

Changes in the electroencephalogram in acute uremia. Effects of parathyroid hormone and brain electrolytes.

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Research Article

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Changes in the Electroencephalogram in Acute Uremia

EFFECTS OF PARATHYROID HORMONE AND BRAIN ELECTROLYTES

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ABSTRACT Studies were carried out in order to evaluate the effects of changes in brain calcium and the influence of parathyroidectomy and administration of parathyroid extract on the electroencephalogram (EEG) of normal and uremic dogs.

Manual analysis of frequency and power distribution of the EEG in uremic dogs revealed a significant increase in both the percentage distribution and the area or power occupied by frequencies below 5 Hz. In addition, high amplitude bursts of delta activity were apparent in the uremic dog. These changes were largely prevented by parathyroidectomy before the induction of uremia, but the administration of parathyroid extract to either normal dogs, or to previously parathyroidectomized uremic dogs, induced EEG changes similar to those noted in uremic animals with intact parathyroid glands. In all groups of animals which showed EEG changes, brain content of calcium was significantly higher than in either normal dogs or previously parathyroidectomized uremic dogs. Changes in arterial pH and bicarbonate, or in the concentrations of Na⁺, K⁺, urea, or creatinine in plasma or cerebrospinal fluid were similar in uremic animals with intact parathyroid glands and in previously parathyroidectomized uremic dogs.

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The results indicate that the EEG changes found in dogs with acute renal failure require the presence of excess parathyroid hormone in blood, and they may be related to the observed changes in brain content of calcium.

INTRODUCTION

It has been shown that there is a significant increase of brain Ca⁺⁺ content in dogs with acute uremia. This phenomenon was prevented by parathyroidectomy but occurred after the administration of parathyroid extract both to normal dogs and uremic animals previously subjected to thyroparathyroidectomy (1). These observations suggested that excess parathyroid hormone is responsible for the observed elevation in brain calcium.

Electroencephalographic changes and various central nervous system abnormalities are noted in patients with uremia (2). With increasing deterioration of renal function, incremental changes in background frequency have been noted (3), and it has been proposed that quantitation of electroencephalographic slowing may provide an objective guide in evaluating the severity of uremia and the management of renal failure (3, 4). Patients with acute or chronic renal failure almost invariably have secondary hyperparathyroidism (5, 6), and similar electroencephalographic abnormalities may be seen both in patients with parathyroid adenoma (7) and in those with renal failure (2, 3). It is possible

that changes in brain Ca^{++} content, or a hyperparathyroid state, may be responsible for the electroencephalographic abnormalities observed in uremia.

The present study was undertaken in order to evaluate the effects of changes in brain Ca^{++} on the electroencephalogram (EEG)¹ of normal and acutely uremic dogs. The influence of parathyroidectomy and administration of parathyroid extract on the EEG was also evaluated.

METHODS

Studies were done in five groups of adult mongrel dogs of both sexes, weighing 15–22 kg, as follows: (a) seven normal dogs; (b) six dogs with uremia of 3.5 days duration; (c) seven normal dogs which received intramuscular injections of parathyroid extract (Eli Lilly & Co., Indianapolis, Ind.), 80 U twice a day for 3.5 days; (d) seven normal dogs which were subjected to thyroparathyroidectomy and received vitamin D₃ (Deltalin, Eli Lilly & Co.) in adequate doses to maintain a serum calcium level of 9–11 mg/dl for 7–10 days and were then made uremic for 3.5 days; (e) and six normal dogs which were first subjected to parathyroidectomy, then made uremic, and received parathyroid extract, 100 U four times a day thereafter. The procedures for induction of uremia and for parathyroidectomy have been described elsewhere (1, 8). The technique for parathyroidectomy involved simultaneous removal of the thyroid gland, and success of parathyroidectomy was ascertained by a fall in plasma Ca^{++} of a least 2 mg/dl within 48 hr.

