Proton Magnetic Resonance Spectroscopy Investigation of Hyperventilation in Subjects With Panic Disorder and Comparison Subjects

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Objective: *The purpose of this study was to investigate differential effects of hyperventilation on brain lactate in patients with panic disorder and comparison subjects as a possible mechanism for explaining previous observations of an excess rise in brain lactate among panic disorder subjects during lactate infusion.* *Method:* *Seven treatment-responsive patients with panic disorder and seven healthy comparison subjects were studied with proton magnetic resonance spectroscopy to measure brain lactate during controlled, voluntary hyperventilation over a period of 20 minutes. Hyperventilation was regulated with the use of capnometry to maintain end-tidal P_{CO_2} at approximately 20 mm Hg during the period of hyperventilation. Blood lactate was measured prior to and at the end of hyperventilation.* *Results:* *At baseline the two groups had similar brain lactate levels. Panic disorder subjects exhibited significantly greater rises in brain lactate than comparison subjects in response to the same level of hyperventilation. Blood lactate levels before and after 20 minutes of hyperventilation were not significantly different between groups.* *Conclusions:* *Controlled hyperventilation increases brain lactate and does so disproportionately in subjects with panic disorder. This increase in brain lactate may result from decreased cerebral blood flow due to hypocapnia, and individuals with panic disorder may have greater sensitivity to this regulatory mechanism.*

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The provocation of panic by intravenous infusion of sodium lactate (1) has been widely used to investigate panic disorder. The rationale originally put forth for infusing lactate was based on earlier observations that individuals with anxiety syndromes, who now would generally be diagnosed as having panic disorder, produce more lactate during moderate exercise than comparison subjects (2–4). Panic patients appear to produce excess blood lactate, pointing to some underlying metabolic or physiologic disturbance, in response to a variety of metabolic or chemical challenges capable of inducing panic in susceptible individuals (5–8). For example, vigorous hyperventilation, preceded by a glucose infusion to enhance metabolic production of lactate, results in greater serum lactate increases among symptomatic panic disorder subjects than among healthy control subjects (8).

One of the more consistent physiologic concomitants of lactate-induced panic is hyperventilation (5, 9, 10). This robust hyperventilatory response is notable because it is decoupled from the usual physiologic regulation (i.e., hypoventilation) that is expected in response

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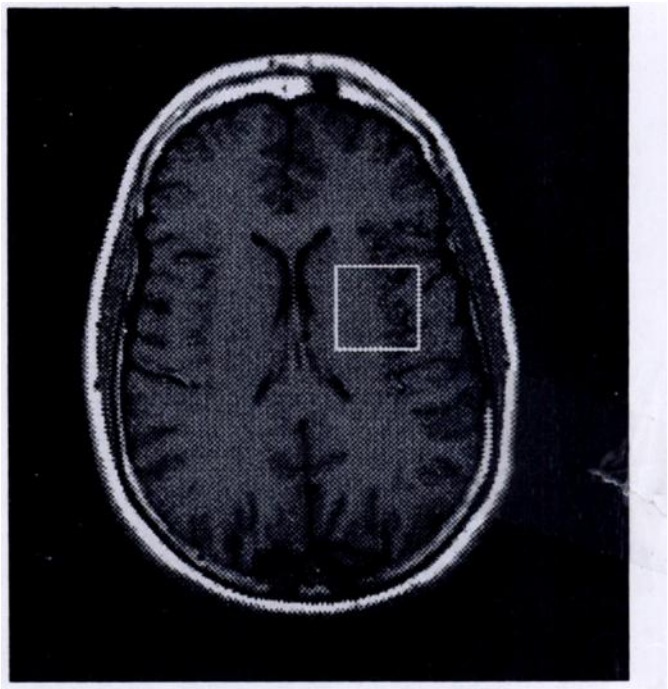
to a metabolic alkalosis, such as is produced by infusion of sodium lactate. It also has been demonstrated that hyperventilation increases brain lactate levels (11, 12). Because patients with panic disorder produce excess blood lactate in response to metabolic challenges and also hyperventilate in response to lactate-induced panic, it is conceivable that these individuals may exhibit greater rises in brain lactate in response to hyperventilation. Thus, a possible mechanism is suggested for the excess rise in brain lactate detected by proton magnetic resonance spectroscopy (^{1}H MRS) in association with a lactate-induced panic response (13). In this study, ^{1}H MRS was used to investigate changes in brain lactate among subjects with panic disorder and healthy comparison subjects in response to controlled, voluntary hyperventilation for 20 minutes. The use of capnometry— continuous determination of end-tidal PCO_2 ($P_{ET}CO_2$)—permitted subjects to regulate their breathing to achieve consistent $P_{ET}CO_2$ levels of approximately 20 mm Hg during hyperventilation. Because of a concern that vigorous hyperventilation might produce a panic response in actively symptomatic panic subjects (14), we studied treatment-responsive, asymptomatic panic disorder patients in an attempt to isolate the effects of hyperventilation on changes in brain lactate.

