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EFFECTS OF YOHIMBINE AND HYDROCORTISONE ON PANIC SYMPTOMS, AUTONOMIC RESPONSES AND ATTENTION TO THREAT IN HEALTHY ADULTS

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Abstract

Rationale—Research in rodents and non-human primates implicates the noradrenergic system and hypothalamic-pituitary-adrenal axis in stress, anxiety, and attention to threat. Few studies examine how these two neurochemical systems interact to influence anxiety and attention in humans.

Objective—To examine the effects of exogenous yohimbine and hydrocortisone, as well as their combination (Y+H) on panic symptoms and attention to social threat cues.

Methods—32 healthy adults underwent a pharmacological challenge in which they were blindly randomized to either: yohimbine, hydrocortisone, Y+H, or placebo. Thirty minutes after drug infusion, attention to threat was measured using the dot probe task, a visual attention task that presents angry, happy and neutral faces and measures the degree of attention allocated towards or away from the emotional faces. Panic and autonomic measures were assessed before and 30 minutes after drug infusion.

Results—There was a significant increase in panic symptoms in the yohimbine and Y+H groups but not in the hydrocortisone or placebo groups. Yohimbine resulted in a greater increase in panic symptoms than Y+H. On the dot probe task, the placebo group exhibited an attention bias to angry faces whereas this bias was absent after yohimbine. When collapsing across groups, increased panic symptoms was associated with less attention to angry faces.

Conclusions—Exogenous hydrocortisone may attenuate noradrenergic-induced panic symptoms. The inverse relationship between panic symptoms and attention to angry faces extends prior research demonstrating attention modulation by stressful conditions.

Keywords

yohimbine; hydrocortisone; panic symptoms; attention; threat cues; adults

INTRODUCTION

The noradrenergic (NA) system and hypothalamus-pituitary-adrenal axis (HPA) interact to mediate an organism's response to danger. Animal data show that these two neurobiological systems activate each other through corticotrophin releasing factor (CRF) mediated pathways connecting hypothalamic CRF neurons with the locus ceruleus (LC) (Chrousos et al. 1998; Dunn et al. 2004). Norepinephrine stimulates CRF release from the hypothalamus and other CRF-containing neurons throughout the brain. Conversely, CRF neurons increase LC firing to stimulate norepinephrine release. Interactions between the NA system and HPA axis are hypothesized to play a key role in facilitating an organism's response to threat by influencing attention allocation (Aston-Jones et al. 1994). In humans, few studies examine how NA-HPA interactions influence anxiety and attention to threat. Understanding these relationships can provide insights regarding the neurochemistry of anxiety disorders.

The NA system is implicated in anxiety, attention, vigilance and arousal (Aston-Jones et al. 1994; Aston-Jones et al. 1998; Southwick et al. 1999; Berridge and Waterhouse 2003). Stress can trigger LC firing and subsequent widespread norepinephrine transmission in the brainstem, amygdala and prefrontal cortex (Liddell et al. 2005). Activity in these regions leads to behavioural responses such as orienting to threat, fear, arousal and inhibition of activity (Gray 1982; Redmond 1987; Coull et al. 2001; Liddell et al. 2005). Yohimbine, an alpha-adrenergic antagonist, is a NA probe that increases norepinephrine, autonomic activity and awareness, thereby producing a panic-like state resembling a classic panic attack (Charney et al. 1984, 1992; Southwick et al. 1999). Adults with panic disorder (PD) and posttraumatic stress disorder (PTSD) exhibit more anxiety and autonomic activity after yohimbine challenge compared to controls (Charney et al. 1984). No studies have examined how yohimbine affects attention allocation to threat; such research can establish links between neurotransmitters, panic symptoms and attention regulation mechanisms.

In humans, the relationship between the HPA axis and fear behavior varies and depends on whether the effects of endogenous or exogenous cortisol are measured as well as the types of psychiatric instruments used. High endogenous basal cortisol is associated with elevated trait anxiety (Brown et al. 1996; Takahashi et al. 2005), behavioral inhibition (Kagan et al. 1987) and threat cue avoidance (Van Honk et al. 1998, 2000). Roelofs et al. (2007) found that subjects with a high cortisol response to stress avoided threat cues before a social stressor but attended to threat cues after the stressor. Conversely, exogenous cortisol acutely reduces subjective fear in phobic individuals (Soravia et al. 2006), the magnitude of emotion-modulated startle responses (Buchanan et al. 2001) and attention bias to threat in anxious individuals (Putnam et al. 2007).

