Effect of Chloride or Glucose on the Incidence of Lactate-Induced Panic Attacks

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Objective: *This study was designed to test the hypothesis that the addition of chloride to a lactate infusion would reduce the frequency of panic attacks.* *Method:* *The subjects included 14 healthy volunteers and 20 patients meeting the DSM-IV criteria for panic disorder. All subjects received an infusion of lactate dissolved in 0.9% sodium chloride and an infusion of lactate dissolved in 5% dextrose in water on separate days in a random-order, double-blind procedure. Blood pressure, heart rate, and panic symptoms were measured at 3-minute intervals during the infusions. The occurrence of panic attacks was ascertained through the subjects' reports of losing control, panicking, or "going crazy" and the presence of at least four Research Diagnostic Criteria symptoms of a panic attack.* *Results:* *Fifteen (75%) of the patients with panic disorder reported a panic attack during one of the infusions or both; no healthy volunteers had a panic attack. The patients with panic disorder were significantly more likely to have a panic attack during the lactate/sodium chloride infusion than during the infusion of lactate/5% dextrose in water. The number of panic attack symptoms reported at 3-minute intervals did not differ between the two types of infusion.* *Conclusions:* *The coadministration of glucose resulted in a reduced sensitivity to the panicogenic effects of lactate. The hypothesis that adding chloride to the infusion would reduce the frequency of lactate-induced panic attacks was not supported.*

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Sodium lactate induces panic attacks in 70%–90% of patients with panic disorder but in less than 10% of control subjects or patients with other mental disorders (1–3), such as obsessive-compulsive disorder (4), social phobia (5), and major depression (6, 7). Attempts to link biochemical changes resulting from lactate administration to the pathophysiology of panic disorder have been inconclusive. Pitts and McClure (1) reported that the addition of calcium chloride to the lactate infusion resulted in panic attacks with fewer and less severe symptoms. Although subsequent studies have discredited calcium as a factor in the etiology of panic attacks (8, 9), the role of chloride in the blockade of lactate-induced panic attacks remains largely unexplored. Its potential significance is emphasized by a study of healthy volunteers which showed that administration of lactate in sterile water resulted in a mean 9.0-meq/liter (SD= 2.4) reduction in plasma chloride concentration, compared to a mean 3.75-meq/liter (SD=1.9) decrease following an infusion of an equal volume of 5% dextrose in water without lactate (10).

Since chloride modulates benzodiazepine binding to the benzodiazepine-GABA-chloride ionophore (11), a decrease in plasma chloride concentration during lactate administration, if reflected in the central nervous system, could lead to a loss of neuronal inhibition. If subjects with panic disorder are uniquely sensitive to decreases in chloride concentrations, then the addition of chloride to the infusion solution should lower the incidence of lactate-induced panic attacks. To test this hypothesis, we manipulated plasma chloride concentrations by administering sodium lactate dissolved in either 0.9% sodium chloride or 5% dextrose in water to patients with histories of panic attacks and to healthy volunteers.

METHOD

All subjects underwent extensive physical examinations to ensure that they were in good health. Persons with histories of seizures or

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major head trauma (defined as a period of unconsciousness exceeding 1 hour) were excluded from participation. All subjects were medication free for 3 weeks prior to the study and had negative urine drug screens.

Psychiatric evaluations were made with the use of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (12), the Michigan Alcoholism Screening Test (13), and a clinical interview by a psychiatrist (D.T.G.). The SADS-L was administered by a trained social worker and subsequently rated blindly by another social worker and a psychiatrist. A consensus diagnosis was reached for each participant. Six panic patients were not administered the SADS-L. In order to utilize the most recent diagnostic criteria for panic disorder (DSM-IV), a retrospective chart review was conducted for each patient.

Twenty patients (seven men and 13 women) met the DSM-IV criteria for panic disorder. Eleven of the 14 patients who had been given the SADS-L met the Research Diagnostic Criteria (RDC) for panic disorder, seven for major depressive disorder, and five for generalized anxiety disorder. Fourteen healthy volunteers (nine men and five women) who were free of any current diagnosis according to the RDC served as the comparison subjects. Three of the healthy volunteers met the RDC for minor depressive disorders that had occurred in the past.