Animals were sedated with one single dose of intravenous diazepam (Valium, Roche Diagnostics Div., Hoffmann-La Roche Inc., Nutley, N. J.), 0.5 mg/kg, then paralyzed with 1 mg/kg of succinylcholine (Anectine, Burroughs Wellcome & Co., Research Triangle Park, N. C.) intravenously, and immediately intubated with an endotracheal tube. Mechanical ventilation was carried out with a Harvard Respirator (Harvard Apparatus Co., Inc., Millis, Mass.) at a rate of 25 strokes/min and tidal vol of 8.5 cm³/kg. Arterial pCO₂ was maintained at about 35 mm Hg by minor changes in the tidal volume.

EEG recordings were made with a Beckman Accutrace 8 channel electroencephalograph (Beckman Instruments, Inc., Fullerton, Calif.) with a time constant of 0.3 s and muscle filter set at 30 Hz, using subdermal needle electrodes. Bipolar longitudinal linkages were used in accordance with the standard 10–20 system (9). Recordings of the right and left frontoparietal, frontotemporal, centro-occipital, and occipitotemporal areas were obtained in all animals.

At least 3–4 h were allowed between the initial administration of IV diazepam and the EEG recordings. During the recordings, attempts were made to maintain a state of alertness of the dogs, by both manual and auditory stimulation. After the EEG had been obtained, the animals were anesthetized with intravenous sodium pentobarbital (20–30 mg/kg) and samples of arterial blood, cisternal cerebrospinal fluid (CSF) and brain white and gray matter were obtained as previously described (8).

Measurements of Na⁺, K⁺, Ca⁺⁺, Mg⁺⁺, and water content were made in brain cortical gray matter and subcortical white matter, and of Na⁺, K⁺, Ca⁺⁺, Mg⁺⁺, PO₄³⁻, and creatinine levels in plasma and CSF. The analytical methods

¹ Abbreviations used in this paper: CSF, cerebrospinal fluid; EEG, electroencephalogram.

have been published elsewhere (1, 8, 10, 11). The EEG activity was analyzed by a visual method of frequency analysis similar to that described by Laidlaw (12) and Engel et al. (13). A representative segment of the record (epoch), of about 30 s duration was selected. This segment was selected from a portion of the record which showed a stable background frequency after a period of time in which sleep-like activity such as sleep spindles or K complexes were absent. Measurements of frequency distribution were made of the right temporoccipital derivation (12). All clearly visible potentials in the frequency classes 1–13 Hz, with an amplitude of at least 1 mm (5 mV) were included in the analysis. A wave was arbitrarily defined as one that returned half the distance to the baseline, and small superimposed waves were not counted (12). As emphasis was placed on the occurrence of abnormally slow activity, frequency classes from 10 to 13 Hz were counted together, and higher frequencies were not counted (12). The number of waves at each frequency class was counted and the percentage of waves having the same duration was calculated. The average amplitude of all the waves at each particular frequency class was then measured in millimeters, and the result was multiplied by the percentage distribution obtained for that frequency class. The resulting number then gave a measure of the area (or power) occupied by each frequency class, for the EEG segment being analyzed (14, 15). The total EEG area of the epoch was then calculated by adding the areas of all the frequency classes present. The percentage of the total EEG area occupied by all waves below 5 Hz was then calculated, for purposes of comparison. When paroxysmal bursts of high amplitude slow (delta) activities were found, a "burst index" was calculated by dividing the total time of burst activity by the total duration of the record (16). In addition, the records were analyzed for the presence of other types of abnormal activity.

RESULTS

Representative electroencephalographic recordings for all groups studied are shown in Fig. 1. The percentage distribution of slow wave activity (below 7 Hz and below 5 Hz) is shown in Fig. 2 and the percent EEG power for frequencies below 5 Hz, divided by total EEG power, is shown in Fig. 3.

In acutely uremic animals, the plasma urea and creatinine concentrations (\pm SE) were 64.7 ± 4.0 mM and 11.9 ± 1.3 mg/dl, respectively. In these animals, there was a highly significant ($P < 0.01$) increase in the percent slow wave activity as compared to normal values (Figs. 1 and 2). Similarly, the percent EEG power for frequencies below 5 Hz was significantly ($P < 0.01$) greater than normal values (Fig. 3).