Dysregulation of the HPA axis and NA system has been implicated in anxiety disorders. For example, PD is characterized by elevated basal cortisol (Wedekind et al. 2000), absence of cortisol elevation during acute panic (Sinha et al. 1999) and clonidine-induced hyperreactivity of the NA system (Coplan et al. 1995, 1997). Heightened NA activity (Southwick et al. 1993, 1997), cortisol elevation (Kolassa et al. 2007) and cortisol reduction (Yehuda et al.

1991, 1992; Rasmusson et al. 2000, 2001) have been reported in PTSD. These data highlight the complex involvement of CRF and LC, amongst other brain systems, in clinical anxiety.

There is a strong relationship between anxiety and the degree of attention allocated to threat cues. In a meta-analysis of 172 studies, Bar-Haim et al. (2007) found that anxious but not healthy subjects exhibit a selective attention bias towards threat on attention paradigms. The direction of threat bias can be modulated by state and contextual factors. For example, situational anxiety increases attention bias to threat (e.g., MacLeod and Mathews 1988; Mogg et al. 1990, 1994), but this bias diminishes if attention is directed towards an internal focus, e.g., self-awareness of physiological symptoms (Mansell et al. 2003), or external threats other than the threat stimuli presented in the attention task (Mathews and Sebastian 1993; Williams et al. 1996).

In this study, we activated the NA and HPA systems with yohimbine and hydrocortisone, respectively, and examined their separate and combined effects on two processes: self-reported physiological panic symptoms and attention to threat cues. Subjects were randomized to one of four conditions: yohimbine, hydrocortisone, yohimbine and hydrocortisone (Y+H), or placebo. All subjects were informed that the IV-infusion of medication might induce a panic attack. Some faced the additional internal distress of experiencing pharmacologic-induced panic symptoms. Attention to threat was assessed using the dot probe task, which measures attention towards angry compared to happy and neutral faces. Angry faces were used as threat cues because attentional biases for these stimuli have been associated with a broad range of anxiety disorders more generally (Roy et al. 2008) as well as with non-clinical state and trait anxiety (Bradley et al. 1998, 2000; Bar-Haim et al. 2007). These stimuli have also been used to examine the relationship between attention bias and HPA axis functioning (Van Honk et al. 1998, 2000).

Our hypotheses predicted between-group differences in panic symptoms, autonomic measures and attention bias. With respect to panic symptoms, yohimbine was expected to demonstrate the greatest increase in panic symptoms whereas placebo would exhibit the least increase. Given prior data reporting fear-reducing effects of hydrocortisone, we predicted that panic symptoms in the Y+H group would increase but to a lesser degree than after yohimbine. We did not expect a significant increase in panic symptoms in either the hydrocortisone or placebo groups. Changes in autonomic measures were expected to parallel the changes in panic symptoms across the groups (Markovitz et al. 1991).

In terms of threat bias, yohimbine was expected to influence the direction of the attentional bias to the angry faces relative to placebo. Our hypotheses for this effect were non-directional since physiological stress may either increase or decrease attention to external threat cues. In the Y+H condition, we predicted that the hypothesized reduced panic symptoms would attenuate the attentional response to angry faces relative to the yohimbine group. We did not expect to find a significant difference in attentional bias between hydrocortisone and placebo because panic/anxiety levels were expected to be low in both conditions and Putnam et al. (2007) found no effect of hydrocortisone on attentional bias in non-anxious individuals. Across all conditions, we hypothesized that physiological panic symptoms would be associated with attention bias to the angry faces.

MATERIALS AND METHODS

Subjects

Thirty-two healthy adults (50% female), ages 22 to 35 years (mean = 26.63 years, SD = 4.30) were enrolled in the study and participated in two separate study sessions. These subjects were recruited through community newspapers, internal websites and other NIH studies. Subjects

were part of a larger pool of subjects who were initially screened by telephone to exclude any possible psychopathology or medical illness. Eligible subjects were scheduled for the first visit at which time the following assessments were performed: Structured Clinical Interview for DSM III-R to confirm the absence of any past or present Axis I psychopathology (Spitzer et al. 1992), a physical exam, electrocardiogram and urine toxicology screen. Each subject's IQ was above 85 as measured by the Kaufman Brief Intelligence Test (Kaufman and Kaufman 1990). Subjects who met eligibility criteria based on the first visit were scheduled for the second visit during which the pharmacological agent was administered.