Written informed consent was obtained from all subjects before the study began. The subjects were on a low-monoamine diet for at least 72 hours prior to the study. Then, after overnight bed rest and fasting, an intravenous cannula was placed in the antecubital fossa and kept open with a slow infusion of 5% dextrose in water. Approximately 1 hour after the placement of the intravenous cannula, a 10-cc/kg infusion of 0.5 M sodium lactate dissolved in either 5% dextrose in water or sodium chloride was administered over 20 minutes, or until the subject requested that the infusion be stopped. Each lactate solution was administered on a separate day in a double-blind, random-order design. The rater of panic symptoms was not blind to the diagnoses.

Before the infusion, all subjects were informed that the administration of sodium lactate could result in a number of somatic symptoms and that these might be similar to those of a panic attack. Subjects were told that if they experienced the onset of a panic attack, they should ask the attending physician to stop the infusion. Occurrence of a panic attack was determined by the presence of at least four RDC symptoms and the patient's reported sense of losing control, panicking, or "going crazy."

Blood samples for chemical analyses were obtained at baseline and immediately after the termination of the infusion. Radioimmunoassays for norepinephrine, epinephrine, and insulin were performed by the Hazleton Corp. (Reston, Va.). Other assays were performed at the pathology department of the National Institutes of Health Clinical Center. Blood was analyzed for glucose, sodium, and chloride levels with the use of a Hitachi autoanalyzer (model 736-30) (Boehringer Mannheim).

Blood pressure and heart rate were measured at baseline and at 3-minute intervals throughout the infusion with a Dinamap recorder (Critikon Co., Tampa, Fla.).

Anxiety levels were measured at baseline with the state and trait portions of the State-Trait Anxiety Inventory (15); the state portion of the inventory was also readministered at the end of the infusion. The Hamilton Depression Rating Scale (16) was administered at baseline. Subjects also indicated the presence or absence of 13 symptoms associated with panic attacks (i.e., dyspnea, chest pain/pressure, choking, dizziness, feelings of unreality, tingling, hot/cold flashes, faintness, trembling, sadness, apprehension, sense of losing control, and fear) at 3-minute intervals throughout the infusion. Although sadness and apprehension are not specific RDC symptoms of a panic attack, they were included to assess the relation between lactate-induced panic and the cognitive states of apprehension and depression. None of the patients reported sadness, and apprehension was not included as one of the four symptoms necessary for making a diagnosis of a panic attack.

Data for men and women were combined for all statistical analyses. All data were analyzed with the 1990 revision of the BMDP statistical software package (17). All tests were two-tailed, with significance set at an alpha level of ≤0.05.

The frequencies of panic attacks on the first and second days of the study, regardless of infusion type, among the patients with panic disorder were compared with the use of the McNemar chi-square test for related samples. Differential responses to lactate/sodium chloride and lactate/5% dextrose in water were also assessed, using the McNemar chi-square test, only in the patients with panic disorder.

Comparisons of diagnostic groups and infusion types at baseline on biochemical, physiological, and psychological measures were analyzed with a mixed-design analysis of variance. Postinfusion biochemical and psychological responses were analyzed with a mixed-design analysis of covariance (ANCOVA), with baseline values used as covariates. Because a number of subjects panicked before completion of the infusion, not all subjects had complete blood pressure and heart rate data for the entire 21 minutes of the study. Maximum and minimum observed blood pressure and heart rate values were compared with an ANCOVA, again with baseline values as covariates.

Symptom frequencies at each time point were analyzed with nonparametric statistics because of the small numbers of subjects who remained at the later time points. Mann-Whitney U tests were used to compare differences between subject groups; different sets of analyses were conducted for each infusion type. Wilcoxon signed-rank tests were used to compare postinfusion responses to lactate/sodium chloride and lactate/5% dextrose in water within each diagnostic group.

RESULTS

No healthy volunteer reported a lactate-induced panic attack. Fifteen (75%) of the patients with panic disorder reported lactate-induced panic attacks: 11 patients during the lactate/sodium chloride infusion only, two during the lactate/5% dextrose in water infusion only, and two during both infusions. Five did not report any panic attacks. These differences in incidence indicated a significantly greater likelihood of having a panic attack in response to lactate/sodium chloride compared to lactate/5% dextrose in water (χ^2=6.23, df=1, p<0.02). The order in which the lactate infusions were administered did not affect the frequency of panic attacks.