In uremic animals who had previously been subjected to parathyroidectomy the concentrations of urea and creatinine in plasma (Table I) were not different from those of uremic animals with intact parathyroid gland function. However, both the frequency distribution (Fig. 2) and the percent EEG power distribution (Fig. 3) in the uremic animals without parathyroid gland function were not different from those of normal animals (Figs. 1–3). When comparing the changes in blood and CSF in uremic animals with intact para-

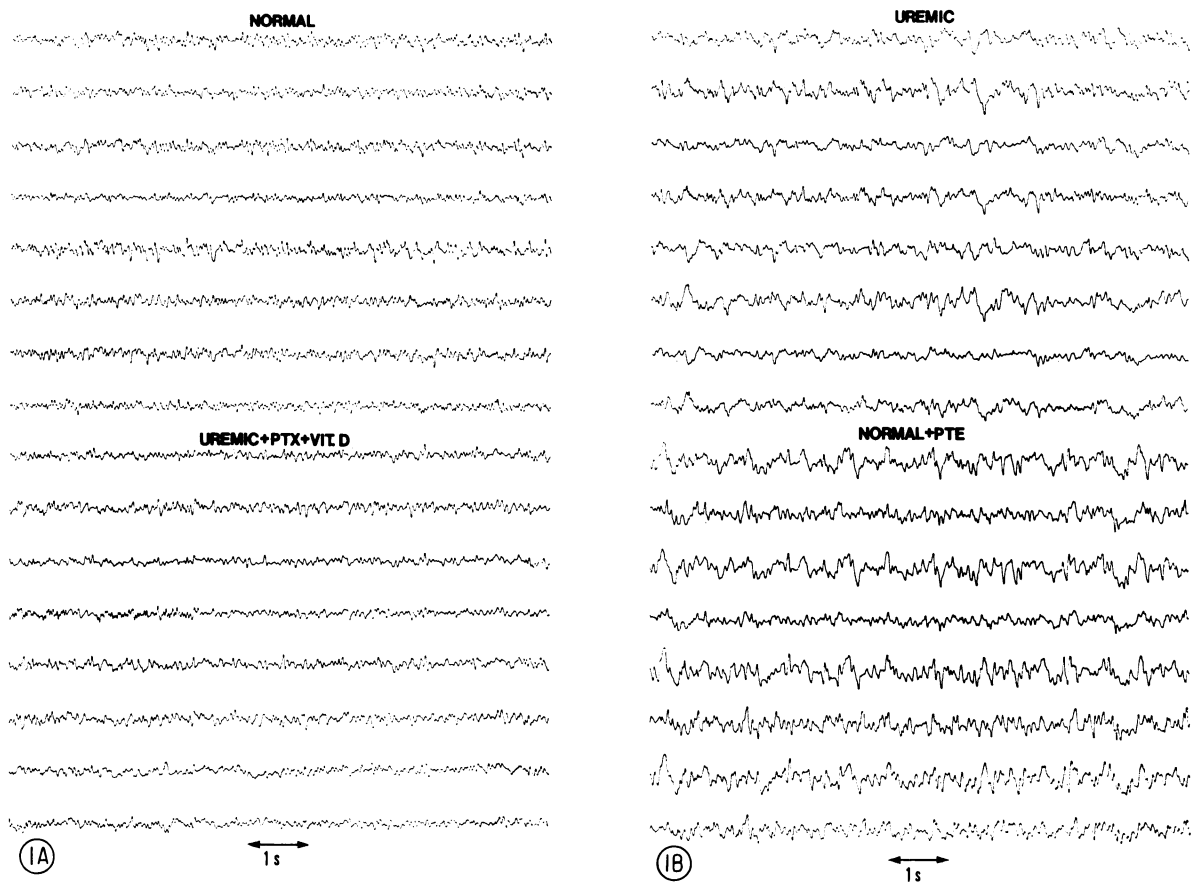


FIGURE 1 Representative samples from electroencephalograms obtained in four experimental groups: (A) normal animals (top) and uremic parathyroidectomized dogs (bottom). (B) Uremic animals with intact parathyroid gland (top) and normal animals receiving parathyroid extract (PTE) for 3 days (bottom). Background frequencies are similar in normal and uremic parathyroidectomized animals, whereas a significant increase in slow wave activity with disruption of background activity is seen in uremic animals and normal dogs receiving PTE. The mean serum creatinine levels in normal dogs (Figs. 1 A, top and 1 B, bottom) was (Mean \pm SE) 0.9 ± 0.1 mg/dl and 1.2 ± 0.2 mg/dl, respectively. The serum creatinine level in both uremic and uremic parathyroidectomized dogs was 11.3 ± 0.7 mg/dl and 10.6 ± 0.6 mg/dl.

