Cholecystokinin and anxiety in normal volunteers: an investigation of the anxiogenic properties of pentagastrin and reversal by the cholecystokinin receptor subtype B antagonist L-365,260

C. LINES, J. CHALLENGOR & M. TRAUB

Merck Sharp & Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK

- 1 Two studies were undertaken to develop a model of experimentally induced anxiety in normal volunteers based on cholecystokinin (CCK) receptor agonism/antagonism.
- 2 In Study 1 rapid intravenous injections of the CCK receptor subtype B (CCK_B) agonist pentagastrin (0.15, 0.3 and $0.6 \mu\text{g kg}^{-1}$) were found to produce dose-related increases in subjective ratings of anxiety compared with placebo.
- 3 In Study 2 the effects of pre-treatment with two doses of the CCK_B receptor antagonist L-365,260 (10 mg, 50 mg p.o.) on the anxiety induced by pentagastrin $0.3 \mu\text{g kg}^{-1}$ i.v. were investigated. Detailed measurements of blood pressure and pulse rate were also undertaken. Pentagastrin produced changes in blood pressure and pulse rate which had a similar time course to that observed for subjective anxiety ratings. L-365,260 reversed both the autonomic and anxiogenic effects of pentagastrin.
- 4 The pentagastrin model would appear to be a useful tool for investigating potential anxiolytics in normal volunteers.

Keywords CCK pentagastrin CCK_B antagonists L-365,260 anxiety

Introduction

Although inappropriate or pathological anxiety is generally accepted as a major cause of psychiatric morbidity, the separate designation of Panic Disorder is relatively recent [1]. The syndrome is characterised by repeated, brief episodes of intense fear, feelings of impending doom and a host of physical symptoms. Since Panic Disorder was recognised as a distinct diagnostic entity in 1980 by the American Psychiatric Association (DSM-III) it has become a focus of increasing attention in the psychiatric literature and a target for pharmacological interventions. The benzodiazepine alprazolam has recently been approved for this indication in the United States and there is evidence that other benzodiazepines, as well as antidepressants, are effective treatments [2].

The unpredictability of spontaneous panic attacks has led investigators to examine alternative models of panic in vulnerable patients. These have included the response to a number of pharmacological challenges

such as sodium lactate, carbon dioxide, yohimbine [3] and, more recently, the cholecystokinin (CCK) fragment CCK-4. CCK is a peptide which is thought to act as a neurotransmitter or neuromodulator in the mammalian nervous system. Two pharmacologically distinct CCK receptors have been identified; the CCK_A subtype predominates in peripheral tissues while the CCK_B receptor (which is pharmacologically indistinguishable from the peripheral gastrin receptor) predominates within the brain [4]. It has been demonstrated that rapid intravenous injections of the CCK_B /gastrin receptor agonists, CCK-4 and pentagastrin, reliably induce panic attacks in patients with Panic Disorder [5–7]. Pre-treatment with the CCK_B receptor antagonist L-365,260 prevents panic attacks in this model [8]. These findings suggest that CCK might be implicated in the pathophysiology of Panic Disorder and indicate a possible novel therapeutic approach involving CCK_B receptor antagonism.

While much valuable information has been gleaned from pharmacological challenge models, the induction of panic attacks in vulnerable patients has significant ethical and practical limitations. Consequently, it would be desirable if a reliable model of Panic Disorder could be developed in normal volunteers. The aim would be to produce sub-maximal anxiety in normal subjects, rather than panic attacks, on the assumption that panic attacks lie at the extreme end of an anxiety continuum. In Study 1 we sought to develop such a model by investigating whether injections of pentagastrin in normal volunteers could induce symptoms typically found in panic attacks. In addition, a novel computerised rating system was used to allow continuous monitoring of anxiety levels.

Methods

Study 1

The study was undertaken at Merck, Sharp and Dohme Neuroscience Research Centre, Terlings Park, Harlow, UK. The protocol was approved by the Terlings Park ethics committee and all subjects gave written informed consent.