Exclusion criteria included a prior history of panic attack, a first degree relative with history of panic attacks, body mass index of 32 or greater, use of steroid-based medication within the past three years, current tobacco use and abnormal sleep patterns which were defined as less than 6 hours of sleep per night, waking up before 5:00A.M. and/or falling asleep after 2:00 AM. All females were between days three and ten of the beginning of their menstrual cycle, not taking hormonal birth control, not nursing and not pregnant based on a urine pregnancy test administered the day of the pharmacological challenge. Subjects were also asked to refrain from eating for three hours before arrival (5 hours before the medications were administered). All subjects provided written informed consent following a description of the procedures, risks and the opportunity to ask questions. The National Institute of Mental Health review board approved all study procedures.

Procedures

For the second visit, subjects arrived at 11:30 AM and were asked to relax for one hour. At approximately 12:30 PM, subjects were escorted to a private room, positioned upright on a bed, and an I.V. was placed in each forearm after which the following baseline assessments were performed: 1) physiological panic symptoms; 2) anxiety and distress; 3) blood pressure and pulse; 4) training on the dot probe task to ensure that subjects could perform the task with the IV in place; 5) seven blood draws from the left forearm for hormone studies, which are currently banked for future analyses. The drug infusion began after these assessments were completed.

Pharmacy services at NIH randomly assigned subjects to medication conditions in two blocks of 16. The subjects were initially divided into groups of 16 and then randomization was restricted within each group so that an equal number of males and females were assigned to each drug condition. Since the sample was small, this strategy ensured that the groups were balanced according to gender. The investigators, clinicians and subjects were blind to drug condition. Only the pharmacists, who had no contact with the subjects, were aware of the assignments.

At approximately 1:15 PM, the challenge agent was infused into the right arm. Yohimbine administration was based on previously established protocols and consisted of an initial dose of 0.125 mg/kg body weight given through an IV bolus for 3 minutes (Goldstein et al. 1991). This was followed by a continuous infusion at 0.001 mg/kg/min for 12 minutes. Based on this protocol, it was anticipated that peak norepinephrine levels would be achieved 15 minutes following the initiation of the infusion and that pharmacodynamic effects could take up to two hours (Charney et al. 1982). Hydrocortisone, 0.5 mg/kg body weight, was infused through an IV bolus over a 2-minute period. In the combined condition, the hydrocortisone infusion commenced 5 minutes after the 3-minute yohimbine infusion began and co-occurred with the 12-minute yohimbine infusion. The amount and rate of hydrocortisone infusion follows the work of a neuroimaging study that examined the effects of this steroid and found reduced glucose uptake in the hippocampus (de Leon et al. 1997). In that study, hydrocortisone 35mg was infused over a 2-minute period to healthy elderly adults. Following the infusion, levels of plasma cortisol peaked after 10 minutes. This rapid rate is in accord with a pharmacokinetic

study of hydrocortisone, which documented peak cortisol levels 10 minutes after hydrocortisone infusion (Derendorf et al. 1991). Saline (0.9%) was administered as a placebo for the same duration as the active drug counterpart.

The dot probe task was administered 30 minutes after drug infusion. Immediately after the task was administered (approximately 35 minutes after the start of the infusion), assessments of physiological panic symptoms, anxiety, distress, blood pressure and pulse were obtained since one of the goals of the study was to examine relationships between subject state and threat bias. The baseline and 30 minute time point data on these variables are presented in Table 1. These same variables were measured again at 60 minutes.

Primary outcome variables

Physiological panic symptoms—Panic symptoms were measured using the Panic Attack Symptom Scale, a self-report scale that asks subjects to rate the intensity of 27 anxiety symptoms using a 4-point scale (1=none, 2=mild, 3=moderate, 4=severe) (Charney et al. 1987). From this original scale, we derived a physiological symptom scale (PSS), which consisted of six panic-relevant internal physiological symptoms (i.e., sweating, heart beat, dizziness, light headedness, tremors/shakiness, and shortness of breath). A composite score of these six symptoms was calculated; the lowest and highest possible score for each subject was 6 and 24, respectively.

