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# Brain Energy State and Lactate Metabolism during Status Epilepticus in the Neonatal Dog: *In Vivo* $^{31}$P and $^{1}$H Nuclear Magnetic Resonance Study[1]

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**ABSTRACT. The purpose of these experiments was to determine whether flurothyl-induced status epilepticus causes progressive decline of brain high-energy phosphates and progressive increase in brain lactate in neonatal dogs who are paralyzed and oxygenated. *In vivo* $^{31}$P nuclear magnetic resonance spectroscopic measurements showed that the fall in brain pH occurred early in the course of seizure. The decline in phosphocreatine was more gradual, *i.e.* 50% reduction, during the 1st h of seizure. There was no reduction in ATP during the 3 h of status epilepticus. *In vivo* $^{1}$H nuclear magnetic resonance measurement of brain lactate disclosed a steep rise that stabilized by 60 min. Brain and blood lactate were closely related during the initial phase of seizure, suggesting rapid efflux of lactate from brain or systemic production of lactate. Blood lactate exceeded brain lactate after 1 h of status epilepticus. The new steady state for cerebral phosphocreatine and lactate during status epilepticus was achieved much more slowly during neonatal status epilepticus than has been reported during status epilepticus in the adult experimental animal. The lack of change in ATP during 3 h of seizure indicates that brain energy state is not radically altered during prolonged seizure if oxygenation is maintained. (*Pediatr Res* 29: 191–195, 1991)**

**Abbreviations**

**PCr, phosphocreatine**
**$pH_i$, intracellular pH**
**NMR, nuclear magnetic resonance**
**GABA, γ-aminobutyric acid**

NMR spectroscopic studies in human neonates (1) as well as in neonatal experimental animals (2) show that brief seizures reduce levels of PCr and elevate levels of inorganic phosphate in brain, but do not perturb ATP. Nonetheless, it is hypothesized that levels of ATP might eventually fall when seizure is prolonged (1–3). We used *in vivo* $^{31}$P and $^{1}$H NMR spectroscopy to test the hypothesis that brain ATP is preserved and brain PCr and lactate do not progressively deteriorate during prolonged status epilepticus in the neonatal dog as long as the animal remains normoxic and normotensive.

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Earlier investigations in the adult rat disclosed that there is a rapid fall in PCr and $pH_i$ as well as a rise in lactate within 5 min of onset of status epilepticus. Thereafter, a new steady state for PCr and lactate was established (4–8). However, these studies in adult experimental animals could not accurately follow the sequential changes in the same animal for a prolonged period of time, but rather relied upon measurements made in multiple groups of animals. Moreover, differences in blood-brain permeability to lactate (9–13) make it difficult to extrapolate data obtained in the adult to the neonate.

In the present study, seizure was induced with the convulsant gas flurothyl (bistrifluoroethyl ether) to avoid parenteral administration of acidic convulsants such as bicuculline or kainic acid. The metabolic effects of flurothyl are of interest because flurothyl retards brain growth in the neonatal rat (14), and produces neuronal necrosis in the adult rat (15). Three types of studies were performed: *in vivo* $^{31}$P NMR to determine brain high-energy phosphate metabolism and brain pH; *in vivo* $^{1}$H NMR to measure brain lactate; and *in vitro* $^{1}$H NMR spectroscopy to quantitate concentrations of PCr, ATP, lactate, glucose, and amino acids.

## MATERIALS AND METHODS

*Animal preparation.* Mongrel dogs (4 to 12 d old) were anesthetized with halothane, 1–4%, while undergoing tracheotomy and femoral arterial catheterization (2, 16). After placement of the catheters, halothane was withdrawn, and the animals were mechanically ventilated to provide normoxia and normocarbia [partial arterial $O_2$ pressure, 80–150 mm Hg (10.7–20.0 kPa); partial arterial $CO_2$ pressure, 30–40 mm Hg (4.0–5.3 kPa)]. Thereafter, ventilator settings were not changed. Muscle paralysis was maintained throughout the experiment by parenteral administration of pancuronium bromide. To reduce pain, animals were ventilated with 30% $O_2$/70% $N_2O$ and topical anesthetic (lidocaine jelly, 1%) was applied to all incision sites. During status epilepticus, loss of awareness was produced by the seizure itself. EEG and blood pressure were monitored continuously with a Grass model 7 polygraphic recorder (Grass Instrument Co., Quincy, MA). Base deficit was calculated from arterial blood gas samples (model ABL 30; Radiometer, Copenhagen, Denmark). Blood glucose and blood lactate were determined with Beckman microglucose analyzer and lactate analyzer, respectively. Animals were subjected to 3 h of seizure, which was induced by continuously vaporizing flurothyl (0.08 mL/min; Flura Corp., Newport, TN) in the ventilator tubing.

