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*J Clin Invest.* 1978;62(1):88-93. <https://doi.org/10.1172/JCI109118>.

### Research Article

Peripheral neuropathy is not an uncommon complication of chronic uremia. Because parathyroid hormone, by raising brain calcium, is partly responsible for central nervous system aberrations in uremia, we studied the relative role of uremia, per se, and(or) parathyroid hormone on peripheral nerve calcium and motor nerve conduction velocity (MNCV). Studies were made in six groups of six dogs each, as follows: (a) normal dogs, (b) thyroparathyroidectomized (T-PTX) animals, (c) dogs with 3 days of uremia produced by bilateral nephrectomy, (d) T-PTX before the induction of acute renal failure, (e) normal dogs receiving 100 U/day of parathyroid extract (PTE) for 3 days, and (f) normal animals receiving 3 days of PTE followed by 5 days without PTE. Calcium content in peripheral nerve (expressed as milligram per kilogram of dry weight) was  $252 \pm 5$  (SE) in normal animals and  $262 \pm 4$  in T-PTX dogs. It was significantly ( $P < 0.01$ ) higher in dogs with acute renal failure and intact parathyroid glands ( $410 \pm 12$ ) and in normal animals receiving PTE ( $362 \pm 7$ ). T-PTX, before acute renal failure, prevented the rise in peripheral nerve calcium ( $262 \pm 4$ ) and PTE withdrawal was followed by the return of peripheral nerve calcium to normal ( $261 \pm 3$ ). The increments in peripheral nerve calcium were associated with slowing of MNCV. It decreased significantly from  $70 \pm 4$  to  $43 \pm 1$  m/s after 3 days of acute uremia in [...]

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# Effect of Parathyroid Hormone and Uremia on Peripheral Nerve Calcium and Motor Nerve Conduction Velocity

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**ABSTRACT** Peripheral neuropathy is not an uncommon complication of chronic uremia. Because parathyroid hormone, by raising brain calcium, is partly responsible for central nervous system aberrations in uremia, we studied the relative role of uremia, per se, and(or) parathyroid hormone on peripheral nerve calcium and motor nerve conduction velocity (MNCV). Studies were made in six groups of six dogs each, as follows: (a) normal dogs, (b) thyroparathyroidectomized (T-PTX) animals, (c) dogs with 3 days of uremia produced by bilateral nephrectomy, (d) T-PTX before the induction of acute renal failure, (e) normal dogs receiving 100 U/day of parathyroid extract (PTE) for 3 days, and (f) normal animals receiving 3 days of PTE followed by 5 days without PTE. Calcium content in peripheral nerve (expressed as milligram per kilogram of dry weight) was  $252 \pm 5$  (SE) in normal animals and  $262 \pm 4$  in T-PTX dogs. It was significantly ( $P < 0.01$ ) higher in dogs with acute renal failure and intact parathyroid glands ( $410 \pm 12$ ) and in normal animals receiving PTE ( $362 \pm 7$ ). T-PTX, before acute renal failure, prevented the rise in peripheral nerve calcium ( $262 \pm 4$ ) and PTE withdrawal was followed by the return of peripheral nerve calcium to normal ( $261 \pm 3$ ). The increments in peripheral nerve calcium were associated with slowing of MNCV. It decreased significantly from  $70 \pm 4$  to  $43 \pm 1$  m/s after 3 days of acute uremia in dogs with intact parathyroid glands and T-PTX before acute renal failure prevented the fall in MNCV. Administration of PTE to normal animals reduced MNCV from  $63 \pm 3$  to  $35 \pm 3$  m/s and the withdrawal of PTE restored MNCV to normal ( $73 \pm 2$  m/s). The results show that (a) excess parathyroid hormone increases peripheral nerve calcium and slows MNCV, (b) T-PTX, previously performed, prevents these

changes in acute uremia, and (c) the withdrawal of PTE administration is followed by a reversal of the abnormalities.

## INTRODUCTION

Several lines of evidence indicate that abnormalities in the central and peripheral nervous system develop in uremia (1, 2). Previous studies from our laboratory have shown that the elevation of parathyroid hormone (PTH)<sup>1</sup> in blood, usually found in uremia (3, 4), may play an important role in the genesis of the derangements in the central nervous system (5). Thus, excess PTH increased the calcium content of the brain (5) and produced typical aberrations in the electroencephalogram (6). Furthermore, these changes were reversed when the state of excess PTH was abolished (7).

