Modulation of Parathyroid Hormone Levels by Calcium Intake

By Ron Gerrits (Modified by Charles S. Tritt)

BI-102

Section 1

Submitted to: Dr. Tritt

Submitted on: Dec.14, 1999

INTRODUCTION

It is currently well known that extracellular calcium levels play a vital role in the body's homeostatis. This work started in the early part of this century when scientists demonstrated the importance of this ion in both skeletal and smooth muscle contraction. Further, more recent evidence by Gerrits has indicated that blood calcium levels may also play a significant role in determining threshold potentials of electrically excitable cells (2). Together with the acceptance that people who drink milk have strong bones, it can be reasonably concluded that calcium levels are of utmost importance to human function.

One area of recent interest is the regulation of calcium concentrations in the human body. Despite a wide variety of calcium intakes amongst individuals, it has been noted by Endemann that blood calcium levels stay quite constant (1). An important question arising from this work is how extracellular calcium levels are kept in a narrow range. A possible explanation has been suggested by Nelson and Paur, who published a study indicating that a novel hormone influences the amount of calcium either deposited into, or resorbed from, isolated bone pieces (3). This hormone, originally purified and Shurr and Danforth, is now termed parathyroid hormone (4), and, although thought to be involved in calcium regulation, has not yet been investigated in humans.

The goal of the present study was to test the overall hypothesis that parathyroid hormone regulates extracellular calcium levels. In particular, the study tested the following specific hypotheses: 1. that parathyroid hormone levels fluctuate inversely proportional to ingested calcium load in humans 2. that removal of the parathyroid gland of a rat will cause neuronal hypoexcitability in animals fed a high calcium diet.

MATERIALS AND METHODS

For the first study, forty-five human subjects (23 male, 22 female) were used. All were in good health as determined by a physical and between the ages of 20 and 25. Control blood samples from each subject were obtained at the start of the protocol and assayed for calcium content and parathyroid hormone by a radioimmunoassay (RIA). The subjects were then put on diets consisting of varying calcium intake, with each subject staying on 1 diet for a 5 day period, before being changed to another diet. The diets were regulated by the amount of milk (of standard calcium content of 20 mEq/L) the subjects were allowed to ingest and ranged from 20 to 60 mg calcium/day, assigned randomly (5 subjects were on each diet at a given time). Blood samples were collected every 5^{th} day for 30 days, 1 hour after the evening meal, and assayed for calcium and parathyroid hormone. At the end of the experiment, the blood calcium and parathyroid levels were averaged from all subjects for each diet and a regression performed on the data. Statistics were done utilizing a repeated measures ANOVA with $p<.05$ considered significant. Data are expressed as mean ± SD.

The second study utilized 30 male Sprague-Dawley rats that were each 7 weeks old at the beginning of the protocol. On day 1 of the protocol, a parathyroidectomy was performed on 15 of the subjects and a sham surgery on the other 15. The animals were then allowed to recover. During this time the animals were on a normal calcium diet (2 mEq/day). On day 8 the rats were implanted with needle electrodes into the phrenic and vagus nerves for electrical recording, and blood samples taken to confirm presence or absence of parathyroid hormone (tested by RIA). The electrodes were then coupled to standard lab amplifiers and recording units. At that point the animals were switched to a

high calcium diet (5 mEq/day) with the neuronal recording running continuously. The number of action potentials/hr were then compared between the two groups and tested for significance with an unpaired t-test, utilizing a p value of 0.05 for significance.

RESULTS

The first experiment tested the effect of varying calcium intakes on the level of parathyroid hormone in adult humans. The results of this experiment are shown in Figures 1 and 2. As can be seen from these figures, parathyroid hormone levels are inversely correlated with both calcium intake and blood calcium levels. This correlation was significant ($p<.005$).

