Information from the clinical interview, lifetime drinking history, and SADS were used to further subdivide the ALCPAN into primary (n = 15) (experienced their first panic attack prior to the onset of alcoholism) and secondary groups (n = 7) (experienced their first panic attack after developing signs and symptoms of alcoholism). The onset of alcoholism was determined by subtracting the number of years of heavy drinking from the patient's present age. Classification of the primary and secondary ALCPAN was performed without knowledge of the lactate response. A definite primary versus secondary category could not be determined for 4 ALCPAN patients. Seven men and 13 women had a history of panic attacks without a diagnosis of alcoholism (PAN). All ALCPAN and PAN patients reported having symptoms compatible with a panic attack on at least one occasion in the 4 months preceding the study.

To utilize the most recent diagnostic criteria for panic disorder, we retrospectively analyzed the data (e.g., panic symptomatology and patterns of alcohol consumption) obtained during the psychiatric interview according to DSM-IV criteria (American Psychiatric Association 1994). Twenty-two of the 26 ALCPAN patients fulfilled DSM-IV criteria for panic disorder. The 4 patients who did not meet criteria for panic disorder had panic attacks associated with alcohol withdrawal. All of the PAN patients fulfilled DSM-IV criteria for panic disorder. Both ALC and ALCPAN fulfilled DSM-IV criteria for alcohol dependence. Information regarding recent and chronic alcohol consumption as well as alcohol-related behaviors was obtained from structured research questionnaires completed by the patients (Eckhardt et al 1978).

Data from 12 ALCPAN, 10 PAN, and 8 HVOL were reported in our previous lactate study (George et al 1989). These patients were included in the present study to increase the statistical power to detect a significant difference in the lactate-induced panic response between PAN and primary ALCPAN. All subjects were recruited and studied using the same protocol. All PAN and HVOL were subjects in another study comparing the effects of glucose and chloride on the incidence of lactate-induced panic attacks (George et al 1995).

Procedure

Actively drinking alcoholics were hospitalized on the National Institute on Alcohol Abuse and Alcoholism research ward at the National Institutes of Health Clinical Center in Bethesda, Maryland. They were free of all medications, including benzodiazepines, for at least 3 weeks prior to the study. Abstinence was assured by staff supervision, serial liver enzyme analyses, random breath alcohol tests, and urine drug screens. Treatment consisted of intensive educational sessions on the disease of alcoholism, daily Alcoholics Anonymous (AA) meetings, biweekly group therapy, family counseling, and individual therapy with a primary nurse and physician. Other subjects were admitted to the research ward on the evening prior to the study.

After an extensive description of the study was given to the subjects, written informed consent was obtained. Subjects were maintained on a low-monoamine diet for at least 72 hours prior to the study. After an overnight bed rest and fast, an intravenous (IV) cannula was placed in the antecubital fossa and kept open with a slow infusion of D5W. Approximately 1 hour after the placement of the IV, a 10-cc/kg body weight infusion of 0.5 mol/L sodium lactate dissolved in NaCl was administered over 20 min or until the subject requested that the infusion be stopped.

Prior to the infusion, all subjects were informed that the administration of sodium lactate could result in a number of somatic symptoms that might be similar to a panic attack. Control subjects were educated regarding the symptomatology of a panic attack. Subjects were told that if they experienced the sense of losing control or panic, they should ask the attending physician to stop the infusion. Occurrence of a panic attack was determined if a subject had: a) at least four RDC panic symptoms; b) the sense of losing control, panicking, or going crazy; and c) likened the lactate response to a previous panic attack. Conditions a) and b) were required for controls to meet criteria for a positive lactate response.

Blood samples for chemical analyses were obtained at baseline and immediately after the termination of the infusion. Radioimmunoassays for norepinephrine (NE) and epinephrine (EPI) were performed by Hazleton Corporation (Reston, VA). pH of venous blood was determined using an Ag/AgCl pH electrode. Lactate was quantified with a spectrophotometric assay.

