Direct effect of phosphate on parathyroid function

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Patients with chronic renal failure develop secondary hyperparathyroidism (HPT-2). Decreased calcitriol production, hypocalcaemia and phosphate retention are the main pathogenic factors involved in the development of HPT-2 in these patients.

The accumulation of phosphate favours HPT-2 through indirect and direct mechanisms [1]. High phosphate inhibits calcitriol production [2–5] which in turn causes hypocalcaemia; furthermore uraemia may directly affect the function of calcitriol and parathyroid (PTH) receptors [6,7]. High phosphate also impairs the calcaemic action of PTH [8,9] which is another cause of hypocalcaemia in renal patients.

Recent studies in animals and patients have confirmed the beneficial effect of dietary phosphorus restriction for the control of HPT-2. Furthermore animal experiments and clinical observations have suggested that high phosphate may have a direct effect on parathyroid glands. These studies demonstrate that dietary phosphorus modulates serum PTH independent of the severity of renal failure and this effect is observed even with no changes in serum calcitriol. In rats with surgically induced renal failure, a high phosphorus diet induces severe HPT-2 compared with a moderate phosphorus diet [10]. Lopez-Hilker et al. [11] showed that reduction of dietary phosphorus reduced PTH independently of calcium and calcitriol, suggesting that control of HPT-2 was a direct effect of the decrease in serum phosphorus. In different studies by Bover et al. [12] and by Yi et al. [13] restriction of dietary phosphorus prevented HPT-2. In patients with moderate renal failure, the serum PTH directly correlated with serum phosphorus in patients with mild renal failure suggesting a predominant effect of phosphorus on HPT-2 [14]. Furthermore, reduction of dietary phosphorus has been shown to be highly effective in reducing PTH [15–17]. Although reduction of dietary phosphorus is effective in the control of HPT-2, poor nutrition as a consequence of protein restriction must not be allowed.

Past and recent reports on calcitriol treatment of HPT-2 have shown that the PTH response to calcitriol treatment is poor when serum phosphorus is high [18,19]. These findings are further evidence of the important role of phosphorus in HPT-2 which, in end-stage renal disease, may not be overcome by the administration of calcitriol.

Hernandez et al. [20] have analysed the changes in serum PTH and PTH mRNA in rats after a meal with a high phosphorus content. The serum PTH increased after the high phosphorus meal with a peak at 8 h and serum calcium and calcitriol remained unchanged. The increase in serum PTH was associated with an increase in the PTH mRNA. In a different study the same authors showed that the high phosphorus meal did not change the parathyroid cell calcium receptor mRNA [21]. These results demonstrate that an oral phosphorus load can directly stimulate the synthesis of PTH.

Recent in vitro studies at this hospital and by others have demonstrated that high phosphate in the medium stimulates PTH secretion and synthesis [22–24]. Interestingly, the in vitro effect of phosphate on PTH secretion is observed in parathyroid tissue preparations and not in dispersed parathyroid cells. This suggests that in order to prove the effect of phosphate, cell to cell contact or cell to cell communication may be required. Another possibility is that in isolated parathyroid cells, the phosphate sensing mechanism is damaged.

Using intact rat parathyroid glands incubated with 1.25 mM calcium and 1, 2, 3, and 4 mM phosphate, we observed that with phosphate concentrations of 3 and 4 mM, the PTH concentration in the medium was increased two- and threefold respectively when compared with 1 or 2 mM phosphate (Figure 1); the stimulatory effect of phosphate on PTH secretion was maintained despite high calcium in the medium; similar results were obtained in bovine parathyroid tissue [24].

The effect of phosphate was also tested in human parathyroid tissue in vitro [25]. The study includes parathyroid glands obtained from patients with primary adenomas and from haemodialysis and kidney transplant patients with diffuse and nodular secondary hyperplasia. The decrease in PTH secretion induced by high extracellular calcium was less in adenomas than in secondary hyperplasia and nodular hyperplasia was less responsive than diffuse hyperplasia. In diffuse hyperplasia, high extracellular phosphate (3 and

To evaluate the acute effect of high phosphate on PTH secretion in vivo, anaesthetized dogs received a continuous i.v. infusion of phosphate for a 2-hour period reaching serum phosphate concentrations of 2, 3, 4, and 5 mM. Calcium chloride was simultaneously infused to maintain a constant serum calcium ‘calcium clamp’. PTH concentration increased significantly in the group of dogs with phosphate concentrations of 4 and 5 mM. The increase in PTH was observed despite there being no change in calcitriol and a normal magnesium concentration [28].

In conclusion, in vitro and in vivo experiments demonstrate that high phosphate has a direct effect on parathyroid cell function and this effect appears to be mediated, at least in part, by a decreased production of AA.

References