It is possible that the excess PTH plays a major role in the etiology of the peripheral neuropathy in uremia. PTH may increase the calcium content of the peripheral nerve and may induce abnormalities in motor nerve conduction velocity (MNCV). The present investigation was undertaken to test this hypothesis.

## METHODS

Studies were made in 36 mongrel dogs of both sexes, weighing 18–22 kg. The animals were divided into six groups of six dogs each, as follows: (a) normal dogs, (b) thyroparathyroidectomized dogs (T-PTX), (c) dogs with 3 days of acute renal failure, (d) dogs which were subjected to T-PTX before the production of acute renal failure, (e) normal dogs which received parathyroid extract (PTE, Eli Lilly and Company, Indianapolis, Ind.), 50 U twice a day for 3 days, and (f) normal dogs which received PTE for 3 days, as described above, followed by 5 days without PTE administration.

Acute uremia was produced by bilateral nephrectomy performed through flank incisions. During the subsequent 3 days of acute uremia, the dogs had free access to food and water. The success of T-PTX was ascertained by a fall in the serum

Dr. Goldstein was a Fellow of the National Kidney Foundation and is currently a recipient of Fellowship 1F32 AM 05754 from the National Institutes of Health.

Received for publication 11 November 1977 and in revised form 16 January 1978.

<sup>1</sup> Abbreviations used in this paper: MNCV, motor nerve conduction velocity; PTE, parathyroid extract; PTH, parathyroid hormone; T-PTX, thyroparathyroidectomized.

calcium of at least 2.0 mg/100 ml within 48 h. The T-PTX animals received oral calcium supplementation to prevent the development of tetany.

The animals were sacrificed 3 days after T-PTX (group B), 3 days after acute uremia (groups C and D), 3 days after PTE administration (group E), and after 5 days of discontinuation of PTE (group F).

MNCV was measured using the Flexline Electromyograph (Medical Instrument Co., Burbank, Calif.) while the animals were under 0.5 mg/kg pentobarbital anesthesia. Ventilation was maintained with a Harvard respirator. (Harvard Apparatus Co., Inc., Millis, Mass.) at a rate of 25 strokes/min. The tidal volume was adjusted to maintain a PCO<sub>2</sub> of  $\approx$  25 mm Hg. Measurements of MNCV were made before subjecting the animals to any experimental procedure (control values) and at the time of sacrifice. In group F, MNCV was also measured at the end of 3 days of PTE administration. Calcium chloride was given intravenously to T-PTX uremic dogs to raise the blood levels of calcium to normal before measurements of MNCV. This was done to prevent changes in MNCV that could be produced by hypocalcemia, per se.

The following technique was used for measurement of MNCV (8). Using a stainless steel intramuscular electrode, the sciatic nerve was stimulated supramaximally (rectangular pulse of 0.1 ms 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 from dividing the

distance in millimeters by the difference between proximal and the distal latencies. This provided the velocity of the fastest conducting fibers. All measurements of MNCV were made at a room in which the ambient temperature was kept between 70 and 74°C and the animals were brought to the room an hour 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  $\approx$  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 h. The tissue was reweighed to determine water content and was then brought to dry ash at 550°C for 24 h. The samples were then extracted in 0.75 N nitric acid for 24 h and measurements of calcium, magnesium, sodium, and potassium were made in the supernates.

Blood samples were obtained before the experimental procedure and at time of sacrifice for the measurements of creatinine, calcium, magnesium, phosphorus, sodium, and potassium. The techniques for the various analytical methods have been detailed elsewhere (9, 10).

## RESULTS

The results are presented in Tables I and II, and Figs. 1–3. The effects of the various experimental procedures on blood chemistry are shown in Table I. T-PTX was followed by a significant ( $P < 0.01$ ) fall in both total and ionized calcium and a modest rise in serum phosphorus. There were marked increments in the blood concentration of inorganic phosphorus during acute uremia. These levels increased from  $4.1 \pm 0.08$  (SE) to

TABLE I  
Effects of Uremia, Parathyroidectomy, and PTE Administration on the Concentration of Serum Electrolytes