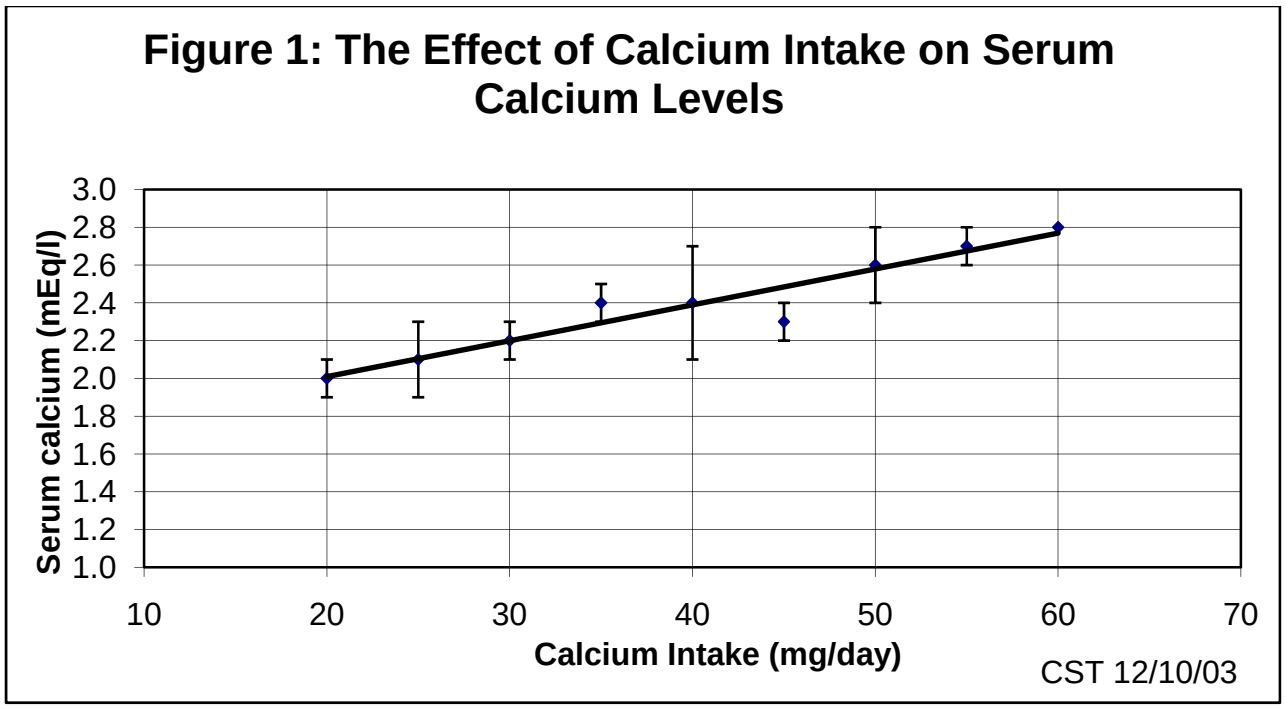
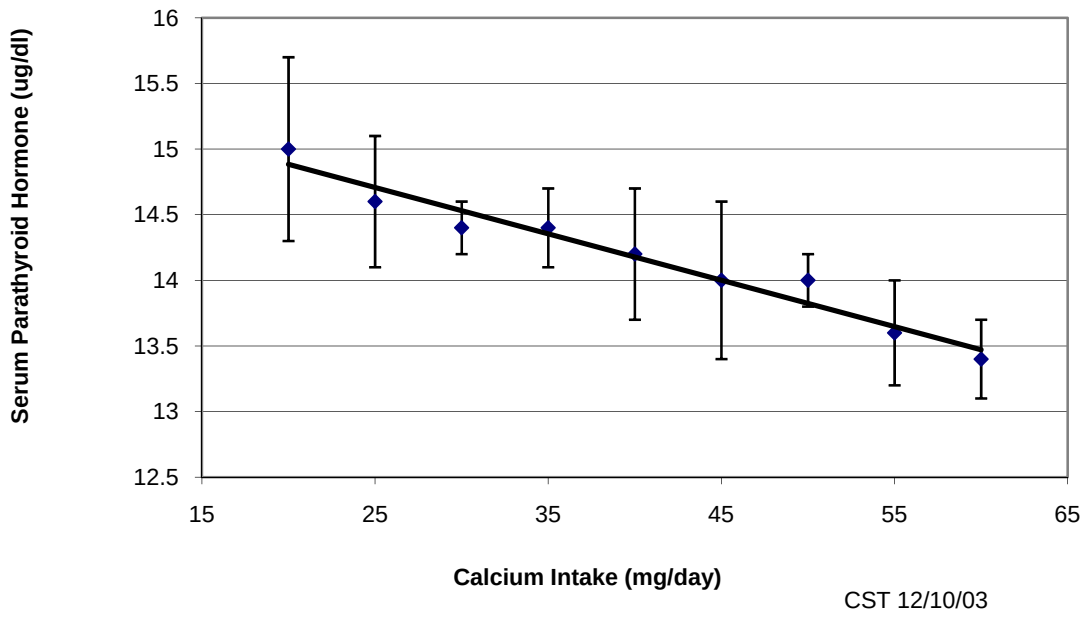