Autonomic measures—Blood pressure and pulse were obtained at baseline, 30 minutes and 60 minutes. Only baseline and 30 minute blood pressure as well as 30 minute pulse were analyzed since data from the other time points were not consistently recorded.

Attention to threat cues—The dot probe task is a visual attention task that has demonstrated biases in attention allocation to threat cues in adult and pediatric anxiety (Mogg and Bradley 2005; Pine et al. 2005; Monk et al. 2006). The stimuli include black and white photographs of happy (positive), angry (threat), and neutral facial expressions portrayed by 64 different actors (half of each gender). An additional 16 actors that portrayed neutral facial expressions were used in filler trials. Each trial begins with a fixation cross appearing in the middle of the screen for 500ms (Figure 1) after which a pair of faces of the same actor simultaneously appears on the left and right sides of the screen for 500 ms; one face displays a neutral expression and the other expresses either an angry or happy expression. Prior data indicates that the 500 ms stimulus presentation is a robust measure of attentional bias towards threat cues across a wide range of studies (Bradley et al. 2000; Mogg et al. 2004; Barhaim et al. 2007). Immediately after the face pair is presented, a single-asterisk “probe” is displayed for 1100 ms on the left or right side of the screen in the location of one of the faces. Subjects are instructed to indicate, as quickly and accurately as possible, whether the probe appeared on the right or the left side of the screen using the keyboard. An incongruent trial presents the emotional face and probe on opposite sides of the screen whereas a congruent trial presents the emotional face and probe on the same side of the screen. Reaction time data for each trial was collected. The inter-trial interval varied randomly between 750 and 1250 ms.

Each subject viewed 80 trials of 80 actors that were presented in a random order for each subject. Trial types included 32 angry-neutral trials and 32 happy-neutral trials; half of these trials displayed the emotional face on the right, and the other half displayed the emotional face on the left. The main trials of interest in this study were the angry-congruent and angry-incongruent trials. Additionally, 16 neutral-neutral trials were presented and served as a general measure of response speed. The task was programmed using E-Prime 1.0 software (Psychological Software Tools, Pittsburgh, PA) and presented on a Dell Inspiron 8100 laptop computer (Round Rock, TX).

Secondary outcome variables

Anxiety and Distress—Anxiety and distress, associated features of panic, were assessed in order to better characterize the panic symptom response. These variables were assessed using self-reported visual analogue scales (VAS) (Charney et al. 1982). The VAS consisted of a 100 mm horizontal line extending left to right with endpoints of 0 (not at all) and 100 (most ever). Subjects were asked to separately rate three anxious feelings (anxious, fearful, and nervous) by making a perpendicular mark on the scale, which provided a millimeter score of their feeling state that moment. The subjective units of distress scale (SUDS) also consisted of a VAS, i.e., horizontal line ranging from 0 (none) to 100% (extremely distressed) (Wolpe 1958). Subjects were asked to rate their degree of distress at the time by placing a perpendicular mark on the scale.

Data analysis

A 2 (time: baseline, 30 minutes) $\times$ 4 (drug condition: yohimbine, hydrocortisone, Y+H, placebo) analysis of variance (ANOVA) was performed to examine group differences in the change in scores from baseline to 30 minutes for each of the following variables: panic symptoms, anxiety, distress, systolic (SBP) and diastolic (DBP) blood pressure. Support for the main hypotheses would be reflected in a significant time $\times$ group interaction resulting from the groups being similar at baseline but differing in response to the infusion, as predicted. For each measure, a significant interaction was explored with two separate one way ANOVAs examining the effects of group at each of the time points, i.e., baseline and 30 minutes. If the time $\times$ group interaction (in the 2 $\times$ 4 ANOVA) and the effect of group at 30 minutes (in the one way ANOVA) were both significant, we conducted 5 planned comparisons to address the primary hypotheses. These comparisons included 4 paired t-tests that examined the change in scores for each drug condition and one independent t-test comparing change scores for yohimbine and Y+H. Group differences in the 30 minute pulse data as well as the 60 minute time point data were examined using one way ANOVA. Cohen's d and partial eta squared values were calculated to determine the effect size of the comparisons. For all ANOVAs, an alpha level of .05 was used. For the planned t-tests, a Bonferroni adjusted alpha of .01 was used to account for the number of tests.

