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The apparent hysteresis in hormone-agonist relationships

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It has been noted in multiple studies that the calcium–PTH axis, among others, is subject to an apparent hysteresis. We sought to explain a major component of the observed phenomenon by constructing a simple mathematical model of a hormone and secretagogue system with concentration dependent secretion and containing two delays. We constructed profiles of the hormone–agonist axis in this model via four types of protocols, three of which emulating experiments from the literature, and observed a delay- and load-dependent hysteresis that is an expected mathematical artifact of the system described. In particular, the delay associated with correction allows for over-secretion of the hormone influencing the corrective mechanism; thus rate dependence is an artifact of the corrective mechanism, not a sensitivity of the gland to the magnitude of change. From these observations, the detected hysteresis is due to delays inherent in the systems being studied, not in the secretory mechanism.

1. Introduction

It is well understood that parathyroid hormone (PTH) secretion is functionally related to the concentration of serum ionized calcium. Studies *in vivo* and *in vitro* have demonstrated that the steady state relationship between calcium and PTH takes the form of a monotonically decreasing saturable curve with half maximal response located below normal serum calcium levels. More interesting and complicated questions surround the dynamic nature of PTH secretion in response to an acute stimulus. These questions fall into one of two basic types: the first concerns a bimodal secretion pattern seen in an initial calcium challenge but not subsequent ones (Schwarz et al., 1998). This pattern has been attributed to "PTH exhaustion", the notion that the parathyroid gland secretes its entire ready-made store of the hormone in an initial pulse. This phenomenon has been modeled previously (Momsen and Schwarz, 1997). The second type of hysteresis observed concerns an apparently different functional relationship between serum ionized calcium and serum parathyroid hormone concentration depending on the situation studied (Toribio et al., 2003;Grant et al., 1990; DeCristofaro et al., 2001). In particular, for a given serum ionized calcium level, PTH concentration is higher with induction of hypocalcemia or hypercalcemia than in recovery from the same (Conlin et al., 1989; Kwan et al., 1993; Schwarz et al., 1998). This hysteresis has led some investigators to conclude that the parathyroid gland is capable of sensing the rate of change of serum ionized calcium and secreting in response to this rate as well as the serum concentration. It is this type of hysteresis that we wish to address with this paper.

The "rate-related" hysteresis has appeared in various protocols.

1. In some studies, calcium is clamped by means of calcium infusion or the infusion of a chelating agent such as EDTA or trisodium citrate. During the recovery from hypo- or hypercalcemia, PTH and serum ionized calcium are monitored. To accelerate recovery of baseline serum ionized calcium levels in some individuals subjected to hypercalcemic clamp, chelating agents were administered, and similarly calcium was given to accelerate recovery from hypocalcemic clamps. Hysteresis was noted between the "natural" recovery and the accelerated recovery (Conlin et al., 1989).
2. In normal humans hypo- and hypercalcemia are induced and recovered from by means of calcium or chelator infusion as above. In all cases, serum PTH concentrations were higher in the inductive phase of each type of protocol than in the recovery phase (Kwan et al., 1993).
3. In human patients with kidney failure of various etiologies, serum ionized calcium levels and PTH levels were monitored in dialysis against high calcium or no calcium dialysate, with return to baseline values. The hysteresis was observed between the stimulus and recovery periods of both increased and decreased serum ionized calcium (Schwarz, 1993).
4. In human patients with renal failure of various etiologies, serum ionized calcium and PTH are monitored in patients undergoing low or high calcium dialysis, and compared to patients undergoing dialysis with dialysate calcium increasing from the low to high level, or vice versa. Hysteresis in the calcium–PTH relationship was observed between the types of stimulation (DeCristofaro et al., 2001).

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Three major conclusions have followed from the described protocols. First is the belief that, in addition to serum calcium concentration dependence, the parathyroid secretes its hormone in response to any decrease in serum ionized calcium, and withholds secretion in response to any increase in the same. Secondly, curve-fitting of the data has suggested that the set point of the PTH–calcium curve moves in the direction of calcium stimulus. Finally, it has been proposed that in addition to sensing the direction of change in serum ionized calcium, the parathyroid gland is able to sense the rate of change and increase the magnitude of its response accordingly.

Our group began with the question of whether some aspect of the homeostatic mechanism controlling calcium might explain the hysteresis with hormonal secretion dependent only on minute to minute serum ionized calcium concentration.

In vivo, the PTH–calcium relationship is very subtle, and subject to other hormonal factors including FGF-23 and 1α,25(OH)$_2$D$_3$ (Torres and De Brauwere, 2011;Ben-Dov et al., 2007) and a model integrating the various aspects of calcium homeostasis would likely obfuscate structural effects in the hormone–secretagogue relationship. Thus, rather than modeling the PTH–calcium relationship specifically, we undertook to construct a simple "ideal" system that contained the same basic elements, namely intake, pool, and clearance functions for the secretagogue, and secretion, pool, and clearance functions for the hormonal responder. In particular, we declined to model storage conditions for the hormone as in Momsen and Schwarz's work (Momsen and Schwarz, 1997) so as to have the most transparent possible model with physiologic relevance. Our hypothesis was that the system would demonstrate hysteresis with respect to induction of and recovery from low and high serum states of the secretagogue with no need to include rate dependent secretion of the hormone. This demonstration does not prove that no rate-dependence exists in the determination of parathyroid hormone secretion in response to a given serum ionized calcium signal, but it does provide a mechanism describing a portion of the observations. Similarly, this demonstration does not seek to explain the lack of peak hormone in subsequent stimulations that have been observed, for example, by Schwarz's group (Schwarz et al., 1998). Similar findings have been reported with respect to calcitonin as well (Wang et al., 2002).