The healthy volunteers had significantly lower diastolic blood pressures at baseline than did the subjects with panic disorder (F=4.97, df=1, 31, p<0.04). Following lactate administration the healthy volunteers had lower minimum systolic blood pressures than the subjects with panic disorder (F=4.55, df=1, 30, p<0.05) (table 1).

At baseline the patients with panic disorder had significantly higher plasma norepinephrine concentrations than the healthy volunteers (F=4.48, df=1, 31, p<0.05), and following each infusion, the patients with panic disorder had higher plasma norepinephrine concentrations than the healthy volunteers (F=4.42, df=1, 28, p<0.05). Plasma norepinephrine concentrations were higher after the lactate/sodium chloride infusion than after the infusion of lactate/5% dextrose in water (F=7.05, df=1, 28, p<0.02) (table 1). Blood glucose concentrations were significantly higher following the infusion of lactate/5% dextrose in water than following the lactate/sodium chloride infusion (F=902.96, df=1, 31, p<0.001). The infusion of lactate/5% dextrose in water also produced greater concentrations of plasma insulin than the lactate/sodium chloride infu-

TABLE 1. Baseline and Postinfusion Measures of 14 Healthy Volunteers and 20 Patients With Panic Disorder Given Lactate/Sodium Chloride and Lactate/5% Dextrose in Water

Variable and Type of Lactate Infusion	Healthy Volunteers				Patients With Panic Disorder			
	Baseline		After 20 Minutes		Baseline		After 20 Minutes	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Physiological								
Blood pressure (mm Hg)								
Systolic								
Sodium chloride	114.00	13.9			119.79	17.5		
Maximum			132.14	13.4			141.63	19.3
Minimum			106.14	16.9			120.10	18.4
5% dextrose in water	112.50	10.4			123.16	17.3		
Maximum			127.50	10.6			143.84	22.2
Minimum			108.57	9.0			120.74	18.4
Diastolic								
Sodium chloride	67.79	11.4			74.79	10.2		
Maximum			76.86	8.3			83.00	7.9
Minimum			60.64	10.8			68.47	8.6
5% dextrose in water	67.21	8.1			74.58	11.3		
Maximum			72.50	6.8			85.10	15.0
Minimum			59.00	8.5			67.21	9.6
Heart rate (bpm)								
Sodium chloride	65.29	8.8			68.89	10.7		
Maximum			100.29	8.5			104.95	13.4
Minimum			65.57	8.9			71.16	12.2
5% dextrose in water	63.00	6.5			67.32	11.0		
Maximum			97.36	8.1			102.21	11.5
Minimum			63.07	7.9			68.86	13.1
Biochemical								
Norepinephrine (pg/ml)								
Sodium chloride	170.57	73.6	255.15	150.0	213.26	76.6	358.72	153.1
5% dextrose in water	156.79	68.6	214.85	157.7	206.42	57.7	285.94	119.5
Epinephrine (pg/ml)								
Sodium chloride	18.71	14.0	29.38	22.0	23.80	16.0	26.37	18.0
5% dextrose in water	20.14	15.4	23.31	21.4	34.15	22.2	22.42	16.3
Glucose (mg/dl)								
Sodium chloride	89.29	11.8	82.07	9.0	92.35	12.8	81.60	8.4
5% dextrose in water	90.71	9.5	260.07	26.8	106.45	36.2	248.05	48.0
Insulin (μU/ml)								
Sodium chloride	9.18	2.1	5.22	2.1	11.54	6.7	7.53	3.8
5% dextrose in water	9.70	3.1	20.68	8.5	9.96	5.1	30.29	15.4
Sodium (mmol/liter)								
Sodium chloride	139.00	2.7	150.00	2.7	140.15	2.4	149.60	4.7
5% dextrose in water	139.07	2.0	145.14	2.6	140.30	2.6	144.95	3.2
Chloride (mmol/liter)								
Sodium chloride	106.71	2.3	101.36	1.7	107.40	2.9	102.95	3.2
5% dextrose in water	107.43	3.2	95.96	3.4	106.50	3.9	98.35	4.2
Venous pH								
Sodium chloride	7.33	0.04	7.44	0.04	7.36	0.03	7.46	0.04
5% dextrose in water	7.34	0.04	7.45	0.05	7.36	0.03	7.46	0.06
Lactate (mmol/liter)								
Sodium chloride	0.53	0.2	7.81	1.9	0.45	0.4	8.21	2.8
5% dextrose in water	0.56	0.2	8.16	1.8	0.49	0.3	11.09	7.6
Psychological								
Hamilton Depression Rating Scale score								
Sodium chloride	0.46	0.5	—	—	8.05	6.2	—	—
5% dextrose in water	1.38	1.6	—	—	7.60	6.3	—	—
State-Trait Anxiety Inventory								
Trait scale score								
Sodium chloride	25.08	3.3	—	—	42.70	11.6	—	—
5% dextrose in water	23.85	2.8	—	—	44.25	12.0	—	—
State scale score								
Sodium chloride	25.93	6.7	43.42	10.6	42.60	11.6	59.55	9.4
5% dextrose in water	26.00	5.3	38.50	15.4	42.85	9.7	61.00	10.8

