Anxiogenic Effects of *m*-CPP in Patients with Panic Disorder: Comparison to Caffeine's Anxiogenic Effects

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The behavioral and neuroendocrine effects of meta-chlorophenylpiperazine (m-CPP), a serotonergic agonist, were compared with the effects of caffeine, an adenosine antagonist, in panic disorder patients. Patients with panic disorder were given single oral doses of 0.5 mg/kg m-CPP, 480 mg caffeine, and placebo on separate days under double-blind conditions. Both m-CPP and caffeine had significantly greater anxiogenic and panic-inducing effects than placebo, although caffeine produced nonsignificantly greater increases on all anxiety rating scales than m-CPP. Both m-CPP and caffeine produced significant equivalent increases in plasma cortisol concentrations, but only m-CPP produced plasma prolactin increases. These findings provide further evidence implicating both the serotonergic and adenosinergic receptor systems in the neurobiology of panic disorder.

Introduction

The involvement of serotonergic pathways in anxiety behaviors has been suggested by several authors (Geller and Blum 1970; Wise et al 1972; Stein et al 1973; Schoenfeld 1976; Stein et al 1977; Simon and Soubrie 1979; Tye et al 1979; Thiebot et al 1982; Glaser and Traber 1983; Engel et al 1984; Traber et al 1984; Brady and Barrett 1985a, 1985b). Chemical depletion of serotonin, surgical lesions of serotonin pathways, and serotonin receptor blockade have been shown to have anticonflict activity similar to that of the benzodiazepines (Stein et al 1973; Schoenfeld 1976; Brady and Barrett 1985a, 1985b). In contrast, increased serotonergic activity via electrophysiological or pharmacological activation has anxiogenic effects, as reflected by increases in the inhibitory effects of punishment in animals (Geller and Blum 1970; Schoenfeld 1976; Tye et al 1979; Brady and Barrett 1985a, 1985b). Some of the recently developed nonbenzodiazepine anxiolytic drugs are selective agonists at the $5HT_{1A}$ binding site and this effect has been related to their anxiolytic properties (Glaser and Traber 1983; Engel et al 1984; Traber et al 1984). Clinical reports indicating antipanic and anti-anxiety efficacy of serotonin reuptake blockers like clomipramine, fluvoxamine, and fluoxetine, and the serotonin precursor, L-5-hydroxytryptophan, also suggest

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a possible role for sertonin dysfunction in some forms of human anxiety (Gloger et al 1981; Kahn and Westenberg 1985).

Recently, several reports have appeared indicating that meta-chloro-phenylpiperzine (*m*-CPP), a novel serotonergic agonist, has anxiogenic effects. The preclinical pharmacology and biochemistry of this drug has been extensively studied (Samanin et al 1979; Fuller et al 1980; Caccia et al 1981, 1982; Hamik and Peroutka 1989).

Mueller et al (1985) first reported a modest, but statistically significant, increase in self-rated anxiety in normal volunteers given *m*-CPP (0.5 mg/kg) orally. Charney et al (1987) reported that *m*-CPP (0.1 mg/kg) given intravenously induced more marked anxiety and elicited panic attacks in both healthy volunteers and patients with panic disorder. More recently, Kahn et al (1988a, 1988b), using a smaller dose of *m*-CPP (0.25 mg/kg) given orally found that only panic disorder patients, and not depressed patients or normal controls, became significantly more anxious with *m*-CPP than placebo, with 60% of the panic patients developing panic attacks. Obsessive-compulsive disorder patients also become significantly more anxious than normal controls when given 0.5 mg/kg *m*-CPP orally (Zohar et al 1987).

In the present study, the effects of *m*-CPP were directly contrasted with those of caffeine, which was found to have potent anxiogenic effects in panic disorder patients (Uhde 1990), and placebo in a carefully selected group of panic disorder patients. We compared the anxiogenic properties of the two drugs both quantitatively and qualitatively in the same patients and assessed the neuroendocrine response to these drugs and its relationship to the behavioral response

Materials and Methods

Panic Disorder Patients

Ten panic disorder patients, 7 women and 3 men, who were consecutively referred by local psychiatrists to the Section on Anxiety and Affective Disorders of the National Institute of Mental Health (NIMH), were screened by 2 clinicians. After it was determined that the patients met DSM-III criteria for panic disorder with or without agoraphobia (DSM-III 1980), they were invited to participate in the study.

Of the 10 referrals, 3 subjects were unable to receive caffeine and thus 7 patients were given the three challenges (*m*-CPP, caffeine, and placebo). The mean age of the 7 patients who received both *m*-CPP and caffeine was 42.0 ± 9.6 years (5 women, 2 men, range 30–57 years). According to previously established life-charting criteria (Uhde et al 1985) the mean duration of illness from the onset of their first panic attack was determined to be 12 ± 7.1 years (range 4–22 years). All but 1 had agoraphobia, or at least multiple phobias with significant avoidance behaviors. None of the patients was depressed during the study period. All patients had normal physical and neurological examinations, and laboratory indices of renal, liver, hematological, and thyroid function were within normal limits. All patients gave written informed consent for their participation in the study and were medication free for at least 2 weeks prior to the study.

Procedures

Oral single-dose drug or placebo was used in all studies under double-blind conditions on separate days with at least 72 hr between procedures. