Role of Parathyroid Hormone in the Decreased Motor Nerve Conduction Velocity of Chronic Renal Failure (43135)

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Abstract. **Certain data support the notion that chronic exposure to excess parathyroid hormone (PTH) is associated with decreased motor nerve conduction velocity, while other studies failed to confirm such an effect. Also, chronic renal failure of 4 months duration in dogs did not elicit changes in MNCV or calcium content of nerve. These discrepancies may be due to differences in other metabolic parameters, such as degree of uremia, serum levels of calcium, phosphorus, or magnesium, and acid-base parameters, or in duration of chronic renal failure. To examine the effect of PTH on peripheral nerve function in renal failure in a more defined biochemical setting, we studied the changes in MNCV and nerve calcium content in dogs with and without excess PTH and with prolonged and similar duration of chronic renal failure (57 ± 1.7 weeks) and comparable biochemical parameters. Dogs with chronic renal failure displayed a significant ($P < 0.01$) decrease in MNCV (before renal failure, 65 ± 1.5 m/sec; after renal failure, 49 ± 3.5 m/sec) and marked elevation in calcium content of peripheral nerve (444 ± 45 mg/kg dry wt). These derangements were not observed in parathyroidectomized chronic renal failure animals; MNCV before renal failure was 66 ± 1.5 m/sec and after renal failure was 65 ± 1.5 m/sec, and nerve calcium content after renal failure was 229 ± 3 mg/kg dry wt. Also, parathyroidectomy of three dogs with preexisting chronic renal failure of 52 weeks was associated with reversal of the abnormalities in MNCV and calcium content of nerve despite an additional period of renal failure of 52 weeks in two of the dogs and 40 weeks in the third. Our data are consistent with the proposition that excess PTH plays a major role in the genesis of peripheral nerve dysfunction in chronic renal failure. This adverse effect of the hormone is most likely mediated by the PTH-induced accumulation of calcium in peripheral nerve.** [P.S.E.B.M. 1990, Vol 195]

Abnormalities in central and peripheral nervous system functions are present in both acute and advanced chronic renal failure (CRF) (1–10). studies suggest that the excess parathyroid hormone (PTH) in these conditions may play a significant role in the neurotoxicity of renal failure (1–4, 8–10).

It is possible that the state of secondary hyperparathyroidism in acute (11), as well as in chronic, renal failure (12–14) leads to impairment in motor nerve conduction velocity (MNCV). Indeed, decreased MNCV in dogs after 3 days of acute uremia or after 3 days of administration of PTH to dogs with normal renal function has been reported (9). This abnormality is prevented by prior parathyroidectomy in the former group of dogs and is reversed by discontinuation of PTH treatment in the latter group of animals (9). These data are consistent with a potential role for excess PTH in the genesis of peripheral neuropathy in acute renal failure. It was suggested that such an effect of PTH is mediated via the accumulation of calcium in the nerves, since the contents of magnesium, sodium, or potassium of the nerve were not altered by acute renal failure. Others, however, were unable to demonstrate derangements in MNCV in patients (3) or dogs (15) with acute renal failure. In this latter study with dogs, nerve calcium was not increased.

Support for a role of excess PTH in the genesis of peripheral neuropathy in CRF is found in the report of Avram *et al.* (2), who described an inverse relationship between MNCV and blood levels of PTH in dialysis patients. These authors also demonstrated an improve-

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ment in MNCV in two patients who underwent parathyroidectomy (8). In contrast, Schaefer *et al.* (16) could not demonstrate a relation between blood levels of PTH and MNCV in patients with chronic renal failure. The reasons for the differences in these studies are not clear but may be related to differences in other biochemical parameters, such as levels of serum calcium, magnesium, and phosphate and acid-base status. Also, one must consider that peripheral neuropathy and derangements in MNCV are part of a chronic progressive process and it is not always possible to correlate such a chronic process with a one-time measurement of blood PTH. Finally, Mahoney and Arieff (15) reported that nerve calcium was normal and MNCV was not decreased in dogs with up to 6 months of CRF. It is possible that a longer duration of CRF is needed for the development of these abnormalities.

