Central Nervous System pH in Uremia and the Effects of Hemodialysis

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ABSTRACT Rapid hemodialysis of uremic animals may induce a syndrome characterized by increased cerebrospinal fluid (CSF) pressure, grand mal seizures, and electroencephalographic abnormalities. There is a fall in pH and bicarbonate concentration in CSF, and brain osmolality exceeds that of plasma, resulting in a net movement of water into the brain. This syndrome has been called experimental dialysis disequilibrium syndrome. The fall in pH of CSF may be secondary to a fall of intracellular pH (pHi) in brain. Since changes in pHi can alter intracellular osmolality in other tissues, it was decided to investigate brain pHi in uremia, and the effects of hemodialysis. Brain pHi was measured by evaluating the distribution of ^{14}C-labeled dimethadione in brain relative to CSF, while extracellular space was calculated as the $^{35}SO_4^=$ space relative to CSF. In animals with acute renal failure, brain (cerebral cortex) pHi was 7.06±0.02 (±SE) while that in CSF was 7.31±0.02, both values not different from normal. After rapid hemodialysis (100 min) of uremic animals, plasma creatinine fell from 11.8 to 5.9 mg/dl. Brain pHi was 6.89±0.02 and CSF pH was 7.19±0.02, both values significantly lower than in uremic animals ($P < 0.01$), and there was a 12% increase in brain water content. After slow hemodialysis (210 min), brain pHi (7.01±0.02) and pH in CSF (7.27±0.02) were both significantly greater than values observed after rapid hemodialysis ($P < 0.01$), and brain water content was normal. None of the above maneuvers had any effect on pHi of skeletal muscle or subcortical white matter.

The data show that rapid hemodialysis of uremic dogs is accompanied by a significant fall in pH of CSF and pHi in cerebral cortex. Accompanying the fall in brain pHi is cerebral edema.

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INTRODUCTION

Dialysis disequilibrium syndrome (DDS)[1] is a well described complication of the treatment of renal failure with hemodialysis (1, 2). The syndrome is most common either in patients undergoing their initial treatment with hemodialysis or in children (3). The usual symptoms of DDS are headache, nausea, restlessness, and lethargy, while seizures and coma may occur (1, 2). In patients with DDS, the electroencephalogram usually shows a characteristic pattern (4) and there is often a fall in pH of cerebrospinal fluid (CSF) both in man (5, 6) and experimental animals (7). We have previously shown that when acutely uremic dogs (bilateral ureteral ligation for 3½ days) are treated with rapid hemodialysis (blood flow = 12 ml/kg per min for 100 min), they may develop experimental DDS. In such animals, there is an osmotic gradient from brain to plasma that results in a net movement of water into brain. The osmole content of brain in animals treated with rapid hemodialysis was significantly greater than that of animals treated with slow hemodialysis (blood flow = 5 ml/kg per min for 210 min), although plasma urea, creatinine, and osmolality fell by the same amount after either dialytic procedure (7). The increased brain osmole content could not be entirely accounted for by changes in brain concentration of Na^+, K^+, Cl^-, Ca^{++}, Mg^{++}, or urea (7, 8).

Along with the increase in brain osmole content, a significant fall in both pH and bicarbonate concentration

[1] *Abbreviations used in this paper:* CSF, cerebrospinal fluid; DDS, dialysis disequilibrium syndrome; DMO, dimethadione; pHi, intracellular pH.

TABLE I

Effects of Uremia and Hemodialysis on Acid-Base Status of CSF and Blood

	CSF									Blood							
	pH		P_{CO_2}		P_{O_2}		HCO_3^-		Lactate	pH		P_{CO_2}		P_{O_2}		HCO_3^-	
	I	F	I	F	I	F	I	F	F	I	F	I	F	I	F	I	F
	mm Hg						*mmol/liter*			*mm Hg*						*mmol/liter*	
Normal, n = 8																	
Mean	7.31	—	41	—	67	—	19.6	—	2.2	—	7.36	—	36	—	77	—	20.6
±SE	0.01	—	1	—	6	—	0.7	—	0.2	—	0.01	—	1	—	6	—	0.8
Uremic, n = 8																	
Mean	7.31	—	41	—	48*	—	19.7	—	2.4	—	7.22*	—	34	—	83	—	13.5*
±SE	0.02	—	1	—	4	—	0.7	—	0.3	—	0.02	—	1	—	6	—	0.8
Uremic + slow hemodialysis, n = 5																	
Mean	7.30	7.27	40	42	55	56	19.6	18.2	2.6	7.23*	7.33	36	37	76	72	14.6*	18.9
±SE	0.01	0.02	3	2	3	3	0.8	0.4	0.4	0.02	0.02	2	2	6	5	0.7	1.3
Uremic + rapid hemodialysis, n = 7																	
Mean	7.33	7.19*	37	43*	55	55	18.9	15.4*	2.2	7.21*	7.31*	35	36	78	74	13.7*	17.7*
±SE	0.02	0.02	2	3	4	3	1.1	0.5	0.2	0.04	0.01	3	1	4	6	1.0	0.7