FIGURE 1. T_1-Weighted Image Demonstrating Localization of Sample Volume for Proton Magnetic Resonance Spectroscopy



METHOD

Subjects

Seven subjects with panic disorder (four male and three female) whose mean age was 40.8 years (SD=6.3) and seven healthy comparison subjects (five male and two female) whose mean age was 35.6 years (SD=5.8) were enrolled in the study. All subjects were Caucasian and college educated, with the exception of one panic subject who had completed only high school. All subjects gave written informed consent for participation in the study, which was approved by the University of Washington Human Subjects Review Committee.

The panic subjects fulfilled all DSM-III-R criteria for panic disorder according to evaluations by a board-certified psychiatrist (S.R.D.) using a semistructured diagnostic interview (15) at the time of initial assessment. There was no current or past history of other clinically significant psychiatric or general medical problems. All but one panic subject had participated in a long-term treatment study of panic disorder (16). At the time of this study, all panic subjects had been asymptomatic for at least the preceding 6 months. Six panic subjects were taking maintenance medication (five were taking fluoxetine, and one was taking desipramine), and one subject was asymptomatic after having discontinued fluoxetine approximately 2 months prior to being studied. The comparison subjects had no history of clinically significant psychiatric illnesses, including panic or anxiety disorder, and were medication free. Medical conditions and contraindications to MRS evaluation, including the presence of a pacemaker, metal implants other than dental work, unstable cardiovascular status, clinically significant pulmonary disease, and severe claustrophobia, were grounds for exclusion from the study.

MRS

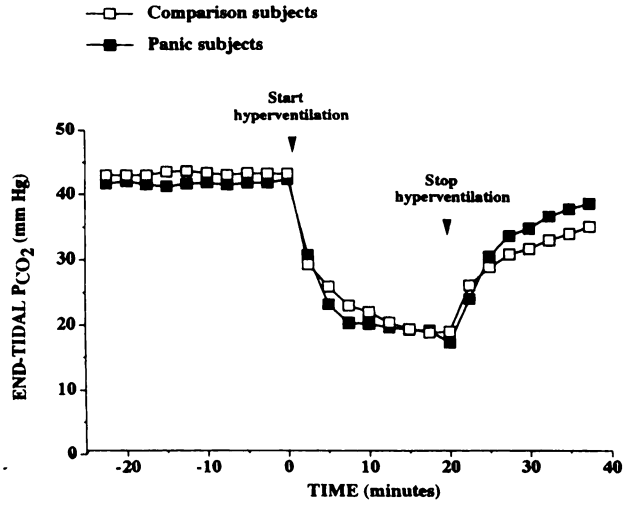
Localized ^{1}H MRS was performed with a 1.5-T magnetic resonance imager/spectroscopy unit (GE Signa) and quadrature head coil located in the Imaging Sciences Research Laboratory at the University of Washington. The method was the same as for our previous human MRS studies evaluating lactate infusion (13, 17), with the exception that newer Signa software—version 5.3—incorporating automatic shimming and water suppression was used. Each study required approximately 1½ hours' confinement in the magnet. A vacuum bag head holder (size 20; Olympic Medical, Seattle) was used to immobilize the head.

Magnetic resonance imaging (MRI) was used for anatomic localization. MRS was performed immediately after the MRI scan. The subjects did not have to be moved, as MRS uses the same instrumentation and head coil as does MRI. The MRI axial images were used to establish a 27-ml volume of interest for spectroscopy in the same region that we reported on for lactate infusion (13, 17). An axial section approximately 25 mm inferior to the intercommissural line was used to set the volume of interest in the left hemisphere, lateral to the midline in an area between the anterior and posterior horns of the lateral ventricle. Localization of a standard 27-ml sampling volume (30×30×30 mm), encompassing the insular cortex and adjacent areas, is shown in figure 1. A large anatomic sampling volume was chosen to maximize the signal-to-noise ratio and corresponding temporal resolution.