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Anxiety levels were rated at baseline with the Spielberger Trait Anxiety Inventory (STAI) (Spielberger et al 1970) and the Spielberger State Anxiety Inventory (SSAI) (Spielberger et al 1970); the SSAI was also administered at the end of the infusion. The Hamilton Depression Index (HDI) (Hamilton 1967) was administered at baseline. At 3-min intervals throughout the infusion, subjects indicated the presence or absence of the following 11 specific panic attack symptoms: dyspnea, chest pain/pressure, choking, dizziness, feelings of unreality, faintness, tingling, hot/cold flashes, trembling, fear, and the sense of losing control.

exists between alcoholism and panic disorder, the nature of this relationship remains ill-defined and controversial (Schuckit and Hesselbrock 1994). Therefore, we chose to approach the issue from a biological perspective by using the pharmacologic probe, sodium lactate. In a previous study (George et al 1989) we reported that alcoholics with either panic disorder or frequent panic attacks (ALCPAN) were less likely to experience a lactate-induced panic attack than nonalcoholics with panic disorder (PAN). This led us to postulate that the pathophysiology of panic attacks in ALCPAN might be different from PAN. A subsequent study by Cowley et al (1989) failed, however, to show a difference in the incidence of lactate-induced panic responses between PAN and ALCPAN. In an attempt to explain these seemingly discrepant results, we postulated that the two ALCPAN groups might have differed in their relative timing of the onset of panic attacks to alcoholism.

The purpose of this study was to increase the number of patients we had studied previously to investigate the lactate response in ALCPAN stratified according to whether they had developed panic attacks before or after the onset of alcoholism. First, based on the results of our previous study, we hypothesized that patients who fulfilled diagnostic criteria for both alcoholism and panic attacks would be less likely to experience a lactate-induced panic attack than patients with a history of panic attacks without alcoholism. Second, patients who had had the onset of panic attacks before the onset of alcoholism would be more likely to have a lactate-induced panic attack than patients who had experienced their first panic attack after the onset of alcoholism. We assumed that secondary panic attacks might have a different etiology (e.g., alcohol withdrawal could be either mimicking the symptoms of panic attacks or actually altering brain function, which could lead to panic attacks), thereby resulting in a reduced response to lactate.

Methods and Materials

Subjects

The majority of both the alcoholic and panic disordered patients enrolled in the study were recruited from newspaper advertisements. The ALCPAN group was comprised of alcoholics and panic disordered patients who were evaluated and found to fulfill criteria for both disorders. All subjects provided a detailed medical history and underwent an extensive physical examination to ensure that they were in good physical health. Subjects with a history of seizures or major head trauma (defined as a period of unconsciousness exceeding 1 hour) were excluded from participation. All subjects were medication-free for at least 3 weeks prior to the study. None had received fluoxetine or monoamine oxidase inhibitors during at least 3 months prior to the study. Alcoholics were abstinent from alcohol for at least 3 weeks (ascertained by random breath testing); other subjects abstained from alcohol for at least 72 hours prior to the study. All subjects had negative urine drug screens and did not fulfill criteria for stimulant or cocaine abuse.

Table 1. Patient RDC Diagnoses Using SADS-L

	HVOL	ALC	ALCPAN	PAN
Total subjects in study	14	14	26	20
Total subjects having SADS	13	12	25	14
RDC DX[a]				
Alcoholism		12	25	
Panic disorder			16	11
Panic attacks			9	14
Panic with agoraphobia			7	5
Phobia		1	7	6
Past		1	4	1
Generalized anxiety disorder			8	6
Major depression disorder				
Past		1	6	1
Minor depression disorder		1	2	1
Past			3	5
Depression not otherwise specified		4		

[a]Same subject may have more than one diagnosis (DX).

Psychiatric diagnoses were based on the Schedule for Affective Disorders and Schizophrenia–Lifetime (SADS-L) (Endicott and Spitzer 1978). The SADS-L was administered by a social worker with extensive training in structured diagnostic interviewing and subsequently blind-rated by another research social worker and a psychiatrist. A consensus diagnosis using research diagnostic criteria (RDC) (Spitzer et al 1981) was determined for each participant. The results from clinical interviews and the Michigan Alcoholism Screening Test (MAST) (Selzer 1971) were utilized to make RDC diagnoses on the 10 subjects who were not administered the SADS-L.

Table 1 shows the RDC diagnoses for all of the subjects who had a SADS interview. Nine men and 5 women were free of any current psychiatric or medical conditions and served as healthy volunteers (HVOL). Eleven men and 3 women fulfilled RDC for current alcoholism (ALC). Twenty men and 6 women met RDC for alcoholism and also had a history of panic attacks, characterized by at least four panic attack symptoms accompanied by an intense fear and a sense of losing control or panic (ALCPAN).