Previously established methods were used to examine the dot probe task reaction time data (Mogg and Bradley 1999; Monk et al. 2006). First, trials in which reaction time data were < 200 ms or > 1000 ms as well as incorrect trials were removed. One-way ANOVA was performed to examine group differences in the mean number of missing data points due to errors and outliers, as well as response speed for neutral-neutral trials. Second, a threat bias score was calculated for each subject by subtracting the subjects' mean reaction time for congruent angry-neutral trials from the mean reaction time for incongruent angry-neutral trials. Positive values of threat bias scores indicate a bias towards angry faces whereas negative values of threat bias scores indicate a bias away from angry faces. One-way ANOVA with follow-up independent t-tests were performed to examine differences in mean threat bias scores across the four conditions. One sample t-tests were used to compare the absolute difference in threat bias score from zero for each condition. Third, in order to determine the specificity of the findings, attention bias for happy faces was examined using similar methods. Pearson's two-tailed correlation was used to examine the relationship between threat bias and the 30 minute mean PSS scores.

Data for several subjects were compromised. During the dot probe task, the computer did not record responses for one male in the hydrocortisone condition. The PSS score for one male in the placebo condition was not obtained. Finally, the nursing sheets containing the blood pressure and pulse measurements from 4 subjects (1 female in the hydrocortisone group, 1 female in the Y+H group, and 1 male and 1 female on placebo) were misplaced.

RESULTS

Physiological panic symptoms

A 2×4 ANOVA of the PSS scores indicated main effects of time and group that were modified by a significant group $\times$ time interaction [$F(3, 27) = 12.34, p < .001$, partial eta squared = .58]. To clarify this interaction, one way ANOVAs of the PSS scores showed that the groups did not significantly differ at baseline [$F(3, 27) = .55, p = .65$] but did significantly differ at 30 minutes [$F(3, 27) = 13.07, p < .001$, partial eta squared = .59]. Within group planned comparisons showed a significant increase in panic symptoms (from baseline to 30 minutes) in the yohimbine ($p = .001, d = 2.84$) and Y+H ($p = .012, d = 1.42$) but not in the hydrocortisone or placebo groups (see Figure 2 for mean change PSS scores). Furthermore, consistent with our hypothesis, the change in PSS score for yohimbine was significantly greater than Y+H ($p < .01, d = 1.56$).

With respect to the secondary variables, analysis of VAS anxiety ratings indicated no main effects but a time $\times$ group interaction [$F(3, 27) = 3.96, p < .05$, partial eta squared = .31]. Follow-up one way ANOVAs revealed no significant baseline [$F(3, 27) = 1.53, p = .23$] or 30 minute [$F(3, 27) = 1.83, p = .17$] group differences. Analysis of the nervous and distress ratings each showed no main effects but both showed the same near significant time $\times$ group interaction [$F(3, 27) = 2.48, p = .082$, partial eta squared = .22]; none of the follow-up ANOVAs were significant for either variable.

Group differences in the 60 minute PSS [$F(3, 27) = .55, p = .65$], fear [$F(3, 27) = 1.63, p = .21$], nervous [$F(3, 27) = 1.46, p = .34$], and distress [$F(3, 27) = 1.77, p = .18$] scores were not significant. There was a near significant difference in anxiety at 60 minutes [$F(3, 27) = 2.61, p = .072$] with the placebo group showing significantly higher anxiety than hydrocortisone ($p = .007, d = 1.62$) and a trend to show higher anxiety than the yohimbine group ($p = .056, d = 1.06$).

Autonomic measures

A 2×4 ANOVA of SBP indicated a main effect of group [$F(3, 24) = 3.21, p < .05$, partial eta squared = .29] that was modified by a near significant time $\times$ group interaction [$F(3, 24) = 2.90, p = .056$, partial eta squared = .27] (see Figure 3 for mean change in SBP). Follow-up ANOVAs showed no significant group differences in baseline SBP [$F(3, 24) = 1.48, p = .24$] but significant group differences at 30 minutes [$F(3, 24) = 4.86, p < .01$, partial eta squared = .38]. Within group comparisons showed that yohimbine was the only group that had a significant increase in SBP ($p < .01, d = 1.40$). The mean change in SBP did not differ between yohimbine and Y+H ($p = .37$).