We performed ^{1}H MRS (Signa software version 5.3) with a volume-localized technique called "point-resolved spectroscopy" (PRESS) (P.A. Bottomley, U.S. patent 4:480-228, 1984). This pulse sequence uses 90°-180°-180° radio frequency pulses for signal generation. MRS volume localization was achieved by using spatial-selective excitation in all three orthogonal planes and paired "crusher" gradients in each plane to spoil residual signal arising from outside the volume of interest. Water suppression, consistently greater than 94%, was obtained by using a succession of three chemical shift selective (CHESS) pulses, each followed by a crusher gradient. We used a repetition time of 2,000 msec, which is in the midrange of commonly used values (18–21). A long echo time (TE) of 272 msec was chosen both to enhance lactate peak resolution and to decrease lipid signal. A spectral width of 2,500 Hz and 2,048 acquisition points were used for signal acquisition. A total of 128 signal acquisitions were made every 5 minutes and averaged for spectral processing.

MRS signals were processed with 1-Hz exponential line broadening, Fourier transformed and zero-order phase corrected. Baseline correction of the region of interest (3.2–1.2 ppm) and digital integration to determine peak area for *N*-acetyl aspartate (NAA) and lactate were performed with software developed in this laboratory (17).

FIGURE 2. End-Tidal P_{CO_2} Levels at Baseline, During 20 Minutes of Hyperventilation, and After Resumption of Normal Breathing for Subjects With Panic Disorder (N=7) and Comparison Subjects (N=7)



Baseline correction of the region of interest was automated using constant parts-per-million windows for fitting. Integration of spectral peak area was done after baseline correction, and peak intensity values were summed over a set range (for lactate, 1.45–1.10 ppm). Lactate peak area was referenced in relation to NAA, which was set at 2.00 ppm.

The NAA spectral peak was used as an internal reference (signal lactate/signal NAA) to standardize ^1H MRS measurements for any differences in magnet shimming between studies or for the effects of line broadening due to head movement during a study. In previous work, NAA signal was found to remain constant during lactate infusion (13, 17, 22). Although this approach has certain inherent limitations (23, 24), which are further discussed below and in the Discussion section, it is the current method of choice for applications such as this project (25, 26).

Lactate concentration was calculated in relation to the NAA spectral peak area. Since direct measurement indicates an average NAA concentration of approximately 6 mmol/liter for the human brain (23, 27), the lactate/NAA ratio was multiplied by 6 mmol/liter to indirectly determine the brain lactate concentration at each time point. This approach must be considered an estimation of absolute lactate concentration because of regional differences in NAA concentration (partial volume effects) and overlap of the NAA signal by other metabolites, but it has been validated against direct measurement of CSF lactate in children with congenital lactic acidosis (28). Additionally, this approach does not allow for the possibility of differential changes in relaxation times due to hypocapnia, which could not be assessed for this study because of the rapid changes in MRS lactate signal.

Hyperventilation

The hyperventilation protocol was designed to closely parallel our experimental design for lactate infusion during MRS evaluation (13, 17). Five sets of ^1H MRS baseline measurements obtained during a 25-minute baseline period of normal breathing were followed by four sets of ^1H MRS measurements acquired during 20 minutes of sustained hyperventilation; $P_{ET}CO_2$ measurements were used to permit subjects to adjust their respiratory rate to achieve consistent $P_{ET}CO_2$ levels of approximately 20 mm Hg. Three additional sets of ^1H MRS measurements were acquired during a recovery period after hyperventilation was stopped. A Puritan Bennett Datex CO_2 monitor, designed for monitoring anesthetized patients during diagnostic MRI, was used to monitor $P_{ET}CO_2$ through a nasal prong (29, 30).

For this experiment, it was essential that $P_{ET}CO_2$ measurements accurately reflect changes in arterial P_{CO_2} (P_aCO_2) in response to hyperventilation. In order to specifically assess $P_{ET}CO_2$-P_aCO_2 gradients under normocapnic and hypocapnic conditions, $P_{ET}CO_2$ and P_aCO_2 were evaluated in a separate group of mechanically ventilated patients undergoing surgical procedures. Patient data on $P_{ET}CO_2$ and concurrently obtained P_aCO_2 were taken at random in a blinded fashion from intraoperative records of 18 cases involving major vascular or intrathoracic surgery at the University of Washington. The $P_{ET}CO_2$-P_aCO_2 gradient within each patient was determined under normal and hypocapnic conditions.

