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Somatosensory evoked potentials in acute renal failure: Effect of parathyroidectomy

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Somatosensory evoked potentials in acute renal failure: Effect of parathyroidectomy. Effects of acute renal failure (ARF) on somatosensory evoked potentials (SEP) were studied in rats. Cervical and cortical SEPs were measured both before and after bilateral ureteral ligation. A significant augmentation of amplitudes and an increase in latencies of the cortical SEP were observed in ARF. The peripheral nerve conduction velocities were unchanged. Serum parathyroid hormone (PTH) levels in uremic rats were significantly elevated after the bilateral ureteral ligation. In previously parathyroidectomized rats, the bilateral ureteral ligation had no effects on amplitudes of SEP or serum PTH levels.

Both acute and chronic renal failure are known to be accompanied with various neurologic symptoms. Encephalopathy seems to be more common than peripheral neuropathy in acute renal failrue (ARF). In chronic renal failrue (CRF), the central nervous system may be damaged but to a lesser degree [1]. In electrophysiological studies, strikingly pathological changes in electroencephalogram (EEG) have been reported both in patients [2] and in animals [3] with ARF.

In recent years, the value of somatosensory evoked potentials (SEP) in determination of peripheral or central nervous disorders has been elucidated. The SEP is a specific electrical activity of the sensory nervous system elicited by somestetic stimulation. The assessment of latencies of various peaks in the SEP is useful to evaluate the conduction velocities of each segment of somatosensory pathway. To study possible effects of ARF on both the peripheral and central nervous systems, we simultaneously recorded SEPs both at the cervical spinal cord and in the cerebral cortex in rats treated with ureteral ligation. In addition, we performed experiments using rats pretreated with parathyroidectomy, to assess a role of parathyroid hormone (PTH) in the neurological disturbance in acute renal failure. Changes in serum-intact PTH levels before and after the ureteral ligation were also evaluated with radioimmunoassay.

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Methods

Surgical procedures

Thirty male Wistar rats weighing 200 to 300 g were separated into three groups.

Uremic rats (uremia). Ten rats were studied for acute uremic experiments. The rat was given anesthesia with ether and was placed on a board in a supine position. A straight incision was made over the midline of the abdominal wall and bilateral ligation of ureters was performed.

Control rats (control). An additional ten rats were subjected to sham operation consisting of the simple abdominal incision and exposure of bilateral ureters under ether anesthesia.

Parathyroidectomized-uremic rats (PTX-uremia). In another ten rats, removal of the parathyroid glands was followed by the same procedures as those in the uremic rats [4]. The success of parathyroidectomy was ascertained by a fall in plasma calcium (Ca) of at least 2.0 mg/dl within 48 hours. These parathyroidectomized animals then received oral calcium supplementation to prevent the development of tetany over a period of 14 days. These treatments resulted in a rise in serum Ca concentration to more than 10.0 mg/dl, thereafter acute uremic experiments were started.

SEP recording

During the recording of the SEP, body temperature of the rat was monitored with a Thermistor Type NPV (Shibaura Electronics Co., Ltd., Japan) and was kept 37.0 ± 1.0°C using Nikon Incubator NP-2 (Nikon Co., Ltd., Japan). A 1500 EMG system II (DISA Elektronik A/S, Denmark) was used for SEP recordings. SEP was elicited by electrical stimulation of the right forepaw and the reference electrode was placed in the olfactory brain. To record the cervical SEP, a stainless steel needle electrode was inserted at the level of the seventh cervical vertebra. The first negative peak of cervical SEP was named "N_{cervix}". Cortical SEP was obtained with a silver needle electrode implanted previously in the left primary somatosensory cortex [5, 6]. The first positive peak was named "P_1", and the largest negative peak was named "N_{max}". Several peaks were shown in the rising flank of the N_{max} (Fig. 1), and the most stable negative peak was named "N_1". Implantations or insertions of electrodes were performed under sufficient ether or chloral hydrate anesthesia, whereas the SEP was recorded in awake stage. Details of the SEP in rats were reported elsewhere [4, 7].