*In vivo $^{31}$P NMR studies. In vivo* $^{31}$P data were collected using a General Electric (Wilmington, MA) CSI II spectrometer based on a 2.0 Tesla 31-cm diameter bore magnet, a 2-cm circular transmit-receiver surface coil tuned for phosphorous, and a pulse-

acquire sequence. Acquisition parameters were: frequency, 34.5 MHz; repetition interval, 1.5 s; sweep width, 5 kHz; pulse width, 45 $\mu$s; digital resolution, 4096 data points; acquisition time, 0.2 s; number of acquisitions, 512. The flip angle was set to be 90° on axis at 2-cm depth using approximately 8 W of radio frequency power. The skin and cranial muscle were not removed because NMR imaging studies showed that most of the NMR signal is derived from the relatively large brain of the neonatal dog (16).

Sets of $^{31}$P NMR spectra were continuously acquired and summed into 15-min epochs. After acquisition, the data were exponentially multiplied to obtain 10-Hz line broadening in the NMR spectra after Fourier transformation. The standard General Electric curve fitting software, CSICAP, was then employed to determine the areas of individual resonances. The positions, heights, and widths of seven Lorentzian lines were individually adjusted until the fit was optimal as determined by the least squares difference from the actual spectrum (see Fig. 2 in ref. 2). Brain $pH_i$ was determined from experimental spectra by measuring the chemical shift of the inorganic phosphate peak with respect to that of PCr, as previously described (2, 17, 18). At the end of the 3-h observation, the animal's brain was frozen *in situ* using a "funnel" freezing technique to "freeze-clamp" levels of PCr and ATP (19).

The relative change of the PCr signal in each serial spectrum was measured with respect to the intensity of the signal in the spectrum obtained immediately before freezing the brain *in situ*. The concentration of PCr was measured in extract with *in vitro* $^1$H NMR spectroscopy (see below). This value was assigned to the intensity of the last spectrum; the preceding spectra were assigned values by the basis of relative change. There was good agreement between the PCr value calculated in this fashion before the administration of flurothyl and the value determined by freeze-clamp and extraction in a separate group of control animals. The same approach was used to quantitate the ATP signals in the *in vivo* $^{31}$P spectra.

*In vivo $^1$H NMR studies.* A separate group of animals was used for the *in vivo* $^1$H NMR to improve temporal resolution and to maximize the signal to noise ratio. *In vivo* $^1$H NMR spectra were obtained with the same spectrometer tuned for hydrogen and a 2-cm circular proton coil. Acquisition parameters were: frequency, 85.6 MHz on resonance on water; pulse sequence $1\bar{3}3\bar{1}$-$\tau$-$2\bar{6}6\bar{2}$-$\tau$-spin echo sequence; repetition interval, 3.6 s; echo time = $2\tau$ = 150 ms; sweep width, 500 Hz; pulse width, 30 $\mu$s; digital resolution, 4096 data points; acquisition time, 2 s; number of acquisitions, 64. The flip angle was set to be 90° on axis at 2-cm depth using approximately 8 W of radio frequency power. The interval between each component pulse of the binomial sequence was selected to produce maximum excitation around 3.4 ppm off the water resonance corresponding to the lactate frequency. Before Fourier transformation, the data were exponentially multiplied to achieve 1-Hz line broadening. To quantitate lactate in brain, the animal was subjected to KCl-induced cardioplegia in the spectrometer after the 3-h period of seizure. The intensity of the lactate signal *post-mortem* was calibrated using the concentration determined in extract by enzymatic analysis.

