Effects of the Cholecystokinin Agonist Pentagastrin in Patients With Generalized Anxiety Disorder

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Objective: The anxiogenic and panicogenic effects of peripheral administration of the cholecystokinin-B receptor agonist pentagastrin and placebo were evaluated in patients with generalized anxiety disorder and normal comparison subjects. Method: Seven patients with generalized anxiety disorder and seven age- and sex-matched normal subjects received an intravenous bolus of placebo and pentagastrin. Results: Panic attacks occurred in five patients with generalized anxiety disorder (71%) and in one normal subject (14%). Patients with generalized anxiety disorder were more likely to report more nonpanic anxiety than were normal subjects. Conclusions: Patients with generalized anxiety disorder appear to exhibit greater subjective sensitivity to pentagastrin than do normal subjects.

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Cholecystokinin tetrapeptide (CCK-4) is a neurotransmitter that has high affinity for the cholecystokinin-B (CCK-B) receptors in the central nervous system and may play a role in the modulation of anxiety in animals and humans (1). Specifically, in patients with panic disorder, an intravenous bolus of CCK-4 or the synthetic analog pentagastrin reliably provokes panic attacks in the majority of subjects (2–4). Since the administration of CCK-4 to healthy normal subjects also induces panic attacks at substantially higher doses than in patients with panic disorder, it is hypothesized that enhanced sensitivity to CCK stimulation may be present in panic disorder (4). To explore whether CCK sensitivity may be present in anxiety disorders other than panic disorder, we compared the panicogenic and anxiogenic effects of pentagastrin and placebo infusion in patients with generalized anxiety disorder and in normal subjects.

METHOD

Seven patients (three women and four men; mean age=41 years, SD=9) who met DSM-III-R criteria for generalized anxiety disorder and seven age- and sex-matched normal comparison subjects (mean age=40 years, SD=10) were included in this study. All subjects were evaluated through use of the Structured Clinical Interview for DSM-III-R, had normal findings on physical examinations and laboratory tests, and provided verbal and written informed consent. The mean age at onset of generalized anxiety disorder was 30 years (SD=13). Patients with a history of panic attacks, current major depression, or other axis I disorders (except dysthymia in one patient with generalized anxiety disorder) were excluded. Study subjects were free of psychotropic medications for at least 1 month before the study. One comparison subject and one patient took angiotensin-converting enzyme inhibitors on a regular basis.

Pentagastrin was prepared to provide 0.6 μg/kg in 0.9% sodium chloride (volume of less than 1 ml) (3). For placebo infusion an equivalent volume of saline was used. Subjects were blind to the order of the infusions. Following a 15-minute rest after the insertion of an intravenous line, patients with generalized anxiety disorder and normal subjects received an intravenous bolus (over 5 seconds) of placebo. A second intravenous bolus containing pentagastrin was administered after 15 minutes (by which time all subjects had returned to baseline), or earlier if symptoms had subsided for at least 5 minutes. Immediately after each injection, subjects were asked to indicate the onset and duration of and to describe the symptoms they experienced following the injections. The times of infusion and onset and cessation of symptoms were measured with a stopwatch. Systolic and diastolic blood pressure and heart rate were monitored by using an automatic sphygmomanometer.

Panic symptoms were evaluated by using the clinician-rated Panic Symptom Scale, a DSM-III-R-derived panic inventory used by Bradwejn et al. (2), which rates the intensity of symptoms from 0 (not present) to 4 (extremely severe). Panic attacks were defined as those meeting the DSM-III-R criteria for a panic attack (i.e., at least four somatic symptoms, abrupt onset, and apprehension and/or fear of at least moderate intensity compared to pre-infusion levels) (2). In addition, the sum of intensity ratings and the total number of symptoms endorsed on the Panic Symptom Scale were obtained. General anxiety was assessed by using a patient-administered 100-mm visual analog scale. The rating clinician was aware of the order of infusions but blind to subject diagnosis (except in one case). The Panic Symptom Scale and visual analog scale ratings (of symptoms at peak intensity) were obtained before (at baseline) and after (once symptoms subsided) each infusion.

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The study employed a two-factor factorial design with the diagnostic group factor having two levels (i.e., patients with generalized anxiety disorder and normal subjects [between-subjects factor]) and the treatment factor having two levels (i.e., pentagastrin and placebo [within-subjects factor]). Two sets of analyses, one considering the treatment factor as comprising independent samples and one considering the matching of subjects within the factor, were carried out. However, the matching of patients and normal subjects resulted in weak correlations among pairs and, hence, loss of statistical power relative to the unpaired approach; thus, results for the independent sample case (but not for matching) are reported.

Mean responses for continuous variables were compared by using a two-factor, repeated measures analysis of variance (ANOVA). A chi-square test was used to compare the proportion of panic attacks for generalized anxiety disorder and normal groups.

For the behavioral variables (number of symptoms, total symptom intensity, and generalized anxiety scores), preliminary comparisons indicated no significant differences in baseline scores for the two groups. Analysis of covariance, which used baseline levels as covariates, gave results similar to those obtained by using ANOVA with postinfusion scores as the dependent variable. Thus, for purposes of comparisons, postinfusion scores are presented. For analyses in which the interaction term (treatment-by-diagnostic group) in the ANOVA was not significant, the F statistic and corresponding p value for main effect comparisons for diagnostic group and treatment are reported. For cases in which the interaction term for diagnostic group-by-treatment was significant, post hoc (simple effect) comparisons were made by using a pooled t test for patients with generalized anxiety disorder versus comparison subjects and the paired t test for placebo versus pentagastrin. The t statistic and p values, corrected for multiple comparisons by using the Bonferroni correction, are presented.

