Behavioral and Neuroendocrine Responses to Sodium Lactate Infusion in Subjects With Posttraumatic Stress Disorder

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Objective: Sodium lactate infusion has induced flashbacks accompanied by panic attacks in male combat veterans with posttraumatic stress disorder (PTSD) and concurrent panic disorder. This study addressed whether sodium lactate induces flashbacks or other intrusive PTSD symptoms in PTSD patients free of concurrent panic disorder. Method: Behavioral, cardiovascular, catecholamine, and cortisol responses to infusion of 0.5 M sodium lactate were compared among seven subjects with PTSD without panic disorder, seven subjects with panic disorder only, and seven healthy subjects. Results: Six of the seven PTSD subjects but no panic disorder or healthy subjects reported flashbacks or other intrusive PTSD symptoms during lactate infusion. Flashbacks were accompanied by substantial anxiety symptoms. Cortisol levels were low in the PTSD subjects. Conclusions: Sodium lactate induces flashbacks in persons with PTSD without comorbid panic disorder. The relationship between anxiety responses accompanying a PTSD flashback and those in a panic attack remains unclear.

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Sodium lactate infusion has induced flashbacks accompanied by panic attacks in male combat veterans with concurrent posttraumatic stress disorder (PTSD) and panic disorder (1). This study sought to determine whether sodium lactate induces flashbacks or other intrusive PTSD symptoms in persons with PTSD without comorbid panic disorder. Effects of sodium lactate on sympathetic nervous system, adrenomedullary, and adrenocortical activity in PTSD were also estimated.

METHOD

The subjects gave written informed consent after the procedures in this study, approved by the University of Washington, had been fully explained. The subjects with PTSD and the subjects with panic disorder met the respective DSM-III-R criteria as determined by standard structured interviews. The seven subjects with PTSD (five men and two women; mean age=45 years, SD=4) had no history of diagnosable panic attacks either in the context of or separate from PTSD symptoms and had no other current psychiatric disorder. Six of these seven subjects had experienced spontaneous flashbacks. The spontaneous flashbacks always had been accompanied by fearfulness, but in no case were the reported anxiety symptoms sufficient to meet the criteria for a panic attack. Spontaneous flashbacks had occurred at least once per week in three subjects and less frequently in the other three during the 6 months before the study. The seven subjects with panic disorder (four men and three women; mean age=39 years, SD=13) had no history of PTSD and no other current psychiatric disorder. The seven healthy comparison subjects (five men and two women; mean age=35 years, SD=8) had no current or past history of psychiatric disorder. Ages and sex distribution did not differ among the groups.

All subjects were in good general health, had been free of drug or alcohol abuse for at least 9 months, and had taken no medications known to affect sympathetic nervous system, adrenomedullary, or adrenocortical activity for at least 4 months.

After fasting overnight, subjects had intravenous catheters placed in each arm at 9:00 a.m. Thirty minutes later, 10 ml/kg of 0.5 M sodium lactate were administered over a period of 20 minutes. For one subject with PTSD, the infusion was terminated after 10 minutes because of intolerable intrusive symptoms. Behavioral ratings, cardiovascular measures, and blood samples for determining plasma norepinephrine, epinephrine, and cortisol levels were obtained before starting and after terminating the infusion.

A flashback was defined as a sense of unreality accompanied by vivid images of a past traumatic situation as though it were actually present. Fifteen minutes after the infusion ended, the subjects with PTSD used a 10-point scale to rate the sameness of an induced PTSD symptom compared to a spontaneous PTSD symptom. Anxiety symp-

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TABLE 1. Endocrine and Cardiovascular Responses of Subjects With Panic Disorder, Subjects With PTSD, and Healthy Comparison Subjects to Sodium Lactate Infusion

	Comparison Subjects (N=7)		Panic Disorder Subjects (N=7)		PTSD Subjects (N=7)[a]	
Measure	Mean	SD	Mean	SD	Mean	SD
Norepinephrine level (pg/ml)						
Baseline	164	48	267	152	320	165
End of infusion	260	147	400[b]	132	397	63
Epinephrine level (pg/ml)						
Baseline	49	36	52	23	75	15
End of infusion	40	35	51	24	80[c]	21
Cortisol level (μg/dl)						
Baseline	8.9	4.7	9.9	5.2	4.6	2.2
End of infusion	9.8	5.5	8.8	3.9	3.6[d]	1.8
Mean arterial pressure (mm Hg)						
Baseline	83.4	7.3	90.3	9.5	97.3	14.1
End of infusion	82.4	7.9	93.0	15.5	100.6	18.0
Heart rate (bpm)						
Baseline	55.6	8.5	75.4	10.1	63.1	7.9
End of infusion	88.7[e]	7.1	103.1[e]	25.7	97.0[e]	14.2