Blood Analysis

Lactate concentrations at baseline and at completion of the 20 minutes of hyperventilation were determined from 2-ml blood samples obtained through a venous cannula and collected into gray-top tubes containing sodium fluoride and potassium oxalate. Blood samples were filtrated by adding 1.5 ml of blood to 3 ml of ice-cold 0.6 mmol/liter perchloric acid and then vortexed, followed by centrifugation and removal of supernatant. L-Lactate levels in the supernatant were assayed by using an automated enzymatic L-lactate dehydrogenase procedure (31).

Statistical Analysis

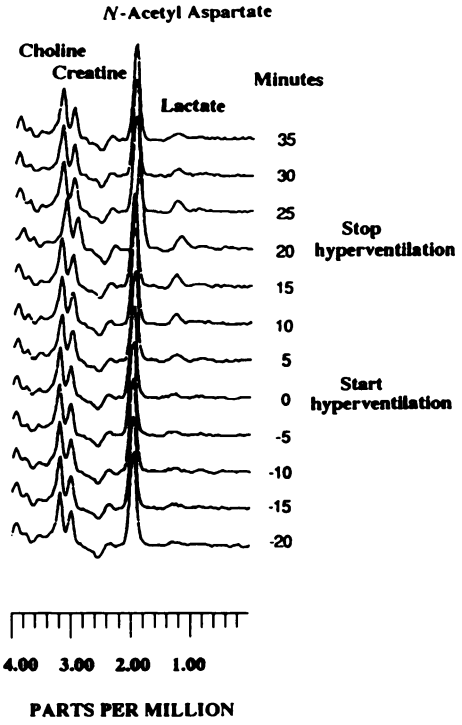
Univariate analysis of variance (ANOVA) for repeated measures was used to compare changes in brain lactate (signal lactate/signal NAA) at 10 time points during the study (four at baseline, four during hyperventilation, and two after return to normal breathing) to preserve complete data sets. Two-way ANOVA for repeated measures allowed assessment of differences in $P_{ET}CO_2$ blood and brain lactate levels over time between comparison and panic subjects and in brain lactate levels between subjects differentiated by gender. One-way ANOVA for repeated measures was used to assess within-subject changes in NAA at the 10 sampling points. ANOVAs were performed using hierarchical techniques. For two-way ANOVA results that reached significance, independent t tests with pooled variances were used to compare signal lactate/signal NAA in the two diagnostic groups at each time point and to assess between-group differences in age and blood lactate levels. Pearson's r was used to assess the correlations between $P_{ET}CO_2$ and P_aCO_2 measurements. Two-tailed statistical tests were performed to determine significance at the level of $p<0.05$.

RESULTS

All subjects completed the experimental procedure. One panic disorder subject and one comparison subject experienced mild to moderate anxiety (overall anxiety rating of 4–6 on a 0- to 10-point analog scale), and one panic subject experienced a panic attack that was described as moderate in severity. All panic and comparison subjects were able to maintain sustained vigorous hyperventilation, with $P_{ET}CO_2$ levels in the 18- to 22-mm Hg range, during the 20-minute hyperventilation period, as shown in figure 2.

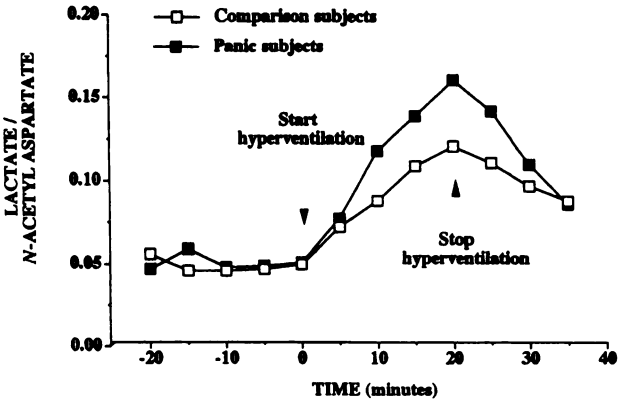
Characteristic MRS brain spectra for a panic disorder subject at baseline and during and after hyperventilation are shown in figure 3. In both groups of subjects, brain lactate began to increase within the first 5 minutes of starting hyperventilation, progressively increased during the entire 20-minute hyperventilation period, and then slowly decreased toward baseline during the posthyperventilation period. We are confident that this peak represents lactate because of the localization of the sampling area away from possible extracranial lipid

FIGURE 3. Consecutive Magnetic Resonance Spectroscopy Brain Spectra for a Subject With Panic Disorder at 5-Minute Intervals Before, During, and After Hyperventilation[a]



[a]Identifiable peaks in the spectra include choline, creatine, *N*-acetyl aspartate, and lactate.