TABLE 1. Behavioral Effects of Pentagastrin Infusion in Patients With Generalized Anxiety Disorder and Normal Volunteers[a]

Measure	Patients With Generalized Anxiety Disorder (N=7)		Comparison Subjects (N=7)	
	Mean	SD	Mean	SD
General anxiety (visual analog scale)[b]	81.0	15.5	37.7	33.9
Number of symptoms (Panic Symptom Scale)	8.9	4.4	6.3	4.4
Symptom intensity (Panic Symptom Scale)	22.3	14.9	12.4	14.9

[a]Five patients with generalized anxiety disorder (71%) and one comparison subject (14%) experienced a panic attack after pentagastrin infusion (χ^2=4.67, df=12, p=0.03).
[b]Significant diagnostic group-by-treatment interaction (F=4.74, df=1, 12, p=0.05; two-factor repeated measures ANOVA. Post hoc comparison showed a significant difference between groups (t=3.07, df=12, p=0.02; pooled t test).

RESULTS

The behavioral effects of pentagastrin infusion in both groups are shown in table 1. No statistically significant differences were observed between the groups for number of symptoms (main effect, diagnostic group: F=1.58, df=1, 12, p=0.23; diagnostic group-by-treatment interaction: F=0.77, df=1, 12, p=0.40) and total symptom intensity (main effect, diagnostic group: F=1.67, df=1, 12, p=0.22; diagnostic group-by-treatment interaction: F=1.38, df=1, 12, p=0.26) after pentagastrin infusion, although for these variables the mean values for patients were 1.4 and 1.8 times higher, respectively, than those for comparison subjects. For the visual analog scale scores, differences between patients and comparison subjects were significant after pentagastrin infusion (diagnostic group-by-treatment interaction: p=0.05) (table 1) but not after placebo infusion (mean=18.1, SD=18.9, versus mean=5.6, SD=3.8) (t=1.72, df=12, p=0.26).

No statistical differences were observed in the mean time to onset of symptoms and total duration of symptoms between patients with generalized anxiety disorder (mean=49.3 seconds, SD=36, and mean=4.9 minutes, SD=1, respectively) and normal subjects (mean=48.6 seconds, SD=33, and mean=4.1 minutes, SD=1.7, respectively) (two-tailed pooled t test; t=0.04, df=12, p=0.97, and t=1.15, df=12, p=0.29, respectively).

There was a statistically significant increase in the number of symptoms (main effect, treatment: F=33.1, df=1, 12, p=0.0001; diagnostic group-by-treatment interaction: F=0.77, df=1, 12, p=0.40) and total symptom intensity (main effect, treatment: F=17.5, df=1, 12, p=0.001; diagnostic group-by-treatment interaction: F=1.38, df=1, 12, p=0.26) after pentagastrin compared to placebo both for patients and normal subjects. For visual analog scale scores (main effect, treatment: F=45.3, df=1, 12, p<0.0001; diagnostic group-by-treatment interaction: F=4.74, df=1, 12, p=0.05), means after pentagastrin infusion were significantly higher than means after placebo for patients with generalized anxiety disorder (pentagastrin: mean=81.0, SD=15.5; placebo: mean=18.1, SD=18.9) (paired t=9.4, df=6, p=0.0002) and were marginally significant for normal subjects (pentagastrin: mean=37.7, SD=33.9; placebo: mean=5.6, SD=3.8) (paired t=2.6, df=6, p=0.08).

DISCUSSION

To our knowledge, this pilot study is the first to evaluate the effects of a CCK agonist in patients with generalized anxiety disorder. We observed that peripherally administered pentagastrin induces panic attacks and increased overall anxiety in patients with generalized anxiety disorder without a history of panic attacks. The difference in the rate of panic attacks between patients and comparison subjects was due to the absence of moderate apprehension and/or fear (required criterion for a panic attack) in comparison subjects after pentagastrin infusion. Although the differences in the number and intensity of the associated somatic symptoms between patients and comparison subjects were not statistically significant, these values were generally higher among patients. Significant differences may have been detected in a larger group. It is of interest that we used the same method of defining panic attacks as other investigators (2–4) and found rates of panic attacks in the patients with generalized anxiety disorder that were

comparable to those observed by Abelson and Nesse (3) in patients with panic disorder; in that study panic attacks occurred in 70% of the patients and 0% of normal subjects after the infusion of 0.6 μg/kg of pentagastrin. This suggests that individuals with generalized anxiety disorder may be similar to those with panic disorder with respect to enhanced sensitivity to the CCK-B receptor agonist challenge. However, other nonpharmacologic factors may also contribute to study results.

Finally, we did not find significant differences in baseline measures for anxiety between patients with generalized anxiety disorder and normal subjects. It is possible that a relatively short resting period before infusions helps reduce anticipatory anxiety in these patients.

In summary, patients with generalized anxiety disorder exhibited greater subjective sensitivity to pentagastrin infusion than did normal subjects. Future research evaluating the effects of CCK-B receptor agonists in a larger group of patients with generalized anxiety disorder in comparison with other anxiety disorders may contribute to our understanding of the potential role of CCK in the pathophysiology of anxiety disorders.

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