

Regional Analyses of CNS Microdialysate Glucose and Lactate in Seizure Patients

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Summary: *Purpose:* To correlate glucose (and lactate) results obtained from microdialysate to recent studies suggesting that glucose transporter activity may be significantly altered in seizures.

Methods: We used a fluorometric technique to quantify glucose and lactate levels in microdialysates collected from two to four depth electrodes implanted per patient in the temporal and frontal lobes of a series of four patients. Hour-by-hour and day-to-day changes in brain glucose and lactate levels at the same site were recorded. Additionally we compared regional variations in lactate/glucose ratios around the predicted epileptogenic region.

Results: Lactate/glucose ratios in the range of 1–2:1 were the most commonly seen. When the lactate/glucose ratio was <1:1, we typically observed a relative increase in local glucose concentration (rather than decreased lactate), suggesting increased

transport, perhaps without increased glycolysis. In some sites, lactate/glucose ratios of 3:1–15:1 were seen, suggesting that a circumscribed zone of inhibition of tricarboxylic acid cycle activity may have been locally induced. In these dialysates, collected from probes closer to the epileptogenic region, the large increase in lactate/glucose ratios was a result of both increased lactate and reduced glucose levels.

Conclusions: We conclude that regional variations in brain extracellular glucose concentrations may be of greater magnitude than previously believed and become even more accentuated in partial seizure patients. Data from concomitant assays of microdialysate lactate and glucose may aid in understanding cerebral metabolism. **Key Words:** Brain microdialysate—Regional variations—Complex partial seizures—Glucose—Lactate—Lactate/glucose ratio.

Dynamic fluorodeoxyglucose–positron emission tomography (FDG-PET) estimations of influx, efflux, phosphorylation, and dephosphorylation have been performed in patients with complex partial seizures (1–3). There is no complete agreement in these studies. However, reports of significantly decreased glucose extraction (1), FDG influx (2), and lumped constant (3) in the epileptogenic areas all are observations that would be consistent with an alteration of brain capillary glucose transporter activity. Furthermore, because the total surface area of brain cell membranes is considerably greater than the surface area of the blood–brain barrier (BBB) membranes, effective rate-limitation of glucose transport could occur more efficiently at the brain capillary endothelial membranes, rather than the membranes of cells in the brain parenchyma (4). It is known from animal model

studies that endothelial glucose transporter maximal velocity is increased by as much as 35% within minutes of an initial seizure (5). However, long-term changes in glucose transport in response to continued intermittent (complex partial) seizures are not yet fully understood.

Recently a form of infantile seizures was described wherein impaired BBB glucose transport, developmental delay, and acquired microcephaly are seen. This condition has been referred to as the glucose transporter protein syndrome, GTPS (6,7), or the Glut1 deficiency syndrome, Glut1DS (8). The diagnostic feature of the syndrome is an unexplained hypoglycorrhachia in the clinical setting of an epileptic encephalopathy (7). Blood glucose levels are normal, but the fact that a low-to-normal CSF lactate together with a persistently low CSF glucose is seen in this syndrome (9) prompted our interest in the study of brain extracellular fluid glucose and lactate in adult complex partial seizures.

Furthermore, it has been shown that extracellular brain-nutrient concentrations can be analyzed in vivo from measurements of brain microdialysate obtained

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from modified depth electrodes (10,11). During et al. (10) characterized ictal and interictal differences in microdialysate and demonstrated that seizures induced a 90% increase in brain lactate levels within the epileptogenic region. They further determined that the increase in lactate persisted for 60–90 min. Fried et al. (11) showed transient ictal increases in glutamate, aspartate, γ -aminobutyric acid (GABA), and taurine (11). Microdialytic monitoring also has been carried out during a variety of neurosurgical interventions (12,13). In many forms of brain insult, such as bypass and aneurysm treatments (14,15), as well as severe head injury (16,17) and subarachnoid hemorrhage (18,19), alterations in both lactate and glucose were reported.

In the present study, we analyzed dialysates from depth electrode/microdialysis probes implanted in patients with intractable complex partial seizures undergoing evaluation for surgical treatment (11). Analyte recovery from different dialysis probes may vary because of probe differences, as well as brain regional differences. Consequently, we analyzed microdialysate glucose relative to lactate as an internal standard. Our objectives were threefold: first, to analyze brain glucose and lactate levels concomitantly in epilepsy patients undergoing dialysate sampling from multiple probes; second, to define possible diurnal alterations or alternatively to determine an absence of diurnal variability in brain glucose (and lactate) levels within epileptogenic regions and adjacent brain; and finally, we sought to determine whether regional lactate/glucose ratios would be uniform or provide information suggesting pathophysiologic alterations in any areas selected for analysis.

METHODS

Patients

All patients studied had long-standing (5–30 years; mean, 11.5 years) epilepsy with failure to achieve control of their seizures with conventional anticonvulsant medications (AEDs), and had experienced repeated seizures of sufficient severity and intensity to limit their lifestyle. The subjects had undergone extensive noninvasive evaluation that did not yield concordant data pointing to a single resectable epileptogenic region. All of the depth electrodes were implanted by the same surgeon (I.F.) in the course of continuing presurgical evaluation. As indicated previously (11), each patient had given fully informed consent to a protocol that was approved by the UCLA Human Subject Protection Committee before being enrolled as a participant in these studies. Stereotactic implantation of depth electrodes was based on analyses of the suspected regions of epileptogenesis, and postsurgical confirmation of probe positions is detailed elsewhere (11). After surgery, patients were transferred to the epilepsy inpatient unit for continuous (video-EEG monitoring) for a period of 1–3 weeks.

Microdialysis

The technical details of the microdialysis probes used were previously described (11). The microdialysis tubing is contained within the same lumen of the electrode as the platinum–iridium microelectrodes. Silica inlet and outlet tubing was connected to either end of a hollow fiber of the cuprophan dialysis membrane ($200 \pm 15 \mu\text{m}$ OD; Akza Nobel Faser AG, Wuppertal, Germany). The distance between inlet and outlet tubing (defining the length of membrane through which dialysis occurred) was 10 mm, and the dialysis membrane positioned at the tip of a modified depth electrode (11). The unit was sterilized with ethylene oxide before surgical implantation.