Table 1. Changes in serum variables in sham-operated (control) and ureteral-ligated (uremia and PTX-uremia) rats

Group	Operation	Na	K	Creatinine	BUN
		mEq/liter		*mg/dl*	
Control	before	142.8 ± 0.68	5.31 ± 0.36	1.32 ± 0.06	21.70 ± 1.00
	after	142.6 ± 0.86	5.32 ± 0.43	1.31 ± 0.08	21.88 ± 1.83
Uremia	before	143.3 ± 1.80	5.57 ± 0.22	1.23 ± 0.03	18.87 ± 1.14
	after	142.6 ± 2.85	6.75 ± 0.68	3.71 ± 0.30[a,c]	126.1 ± 3.73[a,c]
PTX-uremia	before	141.7 ± 0.42	5.37 ± 0.14	1.17 ± 0.06	20.00 ± 3.50
	after	141.1 ± 2.16	6.96 ± 0.29[b,c]	4.29 ± 0.24[a,c]	143.8 ± 9.23[a,b]

Values are means ± SEM.
[a] $P < 0.001$, [b] $P < 0.002$, statistically significant from "before" in each group
[c] Statistically significant from "control after" ($P < 0.001$)

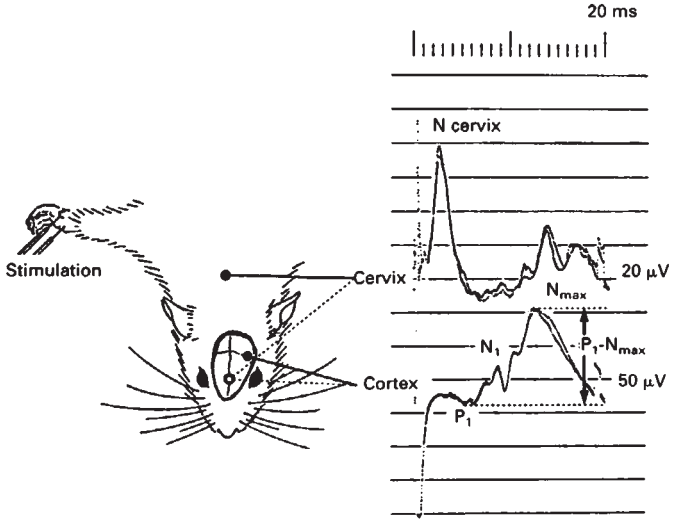

Fig. 1. *Somatosensory evoked potentials recorded at the 7th cervical vertebra and in the primary somatosensory cortex by stimulation of the contralateral forepaw.* In both recordings, the reference electrode was placed 6.5 mm anterior to the bregma.

Data analysis

Blood sampling and SEP recording were performed both before and 24 hours after the ligation of ureters. The serum concentrations of Ca and those of urea nitrogen were measured with RaBA-SUPER SYSTEM (Chugai Pharmaceutical Co., Ltd., Japan). The concentrations of serum creatinine were measured with Sigma Diagnostics Creatinine (Sigma Chemical Co., St. Louis, Missouri, USA). The concentrations of serum Na and K were measured with IL943 Automatic Flame Photometer (Instrumentation Laboratory Inc., USA). The intact parathyroid hormone (PTH) levels were measured with INS-PTH Radioimmunoassay Kit (Nichols Institute Diagnostics, USA).

Statistical significance was assessed using ANOVA.

Results

Changes in the serum concentrations of Na, K, urea nitrogen, and creatinine are shown in Table 1. None of the mean values of Na, of K, of urea nitrogen, or of creatinine concentrations before the bilateral ureteral ligation (or sham operation) was different among the three groups. After the operation, concentrations of K, urea nitrogen, and creatinine in both uremic rats and PTX-uremic rats were higher than those in control rats, while there was no statistically significant difference between those in uremic rats and those in PTX-uremic rats. The serum Ca concentrations in the PTX-uremic rats fell from 11.06 ± 0.49 (mean ± SEM) to 7.35 ± 0.62 mg/dl 48 hours after the parathyroidectomy, then rose to 10.40 ± 0.99 mg/dl with the supply of Ca-rich water. Changes in serum Ca levels and serum PTH levels in both uremic rats and PTX-uremic rats before and after the bilateral ureteral ligation are shown in Table 2. Serum PTH level was significantly increased in uremic rats 24 hours after the bilateral ureteral ligation ($P < 0.001$).