I, initial sample, before hemodialysis; F, final sample, after hemodialysis.
* $P < 0.01$ versus normal animals.
n = number of animals.

of CSF is observed in animals treated with rapid hemodialysis (7). The CSF has thus undergone a net gain in H^+ ion. These H^+ ions could have come from only two places—blood or brain. Since arterial pH rose while that of CSF fell, it is most likely that the increased H^+ ion in CSF came from the brain.

The gain of H^+ ions by CSF thus suggests a possible fall in intracellular pH (pHi) of the brain in uremic animals treated with rapid hemodialysis. It has been demonstrated that a fall in pHi can increase intracellular osmolality in other cell systems, particularly the red blood cells (9). Rapid hemodialysis in some manner may result in a decrease of brain pHi, with a resultant increase of intracellular osmolality in brain. Such a sequence could account for many of the observed manifestations of experimental DDS. It is the purpose of the present experiments to evaluate pHi of brain in uremic animals, and the effects of both rapid and slow hemodialysis.

METHODS

Studies were done in four groups of mongrel dogs of both sexes, 18–26 kg, as follows: (*a*) normal animals; (*b*) dogs with acute uremia of 3½ days duration; (*c*) acutely uremic dogs treated with rapid hemodialysis; (*d*) acutely uremic dogs treated with slow hemodialysis. Groups contained five to eight animals.

In all animals, measurements were made in CSF and arterial blood or plasma of pH, P_{O_2}, P_{CO_2}, bicarbonate, osmolality, urea, creatinine, and radioactivity from [4-*dione*-2-^{14}C]5,5-dimethyloxazolidine-2 ([^{14}C]DMO) and $^{35}SO_4^=$. Both isotopes are from New England Nuclear, Boston, Mass. Lactate was measured both in CSF and in a portion of the cerebral hemisphere rapidly (less than 5 s) frozen in liquid nitrogen.

Acute uremia was induced by bilateral ureteral ligation for 3½ days, at which time plasma urea and creatinine were 65.8 mM and 11.8 mg/dl, respectively. Hemodialysis was carried out with a Travenol RSP unit pediatric coil with 0.6 M^2 surface area at a dialysate flow rate of 500 ml/min (Travenol Laboratories, Artificial Organs Div., Morton Grove, Ill.). Blood flow for rapid hemodialysis was 12 ml/kg per min for 100 min, and for slow hemodialysis, 5 ml/kg per min for 210 min, employing standard dialysate (Diasol, Travenol Laboratories, Deerfield, Ill.). The techniques have previously been described (7).

All animals were studied while under anesthesia (sodium pentobarbital 25 mg/kg i.v.), intubated, and mechanically ventilated while spontaneous respiration was controlled with i.v. succinyl choline, as previously described (7, 10). After intubation, the arterial P_{CO_2} was adjusted to about 35 mm Hg and animals were then given both [^{14}C]DMO, 8 μCi/kg i.v. and 0.1 μCi/kg in the cisterna magna, and $Na_2{}^{35}SO_4$, 20 μCi/kg i.v. and 2.5 μCi/kg into the cisterna magna. The techniques have previously been described (10). The [^{14}C]-DMO was dissolved in 0.4 M "cold" DMO at a concentration of 25 μCi/ml, while the $Na_2{}^{35}SO_4$ was in 100 mM "cold" Na_2SO_4 at a concentration of 50 μCi/ml. The pHi and extracellular space were determined in muscle, gray matter, and white matter by evaluating the distribution of both DMO and $^{35}SO_4^=$ relative to either cortical CSF or plasma; the complete analytical method has been described (10). Briefly, after injecting the isotopes as described above, a 3-h equilibration period was allowed. At the conclusion of the experiment, samples were obtained of both cisternal and cortical CSF, arterial blood, skeletal muscle, brain subcortical white matter, brain cortical gray matter, and cerebral hemisphere, as previously described (7). Triplicate samples, each about