[a]Norepinephrine and epinephrine levels were available for only six PTSD subjects.
[b]Significantly higher than baseline value ($p<0.05$, paired t test).
[c]Significantly higher than value for comparison subjects ($p<0.05$, ANOVA followed by Scheffé's test).
[d]Significantly lower than value for comparison subjects ($p<0.05$, ANOVA followed by Scheffé's test).
[e]Significantly higher than baseline value ($p<0.01$, paired t test).

toms were assessed with the Acute Panic Inventory (2). Global anxiety was rated on a 10-point scale. A panic attack was defined as the abrupt onset of intense fear or discomfort, an increase in at least four Acute Panic Inventory symptoms, and an increase of at least 2 points and an achieved rating of at least 5 points on the global anxiety scale. Heart rate and blood pressure were determined automatically (Dinamap; Critikon, Tampa, Fla.). Mean arterial pressure was calculated as 1/3 (systolic – diastolic) + diastolic pressure. Plasma norepinephrine and epinephrine levels were determined by single isotope radioenzymatic assay and cortisol levels by radioimmunoassay as described in a previous report from this laboratory (3).

Three-group one-way analyses of variance were computed on baseline and postinfusion measures and the differences between baseline and postinfusion measures. Scheffé's method was used for post hoc comparisons. The chi-square test was used to test for different frequencies across groups. Paired t tests were performed on within-group changes from baseline to the end of infusion.

RESULTS

PTSD symptoms occurred during lactate infusion in six of the seven subjects with PTSD but in no subjects with panic disorder or healthy subjects ($\chi^2=16.8$, df=2, $p<0.001$). Flashbacks occurred in four of the subjects with PTSD. Three of the four had had previous spontaneous flashbacks. They rated the induced flashbacks as very similar to their spontaneous flashbacks (mean "sameness" rating=8.3, SD=2.1, on the 10-point scale). A fifth subject with PTSD experienced a dissociative episode following an intrusive combat memory, and a sixth subject with PTSD experienced intrusive combat memories.

Global anxiety and Acute Panic Inventory scores increased significantly in all groups. Increases were substantially greater in the PTSD and panic disorder groups than in the group of healthy comparison subjects but did not differ between the PTSD and panic disorder groups. Five of the seven subjects with PTSD (including all subjects who experienced flashbacks), four of the seven subjects with panic disorder, and no comparison subjects met the a priori criteria for panic during lactate infusion.

Cortisol levels were significantly lower in the PTSD group than in the comparison group at the end of the infusion and tended to be lower in the PTSD group than in the panic disorder group at both time points (table 1). Increases in norepinephrine levels were significant in the panic disorder group. Epinephrine levels were significantly higher in the PTSD group than in the comparison group at the end of the infusion. Heart rate increased significantly but mean arterial pressure was not altered in all groups.

DISCUSSION

This study confirmed the finding that sodium lactate induces flashbacks in subjects with PTSD (1) and extends this observation to PTSD patients without comorbid panic disorder. Despite the PTSD subjects' having no history of panic attacks either separate from or in the context of spontaneous PTSD symptoms, anxiety symptoms meeting the a priori study criteria for panic accompanied the induced flashbacks. Flashbacks and panic attacks may share a common pathophysiology or represent different interpretations of the same phenomenon. Alternatively, the Acute Panic Inventory and the DSM-III-R panic criteria may not be sensitive to real differences between cognitive and autonomic anxiety symptoms occurring during a PTSD flashback and those occurring during a panic attack. During a flashback, anxiety symptoms are an ex-

pected response to reexperiencing a life-threatening situation. Such anxiety responses may be quite different from those occurring during a typical unexpected panic attack that lacks a precipitating threat of danger. Comparing responses to lactate and placebo in larger numbers of PTSD and panic disorder subjects and using instruments sensitive to the potential differences in anxiety symptom precipitants and perceptions between subjects with PTSD and those with panic disorder may clarify this issue.

Our neuroendocrine and cardiovascular results are consistent with previous studies suggesting decreased adrenocortical activity and abnormal autonomic activity in PTSD (4, 5). They provide a rationale for further studies of neuroendocrine responses to sodium lactate in subjects with PTSD.

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