Changes in latencies of the SEP are shown in Figure 2. Neither latencies of the N_{cervix} nor those of the P_1 were changed in all three groups. Latencies of the N_1 were prolonged significantly in the uremic rats (8.02 ± 0.13 to 8.59 ± 0.11 msec, $P < 0.005$) but not significantly in the PTX-uremic rats (7.91 ± 0.16 to 8.37 ± 0.17 msec, $P > 0.05$). Changes in amplitudes of the SEP (P_1-N_{max}) are shown in Table 3. There was a significant augmenation of the amplitudes of P_1-N_{max} in the uremic rats ($P < 0.002$). In the PTX-uremic rats, however, there was no significant change in SEP amplitude ($P > 0.1$). 24 hours after the bilateral ureteral ligation, the mean value of the SEP amplitudes in the uremic rats were significantly higher than those in both the PTX-uremic rats ($P < 0.02$) and in the control rats ($P < 0.002$).

Discussion

In our previous studies on the SEP in the rat [4, 7], latency of the N_{cervix} represents the peripheral nerve conduction time. In the cortical SEP, the P_1 appears to originate from the medial lemniscus and the N_1 is the potential from the primary somatosensory cortex. The N_{max} indicates a summation of polysynaptic evoked potentials from the primary somatosensory cortex.

In the present study, an increased N_1 latency with normal latencies of the N_{cervix} and of the P_1 was demonstrated in the uremic rats. The changes in the SEP latencies suggest that ARF affects mainly the central segments rather than the peripheral ones in sensory pathway. Despite striking abnormalities in the EEG, normal motor nerve conduction velocities (MNCV) have been found in ARF [2, 8]. In contrast, Goldstein, Chui and Massry [9] have reported a reduced MNCV in acute uremic dogs. Because many factors, both technical and physiological, affect nerve conduction velocity (NCV), it is difficult to determine which is responsible for the discrepancies. Body temperature is one of the important factors affecting NCV [10] as well as SEP [11]. Though Goldstein et al [9] were keeping the

Table 2. Effects of bilateral ureteral ligation on serum concentrations of calcium and of parathyroid hromone (PTH)

Group	Ligation	Calcium *mg/dl*	PTH *pg/ml*
Uremia	before	10.43 ± 0.88	8.62 ± 1.29
	after	9.85 ± 0.57	26.84 ± 3.31[a]
PTX-uremia	before	10.40 ± 0.99	5.41 ± 0.80
	after	9.46 ± 0.94	7.53 ± 1.68

Values are means ± SEM.
[a] Statistically significant from uremia before ($P < 0.001$) and from PTX-uremia after ($P < 0.001$)

Table 3. Effects of sham operation (control) and ureteral ligation (uremia and PTX-uremia) on amplitudes of SEP

Group	Operation	P_1-N_{max} μV
Control	before	120.5 ± 10.6
	after	128.1 ± 14.7
Uremia	before	116.8 ± 17.2
	after	274.0 ± 39.1[a]
PTX-uremia	before	127.5 ± 21.8
	after	141.1 ± 27.3

Values are means ± SEM.
[a] Statistically significant from "uremia before" ($P < 0.001$), "PTX-uremia after" ($P < 0.02$), and "control after" ($P < 0.002$)