In order to determine whether CRF and/or excess PTH affects MNCV and/or nerve calcium, one must use an experimental model with prolonged CRF and excess PTH and compare it with another one with comparable duration and degree of CRF but without PTH throughout the entire study period. This study evaluated MNCV and nerve calcium employing such an approach and using the dog as the experimental animal.

Methods

Fifteen female mongrel dogs weighing 18–25 kg were studied. All animals received the same diet, which provided 78 g of protein, 60 g of fat, 5 g of calcium, and 3 g of phosphorus/day (Kal Kan; Kal Kan Foods Co., Inc., Vernon, CA). Baseline studies included the measurements of the plasma concentration of sodium, potassium, bicarbonate, total calcium, magnesium, and phosphorus, serum PTH, and determination of endogenous creatinine clearance.

After these studies, all of the animals underwent left subtotal renal infarction by ligation of five of the six branches of the left renal artery and, in six of the dogs, thyroparathyroidectomy (PTX) was also performed at the same time. The success of the latter procedure was ascertained by a fall in the serum calcium of at least 2 mg/dl. The diet of the thyroparathyroidectomized animals was supplemented with 1–5 g of calcium carbonate to maintain normocalcemia and with thyroxine (0.1 mg daily, 5 days/week). Three weeks later, all of the dogs were subjected to right nephrectomy. Thus, this protocol provided two groups of dogs with CRF: nine dogs with intact parathyroid glands (NPX) and the other six without parathyroid glands (NPX-PTX). All animals were followed closely thereafter for 49–68 (57 ± 1.7) weeks during which measurements of plasma concentrations of calcium, phosphorus, and creatinine were determined several times. Serum PTH and creatinine clearance were measured at the end of the study. In three NPX dogs, PTX was done after 52 weeks of CRF; two of these animals were followed for an additional 52 weeks, and the third one was followed for 40 weeks. All dogs were sacrificed at the end of the study.

The concentrations of phosphorus, creatinine, and bicarbonate were determined by an autoanalyzer (Technicon Instrument Corp., Tarrytown, NY), concentrations of sodium and potassium were measured with an IL flame photometer (model 343; Instrumentation Laboratory, Inc., Lexington, MA), and concentrations of calcium and magnesium were measured with an atomic absorption spectrophotometer (model 503; Perkin-Elmer Corp., Norwalk, CT). PTH was determined by radioimmunoassay according to the method reported previously from our laboratory (12). Free thyroxine index was calculated as the product of T_3 uptake ratio and T_4.

MNCV was measured using the flexline electromyograph (Medical Instrument Co., Burbank, CA) while the animals were under 0.5 mg/kg pentobarbital anesthesia. Ventilation was maintained with a Harvard respirator (Harvard Apparatus Co., Inc., Millis, MA) at a rate of 25 strokes/min. The tidal volume was adjusted to maintain a PCO_2 of 25 mm Hg.

The following technique was used for the measurement of MNCV (9, 17). By using a stainless steel intramuscular electrode, the sciatic nerve was stimulated supramaximally (rectangular pulse of 0.1 msec at 1 Hz frequency) at the level of the sciatic notch (proximal) and the popliteal fossa (distal). Extra precaution was taken to avoid damage of the nerve by introducing the electrode slowly and gradually increasing the voltage until optimum muscle compound action potential was obtained. The muscle pickup electrode (positive) was subcutaneously inserted in the plantar muscle of the rear foot. The indifferent electrode (negative) was attached to the rear foot tendon. Both proximal and distal latencies were measured from the display of the stimulus artifact and muscle compound action potential on the oscilloscope. MNCV was calculated by dividing the distance in millimeters by the difference between the proximal and the distal latencies. This provided the velocity of the fastest conducting fibers. All measurements of MNCV were made in a room in which the ambient temperature was kept between 70 and 74°F, and the animals were brought to the room 1 hr before the measurement.