The dialysis probes were infused at 1.2 $\mu\text{l}/\text{min}$ with a sterilized artificial CSF made of 125 mM NaCl, 2.5 mM KCl, 0.5 mM NaH_2PO_4 , 5.0 mM Na_2HPO_4 , 1.0 mM MgCl_2 , 1.2 mM CaCl_2 , and 200 μM ascorbic acid, pH 7.3–7.4. The dead volume of the outlet tubing ($\sim 25 \mu\text{l}$) was equivalent to a 20-min delay in sampling at the adjusted flow rate. Perfusate delivery was achieved by using minipumps with direct-current motors (CMA-102; CMA, Stockholm, Sweden) to reduce electrical noise affecting microelectrode recordings. Dialysis samples were collected at 30-min intervals by using an automated fraction collector, and vials (containing $\sim 35 \mu\text{l}$) were promptly sealed and stored at -80°C for subsequent analyses. Dialysate flow was interrupted (reduced to 2 $\mu\text{l}/\text{h}$, sufficient to keep the tubing patent) at times by the attending clinical staff, and the first 30-min sample collected after restoring normal flow was not analyzed.

Fluorometric assays

The glucose assay was a modification of the Lowry and Passonneau method (20). All chemicals were obtained from Sigma Chemicals (St. Louis, MO, U.S.A.). For every 50 ml of incomplete glucose assay buffer (25 mM Tris base, 25 mM Tris HCl, 1 mM MgCl_2 , 0.5 mM dithiothreitol, 0.02% sodium azide), 1.2 nmol of nicotinamide adenine dinucleotide phosphate (NADP), and 10 mg adenosine triphosphate (ATP) were added, making up the complete glucose assay buffer. Standards were prepared by diluting a 5.56 mM standard glucose solution and preparing concentrations ranging from 0.0 to 11.12 μM . The complete glucose assay buffer (0.9 ml) was added to 0.1 ml of each of the samples and the known standards. Throughout this study, glucose (and lactate) levels were assayed at a final dilution ranging from 1:30 to 1:100, consistently placing each unknown within the range of the standard curve. Each test tube was directly read in a digital fluorometer (model 450; Sequoia-Turner, Mountain View, CA, U.S.A.) by using a narrow-band excitation filter with 360-nm peak (# 450-101) and sharp cut emission filter that transmits at 450 nm (# 450-123). The fluorometer was zeroed to distilled

water, and the initial reading of relative intensity for each sample was then recorded. For every 50 samples, 0.020 ml of glucose-6-phosphate dehydrogenase (556 units/ml) and 0.050 ml of hexokinase (400 units/ml) was added to 0.50 ml of complete glucose assay buffer. The enzyme solution (0.010 ml) was added to each of the samples and the standards. After a 10-min incubation at room temperature, a second set of readings was taken for each tube and recorded.

The lactate-assay procedure also was modified from Lowry and Passonneau (20). In brief, to 25 ml of buffer solution (25 mM 2-amino-2-methyl-propanol free base, 25 mM 2-amino-2-methyl-propanol HCl, 2 mM glutamate, pH 9.9), 3.3 mg of NAD⁺, 0.060 ml of lactic dehydrogenase (5,400 units/ml), and 0.029 ml of glutamic-pyruvic transaminase (3,333 units/ml) were combined to make a complete lactate assay buffer. 0.9 ml of this solution was aliquoted into borosilicated tubes and incubated for 15 min before initial fluorometric reading. Subsequently, 0.10 ml of standards ranging from 0.0 to 17.76 μ M (dilution of a 2.22 mM standard lactate solution) and samples were added to the tubes and incubated for 15 min before final fluorometric reading.

A standard curve was obtained in each of the assays described earlier by subtracting the initial optical density reading for the each of the known standards from the final reading and plotting these values relative to their respective concentrations. Linear regression analyses gave the slope of each standard curve, which was used to calculate the glucose or lactate concentrations (in duplicate) for each of the unknown samples.

The in vitro recovery rates of glucose and lactate were determined by perfusing dialysate at a rate of 1.2 μ l/min through a probe immersed in standardized solutions of the analytes, as described previously (11). This procedure also established (in vitro) the consistency of sequential glucose and lactate recoveries from cuprophan probes, when both glucose and lactate were assayed fluorometrically. For some probes, in vitro recovery rates of lactate and glutamate also were determined before sterilization and implantation, as described previously (11).

Multiple assays of two (high and low) representative

lactate and glucose standards were performed over a 2-week period to assess interassay variability. The mean coefficients of variation (CVs) for the glucose and lactate assays were 3.2 and 4.2%, respectively. The least significant differences detectable from a mean of duplicate glucose and lactate assays were 0.45 micromoles and 0.87 micromoles, respectively. To compare within-probe variations in glucose or lactate over different monitoring periods, the Student's *t* test was used. Within-patient comparisons of mean glucose/lactate ratios were analyzed by using the Fisher-Tukey multiple mean comparisons test.

RESULTS

Table 1 demonstrates that we examined dialysate from a total of 12 probes implanted into four different patients, with variable numbers (two to four) of dialysis probes operating during the study period. In vivo metabolite levels were assayed in sequential 30-min dialysate samples. The dialysates were typically obtained \geq 24 h after placement of the electrodes, and glucose and lactate samples were collected over 3- to 7-h periods. In vitro studies with a similar cuprophan probe further indicated the consistency of recovery rates at different analyte concentrations. Our in vitro recovery studies for glucose were 46–53%, whereas lactate recoveries (at the same 0.5–5.0 mM concentrations) ranged from 62 to 74%. [In vivo recovery of these analytes is lower (13), and in animal studies, it may be three- to fourfold lower than in vitro (21)].

Patient 1

Patient 1 had three dialysis probes with dialysate samples collected over two different time periods. Shown in Fig. 1A, CNS dialysate glucose concentrations suggested considerable regional variation, ranging from 150 to 900 μ M in this patient. There also was a change in glucose levels over the 7-day interval between the two monitoring periods. Initially, dialysate glucose levels ranged from 350 to 950 μ M, whereas glucose levels were considerably lower (ranging from 150 to 350 μ M) some 7 days later. For each region analyzed, differences in