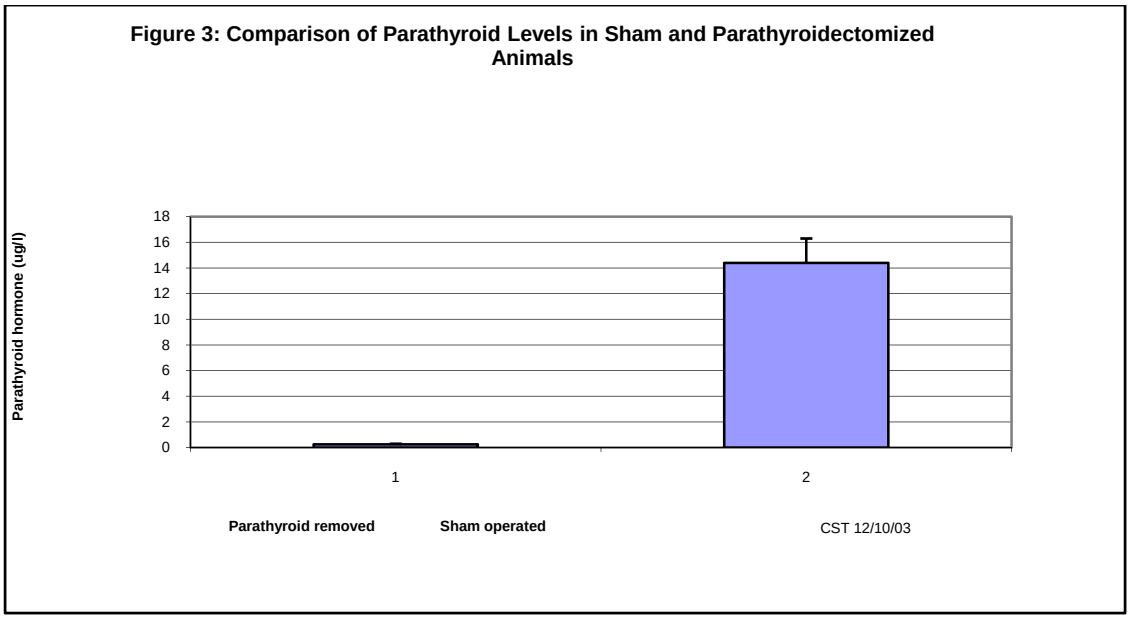
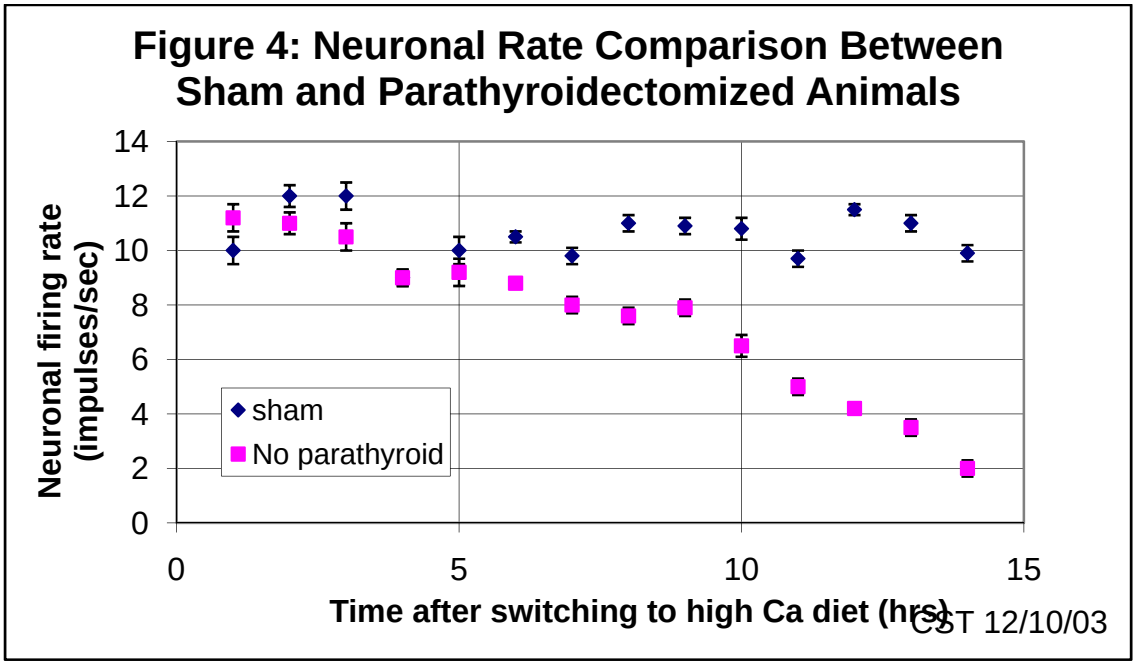