TABLE II

Changes of Intracellular pH in Brain and Skeletal Muscle

	Gray matter				White matter		Muscle
	pHi	ECS	Lactate	H_2O	pHi	H_2O	pHi
		%	*mmol/kg*	*g/100 g dry wt*		*g/100 g dry wt*	
Normal, n = 8							
Mean	7.05	21.9	2.6	399	6.98	201	6.88
±SE	0.01	2.4	0.4	6	0.02	4	0.01
Uremia, n = 8							
Mean	7.06	21.0	2.9	397	6.97	211	6.89
±SE	0.02	2.3	0.3	7	0.01	6	0.02
Uremia + slow hemodialysis, n = 5							
Mean	7.01	22.9	1.9	391	6.95	214	6.86
±SE	0.02	3.8	0.1	7	0.01	5	0.04
Uremia + rapid hemodialysis, n = 6							
Mean	6.89*	17.3	2.6	442*	7.00	237*	6.91
±SE	0.02	3.2	0.2	15	0.06	9	0.04

* $P < 0.01$ vs. normal or uremic animals, or uremic animals treated with slow hemodialysis.
ECS = extracellular space; n = number of animals.

0.1 g, of the outer 0.4 mm of cerebral cortex and of subcortical white matter 0.8–1.2 mm below the brain surface were obtained with a special tissue slicer (11). The samples of brain and muscle (each about 0.4 g) were extracted with 0.5 M perchloric acid as previously described (11). Duplicate aliquots of supernate, plasma, and cortical CSF were treated with $BaCl_2$ to precipitate $^{35}SO_4^=$ but retain ^{14}C. All samples were counted as previously described (11, 12). Subtracting ^{14}C activity from the total radioactivity gave the counts due to $^{35}SO_4^=$ (12). The pH was measured in both arterial blood and cisternal CSF (10). Brain gray matter extracellular space was calculated as the ratio of radioactivity per gram tissue to radioactivity per gram CSF. The intracellular pH was calculated by the distribution of [^{14}C]-DMO in tissue relative to cortical CSF (for gray matter) or plasma H_2O (for white matter or muscle). The formula was modified from that described by Kibler et al. (13), with pH of cisternal CSF for gray matter and arterial pH for muscle and white matter. The bicarbonate concentration in cerebral cortex was calculated from values for cerebral cortex pHi and P_{CO_2} of CSF, as described by Kjällquist et al. (14). Measurements of urea, creatinine, osmolality, pH, P_{O_2}, bicarbonate, and P_{CO_2} were made in CSF and arterial blood by previously described methods (7, 10), and lactate was measured in CSF and brain (10).

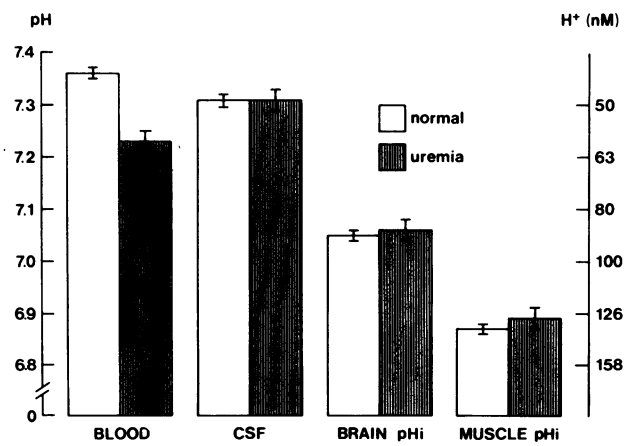

FIGURE 1 The pH of arterial blood and cerebrospinal fluid (CSF), and the intracellular pH (pHi) in brain (cerebral cortex) and skeletal muscle. In animals with uremia (serum creatinine, 11.8±0.4 mg/dl), there was a significant fall in arterial pH. However, there was no change in pH of CSF, or of the pHi in brain or muscle.

RESULTS

The normal values for CSF and arterial blood pH, P_{O_2}, P_{CO_2}, bicarbonate, and lactate are shown in Table I, while control values for pHi of muscle, gray matter, and white matter are in Table II. In the acutely uremic dogs, plasma osmolality (±SE) was 347±6 mosmol/kg, while plasma urea and creatinine were 65.8±0.4 mM and 11.8±0.4 mg/dl, respectively. In animals with acute renal failure, despite a fall in arterial pH from 7.36 to 7.22, there was no change in the pHi of either brain or muscle (Fig. 1). Both the pH and bicarbonate in CSF were normal (Table I), despite the significant fall in plasma bicarbonate concentration.