TABLE 1. Summary of patient data and dialysis probe locations

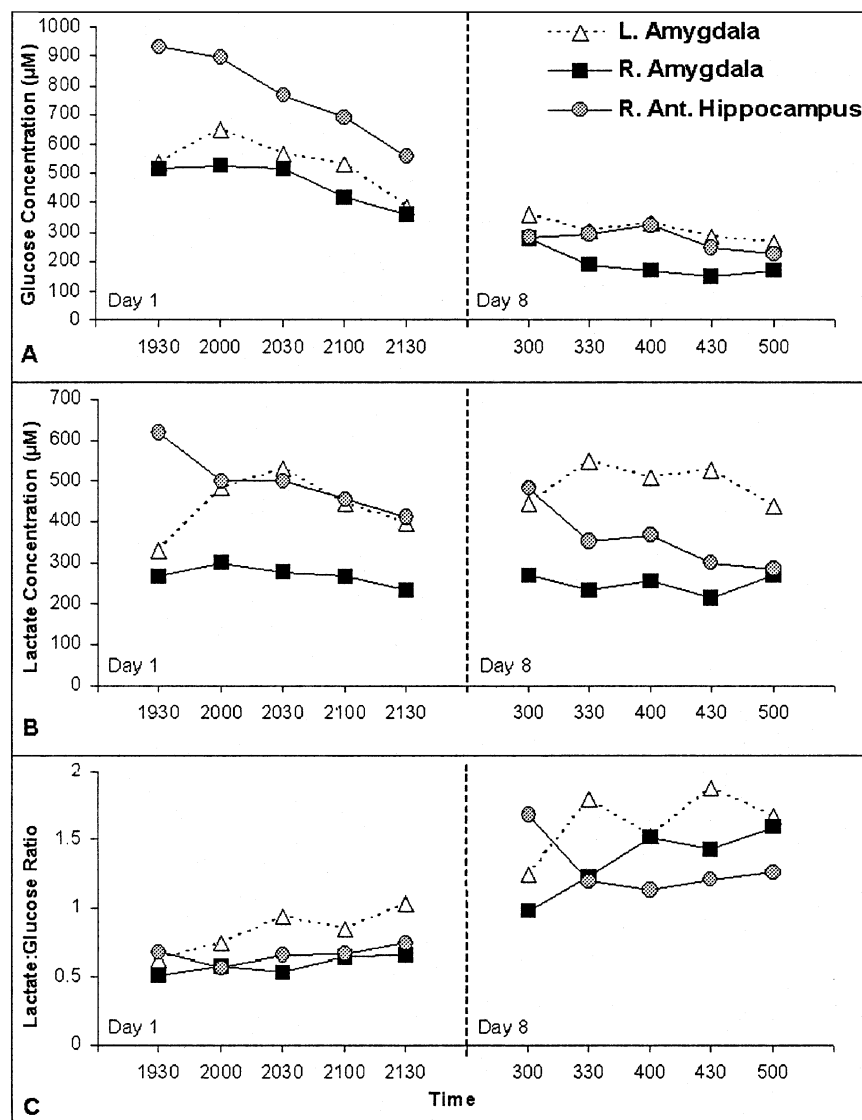
Patient	Age (yr)	Gender	Probe location	Epileptogenic region (duration)	PET hypometabolism	MRI	Surgical procedure	Handedness
1	20	F	RA, RAH, LA	Bilateral temporal (5 yr) ^a	Right temporal hypometabolism	Normal	No resection	Right
2	38	F	LA, ROF, RA, RAH	Right posterior parahippocampal gyrus (6 yr) ^a	Normal	Normal	No resection	Right
3	39	M	LA, RA	Right anterior cingulate cortex, (30 yr) ^a	Normal	Normal	Right medial frontal resection	Right
4	22	M	LOF, LA, RA	Bilateral mesial temporal (5 yr) ^a	Normal	Normal	No resection	Right

All patients were seizure free for \geq 24 h before collecting microdialysates.

RA, LA, right- and left-amygdala, respectively; RAH, right anterior hippocampus; ROF, LOF, right- and left-orbitofrontal region, respectively.

^a Epileptogenic regions confirmed from depth electrode studies.

FIG. 1. Glucose and lactate levels in microdialysate from three different brain regions in patient 1. Dialysates collected in the early evening 2 days after implantation of depth electrodes (**A**, left panel) show that highest and lowest glucose levels were seen in the right anterior hippocampus and right amygdala, respectively. Dialysates collected in the midafternoon 1 week later (**A**, right panel) contained relatively lower glucose levels, but the lowest glucose levels were still seen in the right amygdala. Regional differences in lactate levels also were apparent (**B**), but in samples collected a week later, lactate levels remained relatively unchanged. Lactate/glucose ratios of <1 were recorded during the first monitoring period, whereas in the dialysates collected 1 week later, these ratios were consistently between 1 and 2 in all brain regions (**C**). In the first monitoring period, the lactate/glucose ratios of <1 (**C**) appear to coincide with relatively higher glucose levels (**A**). In this patient, fluorodeoxyglucose-positron emission tomography (FDG-PET) examination indicated right temporal hypometabolism (Table 1). Furthermore, mean glucose levels in two sites close to the area of reduced FDG trapping (the right amygdala and the right anterior hippocampus) differed significantly ($p < 0.05$; t test) by $\sim 40\%$ during the initial monitoring period (Table 3). The same mean $\sim 40\%$ difference ($p < 0.05$) also was seen in the monitoring period 7 days later (Table 3), suggesting that regions of reduced FDG trapping may be associated with alterations in local glucose concentrations.



mean glucose levels on day 1 versus day 8 were significant ($p < 0.05$; t test) whereas changes in lactate levels were not significant. In this patient, one region (the right anterior hippocampus) consistently appeared to exhibit the highest glucose concentration, whereas the right amygdala was consistently lowest, even when dialysate concentrations were assayed a week apart. During both periods of analysis, the mean glucose concentration in the right anterior hippocampus was $\sim 40\%$ greater than that in the right amygdala. Probe differences do not seem to be responsible, because in vitro recovery of lactate and glutamate averaged 25% for the right amygdala probe, 25% for the left amygdala probe, and 38% for the right anterior hippocampal probe. An FDG-PET examination of this patient indicated right temporal hypometabolism (Table 1), possibly suggesting that the extreme differences seen between glucose concentrations in two anatomically close locations (the right anterior hippocampus

and the right amygdala) contributed to the reduced FDG trapping in this region.

Dialysate lactate concentrations exhibited typical regional variations, but changes over the 7-day interval between the two monitoring periods (Fig. 1B) were not significant. In contrast, there was a distinct change in lactate/glucose ratio. These ratios increased from less than 1:1 in the initial period to a range between 1 and 2:1 in the later monitoring period (Fig. 1C), presumably because of a relative decrease in glucose.