thyroid glands, with those noted in uremic animals who had been subjected to parathyroidectomy, there was no significant difference in the arterial pH, $p\text{CO}_2$, or $p\text{O}_2$, or in the concentrations of Na^+ , K^+ , PO_4^{3-} , Ca^{++} , Mg^{++} , or bicarbonate in plasma or CSF (Table I). Although the content of Na^+ and K^+ in brain of uremic animals was lower than those of normal dogs (Table II), there were no differences in these values whether the parathyroid glands were present or previously removed. On the other hand, in uremic animals with intact parathyroid glands, the content of Ca^{++} in both cerebral cortex and subcortical white matter, and Mg^{++} content in white matter, were significantly higher ($P < 0.05$) than those observed in normal animals or in the parathyroidectomized uremic dogs (Table II).

In uremic animals which had previously been subjected to parathyroidectomy and then received parathyroid extract for 3 days, the content of Ca^{++} and Mg^{++} in white and gray matter of brain was not different from that of uremic animals with intact parathyroid gland function (Table II), and was significantly greater ($P < 0.01$) than that found in normal animals. In these animals, the brain content of Na^+ , K^+ , and water was similar to that of uremic animals either with or without parathyroid glands. However, the EEG in these animals revealed frequency distribution and a pattern of percentage EEG power dispersion which were not different from that of uremic animals with intact parathyroid glands (Figs. 2 and 3).