Dogs were then treated with either rapid or slow hemodialysis. After rapid hemodialysis, plasma urea and creatinine fell to 24.4±2.4 mM and 6.4±0.5 mg/dl, respectively. There was no change in the pHi of skeletal muscle. However, there was a highly significant fall ($P < 0.001$) in the pHi of brain (Fig. 2). The pHi in

cerebral cortex was 6.89±0.02 (±SE), versus 7.06± 0.02 ($P < 0.01$) observed in uremic animals. There was a fall in cerebral cortex bicarbonate to 8.0±0.5 mmol/kg H_2O (normal value, 11.3±0.4 mmol/kg H_2O) but no change in brain lactate (Table II). Accompanying the fall in gray matter pHi was a significant ($P < 0.01$) fall in pH of CSF (Fig. 3), from 7.33±0.02 before dialysis to 7.19±0.02 after ($P < 0.001$), while CSF bicarbonate fell from 18.9±1.1 mmol/liter to 15.4±0.5 mmol/liter ($P < 0.001$), and lactate in CSF was unaltered (Table I). In addition to the fall in cerebral cortex pHi, there was also cerebral edema, as defined by an increase in brain water content from 397±7 to 442±15 g/100 g dry wt ($P < 0.01$) in cerebral cortex and 211±6 to 237±9 g/100 g dry wt in white matter ($P < 0.01$).

After dogs were treated with slow hemodialysis for 210 min, plasma urea and creatinine fell by an amount similar to that after rapid hemodialysis. The cerebral cortex pHi fell slightly to 7.01±0.02, not different from normal ($P > 0.09$), but significantly greater ($P < 0.003$) than the brain pHi observed after rapid hemodialysis (Fig. 2). Both the bicarbonate and pH of CSF in dogs treated with slow hemodialysis (18.2±0.4 mmol/liter and 7.27±0.02) were significantly different from values observed after rapid hemodialysis ($P < 0.01$). Animals treated with slow hemodialysis did not develop brain edema (Table II). The pHi in brain white matter did not change after either rapid or slow hemodialysis (Table II).

DISCUSSION

The data presented suggest that in acutely uremic animals treated with rapid hemodialysis, there is a significant increase in brain H^+ ion activity. The increase in H^+ ion is accompanied by an increase in brain osmole content (7), leading to an increase in brain water content. Brain H^+ ion is increased by a significantly lesser increment when uremic animals are treated with slow hemodialysis. The source of the increased brain H^+ ion is not known, but it is probably not due to hypoxia, decreased cerebral blood flow, or increased cerebral lactate production. Cerebral hypoxia is unlikely, as the P_{O_2} in CSF was normal and P_{O_2} of CSF is similar to that of brain (15, 16). Furthermore, cerebral hypoxia should lead to increased brain lactate, and such a phenomenon did not occur (Table II). Similarly, decreased cerebral blood flow probably did not occur, as such a circumstance should lead to a fall in P_{O_2} of CSF, and an increase in brain and CSF lactate (15). In animals treated with rapid hemodialysis, brain and CSF lactate were normal (Tables I and II). Although the exact biochemical sequence leading to an increase in brain H^+ ion is not known, rapid hemodialysis of uremic animals may lead to an increase in brain organic acid(s). In both mammals (17, 18) and amphibians (19) in whom abrupt increases in extracellular osmolality are induced, brain content of amino acids increases. In primates subjected to reversible asphyxia, there is an increase in brain glutamic acid, probably a result of increased conversion from glutamine (20). The presence in brain of strong organic acid(s) would tend to increase osmolality by at least two mechanisms: (*a*) displacement of intracellularly bound K^+ ion from protein anions by H^+ ions, as in the hemoglobin molecule (9, 20); the K^+ ion, osmotically inactive when bound to intracellular protein, may become osmotically active when displaced by a H^+ ion. (b) Production of increased quantities of organic acids, per se, could raise brain osmolality.

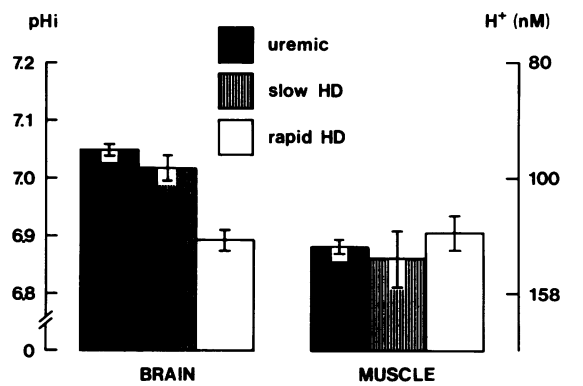

FIGURE 2 The intracellular pH (pHi) of brain (cerebral cortex) and skeletal muscle in uremic dogs, and dogs treated with either rapid or slow hemodialysis (HD). After slow HD, there is a small but not significant fall in brain pHi. After rapid HD, there is a highly significant fall in brain pHi. The pHi of muscle is unaffected by either uremia or HD.