Patient 2

Microdialysate glucose and lactate levels were examined in another patient (bearing four dialysis probes) at two different intervals, 48 h apart. Differences in brain regional glucose concentrations also were seen (Fig. 2A) in the separate 4- to 5-h collection periods between the two monitoring periods. During the initial observation

Patient 2

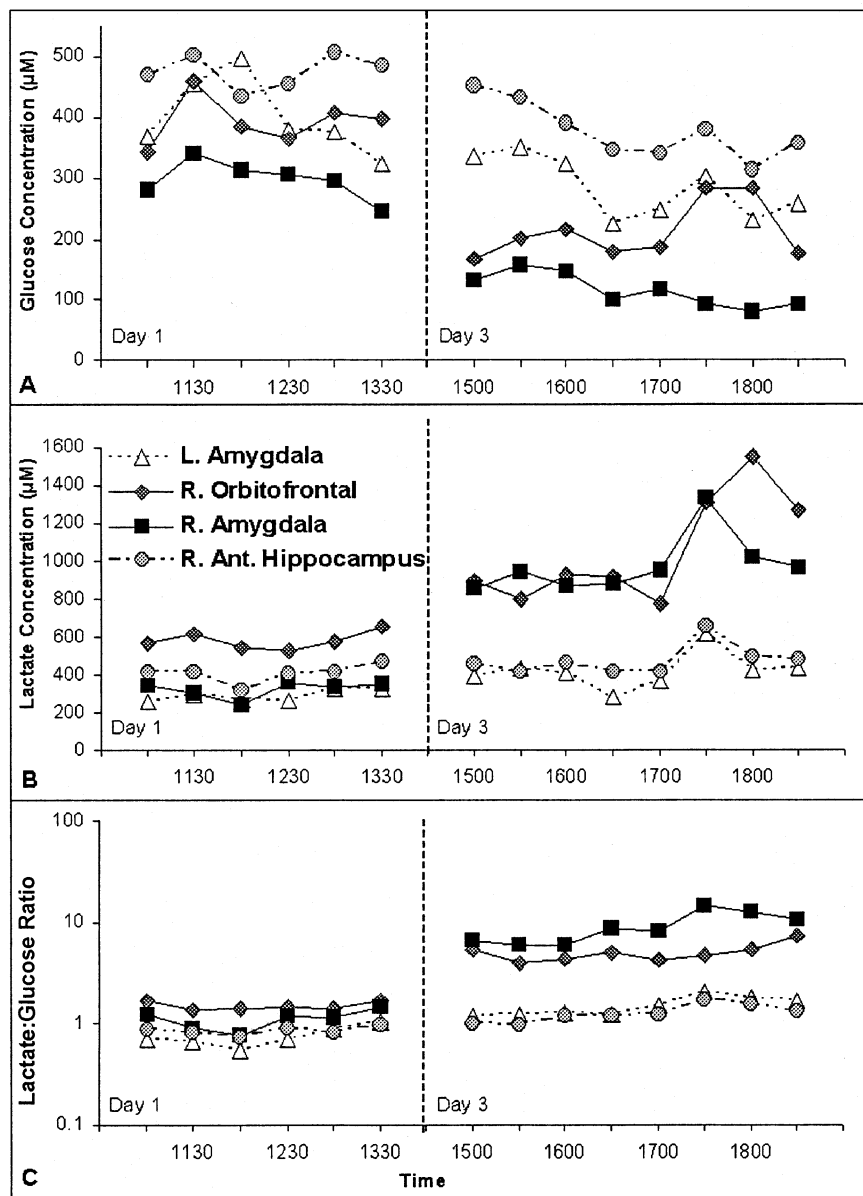


FIG. 2. Glucose and lactate levels in microdialysate from four different brain regions of patient 2. Microdialysate samples were collected over the midday period on day 1, and in the midafternoon 2 days later. **A:** Significant regional differences in glucose concentration are indicated from the four different probes. In both monitoring periods, the relatively lowest glucose levels were consistently seen in the right amygdala, and highest levels were apparent in the right anterior hippocampus and left amygdala. Although glucose concentrations were relatively unchanged (from day 1 to day 3) in the left amygdala and right anterior hippocampus, quantitatively lower glucose concentrations were seen in the right amygdala and right anterior hippocampus on day 1. **B:** Variation in regional dialysate lactate levels ranged from 200 to 600 μM . However, dramatically elevated lactate levels were seen in the right amygdala and right anterior hippocampus during day 3. **C:** Lactate/glucose ratios of 1 to 2 are quite typical. However, the sharply elevated lactate concentrations seen during day 3 in the right amygdala and orbitofrontal sites, coincide with relative reductions in glucose level, resulting in high lactate/glucose ratios ranging from 4 to 12 (Table 3).

period, dialysate glucose levels ranged from 250 to 500 μM , and regional differences in glucose levels were even more distinct (ranging from 100 to 450 μM) 48 h later. Note that the epileptogenic region was clinically identified in the right posterior parahippocampal gyrus (Table 1), and higher glucose levels were apparent in the right anterior hippocampus, with relatively lower glucose seen in the right amygdala (Fig. 2A).

Lactate levels in Patient 2 also exhibited considerable variation, ranging from a minimum of 200 μM to a maximum of 650 μM on day 1, whereas lactate levels in the dialysate ranged from 200 to 1,600 μM during a 4-h monitoring period 2 days later. The two probes that exhibited significantly higher lactate levels (right amygdala

and right orbitofrontal areas, ranging from 800 to 1,600 μM ; Fig. 2B) were coincidentally the two regions exhibiting relatively lower glucose levels in the dialysate (Fig. 2A). A sharp increase in lactate levels was recorded from probes in the right amygdala and right orbitofrontal region, during the second day of monitoring. Clinical records indicated that none of the four patients experienced seizures in the 24 h before microdialysate collection. This suggests that periods of unusually high lactic acid in selected regions (Fig. 2B) may not always be associated with active seizures (10) or trauma (17,19,22). We also examined lactate/glucose ratios in each dialysate sample, and recorded values ranging from 0.5 to 2 in most dialysate samples. However, the right orbitofrontal and right

amygdala regions were remarkable in that lactate/glucose ratios ranging from 4 to 15 were determined in these areas from this patient (Fig. 2C). As noted earlier, the right amygdala and right orbitofrontal region also were coincidentally regions of low glucose, and the change in both analytes contributes to the unusually high lactate/glucose ratios in these selected regions (Fig. 2C). It also is noteworthy that in one instance, increased lactate/glucose ratios were attributable primarily to large increases in lactate levels (in two selected regions, Fig. 2). In contrast, the more modest shift in dialysate lactate/glucose ratios in patient 1 was primarily a function of altered glucose levels (Fig. 1).