Subjects

Sixteen subjects (11 males, 5 females), between the ages of 20 and 48 years, took part in the study. None of the subjects had previously received pentagastrin.

Design

The study employed a double-blind, four period, crossover design. The four treatments consisted of three doses of pentagastrin (0.15, 0.3 and 0.6 $\mu\text{g kg}^{-1}$) and placebo. The treatments were administered according to a Latin Square design and were separated by a washout period of at least 1 week.

Procedure

On each test day subjects had an intravenous cannula inserted into their non-dominant arm. Five minutes later pentagastrin (0.15, 0.3 or 0.6 $\mu\text{g kg}^{-1}$) or placebo was injected as a bolus over 5 s. On commencement of the pentagastrin/placebo infusion subjects were required to rate their anxiety level continuously for 5 min, by using a 'mouse' to control the position of the cursor on a computer-displayed visual analogue scale (VAS). The scale consisted of a horizontal line with the words 'no anxiety' at the left end and 'max. anxiety' at the right end. (Subjects were instructed to regard the extreme right end of the scale as representing the worst possible anxiety they could imagine.) The position of the cursor was recorded every second on a scale of 0–200 units for the duration of the 5 min test period. The primary outcome measures were the area under the anxiety

score over time curve (AUC) and maximum anxiety scores. Latency to onset, defined as time in seconds to the first non-zero rating (i.e. the time the subject first moved the mouse to rate anxiety) and latency to maximum score (i.e. time to peak anxiety) were also measured. For 10 subjects pulse rate data was recorded every 30 s by means of an ear lobe probe attached to a Solex PS300 pulse oximeter. The primary outcome measure was the maximum pulse rate. Immediately following the computerised anxiety rating, subjects were required to complete the Panic Symptoms Scale (PSS) [7]. This scale lists 24 symptoms commonly experienced by patients with Panic Disorder and subjects were required to rate symptom severity on a scale of 0 (not present) – 4 (extremely severe). Subjects were instructed to rate the peak severity of each symptom occurring during the 5 min test period.

Data analysis

Data for each measure, other than PSS item analysis, were analysed by repeated measures ANOVA with a factor of treatment dose. Orthogonal polynomials were used to test for a linear dose trend. In addition, where there was a significant main effect of treatment dose, planned contrasts for all six pairwise combinations of treatments were undertaken using post-ANOVA comparisons. For the PSS item analysis differences between placebo and the highest dose of pentagastrin were analysed for each individual item using Wilcoxon tests. In all cases the level of significance was set at $P < 0.05$. One subject was excluded from the data analysis because the cannula was not inserted properly into his arm for one of the treatment sessions.

Results

Study 1

The mean VAS anxiety ratings at 30 s intervals over the 5 min test period are shown in Figure 1. It can be seen that pentagastrin had a clear cut, dose-related, anxiogenic effect. The mean onset latency was 16 s and the approximate duration was 150 s. Peak anxiety occurred approximately 60 s after the injection. Statistical analysis of the maximum VAS anxiety and AUC scores (Table 1) indicated significant main effects of treatment and significant linear dose trends which accounted for, respectively, 99.8% and 99.7% of the total dose variation. Post-ANOVA testing indicated significant differences for all pairwise comparisons for the two measures.

The results from the PSS were similarly clear cut. Statistical analysis of mean PSS scores (Table 1) indicated a significant main effect of treatment and a significant linear dose trend which accounted for 99.8% of the total dose variation. Post-ANOVA testing indicated significant differences between all pairs of treatments. Mean severity ratings for the

individual items of the PSS following the highest dose of pentagastrin vs placebo are shown in Table 2. It can be seen that mean scores following pentagastrin were higher than those after placebo for all items except 'fear of going crazy'. The pentagastrin vs placebo difference was statistically significant for 16 of the 24 items, i.e.: 'abdominal distress', 'accelerated heart', 'feeling short of breath', 'apprehension', 'nausea', 'unsteady feeling', 'smothering sensation', 'palpitations', 'hot flushes', 'chest discomfort', 'choking feelings', 'numbness or tingling', 'dizziness', 'sweating', 'feeling detached from body' and 'shaking'.