FIGURE 4. Brain Lactate Signal Expressed in Relation to *N*-Acetyl Aspartate Signal and Averaged Over 5-Minute Intervals Before, During, and After Hyperventilation in Subjects With Panic Disorder (N=7) and Comparison Subjects (N=7)



contamination and the use of a 272-msec TE, which is quite long relative to the apparent T_2 of lipid. Effects of "J coupling" for lactate are also minimized at TE=272 msec. Since head movement was controlled with the vacuum bag head holder during hyperventilation, very little line broadening or deterioration in line shape occurred during the experimental procedure (figure 3).

As shown in figure 4, significant differences in brain lactate levels (signal lactate/signal NAA) in response to hyperventilation were observed between panic and comparison subjects according to repeated measures ANOVA (between subjects: F=4.8, df=1, 12, p<0.05; within subjects: F=60.9, df=9, 126, p<0.001; Group by Time interaction: F=2.5, df=9, 108, p=0.01). Baseline brain lactate levels were not significantly different when independent t tests were used to compare panic and comparison subjects at each time point during normal breathing. Consistently higher brain lactate levels were observed among panic subjects at 10 minutes (t=2.6, df=12, p=0.02), 15 minutes (t=2.2, df=12, p=0.05), and 20 minutes (t=2.9, df=12, p=0.01) after starting hyperventilation. During the 15-minute recovery period following hyperventilation, brain lactate levels remained nonsignificantly higher among panic subjects for the first 10 minutes. For all subjects, brain lactate levels progressively decreased toward baseline after hyperventilation was stopped. We observed that the magnitude of the rise in brain lactate of the panic subject who panicked in response to hyperventilation did not differ from that of the other panic subjects, and data from this subject were retained in the data set.

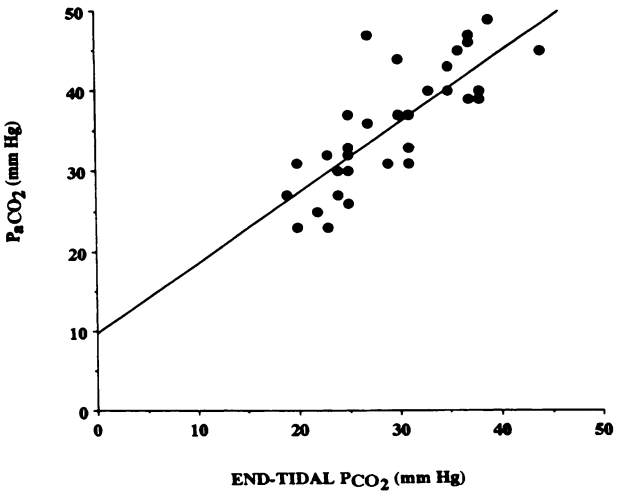
During the experiment, the NAA signal remained stable when evaluated for all subjects combined (F=0.9, df=9, 126, n.s.) and when evaluated separately for panic subjects (F=0.6, df=9, 54, n.s.) and comparison subjects (F=1.1, df=9, 54, n.s.).

The mean estimated brain lactate concentration for the panic disorder subjects rose from 0.31 mmol/liter (SD=0.07) to 0.96 mmol/liter (SD=0.16) during hyperventilation. In contrast, comparison subjects demonstrated a brain lactate rise from 0.30 mmol/liter (SD=0.08) at baseline to a maximum of 0.73 mmol/liter (SD=0.14) at the completion of hyperventilation.

Despite a greater increase in brain lactate among the panic subjects, their blood lactate concentration was not significantly different from that of the comparison subjects at baseline (mean=0.82 mmol/liter, SD=0.27, and mean=0.83 mmol/liter, SD=0.06, respectively; t=0.1, df=8) or after the 20 minutes of hyperventilation (mean=1.18 mmol/liter, SD=0.7, and mean=1.83 mmol/liter, SD=0.7, respectively; t=1.3, df=8). Blood lactate changes in response to hyperventilation were not significantly different between the two diagnostic groups according to repeated measures ANOVA (between subjects: F=1.2, df=1, 7, n.s.; within subjects: F=9.6, df=1, 9, p<0.02). The nonsignificant higher blood lactate concentration among the comparison subjects after hyperventilation is probably attributable to an outlier.

