Research Article

RELATIONSHIP BETWEEN RESPIRATORY, ENDOCRINE, AND COGNITIVE-EMOTIONAL FACTORS IN RESPONSE TO A PHARMACOLOGICAL PANICOGEN

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Background: *The cholecystokinin agonist pentagastrin has been used to study panic attacks in the laboratory and to investigate hypothalamic–pituitary–adrenal axis activity. Its mechanism of panicogenesis remains unclear. Data from other models suggest that respiratory stimulation itself may induce panic, but pentagastrin's effects on respiration are not well established. Data from another model also suggest links between respiratory and HPA axis reactivity and cognitive modulation of both. To further explore these phenomena, we added respiratory measures to a study of cognitive modulation of HPA and anxiety responses to pentagastrin.* **Methods:** *Healthy subjects received pentagastrin and placebo injections, with measurement of cortisol and subjective responses, on two different laboratory visits. They were randomly assigned to receive standard instructions or one of two versions of previously studied cognitive interventions (to either facilitate coping or increase sense of control), given before each visit. Capnograph measures of heart rate (HR), respiratory rate (RR), and end-tidal pCO_2 were obtained on 24 subjects.* **Results:** *Relative to placebo, pentagastrin induced a significant decline in pCO_2 with no change in RR. Cortisol and HR increased, as expected. Cognitive intervention reduced the hyperventilatory response to pentagastrin.* **Conclusions:** *Pentagastrin stimulates respiration, likely via increases in tidal volume. Respiratory stimulation could play a role in its panicogenic potency, though perhaps indirectly. As with HPA axis responses, higher-level brain processes may be capable of modulating pentagastrin-induced hyperventilation. This model may be useful for further study of cortical/cognitive control of interacting emotional, respiratory, and neuroendocrine sensitivities, with potential relevance to panic pathophysiology. Depression and Anxiety 27:1011–1016, 2010.* © *2010 Wiley-Liss, Inc.*

Key words: *HPA axis; respiration; pentagastrin; panic disorder; neuroendocrinology*

INTRODUCTION

Cholecystokinin (CCK) is a widely distributed CNS peptide thought to play a mediating role in anxiety.[1] Human studies have shown that the CCK-B agonists, CCK-4 and pentagastrin, can produce panic attacks in laboratory models,[2–4] but mechanisms of panicogenesis remain unclear. CCK-B agonists may have direct effects on neural regions mediating components of anxiety or panic responses, or simply produce side effects that are interpreted as threatening. Effects on respiration may also play a role. Direct respiratory stimulation can itself induce panic,[5,6] but pentagastrin's

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impact on respiration is not well studied. CCK-B agonists may increase respiration by increasing tidal volume (Vt) and not respiratory rate (RR),[7] though there is some evidence they can increase both Vt and RR. To our knowledge, there has only been one study that examined the effect of CCK-B on end-tidal, partial pressure of carbon dioxide ($P_{ET}CO_2$) and its association with panic-like symptoms in healthy humans. The study found that CCK-B did not affect respiratory parameters,[8] but it used a relatively low dose of the CCK-B agonist in order to demonstrate that increase in general arousal does not drive respiratory parameters, and hypothesized a link between CCK-B panic and respiratory parameters that would likely be seen with higher doses of CCK panicogens. Further understanding the normal respiratory effects of laboratory panicogens is important, because sensitivity to $P_{ET}CO_2$ in brainstem suffocation alarm centers has been proposed as a putative mechanism underlying panic disorder.[9,10]

There is evidence that psychological or cognitive interventions can reduce panic symptom intensity in laboratory models, in part by affecting respiratory measures. Research using the respiratory stimulant doxapram has shown that a cognitive intervention (CI) designed to reduce "catastrophic cognitions" and increase sense of control can significantly attenuate hyperventilatory and panic responses in panic patients.[6] This suggests that respiratory effects of CCK-B agonists may also be modulated by higher cortical processes. The relative contribution of brainstem-level supersensitivities and top-down modulatory dysfunction to respiratory abnormalities in panic has not been extensively examined.