Mean pulse rates at 30 s intervals over the 5 min test period for the 10 subjects in whom pulse rate recording was undertaken are shown in Figure 2. All doses of pentagastrin resulted in increases in pulse rate but the dose-response relationship was less apparent than for subjective anxiety ratings, in that there appeared to be no difference between the two highest doses of pentagastrin. Statistical analysis of the maximum pulse rates (Table 1) confirmed this impression—there was a significant main effect of treatment and a significant linear dose trend which accounted for 87.8% of the total dose variation.

Figure 1 Mean VAS anxiety ratings following i.v. injections of placebo (○), pentagastrin 0.15 µg kg⁻¹ (●), pentagastrin 0.3 µg kg⁻¹ (□) and pentagastrin 0.6 µg kg⁻¹ (■) in Study 1 (*n* = 15 normal volunteers).

All post-ANOVA comparisons were significant except for that between the 0.3 and 0.6 µg kg⁻¹ doses of pentagastrin.

Comment

Study 1

In this study pentagastrin produced a dose-related anxiogenic effect in normal volunteers which, as measured by VAS ratings, occurred approximately 20 s after drug administration, peaked after 60 s and lasted for approximately 150 s. It can be seen from the PSS items listed in Table 2 that the drug induced many of the symptoms associated with Panic Disorder, particularly those of a gastrointestinal and cardiovascular nature. Not surprisingly, given the controlled conditions of the laboratory and the fact that these were healthy volunteers, affective symptoms such as 'fear of dying' and 'fear of going crazy' were not evident. However, several other affective items including 'apprehension' and 'feeling detached from body' were rated significantly higher than placebo. Changes in pulse rates (Figure 2) followed a similar time course to VAS anxiety ratings (Figure 1). The dose-response effect was less apparent but this may simply have been a consequence of the fact that pulse rates were measured in fewer subjects and only at 30 s intervals, so peak effects may have been missed.

Following the demonstration that pentagastrin has clear anxiogenic effects in normal volunteers, a second study was undertaken to examine the pharmacodynamic properties of the selective CCK_B receptor antagonist L-365,260 (chemical name = (3R)-3(*N'*-(3-methylphenyl)ureido)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one) [9] in the model. In addition, pulse rates and systolic and diastolic blood pressures were continuously recorded by means of a Finapres® monitor. Measures of autonomic function and subjective ratings of anxiety were recorded for 5 min before, as well as for 5 min after, the pentagastrin injection. It was anticipated that fear of an unpleasant experience associated with an

Table 1 Mean (s.e. mean) anxiety ratings and pulse rates in Study 1

	Placebo	Pentagastrin 0.15 µg kg ⁻¹	Pentagastrin 0.3 µg kg ⁻¹	Pentagastrin 0.6 µg kg ⁻¹
VAS AUC ¹	1209 (344)	4638 (771)	8648 (1310)	13105 (1942)
Maximum VAS score ¹	10 (3)	46 (7)	84 (11)	115 (8)
PSS score ¹	2.1 (0.9)	7.5 (1.4)	14.3 (2.2)	20.5 (2.7)
Maximum pulse ² (beats min ⁻¹)	79 (4)	94 (5)	107 (9)	107 (6)

¹All pairwise comparisons significant (*P* < 0.05).

²All pairwise comparisons significant (*P* < 0.05) except pentagastrin 0.3 µg kg⁻¹ vs pentagastrin 0.6 µg kg⁻¹.

Table 2 Mean (s.e. mean) PSS item scores in Study 1

	Placebo	Pentagastrin 0.6 $\mu\text{g kg}^{-1}$
Abdominal distress	0.1 (0.1)	1.6 (0.2) ¹
Accelerated heart	0.3 (0.2)	1.6 (0.3) ¹
Feeling short of breath	0.1 (0.1)	1.5 (0.2) ¹
Apprehension	0.2 (0.1)	1.5 (0.2) ¹
Nausea	0.1 (0.1)	1.5 (0.3) ¹
Unsteady feeling	0.1 (0.1)	1.2 (0.3) ¹
Smothering sensation	0.0 (0.0)	1.1 (0.2) ¹
Palpitations	0.3 (0.2)	1.1 (0.3) ¹
Hot flushes	0.2 (0.1)	1.1 (0.3) ¹
Chest discomfort	0.1 (0.1)	1.1 (0.3) ¹
Choking feelings	0.1 (0.1)	0.9 (0.2) ¹
Numbness or tingling in parts of body	0.2 (0.1)	0.9 (0.2) ¹
Dizziness	0.0 (0.0)	0.9 (0.3) ¹
Sweating	0.1 (0.1)	0.7 (0.3) ¹
Feeling detached from body	0.0 (0.0)	0.7 (0.3) ¹
Unreal feeling or disorientation	0.0 (0.0)	0.5 (0.2)
Chest pains	0.0 (0.0)	0.5 (0.2)
Faintness	0.1 (0.1)	0.5 (0.3)
Trembling	0.1 (0.1)	0.4 (0.1)
Shaking	0.0 (0.0)	0.4 (0.1) ¹
Cold chills	0.0 (0.0)	0.3 (0.2)
Fear of doing something uncontrolled	0.1 (0.1)	0.2 (0.1)
Fear of dying	0.0 (0.0)	0.1 (0.1)
Fear of going crazy	0.0 (0.0)	0.0 (0.0)

¹Significantly different from placebo ($P < 0.05$). **Figure 2** Mean pulse rates in Study 1 ($n = 15$ normal volunteers). Legend as for Figure 1.

impending injection might result in an anticipatory anxiety which could be useful for examining any intrinsic anxiolytic effects of L-365,260 (as opposed to antagonism of pentagastrin anxiogenesis).

Methods

Study 2

The study was undertaken at the same site and approved by the same ethics committee as for Study 1. All subjects gave written informed consent.

Subjects

Fifteen subjects (13 males, 2 females), between the ages of 20 and 41 years, took part in the study.

Design

The study employed a double-blind, five period, crossover design. Each subject received the following treatments, which were administered according to a Latin Square design and separated by a washout period of at least 3 days:

Pre-treatment (−90 min)	Challenge (0 min)
Placebo p.o.	Placebo i.v.
Placebo p.o.	Pentagastrin 0.3 $\mu\text{g kg}^{-1}$ i.v.
L-365,260 10 mg p.o.	Pentagastrin 0.3 $\mu\text{g kg}^{-1}$ i.v.
L-365,260 50 mg p.o.	Pentagastrin 0.3 $\mu\text{g kg}^{-1}$ i.v.
L-365,260 50 mg p.o.	Placebo i.v.

The interval of 90 min between pre-treatment and challenge was chosen to coincide with the approximate t_{max} for L-365,260 and was the same as that employed in a previous study on L-365,260 blockade of CCK-4 induced panic attacks in patients [8].

Procedure

Prior to the start of the study all subjects were given a practice session during which they received an injection of pentagastrin 0.3 $\mu\text{g kg}^{-1}$ i.v. On each test day subjects received an oral dose of L-365,260 or placebo and then rested. An intravenous cannula was inserted into one arm 80 min after oral dosing. A warning tone was sounded 9.5 min later and 30 s after this an i.v. bolus of pentagastrin or placebo was administered over 5 s. The subjects rated their level of anxiety, using the same computerised VAS system as in Study 1, for 5 min preceding the start of the pentagastrin/placebo injection and for 5 min afterwards. Immediately following this, subjects were required to complete the PSS. The same outcome measures as for Study 1 were employed.