*In vitro $^1$H NMR studies.* As previously mentioned, the brains of animals used in the *in vivo* $^{31}$P NMR experiments were funnel-frozen *in situ* (19), extracted, and lyophilized. A group of animals that had not been given flurothyl was funnel-frozen and served as a control group. Perchloric acid brain extracts from both the flurothyl-treated animals and the control animals were lyophilized and redisolved in 100 mM phosphate buffer in $D_2O$. Fully relaxed $^1$H spectra were obtained using a $^1$H NMR high-resolution spectrometer [Bruker WM-500 (Bruker Instruments, Inc., Billerica, MA)], 5-mm commercial $^1$H probe, and a one-pulse sequence with low-power presaturation for solvent suppression. Acquisition parameters were: frequency, 500 MHz; temperature, 25°C, pulse, 30°; repetition time, 6 s; accumulations, 160; sweep width, 6 kHz; digital resolution, 32 K; acquisition time, 2.7 s. Resonances were quantitated relative to the added internal concentration standard and chemical shift reference, sodium 3-trimethyl silyl proprionate (20, 21).

These experiments were approved by the Yale University Animal Care Committee and carried out with adherence to "Guiding Principles for the Care of Animals" of the American Physiological Society and in accordance with federal regulations.

## RESULTS

*Systemic changes.* Onset of seizure caused transient increase in mean arterial blood pressure, followed by gradual decline over the next 90 min to significantly lower levels for the duration of the period of study (Table 1). Animals developed significant metabolic acidosis during status epilepticus. Blood glucose rose transiently and then returned toward control values at the end of the 3-h observation. Blood lactate increased 3-fold during the first 15 min of seizure, remained elevated, and began to rise again toward the end of the 3rd h of seizure.

*Cerebral physiologic changes.* The EEG showed low-amplitude (10–30 $\mu$V), 8–11 Hz activity as the dominant rhythm during the control period. Flurothyl produced sharp waves, spikes, and spike/slow wave discharges (50–300 $\mu$V) of varying intensity during the 3 h of seizure (22).

*In vivo $^{31}$P NMR studies.* Serial $^{31}$P NMR spectra disclosed a significant fall in PCr (Figs. 1 and 2). PCr reached a new steady state approximately 60 min after onset of seizure (Fig. 2). Brain

Table 1. *Systemic changes**

| Time (min) | Blood pressure (mm Hg) | Base deficit (mmol $HCO_3$) | Blood glucose (mmol/L) | Blood lactate (mmol/L) |
|---|---|---|---|---|
| 0 | 91 ± 10 | 5.4 ± 1.1 | 7.9 ± 0.6 | 1.3 ± 0.16 |
| 5 | 112 ± 8† | | | |
| 15 | 97 ± 9 | 8.5 ± 3.7 | 12.7 ± 2.1‡ | 3.88 ± 0.62‡ |
| 30 | 91 ± 12 | 15.4 ± 2.0† | 11.8 ± 1.4 | 3.85 ± 0.68‡ |
| 60 | 83 ± 10 | 15.9 ± 1.2† | 11.2 ± 1.4 | 4.58 ± 0.27‡ |
| 90 | 72 ± 8‡ | 17.2 ± 2.1† | 10.5 ± 2.2 | 4.96 ± 0.68‡ |
| 120 | 70 ± 7‡ | 16.5 ± 2.4† | 9.6 ± 2.1 | 4.72 ± 0.71‡ |
| 180 | 69 ± 7‡ | 18.1 ± 3.1† | 8.6 ± 1.8 | 7.02 ± 1.08† |

* Values are Mean ± SEM; analysis of variance (repeated measures); $n = 5$.

† $p < 0.01$ *vs.* 0 min.

‡ $p < 0.05$ *vs.* 0 min.