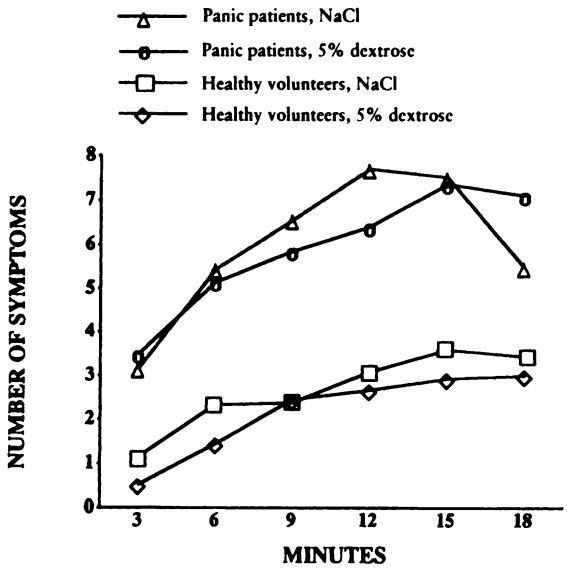
sion ($F=62.52$, $df=1, 19$, $p<0.001$). Serum sodium concentrations were higher following the lactate/sodium chloride infusion ($F=37.09$, $df=1, 31$, $p<0.001$), and serum chloride concentrations were lower following

the lactate/5% dextrose in water infusion (F=46.63, df=1, 31, p<0.001). The patients with panic disorder had significantly higher postinfusion chloride concentrations than the healthy volunteers (F=8.71, df=1, 31, p<0.01) (table 1).

The healthy volunteers had significantly lower baseline state anxiety scores (F=33.82, df=1, 32, p<0.001), trait anxiety scores (F=34.08, df=1, 31, p<0.001), and Hamilton depression scores (F=16.84, df=1, 31, p< 0.001) than the patients with panic disorder. The panic patients also had significantly higher state anxiety scores after the lactate infusion than did the healthy volunteers (F=6.74, df=1, 29, p<0.02) (table 1).

According to the reports of symptoms at 3-minute intervals throughout the infusions, the patients with panic disorder had more panic symptoms at every time point than the healthy volunteers on both infusion days (all U values >18, all p values <0.02). Within-group comparisons according to type of infusion showed no differences in panic symptoms between the two types of infusion (figure 1).

FIGURE 1. Mean Numbers of Panic Symptoms Reported by 20 Patients With Panic Disorder and 14 Healthy Volunteers at Each 3-Minute Interval During 20-Minute Infusions of Lactate/Sodium Chloride (NaCl) and of Lactate/5% Dextrose in Water



DISCUSSION

Infusion of lactate/5% dextrose in water resulted in significantly fewer panic attacks than did infusion of lactate/sodium chloride among patients meeting the DSM-IV criteria for panic disorder. Although the two lactate solutions produced similar numbers of somatic symptoms, the patients with panic disorder who received lactate/5% dextrose in water were less likely to report the sense of losing control or having panic attacks. This finding highlights the potential importance of the solution used to dissolve lactate and suggests that glucose may have an antipanic effect.