In normal animals who received parathyroid extract

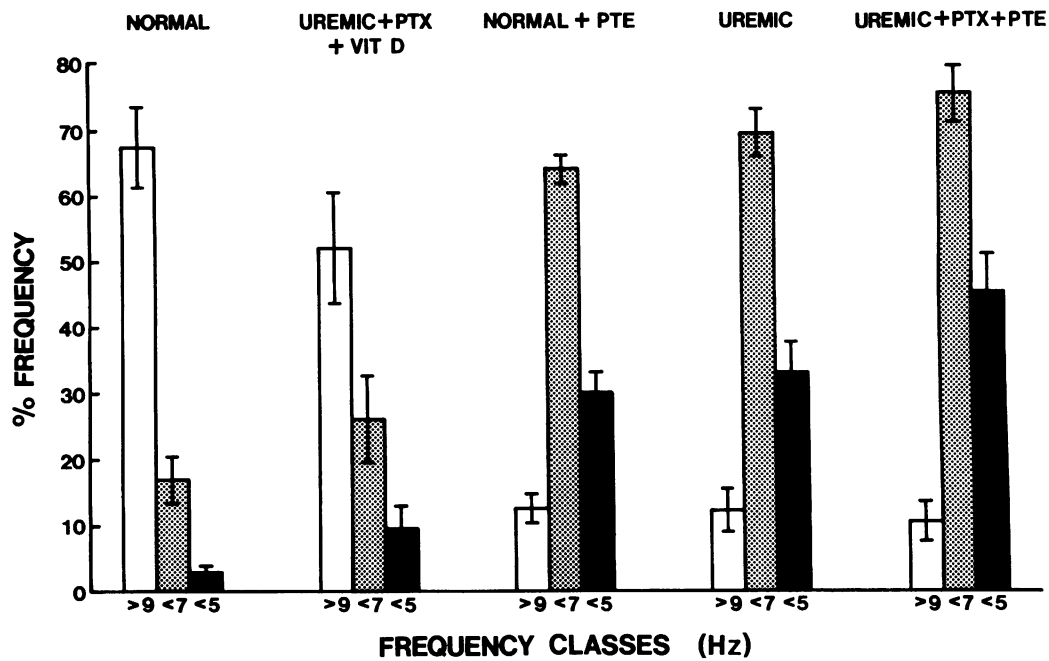


FIGURE 2 Percentage distribution of EEG frequencies from normal dogs, uremic parathyroidectomized dogs (PTX), uremic animals with intact parathyroid glands, and both uremic parathyroidectomized and normal dogs receiving parathyroid extract (PTE). The cumulative distribution for frequency classes above 9 Hz and below 7 Hz and 5 Hz is shown for each experimental group. A similar frequency distribution is seen in normal and uremic parathyroidectomized animals. In both normal and uremic animals with excess blood levels of parathyroid hormone, there is a significant decrease in fast activity (>9 Hz), with an increase in percentage distribution of slower frequency classes (<7 Hz and <5 Hz).

for 3 days, renal function was normal (serum creatinine = 1.2 ± 0.2 mg/dl). The EEG in these animals showed a frequency and percentage EEG power pattern which were not different from that of uremic animals with intact parathyroid glands (Fig. 2 and 3). The content in both white and gray matter of Na^+ , K^+ , and water was not different from normal values (Table II). However, the brain content of Ca^{++} was significantly greater than normal ($p < 0.01$), in both white and gray matter.

The "burst index" (mean \pm SE) in uremic animals with intact parathyroid glands was not significantly different from the values obtained in parathyroidectomized uremic animals treated with parathyroid extract, or normal animals receiving parathyroid extract for 3.5 days ($21 \pm 13\%$; $13 \pm 3\%$; and $12 \pm 4\%$, respectively). However, parathyroidectomized uremic animals not receiving parathyroid extract had a burst index of $3 \pm 0.01\%$, which was significantly less than that of uremic animals with intact parathyroid gland function ($P < 0.05$).

No systematic attempt was made to evaluate behavioral changes in the different groups studied. However, uremic animals with intact parathyroid glands

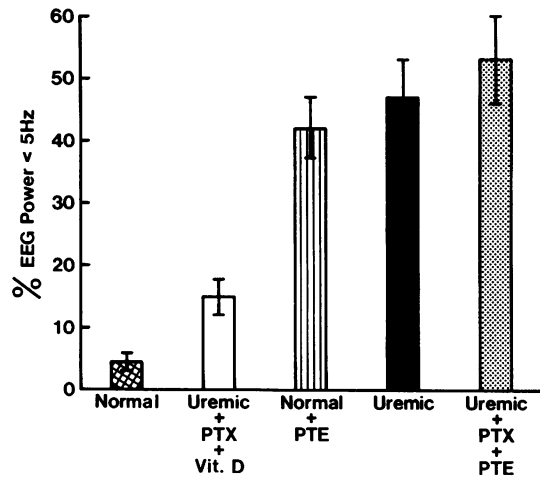


FIGURE 3 Percent EEG power for frequency classes below 5 Hz in five experimental groups of animals. The area (or power) occupied by frequency classes below 5 Hz is similar in normal animals vs. uremic parathyroidectomized animals. The EEG power for frequencies below 5 Hz is significantly increased in uremic animals with intact parathyroid glands and in both uremic parathyroidectomized and normal animals receiving parathyroid extract (PTE).