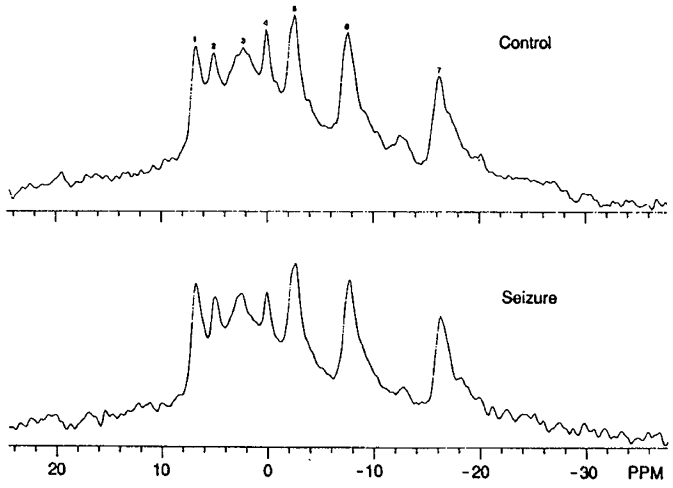


Fig. 1. $^{31}$P NMR spectra before and during flurothyl-induced status epilepticus. The spectra consists of resonances from phosphomonoesters (*1*), inorganic phosphate (*2*), phosphodiesters (*3*), PCr (*4*), and the $\gamma$- (*5*), $\alpha$- (*6*), and $\beta$- (*7*) resonances of ATP. Note the decrease in the intensity of the PCr peak after onset of seizure.

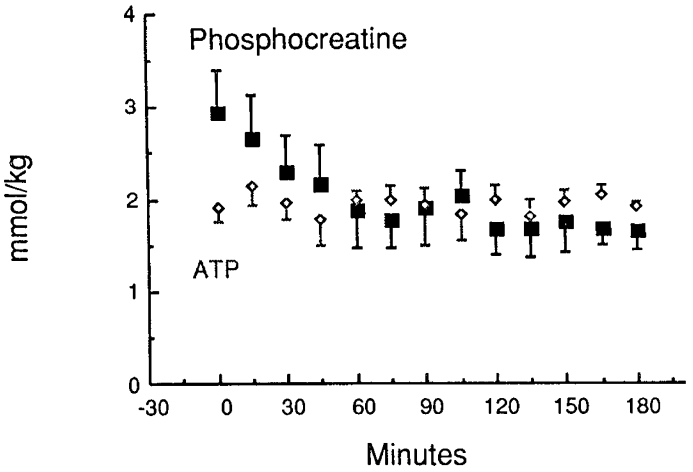


Fig. 2. High energy phosphates during flurothyl seizure. PCr declined by approximately one half during the 1st h of seizure and remained at this reduced value for the next 2 h (analysis of variance: $F$ test, 5.414; $p = 0.0009$). There is no significant change in ATP. Values after 180 min of seizure were: PCr, 1.7 ± 0.2 μm/g; ATP, 1.8 μm/g; creatine, 4.1 ± 0.5 μm/g. Measurements were made on brain extracts using high-resolution *in vitro* $^{1}H$ NMR at 500 MHz ($n = 5$, mean ± SEM).

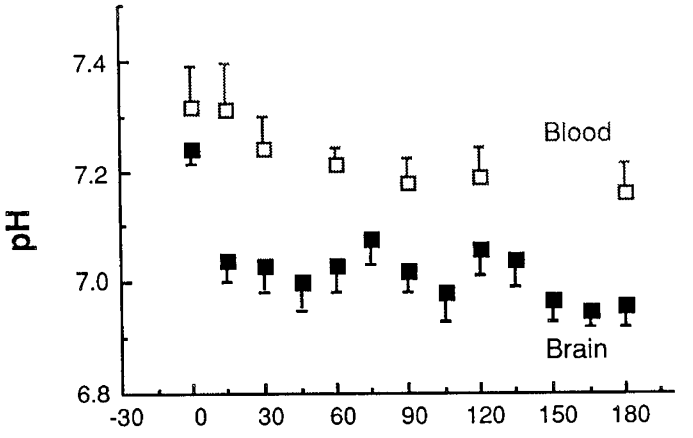


Fig. 3. Blood and brain pH during flurothyl seizure. There is significant decline in brain pH [analysis of variance (Friedman); $\chi^2_r$, 9.08; $p < 0.05$]. Blood pH declined over the 3 h of status epilepticus (analysis of variance: $F$ test, 4.049; $p = 0.0057$; $n = 5$, mean ± SEM).