Patient 3

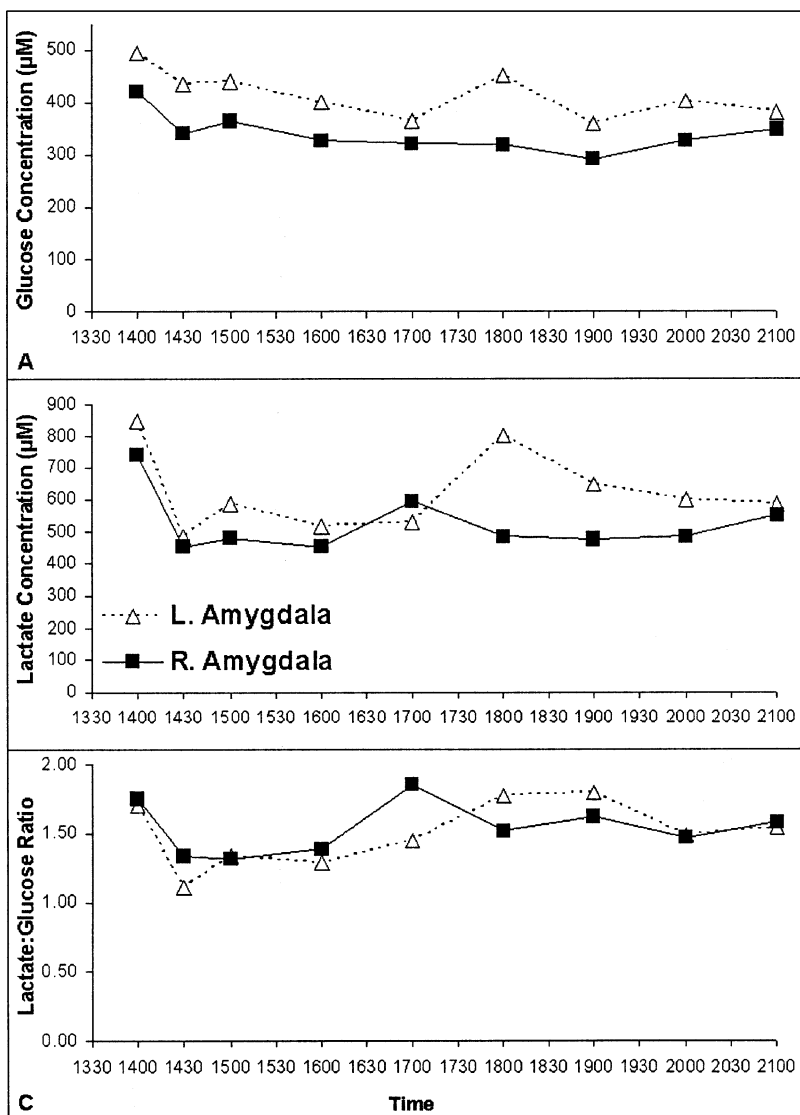
Dialysate glucose and lactate levels also were assayed from the right and left amygdala of a patient whose seizures originated in the right cingulate cortex. Variations in glucose and lactate levels in both left and right amyg-

dala were unremarkable (Fig. 3A and B), in contrast to the data from the patients 1 and 2 (Figs. 1 and 2). Furthermore, over the 7-h monitoring period, lactate/glucose ratios were very similar in these two regions and remained consistently between 1 and 2 (Fig. 3C).

Patient 4

Continuous, extended (32-h) monitoring also was achieved in one patient. In this case, dialysate collections were initiated <24 h after probe implantation, and during the first 6 to 7 h, a general decline in glucose levels was observed in all three regions studied. By approximately noon the day after surgery, glucose levels stabilized in each of the three regions (Fig. 4), consistent with the previous report that microdialysate glucose concentrations do not normalize until 24 h after probe placement (13). For the following 24 h, significantly different regional glucose levels were assayed (Fig. 4A). Dialysate from the right amygdala ranged between 40 and 120 μ M,

FIG. 3. Comparison of microdialysate glucose and lactate levels from the right and left amygdala of patient 3. **A:** Glucose levels were consistently higher in the left than right amygdala over the 7-h monitoring period. **B:** Differences between the left and right amygdala were significantly different from zero. Lactate levels were usually, but not always, greater in the left amygdala than the right. **C:** Lactate/glucose ratios were consistently between 1 and 2, without lateralized differences.



Patient 4

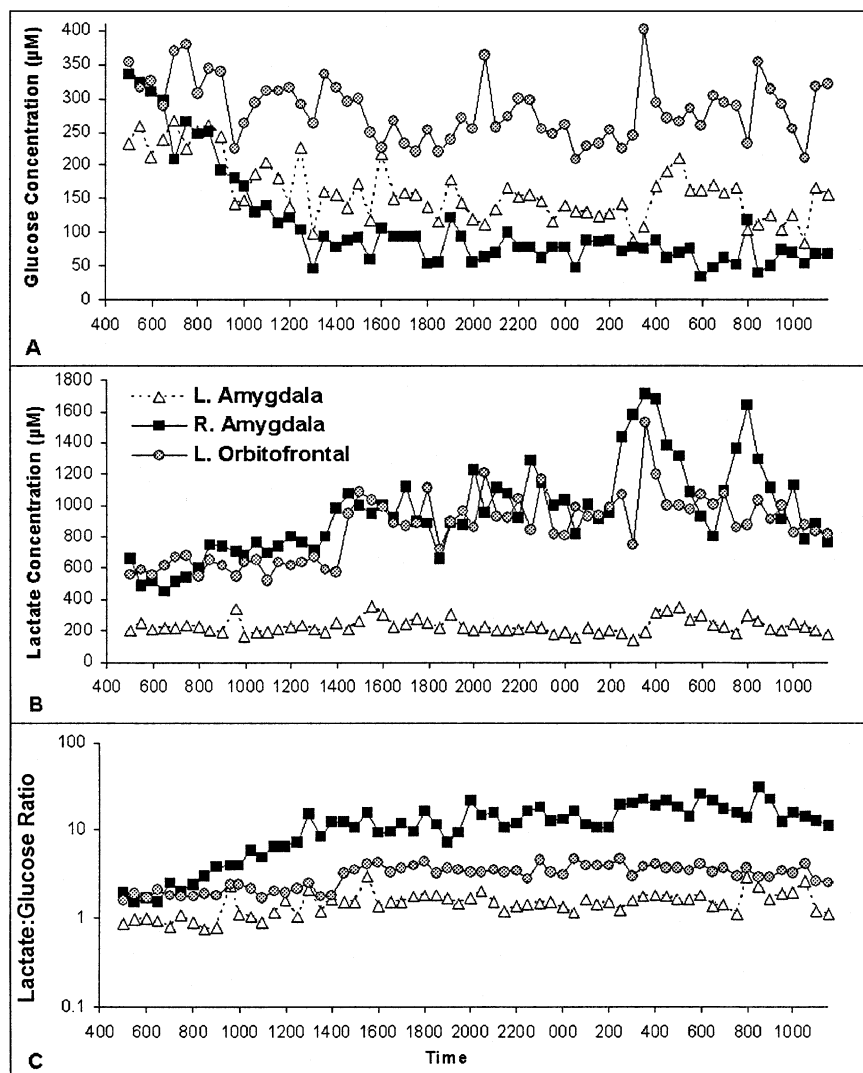


FIG. 4. Glucose and lactate levels in microdialysate from three different brain regions in patient 4. Modified depth electrodes were implanted and dialysate collections from three probes begun ~0500 the following morning. **A:** In all three regions, dialysate glucose concentrations exhibited a decline during the first few hours, which continued until about noon. At this time, distinct regional differences in glucose level became apparent and persisted over the next 24 h. The decline in glucose levels in the first 24 h after probe placement has been seen by others (13) and is believed to represent a normalization occurring after a local reaction to probe insertion. In the following 24 h of monitoring, glucose concentrations were consistently the highest in the left orbitofrontal region, consistently lowest in the right amygdala, and intermediate in the left amygdala. **B:** Lactate levels were lowest in the right amygdala. In the left amygdala and orbitofrontal regions, dramatically elevated lactate levels were seen during the last 24 h of monitoring. **C:** Typical lactate/glucose ratios (ranging from 1 to 2) were observed in the right amygdala, whereas markedly elevated lactate/glucose ratios were apparent in the right amygdala and right orbitofrontal regions.