	Na	K	Ca	Ca <sub>i</sub>	Mg	P	Cr
	meq/liter		mg/100 ml				
Control	144±2	4.5±0.1	9.84±0.17	4.31±0.19	1.86±0.05	4.2±0.30	0.94±0.11
T-PTX							
Base line			9.76±0.11	4.27±0.05	1.61±0.08	3.9±0.09	
3 days PTX	143±2	4.6±0.1	6.04±0.31	2.38±0.11	1.64±0.06	4.7±0.33	0.94±0.04
PTE administration							
Base line			9.89±0.11	4.25±0.05	1.53±0.04	4.1±0.15	
3 days PTE	140±2	4.2±0.1	11.53±0.15	4.96±0.10	1.88±0.19	4.6±0.50	1.1±0.18
PTE withdrawal							
Base line			9.79±0.19	4.32±0.08	1.59±0.04	4.0±0.07	0.9±0.08
3 days PTE			11.39±0.10	5.02±0.04			1.1±0.09
5 days PTE	144±2	4.4±0.1	10.12±0.20	4.46±0.23	1.90±0.11	4.2±0.33	0.9±0.09
Discontinuation							
Acute uremia							
Base line			9.94±0.13	4.24±0.06	1.53±0.08	4.1±0.08	
3 days uremia	142±1	8.3±0.2	10.09±0.41	4.31±0.21	3.00±0.23	14.9±1.41	12.7±0.42
T-PTX—uremia							
Base line			10.05±0.09	4.35±0.09	1.64±0.04	4.0±0.10	
PTX—3 days uremia	143±2	7.7±0.5	5.54±0.39	2.40±0.05	2.95±0.15	8.9±0.50	12.5±0.20
Ca infusion			9.16±0.28	3.78±0.12		8.9±0.50	

Abbreviations used in this table: Ca<sub>i</sub>, ionized calcium; Cr, creatinine. Data are presented in mean±1 SE.

TABLE II  
Changes in Nerve Calcium, Magnesium, Sodium, Potassium, and Water Content

	Ca	Mg	Na	K	Water
	mg/kg dry wt		meq/kg dry wt		%
Control	252±5	229±10	307±6	77±3	68.40±1.15
T-PTX	262±4	227±8	316±15	70±1	69.27±0.49
PTE administration	362±7*	247±4	307±8	70±6	69.54±0.59
PTE withdrawal	261±3	240±6	321±7	70±9	69.83±0.86
Acute uremia	410±12*	245±7	309±9	89±8	69.69±0.56
T-PTX—uremia	261±4	253±8	317±7	83±4	70.79±0.50

Data are presented in mean±1 SE.

\* Data is significantly different from control with  $P < 0.01$ .

14.9±1.41 mg/100 ml ( $P < 0.01$ ) in acutely uremic dogs with intact parathyroid glands, and from 4.0±0.1 to 8.9±0.5 mg/100 ml in T-PTX uremic animals. There were no significant changes in the concentration of serum calcium during acute uremia. The administration of PTE was associated with a modest but significant increment in the levels of both total and ionized calcium. After 5 days of PTE withdrawal, the levels of serum calcium returned to normal.

The various experimental procedures did not significantly alter the water content of the sciatic nerve (Table II). The calcium content of peripheral nerve in dogs with acute uremia and intact parathyroid glands (410±12 mg/kg dry wt) was significantly ( $P < 0.01$ ) higher than that of normal dogs (252±5 mg/kg dry wt), Fig. 1. T-PTX, before induction of acute uremia, prevented the rise in the calcium content of the peripheral nerve (262±4 mg/kg dry wt). T-PTX by itself did not alter the calcium content of the sciatic nerve (261±4 mg/kg dry wt). The calcium content of the peripheral nerve in normal dogs receiving 3 days of parathyroid extract (362±7 mg/kg dry wt) was significantly ( $P < 0.01$ ) higher than normal but lower than that of the uremic dogs with intact parathyroid glands. After 5 days of

withdrawal of PTE, the calcium content of the sciatic nerve (261±3 mg/kg dry wt) was normal.

There were modest increments in the magnesium content of the peripheral nerve in uremic dogs with intact parathyroid glands and those receiving PTE. These changes were not affected by T-PTX or withdrawal of PTE administration. The sodium content of the nerve was not altered by the various experimental procedures although the potassium content displayed modest but inconsistent alterations.

The increments in calcium content of the peripheral nerve were associated with reduction in MNCV (Fig. 2). In the uremic dogs with intact parathyroid glands, MNCV fell significantly ( $P < 0.01$ ) from 70±4 to 43±1 m/s. Uremia in T-PTX dogs did not affect MNCV. The administration of PTE was associated with a significant ( $P < 0.01$ ) decrease in MNCV (from 63±3 to 35±3 m/s). Withdrawal of PTE administration restored MNCV to normal (Fig. 3).