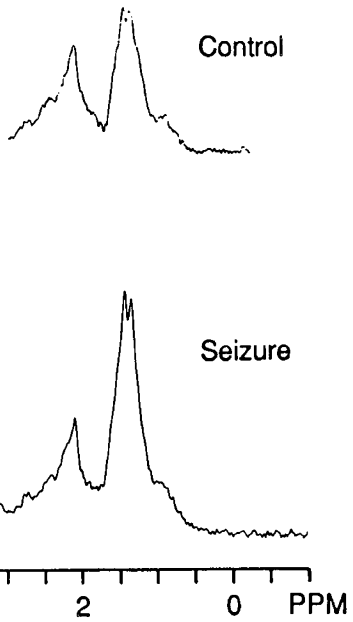


Fig. 4. *In vivo* $^{1}H$ NMR spectra before and during flurothyl-induced status epilepticus. $^{1}H$ spectra showing rise in lactate (the resonance at 1.3 ppm) during seizure. The resonance just beyond 2.0 ppm is that of N-acetyl-aspartate.

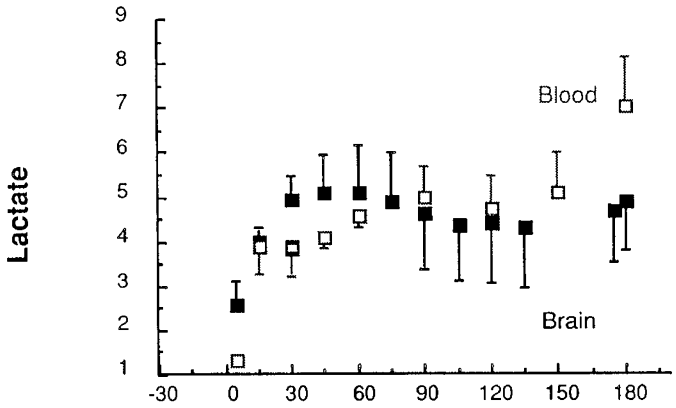


Fig. 5. Brain (mmol/kg) and blood (mM) lactate during flurothyl seizure. There is significant increase in both blood [analysis of variance (Friedman); $\chi^2_r$, 16.95; $p < 0.05$] and brain lactate during the 1st h of seizure [analysis of variance (Friedman); $\chi^2_r$, 8.1; $p < 0.05$]. Brain lactate reached maximum values after 45 min of flurothyl-induced seizure, after which a new steady state was achieved. Values for brain lactate were obtained by calibrating the final postmortem spectrum with the lactate concentration in freeze-trapped brain extract analyzed enzymatically ($n = 4$; mean ± SEM).

pH declined rapidly during the first 15 min of status epilepticus and remained acid (Fig. 3). Arterial pH gradually declined during the 3 h of status epilepticus. There was no significant change in brain ATP (Figs. 1 and 2).

*In vivo $^{1}H$ NMR studies.* *In vivo* $^{1}H$ NMR studies showed that brain lactate increased significantly during the first 45 min of flurothyl seizure (Figs. 4 and 5). During this period of time, the maximum rate of lactate accumulation in brain was 0.2 mmol/kg/min. Arterial lactate rose abruptly during the first 15 min of status epilepticus, then continued to slowly rise, exceeding the concentration in brain by 75 min (Fig. 5). Blood lactate rose more rapidly during the last 30 min of status epilepticus.

*In vitro $^{1}H$ NMR studies.* *In vitro* $^{1}H$ NMR spectroscopic analyses showed that after 3 h of seizure, lactate was significantly increased and PCr significantly reduced (Table 2) compared with a control group of animals. ATP did not change after 3 h of status epilepticus. There were highly significant decreases in aspartate and glutamate and increase in alanine. There was an upward trend in GABA and a downward trend in glucose and taurine. There was good agreement between brain lactate concentration determined by *in vivo* $^{1}H$ NMR, calibrated with an enzymatic analysis of the postmortem extract, and the lactate determined in extract using *in vitro* $^{1}H$ NMR of brain frozen *in situ* during status epilepticus.

