To calculate the slope, maximal PTH is converted to 100% and minimal PTH is represented as a percentage of maximal PTH and the slope is measured directly as a linear measurement in the steepest part of the PTH–calcium curve. This is accomplished by eliminating the asymptotic portions at both ends by subtracting 10% from the maximal PTH and adding at least 10% to the minimal PTH. The resulting measurement should provide a reasonable determination of the change in PTH for the change in serum calcium [5].

In summary, we believe that as recently stated by Brown [12], who first popularized the application of the four-parameter model for the study of PTH–calcium curve, and as we have shown in this editorial, both methods for the calculation the set point of calcium provide similar information in the clinical setting. In addition, we believe that it is time to end this contentious debate about the definition of the set point and proceed with the more exciting subject of learning more about the dynamics of PTH secretion.

References

2. Fitzpatrick LA, Leong DA. Individual parathyroid cells are more sensitive to calcium than a parathyroid cell population. *Endocrinology* 1990; 126: 1720-1727

Editor’s note

Please see also the ‘Exchange of Opinion’ by Goodman (pp. 1725–1727 in this issue).

*Nephrology Dialysis Transplantation* is happy to provide a forum for exchange of opinion on topics where the definite scientific evidence is apparently not yet in. We give the authors of the original article the opportunity to reply.

The set point revisited, again

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The response to our recent editorial [1] about the interpretation of results obtained from in vivo studies of parathyroid gland function in patients with chronic renal failure contains factual errors that warrant attention [2].

When comparing experimental models, an accurate description of the components of each and their underlying tenets is required. Figure 1, which is reproduced from our editorial [1], demonstrates that presenting results according to the four-parameter model does not artificially extend the inverse sigmoidal calcium–PTH curve by setting minimum PTH levels to values of zero; rather, minimum PTH levels at high ionized calcium concentrations are approximately 5% of maximum values in normal subjects, whereas minimum levels are about 20% of maximum in patients with secondary hyperparathyroidism [3]. These findings were initially reported by Ramirez et al. in patients undergoing regular dialysis [3], and they have subsequently been confirmed by Messa and co-workers in...
patients with moderate to advanced renal failure [4]; it is incorrect to imply, however, that similar information has been obtained from studies of subjects with normal renal function using alternative techniques to model PTH release [5,6]. Since the results presented in Figure 1 were derived from direct observation, it is unlikely that the data distort ‘biological reality’.

The two curves depicted in Figure 1 vary somewhat in their configuration, particularly with respect to the magnitude of the non-suppressible component of PTH release, but the corresponding set point values do not differ when evaluated by the four-parameter model as previously reported [3]. Despite opinions to the contrary that are not supported by experimental evidence, the null hypothesis that the set point for calcium-regulated PTH release does not differ in normal subjects and patients with secondary hyperparathyroidism cannot be rejected based upon the data presented [3]. Indeed, set point disturbances were not detectable even in those with advanced secondary hyperparathyroidism [7].

Direct comparisons between patients with secondary hyperparathyroidism and those with normal renal function have not been done using alternative methods to model PTH release. Until such data become available, it is not possible to determine whether set point disturbances can be demonstrated in vivo using these techniques. Methodological considerations have recently been presented that could account for larger differences in set point estimates when the two curves illustrated in Figure 1 are evaluated using alternative models of PTH release rather than the four-parameter model [1]. Meaningful discussions of this predominantly technical matter must await the results of direct in vivo comparisons of parathyroid gland function in patients with secondary hyperparathyroidism and subjects with normal renal function using both the four-parameter model and alternative methods for estimating the set point.

Brown et al. originally described set point abnormalities in parathyroid cells from hyperplastic glands in vivo, but in vivo studies of patients with secondary hyperparathyroidism using the four-parameter model were not reported [8]. In vivo findings in primary hyperparathyroidism were shown, however, to correspond to data obtained in vitro in pathological tissues obtained from the same patients at the time of parathyroidectomy, results that served to validate the four parameter model for in vivo studies [9,10]. Similar comparisons between in vivo and in vitro results using alternative methods to model PTH secretion are not available, and the relationship between in vivo and in vitro findings using these techniques has not been determined. Establishing the level of agreement between in vivo and in vitro results using any of several methods to model PTH release is relevant because the concept that the set point is abnormally high in secondary hyperparathyroidism is based exclusively upon in vitro findings [8,11]. Set point disturbances have yet to be demonstrated in vivo in patients with secondary hyperparathyroidism using the four-parameter model despite the consistent application of this technique for evaluating calcium-regulated PTH release both in vivo and in vitro [3,4].