TABLE I
Changes in Plasma and CSF

	Plasma							CSF			
	Na ⁺	K ⁺	HCO ₃ ⁻	pH	Ca ⁺⁺	Mg ⁺⁺	PO ₄ ⁼	Creatinine	Ca ⁺⁺	Mg ⁺⁺	PO ₄ ⁼
	meq/liter				mg/dl			mg/dl			
Normal, n = 7											
Mean ± SE	147 ± 1	4.02 ± 0.06	20.3 ± 0.6	7.35 ± 0.01	10.6 ± 0.18	1.92 ± 0.04	4.2 ± 0.3	0.9 ± 0.1	4.48 ± 0.10	2.39 ± 0.07	1.2 ± 0.1
Uremia, PTX,* Vit. D, n = 7											
Mean ± SE	138 ± 3‡	6.71 ± 0.16§	15.7 ± 0.4§	7.23 ± 0.01§	9.45 ± 0.39‡	2.24 ± 0.24	10.5 ± 1.3§	10.6 ± 0.6§	4.59 ± 0.47	1.82 ± 0.18‡	3.1 ± 0.8‡
Uremia, n = 6											
Mean ± SE	137 ± 2‡	7.36 ± 0.33§	14.7 ± 0.8§	7.23 ± 0.02§	9.19 ± 0.43‡	2.50 ± 0.14§	11.9 ± 1.3§	11.3 ± 0.7§	4.56 ± 0.28	2.09 ± 0.16	2.1 ± 0.3‡
Normal + PTE, n = 7											
Mean ± SE	142 ± 2	4.14 ± 0.33	18.8 ± 0.8	7.33 ± 0.02	12.5 ± 0.4§	1.63 ± 0.02§	6.3 ± 0.2§	1.2 ± 0.2	5.92 ± 0.32§	2.30 ± 0.06	1.1 ± 0.1
Uremia + PTX + PTE, n = 6											
Mean ± SE	131 ± 3§	6.50 ± 0.53§	15.4 ± 1.2§	7.21 ± 0.02§	9.72 ± 0.35‡	2.76 ± 0.21§	12.8 ± 1.9§	12.4 ± 0.3§	5.79 ± 0.17§	2.64 ± 0.08‡	1.7 ± 0.2‡

* PTE, parathyroid extract; PTX = parathyroidectomy; and Vit. D, vitamin D.

‡ P < 0.05 vs. control.

§ P < 0.01 vs. control.

and previously parathyroidectomized animals receiving parathyroid extract, showed slowed responses to stimulation and were distinctly more lethargic than normal or previously parathyroidectomized uremic dogs.

DISCUSSION

The results of the present study clearly demonstrate that animals with intact parathyroid glands and acute uremia display electroencephalographic abnormalities which are almost completely prevented by previous parathyroidectomy. These changes include a significant increment in the area or power occupied by frequencies below 5 Hz, and in the percentage distribution of frequencies below 5 Hz as well as an increase in the

burst index. The data indicate that these changes in EEG require the presence of excess parathyroid hormone in blood and may be related to the changes in brain content of calcium. Several lines of evidence support this postulate. First, parathyroidectomy before the induction of uremia prevented the occurrence of the electroencephalographic abnormalities when serum calcium was maintained at normal levels; second, the administration of parathyroid extract to previously parathyroidectomized uremic animals was associated with EEG changes similar to those noted in uremic animals with intact parathyroid gland; and third, administration of parathyroid extract to normal dogs without uremia also caused similar abnormalities in