## DISCUSSION

These experiments extend our understanding of the metabolic effects of seizure in the neonate in several respects. First, *in vivo* $^{1}H$ NMR spectroscopy provides determination of rate of lactate

Table 2. *In vitro-$^1$H NMR measurement of brain metabolites (mmol/kg)**

| Metabolite | Control | Flurothyl | *p* |
|---|---|---|---|
| Glucose | 3.1 ± 0.5 | 2.6 ± 0.4 | NS |
| Lactate | 1.8 ± 0.2 | 4.6 ± 0.8 | <0.01 |
| ATP | 1.9 ± 0.1 | 1.8 ± 0.2 | NS |
| PCr | 2.3 ± 0.1 | 1.7 ± 0.2 | <0.025 |
| Creatine | 3.3 ± 0.1 | 4.1 ± 0.5 | NS |
| Alanine | 0.6 ± 0.1 | 1.3 ± 0.2 | <0.005 |
| N-acetyl aspartate | 2.9 ± 0.3 | 3.0 ± 0.2 | NS |
| Aspartate | 2.4 ± 0.2 | 1.1 ± 0.1 | <0.001 |
| Glutamate | 6.7 ± 0.4 | 4.7 ± 0.3 | <0.005 |
| GABA | 1.8 ± 0.1 | 2.2 ± 0.3 | NS |
| Glycine | 1.7 ± 0.2 | 1.6 ± 0.1 | NS |
| Taurine | 7.2 ± 0.5 | 6.2 ± 0.7 | NS |

* Values are mean ± SEM; statistical analysis by two-tailed *t* test for grouped data; number of animals: control, 5; flurothyl, 5.

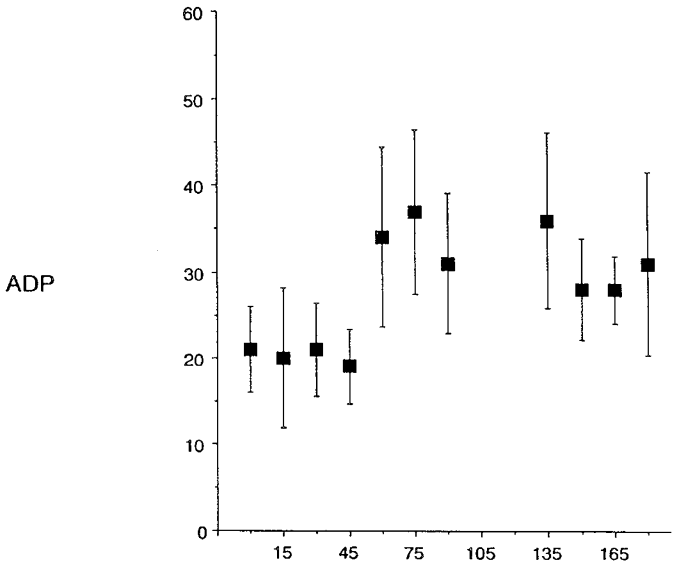


Fig. 6. Calculation of ADP values (mmol/kg) using creatine kinase equilibrium. ADP values (mean ± SEM; $n = 5$) were calculated using the creatine kinase equilibrium:

$$ADP = 6.02 \times 10^{(-10)} \times [ATP] \times [Cr]/[PCr] \times 1/[H^+]$$

ADP values increased abruptly 60 min into status epilepticus.

accumulation *in vivo* during seizure in the neonate. Second, the $^{31}$P NMR data clarify the relationship between PCr and $pH_i$ during prolonged seizure and permit calculation of ADP concentrations. Third, the *in vitro* $^1$H NMR analysis allows quantitation of the *in vivo* signals and provides information about changes in brain amino acids during prolonged neonatal seizure.

*Lactate metabolism during seizure.* There was an initial steep rise in brain lactate associated with intense paroxysmal discharge during the 1st ½ h of seizure. Accumulation of lactate during this period was 0.2 mmol/kg/min. This value is approximately 20% that measured *in vivo* in the adult rabbit (20). Maximum lactate values in the neonatal dog were not obtained until 45 min after onset of seizure. A pseudo-1st order time constant fitted to our data yielded a value of 9 min, which is similar to that calculated in the adult rabbit by *in vivo* $^1$H NMR spectroscopy (20). In contrast, an earlier study using enzymatic analysis noted peak lactate values 5–20 min after onset of seizure in adult rats (4). In all three species, brain lactate values eventually stabilized regardless of the rate at which peak lactate values were achieved and regardless of the intensity of seizure activity. The slower rise in lactate during status epilepticus in the neonatal dog compared with the adult rodent can be attributed to the slower cerebral metabolic rate of the neonate.