On the day of sacrifice and after the measurement of MNCV, the sciatic nerve was dissected and removed. A specimen of the nerve of about 1.0 g was first washed with normal saline, blotted with filter paper, and then placed in a tared crucible. It was weighed to 0.01 mg to determine wet weight and then dried at 105°C for 48 hr. The tissue was reweighed to determine water content and was then brought to dry ash at 550°C for 24 hr.

The samples were then extracted in 0.75 N nitric acid for 24 hr and measurements of calcium were made in the supernatant. All data are presented as the mean ± SE; statistical comparisons between groups were performed by paired or unpaired analysis as appropriate.

Results

The plasma concentration of calcium and phosphorus and the calcium-phosphorus product that were obtained every 4–6 weeks throughout the entire period of the study are shown in Table I. There were no significant differences in these parameters between the NPX and NPX-PTX dogs except for the fall in plasma calcium concentration and the higher values of plasma phosphorus during the first month after parathyroidectomy. The levels of creatinine clearance, the plasma concentrations of electrolytes, and the serum levels of PTH before the induction of CRF and at the time of sacrifice of the six NPX and NPX-PTX dogs are shown in Table II. The 5/6 nephrectomy resulted in marked and significant ($P < 0.01$) reduction in creatinine clearance; however, there was no significant difference in the creatinine clearance between the NPX and NPX-PTX animals before or after induction of CRF. The duration of CRF in the two groups of animals was not different either. Similarly, there were no significant differences among the concentrations of serum sodium, potassium, calcium, phosphorus, magnesium, or free throxine index. The serum concentration of bicarbonate decreased modestly but significantly after the induction of CRF in both groups of dogs. The serum concentration of PTH was elevated after CRF in animals with intact parathyroid glands (168 ± 38 μleq/ml), and the values were 8–25 times higher than normal. The serum levels of PTH were undetectable in the NPX-PTX dogs.

The calcium content of peripheral nerves in NPX dogs (444 ± 45 mg/kg dry wt) was significantly ($P < 0.01$) higher than that of NPX-PTX animals (229 ± 3 mg/kg dry wt). This latter value is even lower than that previously found in normal dogs (252 ± 5 mg/kg dry wt) or in normocalcemic PTX dogs with normal renal function (262 ± 5 mg/kg dry wt) in our laboratory (14).

Figure 1 depicts MNCV before and after more than 1 year of CRF in both NPX and NPX-PTX dogs. There was a significant reduction of MNCV in NPX animals with the mean value changing from 65 ± 1.5 m/sec to 49 ± 3.5 m/sec ($P < 0.01$). In the NPX-PTX dogs, MNCV after CRF (65 ± 1.5 m/sec) was not different from that before renal failure (66 ± 1.5 m/sec).

Table III depicts the biochemical data of the three NPX dogs that were subjected to PTX after 1 year of CRF and followed for an additional 40 to 52 weeks, and Figure 2 shows the change in MNCV induced by this experimental procedure. There were no significant differences in the various biochemical parameters except for the fall in the values of PTH to undetectable levels after PTX. Nerve calcium after PTX in these three dogs was 269 ± 17 mg/kg dry wt—a value not different from that in the other six NPX-PTX animals (229 ± 3 mg/kg dry wt) and significantly ($P < 0.01$) lower than that in NPX dogs (444 ± 45 mg/kg dry wt), despite a more prolonged period of CRF. MNCV in these three animals was normal (65, 62, and 65 ms/sec) before induction of CRF, decreased to 55, 46, and 50 m/sec, respectively, after 1 year of renal failure and excess PTH, and returned to normal values (63, 60 and 60 m/sec, respectively) after PTX, despite an additional 40–52 weeks of renal failure.