Information from the clinical interview, lifetime drinking history, and SADS were used to further subdivide the ALCPAN into primary (n = 15) (experienced their first panic attack prior to the onset of alcoholism) and secondary groups (n = 7) (experienced their first panic attack after developing signs and symptoms of alcoholism). The onset of alcoholism was determined by subtracting the number of years of heavy drinking from the patient's present age. Classification of the primary and secondary ALCPAN was performed without knowledge of the lactate response. A definite primary versus secondary category could not be determined for 4 ALCPAN patients. Seven men and 13 women had a history of panic attacks without a diagnosis of alcoholism (PAN). All ALCPAN and PAN patients reported having symptoms compatible with a panic attack on at least one occasion in the 4 months preceding the study.

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Prior to the infusion, all subjects were informed that the administration of sodium lactate could result in a number of somatic symptoms that might be similar to a panic attack. Control subjects were educated regarding the symptomatology of a panic attack. Subjects were told that if they experienced the sense of losing control or panic, they should ask the attending physician to stop the infusion. Occurrence of a panic attack was determined if a subject had: a) at least four RDC panic symptoms; b) the sense of losing control, panicking, or going crazy; and c) likened the lactate response to a previous panic attack. Conditions a) and b) were required for controls to meet criteria for a positive lactate response.

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Statistical Analyses

Because there was no significant gender effect on the frequency of lactate-induced panic attacks, data for men and women were combined for all analyses. Data were analyzed using the 1990 revision of the BMDP Statistical Software (1990). All tests were two tailed and accepted as significant at a p value of $\leq .05$. Post hoc analyses consisted of pairwise comparisons of diagnostic groups, and were accepted as significant at a p value of $\leq .01$.

Fishers exact (Mehta and Patel 1992) chi-square was used to compare the incidence of lactate-induced panic attacks in ALCPAN and PAN, and in primary and secondary ALCPAN. These statistics were computed for the ALCPAN group based on both the RDC panic attack criteria ($n = 26$) and the DSM-IV criteria for panic disorder ($n = 22$). Since both criteria used to characterize the ALCPAN group yielded the same results, we performed all analyses for the ALCPAN group using the panic attack criteria.

Diagnostic groups were compared at baseline for biochemical and physiological measures with an analysis of variance (ANOVA). Postinfusion biochemical and psychological responses were analyzed with an analysis of covariance (ANCOVA), using baseline values as covariates. Because a number of subjects panicked prior to the completion of the infusion, not all subjects had complete blood pressure and heart rate data. Thus, the end of infusion values for blood pressure and heart rate were compared with an ANCOVA, using baseline values as covariates.

The prevalence of symptom frequencies at each time point was analyzed using nonparametric statistics, because of the small number of subjects remaining at the latter time points. Nonparametric statistics were also used to compare drinking histories. Kruskal–Wallis tests were used to compare differences between groups. Post hoc pairwise comparisons were accepted as significant at a Bonferroni-corrected alpha of $\leq .01$.

Using just the ALCPAN and PAN groups, patients who panicked were compared to those who did not on all measures described above. Analysis procedures were similar to those described above, except that the Mann–Whitney U test was used. To account for any effects of baseline differences, analyses were conducted on change scores. These analyses were considered to be post hoc tests and were accepted as significant at an alpha level $\leq .01$.

Results

Patient Characteristics

The groups differed significantly in age (two-way ANOVA: $F(3, 70) = 3.06, p < .04$). Bonferroni-corrected post hoc analyses indicated that PAN were older than HVOL (mean ages: 41.1 ± 10.4 and 32.4 ± 8.8 years, respectively). There were no significant differences between the groups for either gender or weight.

Lactate Response

No HVOL or ALC either reported or was observed to have a lactate-induced panic attack. Thirteen (65.0%) PAN versus 6 (23.1%) ALCPAN panicked during the infusion ($\chi^2(1) = 8.1, p = .01$), indicating that PAN were more likely to have a panic attack in response to lactate than ALCPAN. The frequency of lactate-induced panic attacks for primary ALCPAN (26.6%) and PAN (65.0%) was also significantly different ($\chi^2(1) = 4.9, p = .04$). Analysis of the ALCPAN group revealed no difference in the lactate-induced panic response between primary and secondary ALCPAN. It is estimated that if the present trends continued, a power of .8 would require 180 patients in each group to detect a difference at the $p < .05$ level.