whereas concentrations of 100–220 μM were seen in the left amygdala, and glucose levels ranged from 200 to 400 μM in dialysate from the left orbitofrontal probe (Fig. 4A).

During the last 24 h of monitoring, lactate levels ranged from 150 to 350 μM in the left amygdala (the area characterized by intermediate glucose levels). In both the left amygdala and left orbitofrontal regions, elevated dialysate lactate levels (ranging from 550 to 1,600 μM) were recorded (Fig. 4B). Coincidentally, these two locations were the sites of relatively higher and lower glucose levels. Lactate/glucose ratios were consistently between 1 and 2 in the left amygdala (Fig. 4C). In contrast, the lactate/glucose ratio was elevated in dialysate from the left orbitofrontal region (ranging from 2.2 to 4.4) and substantially higher (5–25) in the right amygdala. In this patient, there was no evidence of a significant diurnal variation in lactate concentration, glucose concentration, or lactate/glucose ratio.

In each of the patients in whom multiple brain regions were simultaneously analyzed for several hours, one region with significantly lower glucose levels was consistently identified. In addition, mean glucose levels of the right amygdala were always lower than the concentrations assayed at other sites. All of these patients were right-handed, and the right side was coincidentally a site of seizure origin in two of these patients (and in two patients, there was evidence of bilateral seizure onset; Table 1).

This phenomenon is illustrated by inspecting the average mean differences in glucose and lactate levels in the amygdalae (Table 2). The difference in glucose levels (left amygdala minus right amygdala) ranged from a low of 69 ± 32 (patient 25) to a high of 141 ± 50 (patient 14). If probe differences were responsible, one would expect to see the same lateralized increase in lactate levels in left versus right amygdalae, but no distinct laterality of lactate levels was apparent in the amygdalae (Table 2).

TABLE 2. Average left–right differences of dialysate glucose and lactate levels (left amygdala minus right amygdala)

Patient	No. of paired samples	Glucose (μM)		Lactate (μM)	
		Mean	SD	Mean	SD
1	10	90	47	189	100
2	14	141	50	-336	281
3	8	75	29	97	107
4	48	69	32	-819	254

Note that when levels in the left amygdala are subtracted from those in the right, dialysate glucose concentrations in these patients with partial seizures were lower in the right than left amygdala (not significant). In all patients, a positive difference was seen, which was significant from zero. In contrast, left–right differences in dialysate lactate concentrations were not consistently lateralized.

To illustrate time-dependent variation within a given probe, in comparison to apparent variation between brain regions, the mean (\pm SD, and coefficient of variation) dialysate glucose and lactate levels for each of the probes is compared in Table 3. These data suggest that when brain regional lactate/glucose ratios exceed 2.0, there is both an increase in lactate and a relative decrease in glucose levels, within a given region of the brain. Furthermore, in situations in which at least three different regions were studied, significant brain regional differences in lactate/glucose ratios (within a given patient) were apparent (Table 4).

DISCUSSION

In studies of this type, there is a potential for inter-probe variability that may be independent of variability in the actual regional concentration of analytes in the

TABLE 4. Within-patient regional differences in brain lactate/glucose ratios

Patient no.	Brain regions compared	T statistic	p value
1 (Day 1)	RAH versus RA	1.64	Not significant
	LA versus RA	5.86	<0.001
	LA versus RAH	4.22	<0.01
1 (Day 8)	RAH versus RA	0.62	Not significant
	LA versus RA	2.81	<0.05
	LA versus RAH	3.43	<0.01
2 ^a	ROF versus LA	6.26	<0.001
	RA versus LA	4.57	<0.001
	RAH versus LA	0.21	Not significant
	RA versus ROF	5.97	<0.001
	RAH versus ROF	6.48	<0.001
	RAH versus RA	12.4	<0.001
3	RA versus LA	0.40	Not significant
4	LA versus RA	13.5	<0.001
	RA versus LOF	85.4	<0.001
	RA versus LA	98.9	<0.001

Abbreviations are as in Tables 1 and 3. Note that for the majority of sites compared, significant regional differences were apparent.

^a For patient 2, the regional differences shown for pooled data (days 1 and 3) are a confirmation of separate analyses of day 1 or day 3 data (not shown).

extracellular fluid. Sources of variability outside the extracellular fluid may include small variations in pressure and the kinetics of the diffusion of lactate and glucose in different dialysis sites. Recovery also may be affected by changes in supply, metabolism, and in extracellular fluid (ECF) volume (23). Consequently, we can compare (a) changes in lactate and/or glucose within a given probe across time, and (b) changes in the lactate/glucose ratio, with confidence. But possible variability between different probes makes quantitative comparison of absolute regional lactate and glucose concentrations in dialysate samples more problematic.

TABLE 3. Mean dialysate glucose and lactate levels over consecutive 30-min monitoring periods

Patient	Day/Time	No. of samples	Region	Glucose (μM)			Lactate (μM)			Lactate/Glucose		
				Mean	SD	CV	Mean	SD	CV	Mean	SD	CV
1	1 1930–2130	5	RA	468	76	16	268	24	9	0.58	0.06	10
			RAH	768	153	20	497	78	16	0.65	0.07	10
			LA	533	95	18	436	77	18	0.83	0.16	19
	8 0300–0500	5	RA	191	50	26	249	24	10	1.35	0.25	19
			RAH	276	39	14	357	77	22	1.29	0.22	17
			LA	308	39	13	492	49	10	1.62	0.25	15
2	1 1100–1330	6	LA	400	64	16	291	34	12	0.75	0.17	23
			ROF	393	40	10	582	48	8	1.49	0.13	9
			RA	298	32	11	324	47	14	1.11	0.24	22
	3 1500–1830	8	RAH	476	28	6	407	50	12	0.85	0.08	10
			LA	285	49	17	419	94	23	1.49	0.32	22
			ROF	212	47	22	1058	283	27	5.03	1.05	21
3	1 1400–2100	9	RA	114	28	25	981	156	16	9.22	3.27	35
			RAH	377	47	13	474	81	17	1.28	0.27	21
			LA	415	44	11	623	125	20	1.50	0.23	16
4	2 1130–1130 (last 24 h)	48	RA	341	37	11	525	94	18	1.54	0.19	12
			LOF	275	41	15	925	177	19	3.42	0.72	21
			LA	146	31	21	231	49	21	1.63	0.42	25
			RA	77	21	28	1050	258	25	14.73	5.44	37