2. Materials and methods

2.1. Model development

Consider the following simple model: there is an electrolyte A that is absorbed at the constant rate $\alpha=0.5$ unit min^{-1} by the gut, and whose sole clearance is by the kidney realized as a percentage of filtered A. The reference to renal clearance in this way is to create a system of maximal simplicity; metabolic clearance or a more complicated renal mechanism shows the same outcome but with decreased clarity. A decrease in A causes the release of hormone H, which decreases excretion of A (ExA). For simplicity, we will assume that this occurs via endocytosis of active transporters that, in the absence of H, return to the cell membrane at the same rate they were removed. For the purposes of this demonstration, we suppose that H has a circulating half time of 10 min, and that half the change in ExA is achieved in 2.5 min. Thus we have a clearance time constant for H of 0.0625 units min^{-1}, and a delay constant for adjustment of ExA of $k=0.159$. Again, for simplicity, we assume that neither A nor H affects GFR or filtration constants, and that A is filtered freely. Thus we can assume that our test subject has a renal blood flow of 20% of the total cardiac output, with a glomerular filtration rate (GFR) of 0.125 L min^{-1}, and that A is freely filtered. Finally, we define the relations between H, A, and TmA to be

$$ExA_{Target} = 0.5 - 0.01 \times [H]$$

$$\frac{dExA}{dt} = k \times (ExA_{Target} - ExA)$$

$$\frac{dA}{dt} = \alpha - [A] \times ExA \times GFR$$

$$\frac{dH}{dt} = 10 \times \frac{[A]}{5+[A]} - 0.0625 \times H.$$

The first equation establishes a negative linear relationship between excretion and hormone levels. The second equation establishes a delay in the response of ExA to changes in H. The third equation establishes that A is increased in the system only by adding more from the gut, and that it is cleared by the kidney according the linear excretion model. The final equation establishes that H is secreted saturably in response to increases in $[A]$ with half maximal secretion at $[A]=5$ units L^{-1}, a maximal secretion of 2 units min^{-1}, and that it is cleared from the blood at a rate of 6.25% of the total per minute. We will use this simple system to show that variable rates of administration of substance A cause the illusion of multiple secretion curves for H.

2.2. Model protocols

We use four protocols to demonstrate hysteresis without rate dependence. First, we use a stepwise induction of hypocalcemia and stepwise recovery as previously described (Grant et al., 1990). Electrolyte A was lowered in two ways: via a stepped pulse protocol (Protocol 1A) and a continuous protocol (Protocol 1B). In the stepped protocol, α is reduced to -0.2 for 5 min, followed by 25 min in which $\alpha=0.4$, followed by another 5 min pulse of -0.2 with 25 min of $\alpha=0.3$ and so on until $\alpha=0.1$. After 1 h at $\alpha=0.1$, values are returned to baseline by increasing α by 0.1 for 25 min of every 30 min, with 5 min pulses of $\alpha=0.7$. In the continuous protocol, α is decreased by 0.1 units min^{-1} every 30 min. The function α is demonstrated in Fig. 1. The endpoint is $[H]$ as a function of time, and $[H]$ as a function of $[A]$ in each decrement.

The second protocol consisted of decreasing α to bring A to 30% below baseline and maintain this level for 90 min, observing $[H]$. The second part of the protocol is to increase α until $[A]$ rose to 30% above baseline, maintain this value for 90 min, and then reduce α to its normal value, thereby correcting A to baseline while observing $[H]$. In this model, maintaining $[A]$ at ±20% of basal values requires an intake of $\alpha=0.70$ or 0.30 units min^{-1}, respectively. To cause the necessary decline to occur within

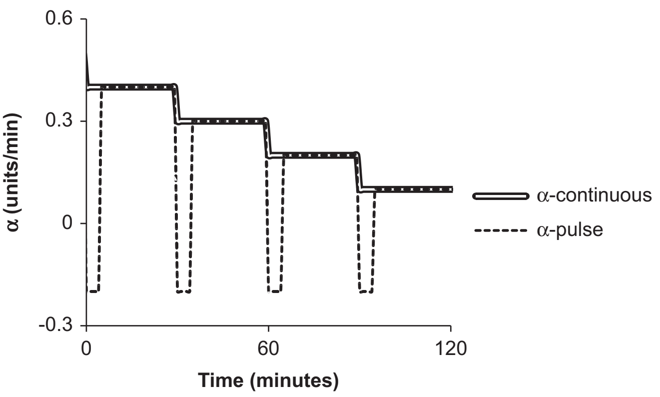

Fig. 1. Time course of the intake parameter α in Protocol 1. The double lined curve is the "continuous protocol" and the dashed line is the "pulsed protocol".