The relationship between brain and blood lactate has not been well delineated in earlier studies of adult animals (4, 20, 23). The rise in arterial lactate during status epilepticus may be due in part to a primary myocardial or skeletal muscle lactic acidosis associated with seizure-induced increase in circulating catecholamines (24). Hypotension due to myocardial failure may also contribute to the terminal increase in arterial lactate (24). The changes in brain lactate in the neonate reflect increased permeability of the neonatal blood-brain barrier to lactate (10–13). Lactate is preferentially utilized by neonatal brain (10–13) and the oxidation of lactate may be 10-fold greater than maximal glucose oxidation (12). During the latter 2 h of status epilepticus, the rising arterial lactate could contribute to the magnitude of the brain lactate concentration.

*Energy state.* Previous investigators have noted that after initial metabolic adjustments during status epilepticus the cerebral energy state rapidly shifts to a new equilibrium (4, 5). For example, PCr values fall to their lowest values within the first 60 s of seizure in the adult rat (4). This *in vivo* NMR study similarly demonstrates that $pH_i$ and PCr levels stabilize, although the plateau was reached substantially more slowly in the neonate, *i.e.* 15 and 60 min after onset of seizure, respectively. There was a more rapid fall in $pH_i$ than PCr during the early phase of seizure.

The lack of change in brain ATP is further evidence that brain energy state is not radically altered during seizure. This study corroborates previous studies in the adult rat (5), rabbit (25), and neonatal dog (16), which showed nonsignificant decrease (10–20% of control values) of brain ATP during seizure.

*Calculation of ADP values using creatine kinase equilibrium.* ADP values, calculated using the creatine kinase equilibrium, remained unchanged during the first 45 min of status epilepticus (Fig. 6). During this period, both PCr and $pH_i$ dropped, whereas ATP remained unchanged (see above). This shows that the decline in PCr reflected the increasing intracellular acidosis.

Lactate increased during the first 30 min of status epilepticus, and calculated ADP remained unchanged. This implies that ADP is not the main stimulus of the relatively greater activation of glycolysis over oxidative metabolism that occurred during these 30 min. Brain lactate levels are determined by the rate of oxidative metabolism, rate of glycolysis, and rate of transport across the blood-brain barrier. Our data suggest that by 60 min, lactate could not leave the brain except by active transport, requiring additional expenditures of energy. Indeed, the data raises the possibility that lactate entered the brain from the systemic circulation.

Because brain lactate levels did not increase further after 45 min of status epilepticus, either oxidative metabolism increased or the rate of glycolysis decreased. The ADP/ATP ratio increased abruptly at the end of the 1st h of seizure. A rise in the ADP/ATP ratio is known to be a powerful stimulator of the pyruvate dehydrogenase complex, which controls the entry of substrate into mitochondria. Oxidative metabolism would increase, matching the rate of glycolysis and stabilizing lactate levels in brain.

*In vitro analysis of amino acids.* After 3 h of flurothyl-induced status epilepticus, the changes in alanine, aspartate, glutamate, and GABA were similar in nature, although milder than those reported after hypoxia in mice (26). Similar alterations in these amino acids along with a 20% decrease in taurine were noted after kainic acid seizure in adult rats (27). Curiously, with allylglycine- and bicuculline-induced seizure, taurine increased by 20–40%. It is widely assumed that the alterations in aspartate and GABA during flurothyl seizure occur because of changes in glutamate metabolism (28). The fall in glutamate could be related in part to increased amidation to glutamine and decarboxylation to GABA. The coupled rise in alanine and fall in aspartate may

be driven by an increase in pyruvate and cytosolic NADH, as reflected by elevation of the lactate:pyruvate ratio (26, 28).

In summary, a new steady state for cerebral PCr and lactate during status epilepticus was achieved much more slowly during neonatal status epilepticus than has been reported during status epilepticus in the adult experimental animal. Brain and blood lactate were closely related during the initial phase of seizure suggesting rapid efflux of lactate from brain or systemic production of lactate. Further $^{1}H$ NMR experiments are planned to investigate the relationship between cerebral and systemic lactate and to determine whether liver and muscle are net producers or consumers of lactate during seizure.

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