TABLE II
Water and Electrolyte Content of the Brain

	Gray matter					White matter				
	Na ⁺	K ⁺	Ca ⁺⁺	Mg ⁺⁺	H ₂ O	Na ⁺	K ⁺	Ca ⁺⁺	Mg ⁺⁺	H ₂ O
	meq/kg dry wt		mg/kg dry wt	%		meq/kg dry wt		mg/kg dry wt	%	
Normal, n = 7										
Mean ± SE	260 ± 6	489 ± 5	270 ± 3	739 ± 11	80.38 ± 0.22	158 ± 5	248 ± 10	159 ± 7	436 ± 10	67.21 ± 0.42
Uremia + PTX* + Vit. D, n = 7										
Mean ± SE	247 ± 7	462 ± 10‡	264 ± 6	743 ± 16	81.23 ± 0.39	148 ± 5	230 ± 8	140 ± 8	427 ± 7	67.44 ± 0.31
Uremia, n = 6										
Mean ± SE	241 ± 7	472 ± 6‡	334 ± 5§	754 ± 5	80.92 ± 0.23	140 ± 4‡	244 ± 10	204 ± 18‡	479 ± 14‡	68.78 ± 0.64
Normal + PTE, n = 7										
Mean ± SE	258 ± 4	482 ± 8	321 ± 10§	745 ± 13	80.56 ± 0.31	163 ± 4	260 ± 6	190 ± 6	474 ± 9‡	68.40 ± 0.84
Uremia + PTX + PTE, n = 6										
Mean ± SE	245 ± 11	456 ± 5	335 ± 14§	748 ± 13	80.68 ± 0.40	140 ± 5‡	241 ± 6	186 ± 7‡	466 ± 8‡	68.75 ± 0.40

* PTE, parathyroid extract; PTX, parathyroidectomy; and Vit. D, vitamin D.

‡ P < 0.05 vs. control.

§ P < 0.001 vs. control.

|| P < 0.01 vs. control.

EEG. In all the groups of animals which showed the electroencephalographic changes, brain content of Ca^{++} was significantly higher than that seen in normal dogs or previously parathyroidectomized uremic animals which had normal EEG. Changes in acid base parameters or in electrolytes, blood urea nitrogen, or creatinine concentrations in blood or CSF could not be implicated as underlying the abnormalities in EEG. There was no significant difference in the aforementioned parameters between the uremic animals with intact parathyroid glands and abnormal EEG vs. previously parathyroidectomized uremic dogs which had normal EEG.

Hagstam (17), in a study of the quantitative changes in EEG frequency distribution of uremic patients, has shown a generalized slowing of EEG frequencies, which was best correlated to both increases in plasma inorganic phosphate levels and low serum Ca^{++} . Since hyperphosphatemia may lower serum Ca^{++} (18), and hypocalcemia stimulates the parathyroid gland (19), it is reasonable to assume that in patients with greater hyperphosphatemia and hypocalcemia, the magnitude of secondary hyperparathyroidism is more pronounced. Under such circumstances, the increment in brain Ca^{++} may be more marked and hence the EEG abnormalities are more evident. In the present study, the plasma inorganic phosphate level in previously parathyroidectomized uremic animals (11.1 ± 2.3 mg/dl) was similar to that of uremic animals with intact parathyroid glands (11.4 ± 1.2 mg/dl), while significantly lower ($P < 0.01$) plasma phosphate levels were found in normal animals receiving parathyroid extract (5.3 ± 0.2 mg/dl). These observations suggest that level of serum phosphorus, per se, is not important but its effect is probably mediated through its influence on serum Ca^{++} and subsequently on parathyroid gland activity. There were small but significant elevations of Mg^{++} content in the brain white matter of uremic dogs with intact parathyroid glands, and after administration of parathyroid extract to either normal or previously parathyroidectomized uremic animals. The significance of this elevation in white matter content of Mg^{++} in relation to the EEG changes described, is unclear.

It is possible that parathyroid hormone, per se, rather than an elevated brain Ca^{++} content, is responsible for the EEG abnormalities observed. To demonstrate such a relationship one would need an experimental model with excess parathyroid hormone but normal brain Ca^{++} content, a combination which we were not able to achieve. The role of parathyroid hormone, per se, in the electroencephalographic changes observed remains unanswered.

Other abnormalities have been demonstrated in the brains of uremic animals. Cerebral blood flow studies

have demonstrated a defect in oxygen utilization of brain (20, 21), while evidence has been presented which suggests that there is a partial block of glucose degradation in the phosphofructokinase step of the glycolytic cycle in brain (2). Elevated levels of both ATP and inorganic phosphate have also been found in brain of such animals (2). Also, in animals with acute uremia, there are alterations in brain permeability to organic acids, carbohydrates, and some electrolytes (23). Either a membrane defect, and/or impairment of the Na^+ pump, with an associated elevation in ATP in brain might also be related to some of the neurological and/or EEG changes seen in uremic patients, although direct demonstration is lacking at this time (2).