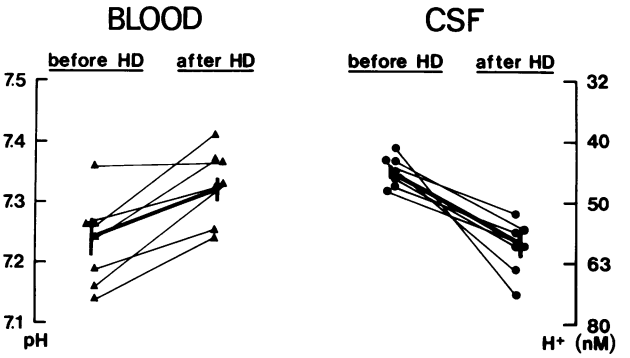

FIGURE 3 Changes in arterial blood and cerebrospinal fluid (CSF) during rapid hemodialysis (HD). During HD, the blood pH increases from 7.22±0.02 to 7.31±0.01, while bicarbonate rises from 13.7±1.0 to 17.7±0.7 mmol/liter. The simultaneously determined pH in CSF falls from 7.33±0.02 to 7.19±0.02, while CSF bicarbonate falls from 18.9±1.1 to 15.4±0.5 mmol/liter. There was no change in arterial blood P_{CO_2}. Heavy lines are mean±SE, while each thin line represents a single dog studied before and after rapid HD.

The water content increased in both gray and white matter of the brain (Table II), although pHi fell only in gray matter. Why pHi did not fall in white matter is not entirely clear, but may be related to the different structural characteristics of the two tissues. White matter consists largely of myelin and fibers, containing little cellular material, while gray matter is largely cellular. The method used to evaluate pHi (10) may not be sufficiently sensitive when only a small portion of the tissue actually consists of cells. The actual increase in white matter water content was less than that observed in gray matter (Table II).

In patients with metabolic acidosis from various causes, it has been shown that when arterial pH is rapidly corrected by infusion of $NaHCO_3$, a paradoxical acidosis may develop in the CSF (16). The fall in pH of CSF is essentially all due to a rise in P_{CO_2} of CSF, secondary to hypoventilation induced by rapid elevation of arterial pH and bicarbonate. In patients with subacute metabolic acidosis, both pH and P_{CO_2} tend to be abnormally low in CSF. Because of the blood-brain barrier, when plasma bicarbonate is elevated with intravenously administered $NaHCO_3$, plasma and CSF bicarbonate levels will not equilibrate for several hours, while P_{CO_2} equilibrates within minutes (21, 22). Thus, when hypoventilation results in a rise of arterial P_{CO_2}, the pH in CSF will fall as CO_2 rapidly diffuses into the CSF (21–23).

In 18 patients with diabetic ketoacidosis in whom pH of CSF was evaluated during therapy (22–24), pH of CSF fell from 7.30 to 7.20 while arterial pH rose from 7.08 to 7.34. However, the fall in pH of CSF was entirely due to a rise in CSF P_{CO_2} (from 24 to 34 mm Hg), as bicarbonate in CSF actually rose slightly (from 10.9 to 12.1 mmol/liter).

The situation during hemodialysis is quite different. Arterial pH is rapidly elevated as a consequence of intravenous administration (through the dialysis membrane) of bicarbonate precursor (lactate or acetate). However, studies of acid-base status in uremic patients treated with dialysis suggest that despite rapid elevation of arterial pH and bicarbonate, hypoventilation is not generally observed (25). In animal studies reported here and elsewhere (7), pH of CSF fell during hemodialysis although arterial P_{CO_2} was maintained at a constant level (Table I).

However, the fall in pH of CSF was primarily due to a fall in CSF bicarbonate (Table I), implying the *de novo* presence of organic acids. Thus, the production of paradoxical CSF acidosis after rapid hemodialysis is not related to systemic hypoventilation and is a different mechanism from that observed after treatment of other forms of metabolic acidosis (22–24, 26, 27).

Whatever the mechanisms, rapid hemodialysis of uremic animals results in a fall in pH of CSF and cerebral cortex pHi, associated with increased brain osmole content and cerebral edema. There is a concomitant fall in pH and bicarbonate concentration of CSF, but no change in skeletal muscle pHi, while pH and bicarbonate of arterial blood rise. This phenomenon appears to be a major mechanism in the pathogenesis of DDS in experimental animals.

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