In addition to the anxiety ratings, pulse rate and systolic and diastolic blood pressures were continuously recorded via a digit by means of a Finapres® monitor (Ohmeda, BOC Health Care) interfaced to a computer, for 5 min before the pentagastrin/placebo injection and for 5 min afterwards. The finger cuff was attached to a finger on the opposite arm to that used for the pentagastrin/placebo infusion and moving the mouse. The primary outcome measures were the maximum readings.

Data analysis

Pre- and post-injection data were analysed separately for each measure (post-injection data only for PSS scores) using repeated measures ANOVA with a factor of treatment. Where there was a significant main effect of treatment, planned contrasts were performed for the following 7 treatment combinations using post-ANOVA comparisons: placebo/placebo 1/5

all other treatments; placebo/pentagastrin vs L-365,260 (10 and 50 mg)/pentagastrin; L-365,260 10 mg/pentagastrin vs L-365,260 50 mg/pentagastrin. As in Study 1 the level of significance was set at $P < 0.05$.

Results

Study 2

Mean VAS anxiety ratings over the 10 min recording period are shown in Figure 3. As expected, pentagastrin had a clear anxiogenic effect. This was com-

Figure 3 Mean VAS anxiety ratings in Study 2 ($n = 15$ normal volunteers). Subjects were pretreated with L-365,260/placebo and received an i.v. injection of pentagastrin/placebo at 0 s. The injection was preceded by a warning tone at -30 s. Treatment groups were placebo/placebo (—), placebo/pentagastrin $0.3 \mu\text{g kg}^{-1}$ (---), L-365,260 10 mg/pentagastrin $0.3 \mu\text{g kg}^{-1}$ (---), L-365,260 50 mg/pentagastrin $0.3 \mu\text{g kg}^{-1}$ (---) and L-365,260 50 mg/placebo (-----). Data are plotted at 30 s intervals between -300 to -30 s/120 to 300 s and at 5 s time points between -30 to 120 s.

pletely blocked by the 50 mg dose of L-365,260 and partially reversed by the 10 mg dose. Analysis of the maximum VAS anxiety and AUC scores (Table 3) indicated that there were no significant pre-injection treatment differences. For the post-injection data there was a significant treatment effect and all the planned contrasts undertaken were significant other than those for placebo/placebo vs L-365,260 50 mg/pentagastrin and placebo/placebo vs L-365,260 50 mg/placebo.

The results for the PSS are shown in Table 3. Statistical analysis of the means indicated a significant treatment effect. All planned contrasts undertaken were significant other than placebo/placebo vs L-365,260 50 mg/placebo.

Mean pulse rates over the 10 min recording period are shown in Figure 4. It can be seen that there was a similar pattern of results to that found for subjective anxiety ratings, in that pentagastrin produced an increase in pulse rate which appeared to be completely blocked by the 50 mg dose of L-365,260 and partially reversed by the 10 mg dose. Analysis of the maximum pulse rates (Table 4) indicated no significant pre-injection treatment differences. Post-injection, there was a significant treatment effect and planned contrasts indicated that only comparisons of placebo/pentagastrin vs the other treatments were significant (i.e. both doses of L-365,260 were equally effective in abolishing the pentagastrin induced increase in pulse rate).

The results for systolic and diastolic blood pressures (Figure 5) were similar to each other. Analysis of the maximum scores (Table 4) indicated no significant pre-injection differences between any of the treatments for any measure. Post-injection, there were significant treatment effects in all cases. Planned contrasts showed that, for both measures, the only significant comparisons were for placebo/pentagastrin vs the other treatments, indicating that both doses of L-365,260 were equally effective in abolishing the increase in blood pressure produced by pentagastrin.