Years of alcoholic drinking for ALC, ALCPAN with positive lactate response, and ALCPAN with negative lactate response were (mean ± SD) 12.2 ± 5.9, 8.8 ± 4.5, and 9.2 ± 7.9, respectively (Kruskal–Wallis chi-square = 2.9, df = 2, $p = .24$). Amount of alcohol consumed per occasion for the last 6 months showed ALC consumed 218.6 ± 130.6 g, ALCPAN with positive lactate response consumed 176.4 ± 144.3 g, ALCPAN with negative lactate response consumed 162.1 ±162.2 g, and PAN consumed 16.1 ± 3.1 g (Kruskal–Wallis chi-square = 24.24, df = 3, $p = .001$). Post hoc pairwise comparisons showed a significant difference of $p \leq .005$ between ALC and PAN, ALCPAN positive for lactate response and PAN, and ALCPAN negative for lactate response and PAN.

Physiological Variables

There were no group differences at baseline for blood pressure or heart rate (see Table 2). Following lactate administration there was a significant group effect for diastolic blood pressure; post hoc tests indicated that the ALCPAN and PAN had higher diastolic blood pressure than the HVOL.

Biochemical Measures

At baseline, ALCPAN had a higher plasma pH than HVOL (see Table 2). This difference was not present following the infusion. There were no differences between groups either at baseline or postinfusion for epinephrine, norepinephrine, or lactate concentrations.

Table 2. Baseline and Postinfusion Means ± Standard Deviations for Biochemical and Physiological Variables

Infusion	HVOL	ALC	ALCPAN	PAN	ANOVA/ANCOVA
Systolic blood pressure (mmHg)					
Base	114.0 ± 13.9	112.5 ± 17.2	117.3 ± 15.5	119.7 ± 17.1	NS
End	123.0 ± 13.1	131.9 ± 17.6	129.2 ± 15.9	132.3 ± 21.6	NS
Diastolic blood pressure (mmHg)[a]					
Base	67.8 ± 11.4	65.9 ± 10.3	71.6 ± 12.0	74.4 ± 10.2	NS
End	65.1 ± 13.2	71.2 ± 8.3	75.6 ± 9.7	75.5 ± 9.3	$F(3, 65) = 3.02$, $p < .04$
Heart rate (beats/min)					
Base	65.3 ± 8.8	62.7 ± 12.1	66.8 ± 9.1	68.8 ± 10.4	NS
End	98.4 ± 9.7	95.3 ± 9.7	97.3 ± 8.2	101.3 ± 13.8	NS
Glucose (mg/dL)					
Base	89.3 ± 11.9	86.1 ± 5.2	94.0 ± 11.6	92.4 ± 12.8	NS
End	82.1 ± 9.0	79.7 ± 5.1	81.3 ± 10.0	81.6 ± 8.4	NS
Epinephrine (pg/mL)					
Base	18.7 ± 14.0	23.8 ± 20.9	20.6 ± 12.2	23.8 ± 16.0	NS
End	28.7 ± 21.3	23.5 ± 13.9	16.7 ± 12.9	26.4 ± 18.1	NS
Norepinephrine (pg/mL)					
Base	170.6 ± 73.6	203.6 ± 100.6	203.4 ± 94.3	213.3 ± 76.6	NS
End	246.8 ± 147.5	266.4 ± 116.1	308.7 ± 175.9	358.7 ± 153.1	NS
Venous pH[b]					
Base	7.33 ± 0.04	7.37 ± 0.02	7.38 ± 0.04	7.36 ± 0.03	$F(3, 45) = 5.86$, $p < .002$[c]
End	7.44 ± 0.04	7.45 ± 0.04	7.47 ± 0.04	7.46 ± 0.04	NS
Lactate (mmol/L)					
Base	0.5 ± 0.2	1.4 ± 2.6	0.6 ± 0.4	0.5 ± 0.4	NS
End	7.8 ± 1.9	6.3 ± 3.3	7.8 ± 3.9	8.1 ± 2.7	NS
HDI[a]					
Base	0.5 ± 0.5	4.1 ± 3.9	7.5 ± 5.7	8.1 ± 6.2	$F(3, 54) = 9.58$, $p < .001$[c]
End	—	—	—	—	—
STAI[a]					
Base	26.0 ± 4.7	36.6 ± 11.2	46.6 ± 7.2	42.7 ± 11.6	$F(3, 46) = 16.25$, $p < .002$[c]
End	—	—	—	—	—
SSAI[a,d]					
Base	25.9 ± 6.7	36.6 ± 9.3	42.3 ± 11.4	42.6 ± 11.6	$F(3, 70) = 9.25$, $p < .001$
End	41.0 ± 11.6	47.6 ± 13.9	64.4 ± 10.4	59.6 ± 9.4	$F(3, 58) = 9.73$, $p < .001$

[a]ALCPAN, PAN > HVOL, post hoc pairwise comparison.
[b]ALCPAN > HVOL, post hoc pairwise comparison.
[c]Variances not equivalent; Brown–Forsyth Equality of Means Test reported.
[d]ALCPAN, PAN > ALC, HVOL post hoc pairwise comparison.