In addition to anxiogenesis, CCK-B agonism also activates the hypothalamic-pituitary-adrenal (HPA) axis, a principal neuroendocrine stress response system,[11–13] but there seems to be little relationship between anxiety and stress system responses.[3,14,15] These data suggest dissociation between autonomic, anxiety, and HPA response to pentagastrin. However, there is evidence that HPA activation and respiratory irregularity are closely linked to each other in panic patients in the doxapram model,[16] suggesting potential value in further examination of cross-system linkages in laboratory models of panic.

To further explore the impact of CCK-B agonism on respiration, we added respiratory monitoring to a larger neuroendocrine study investigating the effects of cognitive/emotional factors as modulators of pentagastrin-induced HPA axis activity in healthy subjects. We examined effects of pentagastrin on respiration and the impact of CI (designed to reduce novelty and increase control and coping) on respiratory responses. We hypothesized that pentagastrin would stimulate respiration, evidenced by reduced $P_{ET}CO_2$, and that CI would attenuate this hyperventilation. Given the limitations of an add-on study, these data must be considered preliminary, but are informative for future studies.

Depression and Anxiety

METHODS

DESIGN

Respiratory data using a hand-held capnograph were obtained on 24 of 40 subjects studied in a pentagastrin challenge paradigm,[17] using a single-blind, placebo-controlled design. The study was reviewed and approved by the University of Michigan Institutional Review Board. Subjects, who were blinded to the condition, always received placebo on the first day and then returned 1–7 days later for the pentagastrin injection. Subjects were randomly assigned to receive either standard instructions or a CI (see below).

SUBJECTS

Subjects were recruited through advertisement and paid $200. Informed consent was obtained after the nature of the procedures was explained. Subjects were 18–44 years old and medically healthy, without history of alcohol or drug dependence, recent drug or alcohol abuse (6 months), or past or present psychiatric disorder (by SCID). They were of normal weight, with low levels of tobacco (one subject 10 cigarettes per day and two subjects 1 cigarette every 1–2 days) and alcohol use (<5 drinks per week), and had normal screening labs. Female subjects were pre-menopausal, not on birth control pills, and were studied in the first 10 days after menstruation onset.

PROCEDURES

Subjects reported at 1 pm for experimental sessions. Use of food and tobacco was prohibited subsequent to their arrival. The investigator administered instructions identically on each visit via a 5 min audio tape for standard instructions or a 9 min tape and a 5 min discussion for the cognitive intervention. An intravenous catheter (saline drip) was inserted into an antecubital vein at approximately 1:30 pm. Subjects rested in bed for 1.5 hr (reading, studying, listening to music) to accommodate to the setting. At 3 pm, a capnograph that samples $P_{ET}CO_2$ and RR via a nasal canula, and HR through pulse oximetry, was attached for continuous monitoring until 5.00 pm. Baseline blood samples were obtained at 3 pm and 3:28 pm. The investigator returned at 3:30 pm (behind a curtain, out of subject's awareness) to inject (over 15 sec) the placebo or pentagastrin (0.06 µg/kg; Wyeth-Ayerst, Philadelphia, PA, or Calbiochem-Novabiochem, Laufelfingen, Switzerland). Blood samples were obtained 3, 5, 10, 20, 30, 45, and 60 min after injection.

INSTRUCTIONS

The Standard Instruction (SI) group received basic instructions describing procedures, apparatus, and common side effects of pentagastrin. The CI group received two additional techniques, labeled "coping" and "control." The coping component included a more detailed description of expectable responses (to reduce novelty) and coaching to attribute these responses to normal reactions to pentagastrin rather than anything dangerous (to facilitate "cognitive coping"). The control component gave subjects permission to use infusion pump controls to stop the drug infusion, if they wished to do so. For the larger neuroendocrine study, the CI group was divided into subgroups (full intervention, coping alone, control alone groups) to dismantle which intervention factor modulates neuroendocrine responses. Details are available elsewhere.[16] Respiratory monitoring was added later in the study only for the last 24 subjects, and for these analyses the CI subgroups were combined.