These data show that within each patient and each study period, mean dialysate glucose levels were consistently lowest in the right amygdala. Note that the coefficients of variation are typically between 10 and 25%, and exceed 30% only for lactate/glucose ratios in the RA of patients 2 and 4, situations characterized by concomitantly low glucose with elevated lactate levels.

Hutchinson et al. (13) studied five patients with head injury or subarachnoid hemorrhage and performed a detailed analysis of probe variability in two identical, adjacently situated microdialysis catheters (of the same length, perfusion rate, and perfusion fluid) over a 15- to 24-h interval. Their analyses of glucose and lactate showed small interprobe differences, ranging from 12 to 25%. Considerably larger differences in regional brain glucose concentrations are seen in patients with complex partial seizures, especially in comparing probes adjacent to the epileptogenic site (30–70%; Table 3). If it is assumed that these regional differences in glucose levels are not due solely to interprobe differences, an alternate conclusion is that glucose levels may be altered in and around epileptogenic areas. This conclusion would be consistent with predictions from previous dynamic FDG-PET analyses (3,24). It also suggests that quantitative electron microscopic immunogold analyses of brain capillary Glut1 glucose transporter expression from seizure resections, showing variable amounts of transporter in different areas have a functional significance (24). The latter study showed that small microvolumes of the brain parenchyma had different capillary Glut1 transporter concentrations and therefore could have markedly different glucose levels. As a consequence, adjacent microvolumes of brain tissue might exhibit highly variable glucose utilization rates, on the basis of capillary supply limitation (24). In the present study, our demonstration of regional differences in glucose/lactate ratios around epileptogenic regions in human brain seems consistent with alterations in glucose metabolism.

The implantation of dialysis probes has been likened to an injury model, in which vasogenic edema is attributed to damage caused by probe insertion (25). Benveniste et al. (26) reported that acutely altered brain glucose concentrations were seen in certain sites. Brain glucose utilization rates also are elevated and did not normalize until 24 h had elapsed in these animal model studies (26). In the human brain, Hutchinson et al. (13) recorded similar findings. They demonstrated that in two adjacent dialysis probes, glucose levels from both probes are characterized by initially high, followed by continually decreasing glucose levels through the first 24 h, and relatively stable and uniform glucose concentrations were recorded for the remainder of the study period. We observed a similar pattern in one of our study patients (patient 4; Fig. 4), in whom probes had been implanted on 1 day, and dialysis commenced at 0500 h the following morning. Decreasing glucose levels were recorded only until about noon on the day after surgery, and during the next 24 h, distinctly different dialysate glucose concentrations (characteristic of each of the sites) were seen in each of the three probes (Fig. 4A). We thus postulate that increased glucose levels attributable to local injury associated with probe insertion were appar-

ently resolved during the second postsurgical day, as previously suggested (13,26).

Sokoloff et al. (27) pioneered the development of methods using the phosphorylation and prolonged tissue retention of tracer levels of deoxyglucose phosphate in measuring cerebral metabolic rates. By using [¹⁸F]fluorodeoxyglucose, together with positron emission tomography, this method was soon applied to humans (28,29). Noninvasive measurements of the cerebral metabolic rate by the FDG method require precise estimation of the net clearance of FDG, and the isotope correction factor, termed the lumped constant (30). Several reports suggested that uncertainty about the estimates of the individual transfer coefficients (describing influx, efflux, and phosphorylation rates of FDG) has little effect on the final result (31–33). However, the latter studies are based on normal rather than on pathological conditions. Our present results, showing regions of highly variable glucose/lactate ratios around the epileptogenic site, suggest that equally variable glucose influx and metabolism may characterize regions in and around the epileptogenic focus. Although FDG-PET continues to aid in the identification of epileptogenic sites, the alterations in glucose influx make accurate estimations of the lumped constant problematic even during normal (interictal) periods in patients with complex partial seizures.

The use of lumped constants for estimating brain glucose utilization rates with hexose analogues (such as FDG or 2-deoxyglucose) assumes that brain glucose is uniformly distributed in intra- and extracellular spaces of the brain, without significant regional variations. Furthermore, it has been traditionally assumed that glucose exchange between blood and brain was symmetrical. When glucose influx and efflux were equal, the partition volume for glucose and FDG was shown to be the same (34). But quantitative electron microscopic studies show a distinct 3:1 abluminal/luminal asymmetry in (low glucose transporter-expressing) type B capillary membranes. The asymmetry in high glucose transporter-expressing type A endothelia (1:2 abluminal/luminal membrane Glut1) exists in the opposite direction (24). Localized differences in the proportions of these two configurations of glucose transporter-expressing capillaries could contribute to the different glucose concentrations recorded in different brain regions of the patients examined in the present study (Table 3). This observation seems consistent with the prior dynamic FDG-PET studies of Reutens et al. (3), who observed that changes in the lumped constant were seen in epileptogenic areas of their patients.

In one patient (patient 4), in whom we determined glucose and lactate concentrations over an extended (29-h) period, there was no evidence for a significant diurnal rhythm for any of the measures tested in the amygdalae or orbitofrontal cortex. Although preliminary, these data

seem to indicate that within a given region, brain glucose levels remained quite constant throughout the sleep-wake cycle (Fig. 4). In contrast, there is a strong diurnal component to peripheral blood glucose levels in humans (35), and FDG-PET studies suggest diurnal variations in cerebral glucose utilization in several neural structures, including the amygdala (36). Studies in rats also have shown relatively little diurnal variation in brain glucose levels, whereas plasma glucose levels and brain glucose utilization rates exhibit a marked diurnal periodicity (37).