In assessing our findings, we noted that other studies that used lactate/5% dextrose in water found much higher rates of lactate-induced panic attacks (18–21). Although most of those studies used criteria similar to ours in judging the occurrence of a panic attack, they found higher rates of panic attacks following placebo than we found following lactate/5% dextrose in water. This suggests that either the patients included in those studies had a more severe form of panic disorder or the environment in which the studies were conducted facilitated panic attacks. Further, as a result of our unique study design, it is also possible that we were able to appreciate more subtle but important differences in the cognitive sense of losing control, which might not have been apparent if only one lactate infusion had been administered to each subject. In general, the incidence of panic attacks following infusion of lactate/sodium chloride that we observed in this study was comparable to that in other studies (1–3), suggesting that our method of selecting subjects and the technique used to judge panic attacks were valid.

Previous attempts to examine the effects of glucose (22) and insulin (23), as well as the effects of lactate on peripheral glucose (24) and insulin concentrations (25), have not shown a clear-cut relation between panic attacks and changes in plasma glucose concentrations. However, it should be noted that these studies were predicated upon an extensive literature linking episodically occurring anxiety symptoms with hypoglycemia rather than the possibility that hyperglycemia could play a role in preventing lactate-induced panic attacks (26, 27).

There are a number of interesting possible ways in which glucose could block the lactate-induced sense of "losing control" in patients with panic disorder. For example, glucose affects the activity of sulfonylurea-sensitive ATP-gated potassium ion channels that are present on neurons in numerous brain regions (28, 29). Current knowledge suggests that glucose enters the cell and generates ATP, which in turn closes the channel. In vitro studies performed on substantia nigra neurons have shown that hyperglycemia causes the release of both GABA (30) and dopamine (31). Although studies have not directly characterized the effect of glucose in other brain regions, it is plausible that neurons with sulfonylurea-sensitive ATP-gated potassium ion channels, which either are present in or project to such brain regions as the cingulate gyrus, prefrontal cortex, and limbic system, could alter the perception of a panic attack through changes in GABA and/or dopamine concentrations.

The possibility that ATP-gated potassium ion channels have a role in the etiology of panic attacks is also compatible with the "suffocation" model of Klein (32), which holds that patients with panic disorder are supersensitive to rises in CO_2. Amoroso et al. (30) demonstrated that substantia nigra slices that are bathed in an anoxic medium (nitrogen, CO_2, glucose) show a de-

crease in intracellular ATP, which results in the opening of the ATP-gated potassium ion channels. This process is largely reversed when the concentration of glucose in the medium is increased.

The effect of glucose on the adrenergic system is also of interest given the results of our study, as well as others (33–36), suggesting that alterations in norepinephrine may be involved in the pathogenesis of panic disorder. Studies performed in rats show a strong inverse relation between blood glucose and noradrenergic activity in the hypothalamus (37). Similarly, in human beings the administration of 2-deoxy-D-glucose, a glucose analogue that causes intracellular glucose deprivation, results in activation of the sympathetic nervous system (38). Thus, these studies, coupled with evidence that hyperglycemia attenuates sympathetic nervous system activity, as measured by vasodilation following precipitated morphine withdrawal in rats (39), support our findings of lower plasma norepinephrine concentrations in patients with panic disorder after lactate/5% dextrose in water than after lactate/sodium chloride.

The apparent dissociation between the somatic symptoms of a panic attack and the cognitive sense of losing control during the infusion of lactate/5% dextrose in water is also interesting and has implications for cognitive theories put forth to explain panic disorder. If lactate-induced panic attacks result from the "catastrophic misinterpretation" of bodily sensations (40), then both types of lactate infusion, which resulted in similar somatic symptoms, should have resulted in comparable rates of lactate-induced panic attacks. Since this was not the case, we are left with the possibility that glucose inhibits the central effects of lactate, perhaps by altering the responsiveness of the noradrenergic, GABA, and/or dopaminergic systems as previously described.

The fact the subjects had a higher rate of panic attacks when receiving lactate/sodium chloride than when receiving lactate/5% dextrose in water argues against our original hypothesis that the addition of chloride to the infusion would block lactate-induced panic attacks. However, it is possible that the peripheral administration of chloride was insufficient to cross the blood-brain barrier and have a biological effect in the central nervous system.

In conclusion, we observed that patients with panic disorder were less likely to experience a sense of losing control after lactate/5% dextrose in water than after lactate/sodium chloride. If this finding is replicated, then future mechanistic studies are indicated to investigate how glucose blocks the sense of panic and losing control.

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