Figure 2: The Effect of Calcium Intake on Serum Parathyroid Hormone Levels



The second experiment investigated the effect of a high calcium intake on neuronal activity in parathyroidectomied rats. Figure 3 illustrates that parathyroidectomy decreased blood parathyroid levels to nonmeasurable levels as compared to the sham operated group. Figure 4 compares the neuronal firing rates from animals with and without parathyroid hormone. Neuronal firing rate decreased in all animals which had received a parathyroidectomy as compared to the controls ($p<.02$). All animals that had undergone parathyroidectomy died between 10 and 24 hours after being switched to the high calcium diet.





DISCUSSION

The goal of the present study was to test the overall hypothesis that parathyroid hormone regulates extracellular calcium levels. In particular, this study tested the following specific hypotheses: 1. that parathyroid hormone levels fluctuate inversely

proportional to ingested calcium load in humans 2. that removal of the parathyroid gland of a rat will cause neuronal hypoexcitability in animals fed a high calcium diet.

As depicted in Figures 1 and 2, when human subjects were placed on variable calcium intakes, their level of blood parathyroid hormone varied inversely to their calcium intake. This provides evidence that calcium intake affects blood parathyroid hormone levels. Not discernable from this study is whether it is the oral calcium intake, the amount of calcium absorbed via the gastrointestinal system, or both that is responsible for parathyroid hormone regulation and/or how these variables may interact. A recent study by Gerrits et. al. provides evidence that parathyroid hormone may regulate calcium absorption in the GI tract (2). Together with the results from the present study this suggests a complex interplay of blood calcium levels and parathyroid hormone. More studies will have to be done to resolve the details.

It was hypothesized that parathyroidectomy would cause neuronal hypoexcitability in animals fed a high calcium diet because Gerrits has previously shown that high serum calcium levels raises threshold potential in nerves (2). Without calcium regulation via parathyroid hormone, it was predicted that serum calcium levels would rise when combining a high calcium diet with no parathyroid hormone. This hypothesis was supported as evidenced from Figures 3 and 4, which indicate a lack of parathyroid hormone in the blood, as well as a decrease in neuronal activity. In fact, this effect was so marked that none of the parathyroidectomied animals lived longer than 24 hours after being placed on a high calcium diet. It was suspected that the deaths resulted from an inability to sustain viable respiration caused by decreased activity of the phrenic nerve (as indicated by figure 3). One shortcoming of this experiment is that serum calcium levels

were not measured in the rodents, and therefore it is ultimately unknown if blood calcium levels were affected by parathyroidectomy. It is possible that neuronal hypoexcitability was caused by another, yet unknown factor, regulated by parathyroid hormone. The authors admit the possibility of this occurring, but feel it much more likely that the neuronal effects were caused by calcium changes caused by lack of parathyroid hormone.

Overall these studies lead to the conclusions that parathyroid hormone is regulated, at least in part, by serum calcium levels. Furthermore, this regulation is paramount to organismal homeostasis as indicated by the rapid death of animals not having a parathyroid gland. These results suggest that parathyroid hormone is critically important in regulating serum calcium levels, although the specific mechanisms still need to be investigated.

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