MEASURES, INSTRUMENTS, ANALYSES

The Beck Depression Inventory (BDI), Spielberger State-Trait Anxiety Index (STAI), and Anxiety Sensitivity Index (ASI) were administered at screening. Visual analog scales (100 mm lines anchored from "not at all" to "most ever") for anxiety, fear, nervousness, and calm were combined to quantify subjective anxious distress during the experiment. Panic symptoms and pentagastrin side effects were rated on a 4-point scale (none, mild, moderate, severe) using a modified acute panic inventory,[3] and summed to quantify total symptom intensity. $P_{ET}CO_2$, HR, and RR were recorded using a TIDAL WAVE Sp Handheld Mainstream Capnograph with Pulse Oximetry and Sidestream Sampling (Model 715/B) (Respironics Novametrix, CT). Cortisol was assayed using the Coat-Account assay from Diagnostic Products Corporation (Los Angeles, CA) with a sensitivity of 0.2 μg/dl.

Respiratory data were collected for 6 min before and 3 min following pentagastrin infusion. The 3 min cutoff was necessary because subjects verbally described symptoms between 3–5 min after infusion, and speaking disrupts capnograph accuracy. Respiratory and cardiac data were averaged at 64 sec intervals, as the device recorded values every 8 sec. Outliers were excluded as follows: $P_{ET}CO_2$ <10 and >50, RR <3 or >30, HR <30 or >160. Repeated measures analyses of variance (RM-ANOVAs) were used to evaluate treatment (placebo versus pentagastrin), time (pre- to post-injection), and interaction effects for heart rate, $P_{ET}CO_2$, and cortisol. Between subjects RM-ANOVA was used to evaluate group (SI versus CI), time, and interaction effects for $P_{ET}CO_2$. Response measures (post-pentagastrin peak minus baseline) were used in regression analyses.

RESULTS

Subjects were 25.1 ± 7.6 (SD) years old, with equal percentages of males and females (50%) in the SI ($n = 6$) and CI ($n = 18$) groups. CI subgroups did not differ from each other on baseline measures or cortisol, $P_{ET}CO_2$, HR, RR, anxious distress, or panic symptom responses to pentagastrin ($P>.3$). There were no differences between SI and CI groups in age, weight, pentagastrin dose, stress rating, ASI (6.16 ± 7.78 versus 11.22 ± 4.67) or BDI (1.16 ± 2.04 versus 0.94 ± 1.35). The two groups did differ in STAI-trait anxiety (34 ± 13.49 versus 25.72 ± 3.38; $t_{22} = 2.44$, $P<.03$).

RESPONSE TO DRUG

Subjects responded differently to pentagastrin than placebo in heart rate (drug-by-time interaction, $F_{3,69} = 35.55$, $P = .0001$), cortisol ($F_{6,132} = 23.91$, $P = .0001$), and $P_{ET}CO_2$ ($F_{3,69} = 8.28$, $P = .0001$), owing to pentagastrin-induced elevations in HR and cortisol and a fall in $P_{ET}CO_2$ (Fig. 1), with no placebo day changes. Mean baseline $P_{ET}CO_2$ was 41.6 mmHg, which dropped to a mean trough of 38.4 within 3 min post-pentagastrin. The average $P_{ET}CO_2$ drop was 3.2 mmHg with a range of 0.1–13.9. Despite evidence of respiratory stimulation (fall in $P_{ET}CO_2$), RR did not change with pentagastrin, but rose slightly with placebo (Fig. 1; drug-by-time interaction effect marginally significant, $F_{3,69} = 2.54$, $P = .06$). Subjects reported greater panic symptom intensity 3 min after pentagastrin ($M = 10.67$ $SD = 7.0$) compared to placebo ($M = 0.83$ $SD = 1.71$) ($t_{23} = 7.35$, $P = .0001$). Three out of 24 subjects had a panic attack (at least 4 symptoms rated mild or higher on the acute panic inventory and 2-point or greater increase in anxiety/fear).