Behavioral Variables

There were significant group differences at baseline for measures of mood (see Table 2). ALCPAN and PAN had significantly higher baseline state and trait anxiety ratings as well as Hamilton depression ratings than HVOL. Following the infusion, ALCPAN and PAN reported higher levels of anxiety than ALC and HVOL. ALCPAN and PAN reported more lactate-induced symptoms at each 3-min time point (except T = 6 min) than HVOL or ALC (Kruskal–Wallis ANOVA, $p < .05$). There were no differences between ALCPAN and PAN (see Figure 1).

Panic Attack versus No Panic Attack

When the patients from the PAN and ALCPAN groups were compared according to whether they had or did not have a lactate-induced panic attack, there were no baseline or postinfusion differences for the physiological, biochemical, and behavioral variables studied.

Discussion

In this study, we again found that alcoholics with either panic disorder or frequent panic attacks were significantly

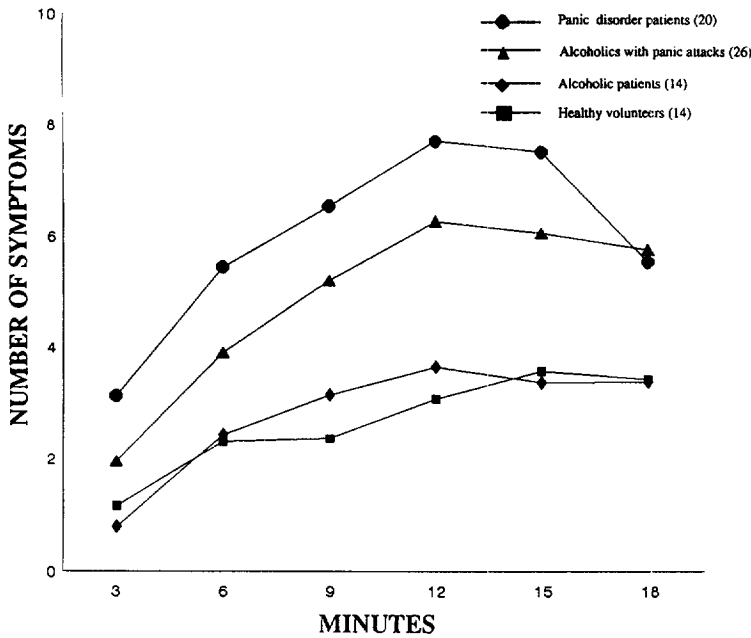

Figure 1. Mean number of symptoms reported at each 3-min interval during the lactate infusion.

less likely to experience a lactate-induced panic attack than nonalcoholic patients with panic disorder. By adding to the number of panic patients that we initially studied (George et al 1989), we were able to subdivide the ALCPAN into groups, based on their relative time of onset of panic attacks to alcoholism, and show that primary ALCPAN were less likely to have a lactate-induced panic attack than PAN. This finding was contrary to our original hypothesis and obviated the need to acquire a much larger sample of ALCPAN to detect a difference between primary and secondary ALCPAN. Comparisons between ALCPAN and PAN for various biochemical, physiological, and behavioral variables failed to show any significant differences between the groups. These findings give additional support for the possibility that the pathophysiology of panic attacks in patients with alcoholism may be different from that in patients with panic attacks without alcoholism.

Why ALCPAN are less likely to panic or experience loss of control during lactate administration is not elucidated by the current data. From a cognitive perspective, the results do not support the concept that repeated episodes of alcohol withdrawal, characterized by numerous symptoms typically associated with panic attacks (George et al 1988), sensitized either ALC or ALCPAN to overreact to the somatic effects of lactate with a "catastrophic misinterpretation" and experience panic; however, it is possible that repeated symptoms of alcohol withdrawal might have desensitized ALCPAN to the effects of lactate, which could explain the decreased reaction. Partially contradicting this interpretation, we did not find a significant difference for either the number of lactate-induced symptoms between ALCPAN and PAN or the amount of alcohol consumed between the ALCPAN who had a lactate-induced panic attack and the ALCPAN who did not have a panic attack.