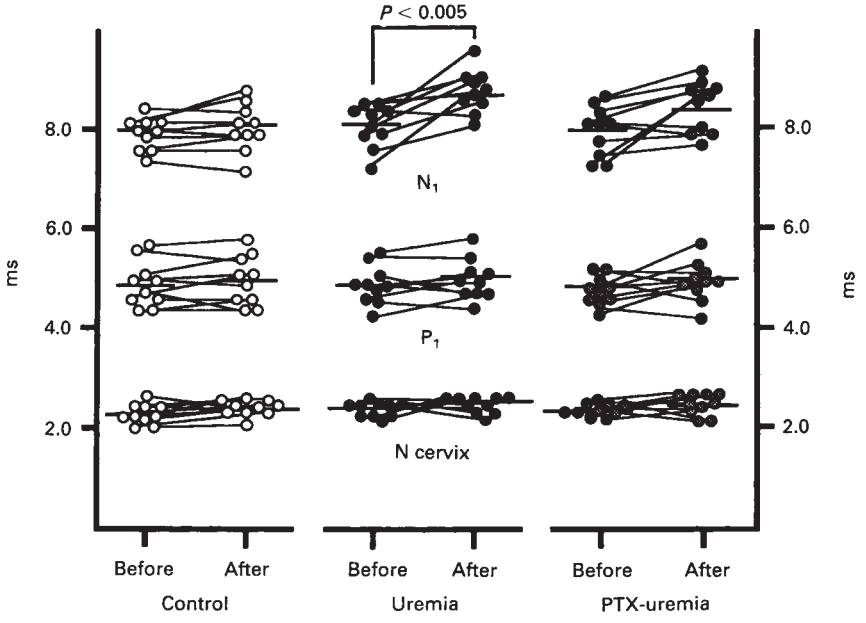

Fig. 2. *Effects of sham operation (control rats) and ureteral ligation (uremic and PTX-uremic rats) on peak latencies of the somatosensory evoked potentials.*

ambient temperature constant, they had not mentioned the body temperature of the animals which might be decreased in acute uremia. Their use of bilateral nephrectomy to induce ARF also might have some different effects on NCV than the ureteral ligation model we used [8].

Amplitudes of the cortical SEP were markedly augmented in uremic rats. The amplitude of cortical SEP seems to be influenced by the neuronal excitability of the cerebral cortex. The amplitude of cortical SEP is suppressed dose-dependently by anesthetic agents [4, 7, 12, 13]. On the contrary, an increase in the SEP amplitude has been observed in patients [14] as well as in animals [4] with acute hypocalcemia. The increased SEP amplitude in rats with ARF observed in the present study resemble those in hypocalcemic rats [4] except for delayed latencies of the cortical SEP. Some of the neurologic signs encountered in ARF seem to be similar in the neurologic hyperexcitability to those in hypocalcemia [15], except that the symptoms in uremic patient do not respond to injection of calcium [1]. Myoclonus, convulsion and tetany are common in uremia and those symptoms probably signify central and peripheral neuronal irritability [1]. An augmentation of SEP amplitude in uremic rats might indicate a neuronal hyperexcitability of cerebral cortex or a decrease in the cortical suppression of the reticular system of the brain-stem in uremia [16].

The pathogenesis of neurologic abnormalities in uremia is still unknown, though many kinds of metabolic abnormalities have been proposed [1]. A marked elevation in the blood level of parathyroid hormone (PTH) is one of the major abnormalities in uremia [17]. In our study, serum concentrations of PTH were markedly elevated after the bilateral ureteral ligation. Our results agree with an observation of other authors [18, 19]. Although the influence of PTH on the peripheral nerve conduction velocities remains controversial [9, 16, 20–22], either the removal or suppression of the parathyroid glands prevents the appearance of the EEG abnormalities in ARF [3, 23]. PTH is also known to be important in abnormality of calcium (Ca) metabolism in acute uremic brain [24, 25]. PTH may increase intracellular Ca concentration, may increase intracellular-extracellular Ca ratio, and may consequently modify the permeability of the cell membrane [17]. In our study, the parathyroidectomy prevented the increase in SEP amplitudes as well as the increase in serum PTH levels in ARF. Our results seem to support the hypothesis that the elevation of serum PTH level causes at least a part of the CNS deterioration in ARF.

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