The CI significantly reduced the $P_{ET}CO_2$ response to pentagastrin (Fig. 2; group-by-time interaction $F_{3,66} = 3.30$, $P = .03$), but not HR ($F = 0.208$, $P = .89$) nor RR ($F = 0.89$, $P = .45$). STAI-trait anxiety was elevated in the SI group (see above) and controlling for this variable in a repeated measures ANCOVA undermined the significance of the $P_{ET}CO_2$ group-by-time interaction ($F_{3,63} = 1.26$, $P = .30$). The direct relationship between STAI-trait and $P_{ET}CO_2$ was relatively weak ($r = .384$, $P = .07$, $n = 24$), especially within the CI group ($r = .064$, $P = .8$, $n = 18$).

CORRELATIONS

The $P_{ET}CO_2$ response to pentagastrin correlated with panic symptom intensity ($r = .709$, $P = .0001$, $n = 24$), but not with anxious distress ($r = .329$, $P = .117$, $n = 24$). The RR response did not correlate with panic symptom intensity ($P>.59$) or with anxious distress ($P>.37$). The cortisol response was significantly correlated with the
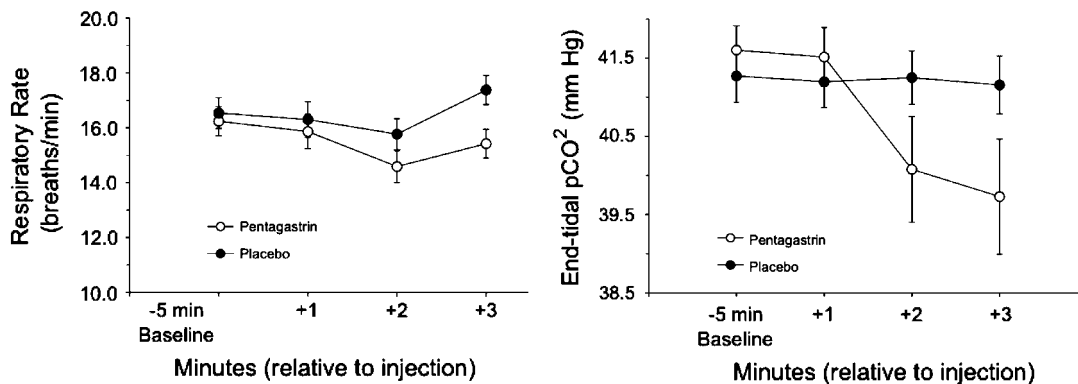

Figure 1. Left panel: Respiratory rate for 24 subjects before and after drug injection on pentagastrin and placebo days (means±SE). Right panel: $P_{ET}CO_2$ levels before and after injection for 24 subjects on pentagastrin and placebo days (means±SE).
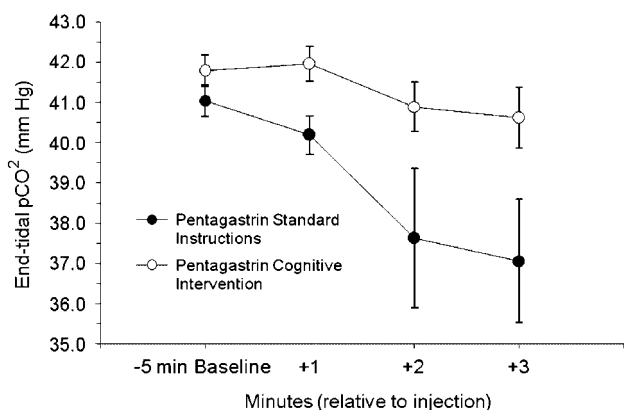
Figure 2. $P_{ET}CO_2$ levels (means $\pm$ SE) on pentagastrin day for the Standard Instruction group ($n = 6$) and the Cognitive Intervention group ($n = 18$). The cognitive intervention was designed to enhance coping and sense of control.