Table 3 Mean (s.e. mean) anxiety ratings in Study 2

	Placebo/ Placebo	Placebo/ Pentagastrin $0.3 \mu\text{g kg}^{-1}$	L-365,260 10 mg/ Pentagastrin $0.3 \mu\text{g kg}^{-1}$	L-365,260 50 mg/ Pentagastrin $0.3 \mu\text{g kg}^{-1}$	L-365,260 50 mg/ Placebo
<i>Pre-injection</i>					
VAS AUC	1287 (665)	2580 (1225)	1703 (994)	1056 (878)	1573 (1090)
Maximum VAS score	10 (4)	15 (5)	9 (4)	7 (3)	8 (4)
<i>Post-injection</i>					
VAS AUC ¹	1703 (859)	11213 (1814)	3953 (1323)	2179 (1044)	1905 (974)
Maximum VAS score ¹	16 (7)	123 (14)	39 (7)	16 (5)	14 (5)
PSS score ²	1.1 (0.5)	19.3 (3.2)	7.0 (1.4)	3.0 (0.8)	0.6 (0.3)

The following planned contrasts were undertaken if there was a significant main effect of treatment: placebo/placebo vs all other treatments; placebo/pentagastrin vs L-365,260 (10 and 50 mg)/pentagastrin; L-365,260 10 mg/pentagastrin vs L-365,260 50 mg/pentagastrin.

¹All planned contrasts significant ($P < 0.05$) except placebo/placebo vs L-365,260 50 mg/pentagastrin and placebo/placebo vs L-365,260 50 mg/placebo.

²All planned contrasts significant ($P < 0.05$) except placebo/placebo vs L-365,260 50 mg/placebo.

Discussion

In Study 2, the utility of the pentagastrin model was further established by the demonstration that the CCK_B receptor antagonist L-365,260 produced a dose related reversal of pentagastrin's anxiogenic effects in normal volunteers (although the dose-response relationship was only apparent for subjective ratings of anxiety and not autonomic measures). These data are in agreement with results from patient studies showing that CCK-4 induced panic attacks can be blocked by L-365,260 [8] and indicate that the pentagastrin model may provide a reliable and easily quantifiable method for the preliminary assessment (e.g. dose finding, duration of action, time to peak effects) of potential anxiolytic agents in normal volunteers. Of course, the conclusions that can be drawn from the present study about the utility of the

model in this regard are limited by the fact that here the actions of an antagonist vs an agonist of the same receptor subtype were being examined. Future studies should determine whether standard anxiolytic agents such as benzodiazepines are also capable of reversing pentagastrin induced anxiety.

Figure 4 Mean pulse rates in Study 2 ($n = 15$ normal volunteers). Legend as for Figure 3.

Figure 5 Mean systolic and diastolic blood pressures in Study 2 ($n = 15$ normal volunteers). Legend as for Figure 3.

Table 4 Mean (s.e. mean) blood pressures and pulse rates in Study 2

	Placebo/ Placebo	Placebo/ Pentagastrin 0.3 µg kg ⁻¹	L-365,260 10 mg/ Pentagastrin 0.3 µg kg ⁻¹	L-365,260 50 mg/ Pentagastrin 0.3 µg kg ⁻¹	L-365,260 50 mg/ Placebo
<i>Pre-injection</i>					
Maximum pulse (beats min ⁻¹)	80 (4)	79 (4)	78 (3)	76 (2)	77 (3)
Maximum systolic (mm Hg)	159 (4)	158 (3)	157 (5)	154 (6)	154 (5)
Maximum diastolic (mm Hg)	86 (3)	88 (3)	85 (3)	86 (4)	82 (3)
<i>Post-injection</i>					
Maximum pulse ¹ (beats min ⁻¹)	84 (4)	108 (4)	85 (4)	80 (3)	79 (4)
Maximum systolic ¹ (mm Hg)	159 (5)	174 (6)	156 (5)	156 (7)	157 (4)
Maximum diastolic ¹ (mm Hg)	83 (3)	94 (4)	82 (3)	82 (4)	82 (2)

The following planned contrasts were undertaken if there was a significant main effect of treatment: placebo/placebo vs all other treatments; placebo/pentagastrin vs L-365,260 (10 and 50 mg)/pentagastrin; L-365,260 10 mg/pentagastrin vs L-365,260 50 mg/pentagastrin. ¹Planned contrasts of placebo/pentagastrin vs other treatments significant ($P < 0.05$).