## DISCUSSION

The results of the present study clearly demonstrate that acute uremia is associated with a significant and

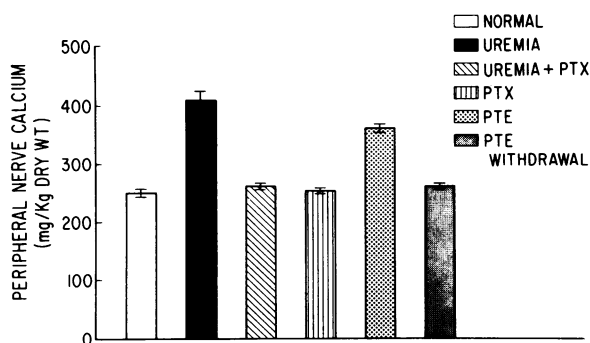


FIGURE 1 The effect of acute uremia, thyroparathyroidectomy (PTX), PTE administration and PTE withdrawal on peripheral nerve calcium. The brackets represent ±1 SE.

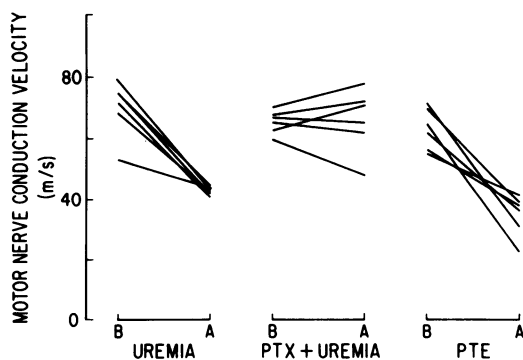


FIGURE 2 The effect of uremia, thyroparathyroidectomy (PTX), and uremia, and PTE administration on motor nerve conduction velocity. B represents value before the experimental procedure and A at the time of sacrifice of the animals.

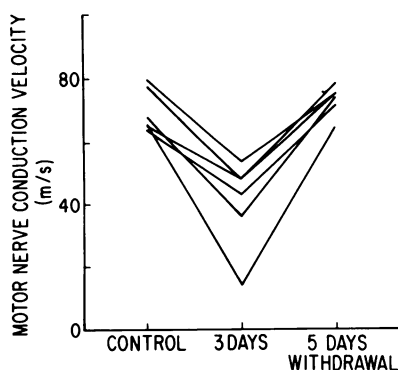


FIGURE 3 The effect of PTE administration for 3 days and its withdrawal for 5 days on motor nerve conduction velocity.

marked (60%) increase in calcium content of the sciatic nerve. Several factors may be involved in this phenomenon. These include elevations in the blood levels of PTH that usually occur in acute renal failure (11), an elevation in calcium-phosphorus product, or uremia, per se.

Our data strongly support that excess PTH is a major determinant underlying the increment in nerve calcium in uremia. This conclusion is supported by three findings. First, T-PTX, before the induction of uremia, prevented the rise in nerve calcium; second, the administration of PTE to dogs with normal renal function produced a significant and marked elevation in nerve calcium; and, third, the calcium content of nerve returned to normal after the state of excess PTH was abolished. This phenomenon is in agreement with previously reported data which showed that PTH increases the calcium content in aorta (12), skin (13), cornea (14), brain (5), and heart (15).

Acute uremia is associated with an elevation in the calcium-phosphorus product and such a change may predispose to calcium deposition in soft tissues (16) and, hence, a rise in nerve calcium. In our studies, T-PTX dogs with acute uremia had a calcium-phosphorus product of  $82 \pm 7$ , but a normal nerve calcium, whereas normal dogs receiving PTE had a calcium-phosphorus product of  $53 \pm 5$  and a markedly elevated nerve calcium. Thus, an increase in nerve calcium can occur in the absence of high calcium-phosphorus product and nerve calcium can be normal in the face of elevated calcium-phosphorus product. It is of interest, however, that the uremic dogs with intact parathyroid glands had the highest calcium-phosphorus product and the highest nerve calcium content. This observation suggests that a markedly elevated calcium-phosphorus product could also participate in the process leading to a rise in nerve content of calcium.

Finally, it seems that uremia, per se, does not play a major role in the rise of nerve calcium content since T-PTX dogs with uremia of similar degree to that of

dogs with intact parathyroid glands had normal calcium content in their nerves.