$P_{ET}CO_2$ response ($r = .417$, $P = .048$, $n = 23$), but not with the RR response ($P = .48$).

To insure that significant correlations were not secondary to SI/CI group differences, they were repeated in the CI group alone ($n = 18$). $P_{ET}CO_2$ remained correlated with panic symptom intensity response ($r = .64$, $P = .015$) and cortisol ($r = .564$, $P = .015$).

DISCUSSION

These data indicate that pentagastrin is a respiratory stimulant that can produce transiently increased ventilation in healthy subjects and suggest that it does so by increasing tidal volume. Unfortunately, we did not have the instrumentation to record Vt, so direct evidence for its increase is still needed. Nonetheless, the fall in $P_{ET}CO_2$ without change in RR strongly suggests that Vt increased. The only study to our knowledge that looked at the impact of a related CCK-B agonist (CCK4) on $P_{ET}CO_2$ found no effect.[8] An earlier study that did not measure $P_{ET}CO_2$ did directly demonstrate hyperventilation in response to CCK4, driven by Vt and not RR.[7] However, another study using pentagastrin showed changes in both Vt and RR in healthy subjects.[18] These discrepancies may reflect differences in drug doses or subject characteristics. The Schruers et al. study purposely used a low drug dose to examine effects of arousal and showed no effect on respiratory parameters despite small but statistically significant effects on heart rate, panic, and anxiety symptoms. The Lara et al. study used a higher dose and examined only those subjects who responded to pentagastrin with panic, and was the only one to show an effect on RR. The CCK4 study and our study included many subjects who did not panic. Increased RR may be a function of panic and not a direct drug effect, whereas reduction in $P_{ET}CO_2$, likely owing to Vt increase, may be a direct drug effect that is dose dependent. A recent study of blood phobia suggests

that Vt increase may be more strongly linked to physical symptoms (e.g., dizziness and feeling faint) than RR, and may play a more prominent role in anxiety.[19] If pentagastrin directly stimulates increases in tidal volume, this may well contribute to its panicogenic potency in vulnerable subjects, with additional respiratory drive that leads to increased RR appearing secondarily when panic in fact occurs.

If respiratory stimulation does contribute to pentagastrin-induced panicogenesis, the precise pathway remains unclear, and this study of healthy subjects can provide only limited information. However, the correlation between $P_{ET}CO_2$ and panic symptom intensity was driven in our subjects entirely by physical symptom ratings, in the absence of any link to anxious distress. Though the total amount of hyperventilation produced was relatively mild (mean drop of 3.17 mmHg in $P_{ET}CO_2$), those subjects with the greatest falls were the ones who reported developing physical symptoms. This suggests that if respiratory stimulation plays a role in pentagastrin's panic symptom generation it might do so indirectly through hyperventilation-related physical sensations, rather than via a direct link between respiratory control centers and anxiogenesis. Such physical sensations may have particular salience to panic-prone people, either because they are reminiscent of previously experienced panic attacks or because they may have particular salience to processors in the brain that attach affective tone to bodily sensations (see below). Such indirect pathways are consistent with growing evidence that respiratory abnormalities are not a fundamental feature of patients with panic disorder,[20,21] so respiratory centers may not play as central a role in panic as once thought.[9]

Other pathways are clearly possible and further research is needed. The link between hyperventilation and physical symptoms in this study was correlational and the overall group reductions in $P_{ET}CO_2$ were not large, so it is possible that the physical sensations reminiscent of panic reported by our subjects were not a consequence of hyperventilation itself. Pentagastrin could produce panic through other pathways, such as hypersensitive CCK-B receptors in the amygdala,[22] which could cause both increased respiratory drive and physical sensations, even without a direct link between the two.