Table I. The Serum Levels of Calcium, Phosphorus, and Calcium-Phosphorus Product Obtained Throughout the Entire Period of the Study[a]

Study peroid[b]	SCa[c] (mg/dl)		SP (mg/dl)		CaXP product	
	NPX	NPX-PTX	NPX	NPX-PTX	NPX	NPX-PTX
Before NPX or PTX	10.3 ± 0.20	10.4 ± 0.10	4.0 ± 0.29	4.6 ± 0.25	48 ± 2.9	44 ± 2.7
Two weeks later	10.1 ± 0.41	7.4 ± 0.45[d,e]	4.8 ± 0.27	5.8 ± 0.27[d,e]	47 ± 2.2	43 ± 2.7[d]
One month after NPX	10.1 ± 0.16	8.0 ± 0.36[e]	4.5 ± 0.23	5.9 ± 0.24[e]	46 ± 2.7	47 ± 0.6
	10.0 ± 0.23	9.3 ± 0.18	4.1 ± 0.28	4.9 ± 0.27	41 ± 3.5	46 ± 1.9
	9.9 ± 0.26	9.7 ± 0.21	4.2 ± 0.24	4.6 ± 0.26	40 ± 2.1	44 ± 1.5
	9.9 ± 0.34	9.7 ± 0.35	4.3 ± 0.63	4.4 ± 0.25	42 ± 4.0	44 ± 1.5
	9.9 ± 0.11	9.7 ± 0.15	4.1 ± 0.27	4.5 ± 0.11	40 ± 2.5	43 ± 1.0
	9.9 ± 0.19	10.2 ± 0.17	3.8 ± 0.28	4.3 ± 0.20	38 ± 3.0	44 ± 1.5
	10.0 ± 0.27	10.5 ± 0.34	3.9 ± 0.29	4.2 ± 0.15	39 ± 3.4	44 ± 1.6
	10.1 ± 0.21	10.6 ± 0.28	3.9 ± 0.29	4.2 ± 0.17	40 ± 4.7	43 ± 1.6
	10.2 ± 0.12	10.3 ± 0.16	4.0 ± 0.50	4.3 ± 0.27	40 ± 1.2	43 ± 2.1

[a] Data are presented as mean ± SE.
[b] The 4th to 11th sets of data were obtained at intervals of 5–6 weeks throughout the study.
[c] SCa, serum calcium; SP, serum phosphorus.
[d] After parathyroidectomy.
[e] $P < 0.01$ from values in NPX dogs.

Table II. Serum Electrolytes, PTH, MNCV, and Calcium Content of Peripheral Nerves in NPX and NPX-PTX Dogs[a]

	Before CRF		After CRF	
	NPX	NPX-PTX	NPX	NPX-PTX
Duration (weeks)			57 ± 6.4	58 ± 6.2
Creatinine clearance (ml/min)	58.6 ± 1.70	59.7 ± 2.60	14.5 ± 3.70	13.2 ± 3.10
Sodium (mEq/liter)	150 ± 0.5	148 ± 1.2	149 ± 1.2	146 ± 1.2
Potassium (mEq/liter)	4.4 ± 0.07	4.4 ± 0.13	4.6 ± 0.09	4.5 ± 0.11
Bicarbonate (mEq/liter)	21.5 ± 0.60	22.6 ± 0.60	18.5 ± 0.60	19.7 ± 0.50
Calcium (mg/dl)	10.2 ± 0.11	10.3 ± 0.10	10.1 ± 0.10	10.0 ± 0.20
Phosphorus (mg/dl)	4.3 ± 0.30	4.6 ± 0.30	4.6 ± 0.20	4.5 ± 0.30
Calcium-phosphorus product	44 ± 2.8	47 ± 2.6	46 ± 2.8	45 ± 2.8
Free thyroxine index	2.13 ± 0.07	2.11 ± 0.07	2.05 ± 0.08	2.02 ± 0.06
Magnesium (mg/dl)	1.9 ± 0.03	1.9 ± 0.06	2.0 ± 0.03	1.9 ± 0.10
PTH (μleq/ml)	12.5 ± 3.00	12.3 ± 2.95	168 ± 38[b]	Undectable
MNCV (m/sec)	65 ± 1.5	66 ± 1.5	49 ± 3.5	65 ± 1.5
Calcium content of peripheral nerve (mg/kg dry wt)			444 ± 45[b]	229 ± 3

[a] Data are presented as mean ± 1 SE.
[b] $P < 0.01$ versus NPX-PTX.