Unlike the data for SPB, there was no time $\times$ group interaction for DBP [$F(3, 24) = 1.53, p = .23$]. A main effect of time [$F(3, 24) = 7.18, p < .05$, partial eta squared = .23] emerged with higher DBP at 30 minutes compared to baseline ($p < .01, d = .45$). A main effect of group [$F(3, 24) = 3.57, p < .05$, partial eta squared = .31] also emerged with higher DBP for Y+H ($p < .05, d = 1.28$).

There was no effect of medication on the 30 minute pulse data [$F(3, 23) = 0.80, p = .51$].

Attention to threat cues

The groups did not differ significantly in the amount of RT data that was missing due to errors and outliers [$M = 6\%$, $SD = 2.03$; $F(3, 27) = 1.47, p = .24$] or in overall mean RT for neutral-neutral, incongruent angry-neutral and congruent angry-neutral trials [$F(3, 27) < 1$].

One-way ANOVA showed a significant group difference in mean threat bias scores [$F(3,27) = 4.60, p = .01$, partial eta squared = .34] (see Table 2 for trial data and Figure 4 for threat bias scores) with planned comparisons indicating a significantly higher mean threat bias score for placebo compared to yohimbine ($p = .001, d = 2.18$) as well as Y+H ($p < .01, d = 1.70$). Furthermore, one-sample t-tests indicated that the mean threat bias score for placebo significantly differed from zero ($p < .001$), whereas bias scores for the other conditions did not differ from zero. Group differences between hydrocortisone and placebo, as well as between yohimbine and Y+H, were not observed. One-way ANOVA for the happy faces did not reveal any group differences [$F(3, 27) = .55, p = .65$].

Relationship between PSS and threat bias

When collapsing across conditions, a significant inverse correlation was present between mean threat bias scores and mean PSS scores [$r(30) = -0.50, p < 0.01$] (Figure 5). Therefore, as the degree of panic symptoms increased, threat bias towards the angry face decreased among the whole group.

DISCUSSION

This study used two pharmacological probes, yohimbine and hydrocortisone, to examine the functional interactions of the HPA axis and NA system. As predicted, we found significant between group differences in both panic symptoms and threat bias. Yohimbine resulted in the greatest increase in panic symptoms and the smallest threat bias whereas placebo yielded the fewest panic symptoms and greatest threat bias. The Y+H condition resulted in an increase in panic symptoms but to a lesser degree than yohimbine. The panic-reducing effect in the Y+H condition may be due to hydrocortisone's negative feedback to the hypothalamus resulting in decreased CRF activity and subsequent anxiety (Mathew et al. 2008). Hydrocortisone also acutely elevates mood which can dampen panic perception. This anti-depressant like effect can result from increased beta endorphins (Goodwin et al. 1992), modulation of other neurotransmitters such as serotonin (Young et al. 1994a, 1994b; Laaris et al. 1999) and dopamine (DeBattista et al. 2000), or impaired memory retrieval which blunts memory for panic symptoms (Monk and Nelson 2002; Soravia et al. 2006).

Our data show an inverse correlation between threat bias and PSS, which concurs with prior data reporting suppressed attention bias on laboratory tasks (e.g., emotional stroop and dot probe) when psychological or cognitive stressors are simultaneously present (Mathews and Sebastian 1993; Mogg et al. 1993; Amir et al. 1996; Constans et al. 2004). For example, threat bias was absent or reduced in snake-fearful subjects who were tested in the presence of a boa constrictor and anticipated touching the snake after the task (Mathews and Sebastian 1993), and in socially anxious subjects who were later asked to give a speech (Amir et al. 1996, Mansell et al. 1999). Using a modified dot probe task, high socially anxious subjects exhibited an attention bias to angry faces when neutral but not threat prime words preceded each trial (Helfinstein et al. 2008). Our findings demonstrate that physiological stress similarly diminishes threat bias.