It is possible that the EEG abnormalities seen in uremia could be due to changes in the intra- to extracellular ratios for Ca^{++} in brain. However, it is not known what fraction of the brain intracellular Ca^{++} is present in the ionized form in uremic animals. Furthermore, a large fraction of intracellular Ca^{++} is probably bound to subcellular fractions in brain. Calcium-binding vesicles associated with the activity of a number of enzymes have been found in endoplasmic reticulum in dog brain (24) and in microsomes and synaptosomes in rat brain (25, 26). Additionally, membrane phospholipids also bind Ca^{++} (27). The effects of changes in intracellular pH in uremic brain, if any, on the binding properties of Ca^{++} , are also not known. Until these factors are clarified, the relationship between changes in EEG activity and intra- to extracellular ratios for any electrolyte can only be speculative.

Although the mechanism by which an increase in brain Ca^{++} results is the observed EEG changes (Fig. 1) is unknown, it may be due to interference with the metabolism of high energy phosphate compounds. It has been shown that under resting conditions, the concentration of free ionized Ca^{++} in cell cytoplasm is probably less than 0.01 mM (28). In some cell systems, (adrenal medulla) the secretion of neurotransmitters (norepinephrine) is intimately dependent on the presence of Ca^{++} (29), and Ca^{++} may well be essential for neurotransmitter release in other cells. In peripheral nerve terminal cytoplasm, for example, the adhesion of synaptic vesicles to the nerve-ending membrane appears to be dependent on an increase in the concentration of ionized Ca^{++} (30). Also, in the brain, microsomal activity of Na^+ -dependent ATPase can be inhibited by an increase in the concentration of free Ca^{++} (31, 32). Parathyroid hormone has been shown to enhance entry of Ca^{++} into several cell systems, including skin (33), aorta (34), cornea (35) and kidney (36). This phenomenon may be related to a direct effect of parathyroid hormone increasing the permeability of cell membrane of Ca^{++} (37). On the other hand, parathyroid hormone

also stimulates adenylyl cyclase activity, producing cyclic AMP (38), which may act to shift Ca^{++} from microsomes to cytosol, thus increasing the concentration of free intracellular Ca^{++} (39). It is thus possible that the observed increase of brain Ca^{++} in the presence of excess parathyroid hormone may in some manner alter the release of neurotransmitters and/or activity of $\text{Na}^+\text{-K}^+$ ATPase, which may be related to some of the neurological and electroencephalographic changes observed in uremia.

Normal EEG activity depends on the integrity of cerebral cortex and of deep diencephalic and brain stem structures. Most conditions which affect consciousness also affect the EEG, and a normal EEG in an unresponsive patient rules out metabolic brain disease as the cause (40).

In metabolic brain disease, a diffuse and symmetrical slowing of the EEG usually parallels the severity of the encephalopathy (41). Initially, there is a reduction in alpha frequency, and with more severe cerebral depression the background alpha activity is replaced by high amplitude slow activity, and paroxysmal bursts of high voltage slow waves (40, 41). Although the EEG is always slow in metabolic coma, very slow coma-like records may persist for some time during clinical recovery and after patients reawaken (40).

Similar nonspecific electroencephalographic changes are seen in acute and chronic uremia (2), and progressive slowing of background frequencies have been correlated with deterioration of renal function (3). It has been suggested (3, 4) that changes in EEG activity may be a useful parameter in the evaluation of patients with progressive renal failure and their response to treatment.

The observed correlation between increased parathyroid hormone activity and the electroencephalographic changes in acute uremia, may reflect a direct effect of parathyroid hormone on brain metabolism. It is possible that correction of secondary hyperparathyroidism in some patients with renal failure may modify or prevent some of the neurological and electroencephalographic abnormalities of uremia, but further investigation is needed in this area.

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