As with doxapram, a CI designed to reduce novelty and increase coping and sense of control significantly attenuated the hyperventilation produced by pentagastrin. This suggests that whatever the mechanism of CCK-B-mediated respiratory stimulation, top–down modulation through higher-level processing of the sensory experiences can attenuate it. The strength of this conclusion is weakened by the fact that some of the variance in respiratory response was captured by a group difference in trait anxiety. Further work with larger and better matched groups is needed to clarify whether CI reduced hyperventilation in the CI group

or trait anxiety increased hyperventilation in the SI group. Interestingly, neither state nor trait anxiety directly predicted respiratory response. We hypothesize that both the CI and trait anxiety contributed to the group difference detected but, with a small sample, we did not have sufficient power to see the independent effects of both. Though there are a variety of mechanisms through which trait anxiety could impact respiration, a trait anxiety effect, like the CI effect, is compatible with the hypothesis that higher order, cortical, and/or limbic inputs can modulate outputs of physiological control centers and may be relevant to psychophysiological abnormalities detected in patients with anxiety disorders.

Growing evidence supports the hypothesis of bi-directional interaction between cortical–limbic/cognitive–emotional control circuits in the brain and respiratory phenomena. Shortness of breath or air hunger is a highly distressing experience that activates limbic and paralimbic brain regions, including anterior insula and cingulate, amygdala, thalamus, and basal ganglia.[23,24] As with pain, the affective dimension of this experience is processed separately from the sensory intensity dimension,[25] with affective evaluation processed through limbic pathways (involving insular cortex, amygdala, cingulate cortex, and medial thalamus).[26] These limbic regions are in turn linked to respiratory control centers, providing a loop through which affective experience can be generated by respiratory-related sensations and can in turn shape autonomic and respiratory responses.[27,28] Intriguingly, limbic regions involved in emotional processing, such as insula, amygdala, and hippocampus, may be particularly involved in modulating the phasic aspects of breathing that produce sighs,[29–32] which may have particular relevance to anxiety disorders.[33,34] There is evidence that these same regions provide cognitive–emotional modulation of HPA axis activity,[35] and shared links to the same cognitive–emotional control regions may create the link between HPA axis reactivity and $P_{ET}CO_2$ seen in this study. An even stronger link between the HPA axis and respiration was seen in our doxapram study, where the respiratory-dependent variable was rhythm irregularity created by sighs.[16] A similar link may well have been seen here, but the capnograph unfortunately did not provide us with the Vt date needed to track sighs. Deeper understanding of potential linkages between anxiety, sighs, and HPA axis activity that may be created by shared modulation through top–down cognitive control regions of the brain could be extremely helpful in efforts to dissect the central pathophysiology of a number of psychiatric disorders.[36]

These data have significant limitations, including a small sample size, an unexpected group difference in trait anxiety despite random assignment, and an absence of Vt measures. However, they have implications for future studies. Potential links between HPA axis reactivity and respiratory abnormalities in anxious patients may be particularly useful clues to pursue, because shared input from cortical–limbic processors may provide the common thread that helps locate the real source of the dysregulation that creates abnormalities in both systems. Further study of the interactions between HPA axis and respiratory dysregulation in psychiatric disorders may be quite fruitful. It will be important in future work to utilize technology that allows simultaneous measurement of tidal volume, $P_{ET}CO_2$, RR, and HPA axis hormones.

CONCLUSION

We found that in a healthy population, pentagastrin stimulates respiration, likely via increases in tidal volume, and that respiratory stimulation could play a role in its panicogenic potency through hyperventilation-related physical sensations. Additionally, pentagastrin-induced hyperventilation can perhaps be modulated by a CI, which also attenuates both panic and HPA responses. Although the strength of this conclusion is weakened by a trait anxiety confound between groups, the trait anxiety effect, like the CI effect, is compatible with the hypothesis that higher order, cortical, and/or limbic inputs can modulate outputs of physiological control centers and may be relevant to psychophysiological abnormalities detected in patients with anxiety disorders.

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