From a biological perspective, the distinction regarding the sense of lactate-induced panic between ALCPAN and PAN parallels the results of another study in which we demonstrated that the coadministration of glucose and lactate to PAN patients blocked the subjective sense of panic without affecting the somatic symptoms associated with lactate administration (George et al 1995). In that study, we postulated a link between the sense of panic and the release of various neurotransmitters, primarily gamma-aminobutyric acid (GABA) (Amoroso et al 1990) and dopamine (Hausser et al 1991), which results when glucose [via increasing adenosine triphosphate (ATP) production] facilitates the opening of ATP-gated K^+ channels present on the membranes of many central nervous system (CNS) neurons (Mourre et al 1989, 1990). Our present results lead us to postulate that lactate itself, given its association with anaerobic metabolism and low ATP states, might also affect these channels. If this is the case, it is possible that the ATP-gated K^+ channels present in PAN and ALCPAN patients might differ in their relative sensitivity to lactate. Whether excessive alcohol consumption could give rise to this postulated difference or whether this postulated difference might somehow predispose to alcoholism is unknown.

In assessing these results, it is important to note the complexity of diagnosing panic disorder in patients with a

concurrent diagnosis of alcoholism. Both the SADS as well as DSM-IV preclude making a diagnosis of panic disorder in patients who have a medical condition, such as alcohol withdrawal, which could mimic the symptoms of panic. Therefore, for actively drinking ALCPAN, we only studied those patients who had both a history of panic attacks during periods of sobriety as well as recent symptoms compatible with panic attacks when they were drinking. Although it is possible that prolonged alcohol withdrawal could have confounded the diagnosis of panic in some of these patients, this seems unlikely, since the panic attacks were typified by a crescendo of symptoms and a sense of panic or losing control that was distinctive and not present in alcoholics without a diagnosis of panic. To assure that our findings were not an artifact of the diagnostic criteria used to characterize panic, we analyzed the frequency of lactate-induced panic attacks using both the diagnostic criteria for just panic attacks as well as DSM-IV criteria for panic disorder. Since we did not find a significant difference between the results applying these two sets of criteria, we chose to characterize the patients using panic attack criteria. Lastly, categorizing ALCPAN into primary and secondary groups, based on the relative onset of panic disorder to alcoholism, was retrospective and subject to patient recollection. For most ALCPAN the onset of panic was a very memorable event, which allowed the patients to determine the date of onset with apparent accuracy. Our ability to diagnose the onset of alcoholism was, however, less precise and made it impossible for us to determine the relative onset of each disorder in 4 ALCPAN. Therefore, these patients were not used in the primary/secondary analysis.

Although the rater was not blind to the diagnosis in the present study, the impact of this possible bias is lessened by: a) the observed finding between primary ALCPAN and PAN was contrary to the anticipated result; b) the classification of ALCPAN into primary and secondary groups was made independent of lactate response; and c) the diagnosis of lactate-induced panic attack was only made if the patients stated they had a panic attack. Given that most ALCPAN were consuming alcohol until they were admitted to the hospital, it is difficult to make a direct comparison between the ALCPAN and PAN regarding the actual frequency and severity of the panic attacks. Since lactate response has been shown to be independent of panic attack frequency (Cowley et al 1987), it is unlikely that the reduced response in ALCPAN is attributable to a less severe form of panic. Although it is possible that differences in age as well as the presence of other concurrent diagnoses could have influenced our findings, we are unaware of any literature that supports this possibility.

The use of the pharmacologic probe, sodium lactate, offers an additional and complementary method to epidemiological/family studies, which have been traditionally employed to study the relationship between alcoholism and panic disorder. Consistent with the findings of our previous study (George et al 1989), ALCPAN, compared to PAN, had a reduced frequency of lactate-induced panic attacks. Analysis of ALCPAN according to the relative onset of panic to alcoholism revealed primary ALCPAN also had a reduced incidence of lactate-induced panic attacks. This decrease in sensitivity to lactate is not explained by a misdiagnosis of panic (e.g., alcohol withdrawal either mimicking or giving rise to panic), since primary ALCPAN had the onset of panic attacks prior to alcoholism. Rather, the data suggest that either alcoholism alters the lactate response in patients with panic disorder, or ALCPAN represent a distinct comorbid disorder different from the two component disorders.

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