The higher brain lactate levels among the panic subjects in response to hyperventilation could not be accounted for by differences in hyperventilation, as measured by $P_{ET}CO_2$ levels, according to repeated measures ANOVA (F=0.0, df=1, 12, n.s.) (figure 2). The 5 years' difference in age range between groups was not significant by independent t test (t=1.64, df=12). Further assessment of possible age-related effects, with age as a covariate, was not feasible because of the small study group size. Differences in gender distribution between

FIGURE 5. End-Tidal Pco_2/Arterial Pco_2 (P_aco_2) Gradient Under Both Normal and Hypocapnic Conditions in 18 Surgical Patients



the comparison group and the panic group were not significant (Fisher's exact test, two-tailed). To assess further the relation between gender and brain lactate changes during hyperventilation, we compared the brain lactate levels before, during, and after hyperventilation of the subjects differentiated by gender, irrespective of psychiatric diagnosis. According to repeated measures ANOVA, there were no significant gender differences in brain lactate response to hyperventilation ($F=2.7$, $df=1, 12$).

Simultaneous measurements of $P_{ET}CO_2$ and P_aCO_2 taken from intraoperative records of the 18 surgical patients under both normocapnic and hypocapnic conditions indicated a linear relation between $P_{ET}CO_2$ and P_aCO_2 measurements, as shown in figure 5 (Pearson's $r=0.79$, $df=34$, $p<0.001$). Since the most convincing way to evaluate the $P_{ET}CO_2$-P_aCO_2 gradient is to make comparisons within each individual, this was approached by expressing the $P_{ET}CO_2$-P_aCO_2 gradient as the percent difference ($P_aCO_2 - P_{ET}CO_2/P_aCO_2 \times 100$) in both normocapnic and hypocapnic conditions. Our supposition that the $P_{ET}CO_2$-P_aCO_2 gradient does not change significantly with hyperventilation would be supported if the percent differences were the same for hypocapnia and for normocapnia (i.e., if the ratio approached 1.00). The ratio between hypocapnic and normocapnic conditions was 0.75 (SD=0.22), which suggests that hypocapnia did not interfere with valid interpretation of $P_{ET}CO_2$ measurements.

DISCUSSION

These results confirm previous reports (11, 12) that vigorous hyperventilation increases brain lactate levels. In this study, brain lactate rose progressively in all subjects during a 20-minute period of sustained, voluntary hyperventilation and then steadily decreased as normal breathing was resumed. Individuals with a diagnosis of panic disorder demonstrated significantly greater increases in brain lactate in response to hyperventilation than healthy comparison subjects.

As we have noted previously (13, 17, 22), MRS measurements based on metabolic ratios, although widely used, are not without methodological difficulties. It is possible that a portion of the lactate signal is "invisible" to ^1H MRS because of restricted molecular motility, which could be influenced by the relaxation times used in this experiment (26, 32–34). Measurements of T_1 for brain lactate and NAA appear to be approximately the same (in the range of 1,500 msec for humans), but T_2 for lactate has been difficult to determine other than for persistent pathological conditions (19, 26, 32–35). In this study, T_2 for lactate could not be accurately determined because of the rapid changes in brain lactate concentration; thus, differences in T_2 between NAA and lactate may have affected the accuracy of brain lactate quantification. It is also possible that differences between patients with panic disorder and comparison subjects during hyperventilation in part reflect differential changes in tissue pH in response to hyperventilation, which could alter relaxation times or chemical shift and, thereby, measurement of metabolite ratios (36). Differences in NAA concentration as a result of the nonsignificant differences in age range or variations in the relative proportions of gray and white matter in the volume of interest (partial volume effects) may have influenced the measurement of NAA (37), although there was no evidence of any group differences in metabolite ratios at baseline or systematic differences in NAA during the course of the experiment.