It has been suggested that set point values obtained using alternative methods to assess parathyroid gland function in patients undergoing regular haemodialysis correspond quite well to those determined using the four-parameter model. This contention is based, however, upon recently published studies in which total rather than ionized serum calcium levels have been measured [2,12]. Earlier studies from this group of investigators that purportedly utilized ionized calcium measurements are not cited [2,6,12–15], whereas unpublished data using ionized calcium determinations are presented in Figure 2. The calculations used for determining the set point also differ substantially among reports [2,6,12–16], but the impact of these methodological variations on set point estimates has not been addressed. Accordingly, these investigators have variously described decreases [14], no change [13] or increases [12] in set point values after calcitriol therapy in patients with secondary hyperparathyroidism.

Since parathyroid cells respond to changes in ionized calcium concentration, direct measurements, rather than indirect estimates, of this critical determinant of PTH release are preferred when evaluating the secretory behaviour of the parathyroid glands. Because the key modifier of PTH release, i.e. the concentration of ionized calcium in serum, has not been directly assessed, the physiological importance of studies based upon measurements of total serum calcium is necessarily quite limited. We have found much weaker agreement between set point estimates determined using the four-parameter model and those obtained by the alternative method, r = 0.30, in studies using measurements of ionized calcium.

With any approach to data analysis, the limitations of the method employed must be recognized. Figure 3A from the accompanying article illustrates the difficulties encountered and the potential for erroneous conclusions when such constraints are not acknowledged. Three putative calcium–PTH curves are depicted; the slope of the mid-portion of each curve is virtually identical. Unfortunately, none of the three curves accurately reflects data obtained in human subjects.

As noted previously, the degree to which serum PTH levels can be suppressed at high ionized calcium concentrations is substantially less than normal in patients with secondary hyperparathyroidism (Figure 1) [3,4]. The larger non-suppressible component of PTH release in subjects with hyperplastic parathyroid glands changes the configuration of the inverse sigmoidal calcium–PTH curve, resulting in a slope along the mid-portion of the curve that is less in patients with secondary hyperparathyroidism than in normal subjects (Figure 1). Similar qualitative changes in the slope of the ionized calcium–PTH curve have been noted after treatment with calcitriol in patients with
overt secondary hyperparathyroidism [17]. There are no published data, however, from in vivo studies of parathyroid gland function in a variety of clinical disorders that correspond to the curves depicted in Figure 3A.

Patients in whom serum PTH levels rise to values of 1000 pg/ml, or 100 pM, in response to hypocalcemia do not exhibit reductions in serum PTH levels to values as low as those depicted in Curve A of Figure 3A when serum calcium levels are raised [3]; such changes are seen only in subjects with normal renal function in whom serum PTH levels are much lower. Differences in the magnitude of the non-suppressible component of PTH release such as those depicted in Curves B and C of Figure 3 also modify the slope of the mid-portion of each corresponding inverse sigmoidal curve when assessed in vivo as illustrated in Figure 1. Projections based upon the hypothetical analysis described in Figure 3 have little physiological meaning since they are not based upon direct experimental observation.

Recent reports using alternative methods to model PTH secretion in vivo have suggested that set point values vary directly with the basal level of calcium in serum [12]. If correct, the meaning of the set point as measured in vivo by this approach differs markedly from that determined in vitro, where the set point is considered to represent an intrinsic property of the parathyroid cell which defines its secretory response to changes in ionized calcium [11,18]. Thus, in vivo estimates of the set point using this alternative model probably do not describe an integral component of parathyroid gland function.

In previous publications, we have emphasized the inherent limitations of the four-parameter model when applied to studies of parathyroid gland function in vivo [3,7,17,19]. The assumptions that underlie the four-parameter model and other methods for characterizing calcium-regulated PTH release differ substantially for in vitro and in vivo studies. Recognizing these limitations would not only eliminate much of the confusion that currently surrounds the set point concept but also clarify our understanding of parathyroid gland physiology in secondary hyperparathyroidism due to chronic renal failure.

In addition to concerns about marked inconsistencies among published reports from a single group of investigators using an alternative approach to assess parathyroid gland function, several of their key findings have not been confirmed by other investigators [17,19], some of whom used the same alternative experimental method [20]. It is unlikely, therefore, that additional studies employing this alternative approach to modeling calcium-regulated PTH release will provide valuable new information about the regulation of PTH secretion in either normal or pathological conditions.

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References