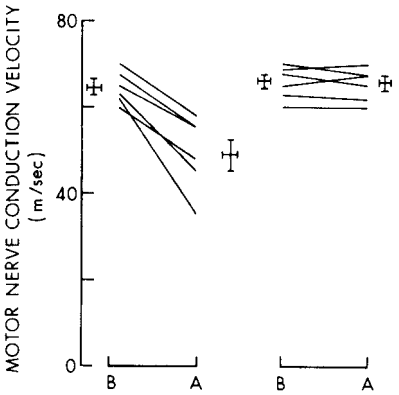

Figure 1. The effect of CRF on MNCV in animals with CRF (left panel) and those with CRF and parathyroidectomy (right panel). Each line represents a study in one dog. B indicates before renal failure and A indicates after renal failure. Brackets denote mean ± 1 SE.

Discussion

The results of this study show that CRF of a 1-year duration or more in dogs with elevated serum levels of PTH is associated with a significant increment in calcium content of the sciatic nerve. This rise in nerve calcium could be due to a rise in calcium-phosphorus product in blood and/or to the state of secondary hyperparathyroidism. The values of the calcium-phosphorus product in the blood of the NPX dogs throughout the entire study period were not elevated and were not different from those observed before the induction of CRF or from those of the NPX-PTX dogs. The demonstration that the nerve calcium content in NPX-PTX dogs was not elevated despite similar degree and duration of renal failure and similar levels of serum electrolytes indicates that the elevation of blood levels of PTH in the NPX dogs is primarily responsible for the high calcium content of the peripheral nerve in this latter groups of dogs.

PTH is known to enhance entry of calcium into many cells and has been implicated in the genesis of the rise in calcium content in aorta (18), skin (19), cornea (20), brain (1, 4), and heart (22) of animals or humans with CRF. Recently, it was found that chronic exposure to excess PTH in the presence (23) or absence (24) of CRF is associated with elevated resting levels of cytosolic calcium in pancreatic islets and of brain synaptosomes as well (25). All of these observations and the result of this study taken together support the notion that the rise in calcium content of the peripheral nerve in CRF is most likely mediated by the high blood levels of PTH. Further support for this postulate is found in the observation that nerve calcium was normalized after PTX of animals with preexisting CRF.

It is of interest to note that this rise in nerve calcium could be potentially reversible. This notion is supported by the results of our studies in the three dogs who had CRF and elevated serum levels of PTX for a year and were then subjected to PTX and followed for an additional 40 to 52 weeks. Although the nerve calcium content at the end of 1 year of renal failure in these three dogs was not measured, we can assume with certainty that it was elevated as it was in the other six dogs with 1 year of CRF. PTX and the correction of the state of secondary hyperparathyroidism apparently reversed the changes in nerve calcium in these three dogs despite the additional prolonged period of CRF.

