial disease may occur in patients with uremia. Its pathogenesis has been ascribed to hypertension, anemia, accelerated atherosclerosis, acidosis, and electrolyte disorders. It may be that PTH adversely affects cardiac function in uremia by increasing calcium deposition in the myocardium and coronary vessels (3). Bogin et al (19) found that both intact PTH and 1-34 PTH in a dosc-dependent manner, but not the 53-84 fragment, increased the number of beats in heart cells in culture. This effect of PTH required Ca^{2+} and was abolished by verapamil but not by α or β blockers. Serum from uremic rats also increased the number of beats but only if it contained PTH. It was also proposed that PTH, via calcium, decreases myocardial synthesis of ATP by inhibiting mitochondrial respiration and uncoupling oxidative phosphorylation (3). Improved left ventricular function after parathyroidectomy has been described in dialysis patients (20).

Hyperparathyroidism may play a role in the reduced pressor response to norepinephrine observed in uremia (21). This effect of PTH may be due to its direct action on blood vessels, probably as a consequence of increased production of vasodilatory prostaglandins (22). These data suggest that PTH may contribute to the pathogenesis of autonomic nervous system dysfunction present in chronic renal failure (23).

ROLE IN GLUCOSE INTOLERANCE AND HYPERLIPIDEMIA

PTH may play a role in the glucose intolerance that occurs in uremic patients, because this abnormality has been described in patients with primary hyperparathyroidism. Although one group (24) reported an increase in hepatic gluconeogenesis in response to PTH 1-84, these findings were not confirmed by others (25). Recently, Akmal et al (26) examined the role of PTH in glucose intolerance in dogs with chronic reduction in renal mass with or without parathyroid glands. The authors concluded that glucose intolerance does not develop in uremic dogs in the absence of PTH.

PTH did not affect the metabolic clearance of insulin or its effect on tissues; however, in the absence of PTH there was increased insulin secretion. Thus, PTH may decrease insulin secretion in uremia. Mak et al (27) found improved glucose tolerance in uremic children after normalization of PTH levels, apparently because secretion of insulin was increased.

Hyperlipidemia is common in uremic patients and animals with experimental renal disease. Evidence exists that PTH may have lipolytic activity and influence the function of adipose tissue (3). Parathyroidectomy partially prevented the hyperlipidemia that follows bilateral nephrectomy in rats (3). Similar results were obtained in rats with 2/3 nephrectomy. On the other hand, patients with primary hyperparathyroidism may have low levels of serum lipids and lipids may actually rise after removal of parathyroid adenomas (28).

OTHER MANIFESTATIONS OF UREMIA

PTH seems to play a role in the metastatic calcification and the pruritus of uremia, which are apparently related to increased deposition of calcium in the skin. Pruritus improves after parathyroidectomy, which also decreases soft-tissue calcification as assessed radiologically. Skin and soft-tissue necrosis are serious and progressive complications of uremia; healing may only occur after parathyroidectomy. In uremic patients, severe complications may occur if calcium is deposited in the heart (arrythmias, congestive heart failure) or lung (decreased vital capacity, pulmonary fibrosis).

OVERVIEW

Although some of the complications of uremia, such as osteitis fibrosa cystica, are clearly attributable to PTH, other clinical and laboratory findings of uremia (especially the anemia) cannot be unequivocally ascribed to PTH. To establish which organs are affected by PTH in uremia, it will be necessary to demonstrate the presence of specific receptors of the hormone in such organs. Evidence suggesting the presence of PTH receptors has been obtained for kidney, bone, liver, mononuclear cells, human skin fibroblasts, and probably vascular endothelium. To the best of our knowledge there is no evidence for the presence of PTH receptors in heart, skeletal muscle, red blood cells, or islets of Langerhans. Until such information is available, it remains difficult to infer a role for PTH in some of the uremic manifestations occurring in such organs. Another important and unresolved question is whether or not C-terminal fragments of PTH have biological

effects that are not mediated via cyclic AMP. These uncertainties must be resolved to establish more clearly the role of PTH as a "uremic toxin."

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