A most interesting feature of the present study is the observation that a rise in the calcium content of nerve was associated with a reduction in MNCV. The abnormality in MNCV occurred only in those experimental conditions where nerve calcium was elevated and MNCV became normal when the rise in nerve calcium was reversed. The mechanisms by which an increase in calcium content of nerve results in reduction in MNCV are not obvious. However, certain available data may provide explanation for this phenomenon. The data of the present study did not define where the increased calcium is located. Theoretically, it could be in the interstitium, Schwann cells, or axonal cytoplasm. The consequences of the changes in calcium content in these various sites may be different.

Two lines of evidence vitiate the possibility that the increase in calcium is within the axonal cytoplasm. First, the axonal membrane serves as an effective barrier to calcium ion maintaining axoplasmic concentration of calcium within narrow limits (17). Second, an increase in the calcium content of the axonal cytoplasm is associated with swelling of the axon followed by fragmentation of the myelin sheath (18-20). The rapid reversibility of the changes in MNCV in our studies suggest that the reduction in MNCV is not due to anatomical disruption of the integrity of the myelin.

An alternative explanation is that calcium accumulates in areas outside the axon such as the interstitium or the Schwann cells, and slows the rise time of action potential at the nodes of Ranvier and, as such, slows MNCV. It should be mentioned, however, that Dayan et al. (21) studied nerve biopsies from patients with acute renal failure and found that segmental damage to the Schwann cell-myelin sheath occurred as early as 4 days after the onset of the disease; evidence for rapid repair manifested by remyelinated segments were noted within 10 days of the onset of acute renal failure. These data suggest that certain metabolic or toxic consequences of acute renal failure can affect the Schwann cells and the damage could be reversible since repair may proceed quickly and simultaneously.

Although our studies suggest an association between the increased calcium content of nerve and the slowing of MNCV, it is possible that other factors may play a role in the reduction of MNCV. 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 which we are unable to achieve.

Lindholm (22) reported that hyperkalemia may affect MNCV and found that an increase of 1 meq/liter is associated with a decrease of 2.1 m/s in MNCV. However, his patients had renal failure and, most probably,

had a state of excess PTH. It does not seem that hyperkalemia could have played a role in our finding since the elevation in serum potassium in T-PTX uremic dogs ( $7.7 \pm 0.5$  meq/liter) was not different from that in uremic dogs with intact parathyroid glands ( $8.3 \pm 0.2$  meq/liter) while MNCV was reduced only in the latter animals. Furthermore, the normal dogs receiving parathyroid extract had decreased MNCV, but without hyperkalemia.

Theoretically, hypermagnesemia could have contributed to our findings. This, however, seems remote. There were no significant differences between the levels of serum magnesium in uremic dogs with ( $3.00 \pm 0.23$  mg/100 ml) or without ( $2.95 \pm 0.15$  mg/100 ml) parathyroid glands, but MNCV was reduced only in those with intact glands. Furthermore, the studies of Hollinrake et al. (23) showed that the concentration of magnesium in blood was not different in uremic patients with or without peripheral neuropathy.

A discussion of the relevance of our observations to peripheral neuropathy in uremia is in place. Patients with chronic renal failure have peripheral neuropathy with reduced MNCV (1, 2) and marked elevation in blood levels of PTH (3, 4). It is, therefore, possible that prolonged exposure of peripheral nerves to excess PTH, as in uremia, may result in accumulation of calcium in critical areas within the nerve and contribute to the pathogenesis of peripheral neuropathy. Avram et al. (24) found that MNCV was reduced in dialysis patients with elevated blood levels of PTH although MNCV was within the normal range in age-matched dialysis patients who had markedly lower levels of PTH.

The mechanisms of peripheral neuropathy in uremia are not, as yet, elucidated. Several investigators have found that the nerves in uremic patients with peripheral neuropathy display segmental demyelination and axonal degeneration and fragmentation (21, 25, 26). It is possible that marked and chronic elevation of blood levels of PTH may enhance entry of calcium into Schwann cells or into the axonal cytoplasm and contribute to the structural damage noted in the nerves. Such an effect of PTH to increase calcium content of cells have been shown to occur in the organs, such as the kidney (27), cornea (14), and even the brain (5).

#### ACKNOWLEDGMENTS

We are very grateful to Mrs. Gracy Fick, Mrs. Jamie Jimenez, and Mrs. Alice Moomjean for their secretarial assistance.

This work was supported by grant RO1-AM 18959 and contract NO1-AM-7-2218 from the U. S. Public Health Service.

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