In this study, $P_{ET}CO_2$ measurements were used to regulate breathing rates to ensure consistent levels of hyperventilation and to assess the relation between hypocapnia and brain lactate levels. As we have demonstrated, the $P_{ET}CO_2$-P_aCO_2 gradient within each subject, when determined under both hypocapnic and hypercapnic conditions, remained stable, indicating that $P_{ET}CO_2$ accurately reflects changes in P_aCO_2. The Puritan Bennett Datex CO_2 monitor can aspirate expired gases at high flows (150 ml/minute), which was necessary to permit real-time regulation of hyperventilation (38). A long length of nylon gas-sampling tubing, used because of the magnet environment, has been found not to decrease monitoring sensitivity (39). In contrast to radial artery cannulation for P_aCO_2 measurements, which can increase anxiety and physiologic arousal (40–42) and does not provide continuous, real-time information, $P_{ET}CO_2$ monitoring is unlikely to increase baseline anxiety levels (41). Other noninvasive measures of ventilation, such as inductive plethysmography, fiber-optic monitoring of respiratory motion, chest bellows, and the apnea mattress, are compatible with magnetic resonance and relatively risk free, but they are not sufficiently sensitive or specific for CO_2 to assess its role in the production of brain lactate changes or ensure consistent voluntary hyperventilation (43–45).

In previous work that applied ^1H MRS to measure changes in brain lactate during intravenous infusion of

sodium lactate, we noted brain lactate rises in rats (22) and healthy volunteers (17) and disproportionately greater rises in panic patients who panicked in response to lactate (13). In those studies, subjects were breathing freely, and effects of possible hyperventilation, in particular among the panic subjects, may have contributed to the observed rise in brain lactate during lactate infusion. However, lactate infusion in mechanically ventilated monkeys also increased directly sampled cisternal fluid lactate when ventilatory effects were held constant (46). In that study, stable cisternal P_{CO_2} levels during lactate infusion indicated that central hypercapnia resulting from systemic metabolism of elevated blood lactate is not the causal mechanism for hyperventilation during lactate infusion in free-breathing subjects.

As hyperventilation or, more specifically, hypocapnia is a potent stimulus for decreasing cerebral blood flow (CBF), this may be the mechanism responsible for brain lactate elevations in response to hyperventilation. Blood P_{CO_2} has long been recognized to be one of the primary physiologic regulatory mechanisms for CBF (47, 48). It is curious that clinically asymptomatic panic subjects should demonstrate significantly greater increases in brain lactate during sustained hyperventilation. Transcranial Doppler ultrasonography measurement of changes in basilar artery blood flow velocity during brief hyperventilation suggested that both untreated and treated panic patients may be particularly sensitive to the effects of hypocapnia on reducing CBF (49), although questions about the methodology, including the lack of a control for level of hyperventilation, have been raised regarding that study's conclusions (50). A greater reduction in CBF in response to hypocapnia would be the most parsimonious explanation for why panic subjects exhibited significantly greater increases in brain lactate during hyperventilation. Alternatively, panic subjects could have experienced greater CNS activation, resulting in greater brain metabolic activity and, consequently, greater brain lactate production, despite their asymptomatic clinical status and an overall lack of differences in clinical response to the hyperventilation.

Brain lactate production in response to hyperventilation may have been similar for all subjects but metabolized differently by panic subjects or more slowly cleared by blood because of blood-brain barrier differences. These possibilities, however, are discounted by the similar slopes for decrease in brain lactate in both groups of subjects following resumption of normal breathing. Although we know of no established mechanism whereby the medications these patients were receiving may have affected CBF response to hypocapnia, it is conceivable that this may be a confounding variable that influenced our findings. One unmedicated panic subject, however, demonstrated a rise in brain lactate similar to that of the medicated panic subjects, which was substantially greater than that of the comparison subjects.

These results may in part explain our findings of an excess increase in brain lactate in association with a lactate-induced panic response (13). However, in that study, increases in brain lactate were higher than could be accounted for solely on the basis of the magnitude of the rise in brain lactate measured in response to hyperventilation. As hypocapnia appears to increase blood-brain barrier permeability (51), this may be an additional component responsible for the excess rise in brain lactate observed during panic in response to intravenous lactate infusion (13). However, the time course for changes in brain lactate during hyperventilation is substantially different from that which occurs in response to lactate-induced panic, where brain lactate levels progressively increase after lactate infusion is stopped (13). In this regard, further work will be necessary to elucidate the mechanism(s) for excess rises in brain lactate in response to hyperventilation, as well as in response to lactate infusion, among panic subjects and to relate those findings to the underlying pathophysiology of panic.

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