Several cognitive models may explain the attenuated attention bias during stress. One model posits that since attentional resources are finite, subjects must prioritize resources and process the most anxiety-provoking stimulus when simultaneously experiencing multiple stressors (Moran and Desimone 1985; MacLeod and Rutherford 1992). In our study, panic symptoms may have been perceived as more threatening than the angry faces, which led attention to shift from external threat to internal panic symptoms. Another possibility is that subjects expended more cognitive effort in completing the task in order to minimize attention to the angry faces (Williams et al. 1996); this hypothesis is unsupported by our data since the overall response speed during angry-neutral trials was not faster after yohimbine compared to the other groups.

Finally, subjects may have engaged defensive mechanisms such as escape and avoidance (McNaughton and Corr 2004). This hypothesis could be tested using eye-tracking measures to delineate whether attentional shifts during stress are due to orienting or disengagement mechanisms (Fox et al. 2001).

There are two noteworthy observations about our data. First, the placebo group exhibited an attentional bias to angry relative to neutral faces (i.e., threat bias score was significantly greater than zero) which contrasts with data in healthy adults indicating no bias for angry faces (i.e., bias scores did not differ from zero; Bradley et al. 1999; Chen et al. 2002; Mogg et al. 2004). Unlike in prior studies, the placebo group was exposed to multiple external stresses (e.g., medical monitoring, threat of impending panic attack), which may have resulted in this finding. Second, although yohimbine increased panic symptoms, anxiety and distress did not increase. This finding may relate to the VAS, which as a single item measure may be less reliable than established anxiety scales (e.g., State Trait Anxiety Inventory, Spielberger et al., 1983) in measuring state anxiety (Nunnally and Bernstein 1994; Streiner and Norman, 1995). Alternatively, provoking physiological symptoms may not have produced substantial anxiety given that subjects were healthy and pre-warned about the potential effects of the challenge agents. These data stress the importance of using anxiety instruments with known psychometric properties to measure responses to challenge agents and external stressors, as well as facilitate cross-study comparisons.

Despite the panic-reducing effects of hydrocortisone, neither blood pressure nor pulse decreased in the Y+H group, relative to the yohimbine group. Since the PSS is a self-report measure of physiological symptoms, it is possible that hydrocortisone diminishes the subjective experience of panic without affecting autonomic arousal. This dissociation hypothesis requires further testing using a more comprehensive physiological battery.

This healthy subject model of NA-HPA interaction has potential utility for generating hypothetical models of anxiety disorders based on derangements in the HPA axis, NA system and/or their interactions. For example, if anxious subjects had participated in our study, we would have expected this group to manifest elevated not reduced panic symptoms in response to Y+H due to sustained unregulated CRF-NE activity. Considerable data supports NA-HPA dysregulation in anxiety (Charney et al. 1986, 1992; Coplan et al. 1995). Following clonidine challenge, Coplan et al. (1995) reported positive correlations between MHPG and cortisol in the control but not PD group; this “uncoupling” of the HPA axis and NA system in PD may be mediated by down regulation or desensitization of postsynaptic hypothalamic CRF receptors. Another model posits that CRF hyposecretion or resistance may lead to excessive noradrenergic output and sustained anxiety (Dunn et al. 2004). Finally, feed-forward models of CRF-NE interactions as well as persistent HPA activity are also implicated in the pathophysiology of severe anxiety (Koob 1999; Makino et al. 2002).

This study has several limitations. First, the PSS, anxiety and distress scales each measured a restricted set of symptoms. Conducting a more comprehensive panic assessment that includes measures of cognitive and affective symptoms would better characterize the effects of the challenge agents and also enable analyses based on full blown panic attack status. Second, other emotional factors (e.g., trait anxiety, anxiety sensitivity) that could have influenced responding were not precisely measured (Byrne et al. 1995; Mogg and Bradley 1999; Nay et al., 2004; Vermeulen et al. 2007). Third, the sample was small and selected subjects who volunteered to participate in a highly stressful experiment. Subjects were therefore prepared to experience panic, which could have either diminished or exaggerated responses on the PSS and the dot probe task. Future studies incorporating real world contexts, paradigms and stimuli would enhance the generalizability of these findings. Finally, multiple action sites of each

challenge agent limits conclusions about the specificity of the brain systems involved in generating responses (Powell et al. 2005).

In summary, our data suggest that hydrocortisone attenuates yohimbine induced panic symptoms in healthy subjects. Additionally, there was an inverse relationship between panic symptoms and threat cues. These data highlight the need to consider interactions between the HPA axis, NA system and attention regulation mechanisms in the pathophysiology of anxiety disorders.