Our results are different from those reported by Mahoney and Arieff (15), who did not find a rise in peripheral nerves in dogs with CRF of 4 months' duration. The reasons for this difference between our data and theirs could be because of the shorter duration of

Table III. Serum Electrolytes, PTH, MNCV, and Calcium Content of Peripheral Nerve after PTX of Animals with Preexistent CRF[a]

	Before CRF	After CRF	After PTX and CRF
Creatinine clearance (ml/min)	54.0 ± 1.20	14.0 ± 1.20	11.0 ± 0.60
Sodium (mEq/liter)	149 ± 0.70	149.6 ± 0.90	148.0 ± 1.00
Potassium (mEq/liter)	4.1 ± 0.18	4.3 ± 0.20	4.0 ± 0.16
Bicarbonate (mEq/liter)	23.0 ± 0.60	22.3 ± 0.90	21.3 ± 0.90
Calcium (mg/dl)	10.3 ± 0.15	10.2 ± 0.15	10.0 ± 0.17
Phosphorus (mg/dl)	3.7 ± 0.12	3.9 ± 0.15	4.1 ± 0.12
Magnesium (mg/dl)	2.03 ± 0.18	1.97 ± 0.03	1.93 ± 0.01
PTH (μleq/ml)	5.0 ± 2.00	73 ± 19.50[b]	Undectable
Calcium content of peripheral nerve (mg/kg dry wt)			269 ± 17

[a] Data are presented as mean ± 1 SE.
[b] $P < 0.01$ versus after PTX and CRF.

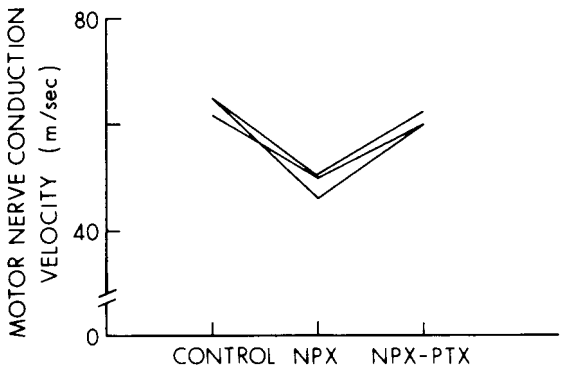

Figure 2. The effect of CRF (NPX) and parathyroidectomy (NPX-PTX) on MNCV in three animals which were subjected to parathyroidectomy after 52 weeks of CRF and followed for an additional 40 (one dog) and 52 weeks (2 dogs). Control indicates values before CRF. Each line represents a study in one dog.

renal failure in their (15) study. In addition, they did not report the levels of PTH in their study, and it is possible that the concentrations of the hormone in the blood of their animals were not elevated to the same degree as it was in the blood of our animals because of the shorter duration of the renal failure.

The mechanisms through which an increase in calcium content of nerve produces prolongation of MNCV are not evident. Theoretically, calcium may accumulate in the interstitium of the nerve, in the Schwann cells, and/or in the axonal cytoplasm. An increase in calcium content of the nerve interstitium and Schwann cells may affect the functional integrity of Schwann cell system and may result in slowing of the rise time of action potential at the nodes of Ranvier and, as such, slows MNCV. Dinn and Crane (26) studied the histology of sural nerve at autopsy of seven dialysis patients. They found segmental demyelination and these changes varied from widening of the nodes of Ranvier to partial or complete loss of myelin of an internodal segment. It is also possible that the chronic exposure to PTH is associated with an elevation in the resting levels of calcium of the axonal cytoplasm. Such an effect of excess PTH on resting levels of cytosolic calcium was reported in another nervous system structure, the brain synaptosomes (25).

Although the results of our studies provide evidence for the role of increased calcium content of nerve in the genesis of the prolonged MNCV of CRF, it is possible that other biochemical changes may be important. Our data rule out a role for the changes in concentrations of serum phosphorus, calcium, magnesium, potassium, sodium, or bicarbonate, since these parameters were not different between the NPX and the NPX-PTX dogs. Excess PTH, per se, rather than elevated nerve calcium may be responsible. To demonstrate such a relationship one would need an experimental model with excess PTH but normal nerve calcium content, a combination that we were unable to achieve. It should be mentioned that PTH may affect phospholipid turnover (27–30) and/or content (27, 31) of several cells. If PTH also induces changes in phospholipid metabolism of peripheral nerves, one might expect that such an action may affect nerve function.

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