In previous measurements of lactate levels in patients with complex partial seizures, During et al. (10) reported that preictal lactate concentrations (150–250 μM) doubled after a seizure, and gradually returned to normal in ~ 2 h. The increase to remarkably high lactate levels that we observed interictally (Fig. 2B) has been previously associated with EEG-demonstrable increases in spiking (10). During et al. (10) implanted a 30-mm dialysis probe, whereas a smaller (10-mm) dialysis membrane was noted in the present study, and differences in our lactate levels (Table 3) can be attributed to the dialysis probes. When electrodes are introduced occipitally through the long axis of the hippocampus, with 30-mm dialysis tubing, it is not possible to sample the amygdala or subregions of the hippocampus exclusively (11). Hutchinson et al. (13) also demonstrated that membrane lengths and perfusion rates also significantly affect analyte recovery. In studies of patients with severe head injuries, microdialysate lactate levels ranging from 500 to 2,000 μM by Zauner et al. (22) and 200 to 3,600 μM by Menzel et al. (16) have been reported, and small (10-mm) microdialysis probes were used in both studies. In minimally traumatized cortex, microdialysate lactate levels from 4-mm probes implanted in brain tissue adjacent to an aneurysm averaged $227 \pm 30 \mu\text{M}$ ($\pm\text{SD}$, $n = 10$) (14). Localized brain regions may therefore be characterized by quite extreme changes in both glucose and lactate levels, and we suggest that the rather simple determination of lactate/glucose ratios would permit a more meaningful comparison between different regions as well as different studies.

Human brain lactate and glucose concentrations have been determined from the same microdialysate in a variety of neurosurgical procedures, and technical differences between the different studies tend to be normalized when the ratios of these two analytes are compared. In cases of severe acute head trauma, mean lactate/glucose ratios of $\sim 1:1$ were reported in patients with a good outcome, $1-2:1$ in patients with moderate to severe disability, and $>2:1$ in patients with poor (death/vegetative) outcomes (22). Studies of Menzel et al. (16) similarly indicate mean lactate/glucose ratios of $1-2:1$ in their head-injury patients. Of more relevance to the present study, however, are the analyses of minimally damaged cortex carried out by Reinstrap et al. (38), Langemann et

al. (39), and Bachli et al. (14). Microdialysate lactate and glucose concentrations were measured before probe removal, in a series of patients in which the neurosurgical intervention was to treat an unruptured aneurysm. Mean lactate/glucose ratios of 0.86 ± 0.11 were recorded (14). It also was shown in one patient that in the 2 h of retraction during surgical treatment of an aneurysm (in the posterior communicating artery), lactate/glucose ratios were consistently $>2:1$, but rapidly changed to $<1:1$ in the 3 h after retraction pressure was withdrawn, and the ischemic stress is removed (14). Reinstrap et al. (38) reported baseline values of glucose ($1.7 \pm 0.9 \text{ mM}$) and lactate ($2.9 \pm 0.9 \text{ mM}$) in nine patients and saw a lactate/glucose ratio of 1.7. In anesthetized patients, the lactate/glucose ratio of minimally disturbed brain (1.17) was slightly lower (39). Data from our patients seem to suggest that dialysate lactate/glucose ratios fall into one of three separate groups (Table 3). First, lactate/glucose ratios of <1 were occasionally recorded (Fig. 2), and this occurrence seems to be associated with elevated brain glucose levels. Second, lactate/glucose ratios of $1-2:1$ were the most frequently recorded, in the present study (Figs. 1–3) and in others (16,22,38,39), suggesting this represents the usual state of glucose use. Third, lactate/glucose ratios of >2 (Figs. 2 and 4) were observed in selected regions, presumably linked with some sort of pathophysiologic event. In epilepsy patients, these markedly elevated lactate/glucose ratios are coincident with elevations in lactate levels (Figs. 2 and 4; Table 2), and increased spiking activity is associated with similar increases in lactate (10). However, in aneurysm patients, the transiently elevated lactate/glucose ratio was associated with an ischemic response (to retraction pressure) and were coincident with a reduction in brain glucose. Some minutes after retraction pressure was eased, dialysate glucose levels increased, and the lactate/glucose ratio normalized (14). The reduction in brain glucose may be attributable to the well-established acute downregulation of BBB glucose transport seen in anoxia, which normalizes after the stress is relieved (40). Ischemia due to retraction pressure also was seen to increase microdialysate lactate/glucose ratios in another study (15). Thus elevated (>2) lactate/glucose ratios occur in brain via different mechanisms. In epilepsy patients, they are attributable to increased lactate accumulation, presumably associated with reduced oxidative activity. In contrast, the transiently elevated lactate/glucose ratios that accompany retraction ischemia apparently are explained by transient downregulation of glucose transport.

In conclusion, regional variations in brain extracellular glucose concentrations may be of greater magnitude than previously established. In two of the four patients with partial seizures whom we examined interictally, regional lactate/glucose ratios differed by log orders of magnitude, and changes in the lactate/glucose ratios are be-

lieved to involve alterations in both regional brain glucose and lactate. Changes in brain glucose are presumably attributable to alterations in brain capillary glucose transporter expression described in previous quantitative immunogold electron microscopic studies of seizure resections (24). The elevated regional lactate levels that also were recorded in two of the four patients examined is seemingly consistent with the observation of During et al. (10), who demonstrated that increases in lactate were seen both ictally and in the absence of active seizures. Furthermore, we observed lower glucose concentrations in the right amygdalae (Table 2) in patients with a right (or bilateral) epileptogenic focus (Table 1), and relatively lower glucose metabolism has been seen by others in the (right) hippocampus, ipsilateral to temporal lobe epileptogenic zones (41). An underlying common mechanism may therefore explain our observation of asymmetric glucose levels in left compared with right amygdalae (Table 2), as well as the Asymmetry Index in hippocampal glucose metabolic rate (and hippocampal volume), reported in patients with temporal lobe epilepsy (41). The present study establishes that modified depth electrodes can be adapted to compare dialysate analyte concentrations diurnally, and in several different brain regions simultaneously. Concomitant assays of microdialysate lactate and glucose may augment FDG-PET analyses of cerebral metabolism in seizure disorders, and help identify sites where rates of glucose transport, glycolysis, and oxidative metabolism may differ.

Since the manuscript was accepted for publication, another study has analyzed lactate and glucose concentrations from microdialysate probes located in non-epileptic regions of patients with complex partial seizures (42). When plasma glucose levels were normal (5.5 mmol/L) the dialysate lactate/glucose ratios averaged 1.7 ($n = 12$). When hyperglycemia was induced (plasma glucose level = 11.5 mmol/L) the microdialysate lactate/glucose ratio was 0.95. However, in hypoglycemic conditions (plasma glucose = 3 mmol/L) microdialysate lactate/glucose ratios averaged 6.1 (42). These observations are consistent with our suggestion that microdialysate lactate/glucose ratios of 1 to 2 would be anticipated under normal conditions, and brain microdialysate lactate/glucose ratios above or below the 1 to 2 range are associated with pathophysiological events.

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