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Figure 1.
Illustration of congruent and incongruent trials in the dot probe task.

Figure 2.

Mean change in panic symptom scale scores across medication groups*

*Mean change in panic symptom scores and standard error bars are presented for each condition. Panic symptoms were measured immediately after the dot probe task was administered. The mean change in panic symptoms (from baseline to 30 minutes) was significant for yohimbine ($p = .001$, $d = 2.84$) and Y+H ($p = .012$, $d = 1.42$) but not hydrocortisone or placebo. The mean change in panic symptoms for yohimbine was significantly greater than Y+H ($p < .01$, $d = 1.56$).

Figure 3.

Mean change in systolic blood pressure across medication groups*

*Mean change in blood pressure and standard error bars are presented for each condition. Blood pressure was taken after the dot probe task. Within group comparisons showed that yohimbine was the only group that had a significant increase in SBP ($p < .01$, $d = 1.40$). The mean change in SBP did not differ between yohimbine and Y+H ($p = .37$).

Figure 4.

Mean threat bias scores on the dot probe task administered 30 minutes after drug infusion*

* Mean threat bias scores and standard error bars are presented for each condition. Mean threat bias scores were calculated by subtracting the mean reaction time for angry-congruent trials from the mean reaction time for angry-incongruent trials. Positive values reflect an attention bias towards threat cues. Significant group differences are indicated (* $p < .05$, ** $p < .01$).

Figure 5.

Scatterplot illustrating the relationship between mean threat bias scores and mean panic symptoms scores in the whole group (n = 30). A significant inverse correlation between these two variables was present ($p < .01$).

Table 1
Baseline and 35 minute assessments of panic, anxiety and distress across the groups[†]

	Yohimbine	Hydrocortisone	Yohimbine/Hydrocortisone	Placebo
PSS score *				
Baseline	6.38 (.74)	6.13 (.35)	6.38 (.74)	6.57 (.79)
30 minutes	13.5 (3.46)	6.75 (1.16)	8.75 (2.25)	7.00 (2.24)
Anxiety rating				
Baseline	7.38 (8.85)	14.75 (24.93)	28.50 (27.50)	24.57 (20.44)
30 minutes	37.50 (32.12)	12.88 (13.27)	25.38 (20.55)	18.00 (17.87)
Fear rating				
Baseline	3.12 (5.00)	3.38 (5.45)	10.75 (13.35)	14.29 (21.25)
30 minutes	16.00 (30.41)	7.50 (10.00)	17.62 (22.94)	12.29 (9.83)
Nervous rating				
Baseline	3.12 (4.32)	11.62 (17.43)	18.25 (29.45)	24.71 (22.99)
30 minutes	19.75 (29.28)	11.12 (12.67)	25.00 (29.03)	13.14 (12.89)
Distress rating				
Baseline	3.63 (4.90)	5.88 (7.00)	8.88 (9.80)	13.29 (12.98)
30 minutes	21.38 (23.98)	7.88 (12.27)	14.00 (14.02)	13.57 (13.24)

[†] Assessments were obtained immediately after the dot probe task.

* There was a significant increase in panic symptoms in the yohimbine ($p = .001$, $d = 2.84$) and Y+H ($p = .012$, $d = 1.42$) groups. Yohimbine resulted in a greater increase in panic symptoms than Y+H ($p < .01$, $d = 1.56$).

Table 2

Reaction time data (Mean, SD) from the dot probe task across the four medication conditions

	N	Angry Face and Probe on Different Side (Incongruent)	Angry Face and Probe on Same Side (Congruent)
Yohimbine	8	450.55 (119.80)	446.84 (115.06)
Hydrocortisone	7	546.80 (123.28)	524.58 (126.45)
Yohimbine/Hydrocortisone	8	460.37 (178.67)	451.68 (180.74)
Placebo	8	510.25 (59.64)	464.16 (48.72)

* Mean threat bias score was calculated by subtracting the mean reaction time for congruent trials from the mean reaction time for incongruent trials. Placebo had a significantly higher mean threat bias compared to yohimbine ($p = .001$, $d = 2.18$) as well as Y+H ($p < .01$, $d = 1.70$).