In this study subjective ratings and autonomic signs were measured for 5 min before as well as for 5 min after the pentagastrin injection. The aim of this experimental design was to determine whether subjects experienced a period of anticipatory anxiety which might allow an examination of any intrinsic anxiolytic properties of L-365,260 (as opposed to pentagastrin antagonism). It can be seen from Figure 3 that subjects did become somewhat more anxious as the injection approached. However, the increase was slight and probably not sufficient for any anxiolytic effects to be detected. Certainly, pre-treatment with L-365,260 did not result in significantly different pre-injection subjective rating scores or autonomic changes compared with placebo. A similar pattern was found for pulse rates (Figure 4). Systolic and diastolic blood pressures showed a slightly different pattern of results (Figure 5). Both measures rose up to 30 s prior to the injection but then, following the sounding of the warning tone, fell quite sharply. This may be attributable to deep inspiration after the warning tone. The effect was apparent across all treatment groups and there was no indication of any differential response in those subjects pre-treated with L-365,260.

The continuous measurement of pulse and blood pressure in Study 2 allowed a detailed comparison of autonomic vs subjective anxiogenic effects of pentagastrin and anxiolytic effects of L-365,260. It can be seen from Figures 3, 4 and 5 that pentagastrin produced increases in subjective anxiety ratings, pulse rates and systolic and diastolic blood pressures which occurred simultaneously and had a similar duration. There was no evidence that L-365,260 had differential effects on autonomic vs affective components of anxiety. Although findings of temporal dissociations would have been of theoretical interest, it is important to note that the failure to distinguish autonomic and subjective events appears to be true of Panic Disorder itself [3, 10]. The present studies do not localise pentagastrin induced anxiety to either peripheral or central mechanisms. However, the latter are suggested by the observation that bolus injections of gastrin-17, a potent CCK_B/gastrin receptor agonist which does not penetrate the blood-brain barrier,

increases gastric acid secretion but does not have anxiogenic effects in man [11].

The encouraging findings with L-365,260 in the present study are in contrast to recent results from a pilot, double-blind, placebo-controlled, 6 week, clinical trial of L-365,260 (30 mg four times daily) in 83 Panic Disorder patients which showed little evidence of efficacy [12]. However, interpretation of the data from this small trial is complicated by a number of factors, including the possibility of reduced compliance due to the fact that patients were required to ingest three capsules of L-365,260 four times each day (because of poor solubility). Even if such frequent dosing were adhered to, plasma levels associated with the blockade of CCK-4 induced panic would only have been maintained for a portion of the treatment period. Laboratory models have an advantage over clinical trials in this respect as compliance can be ensured, assessments can be timed to coincide with peak plasma levels, more detailed/accurate measurements can be undertaken and safety parameters can be carefully monitored so that it may be possible to administer higher doses of the test compound than would be considered prudent in an out-patient setting. Interestingly, a recent study which examined the effects of pre-treatment with L-365,260 50 mg on a sodium lactate challenge in Panic Disorder patients using the computer VAS system described here, did find some evidence of efficacy [13]. These findings are potentially important because the sodium lactate model is the best established procedure of its kind [14] and sodium lactate has no known direct influence on CCK neurotransmission. If these results are replicated in other models it may suggest that higher doses of L-365,260 than those investigated in the clinic to date, or other CCK_B antagonists, could be effective in Panic Disorder.

In conclusion, injections of pentagastrin in normal volunteers result in brief periods of anxiety, the objective and subjective signs of which can be easily quantified. Pre-treatment with the CCK_B antagonist L-365,260 blocks these anxiogenic effects. The pentagastrin model would appear to be a useful tool for the preliminary assessment of novel anxiolytic agents in normal volunteers.

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(Received 10 October 1994,
accepted 1 November 1994)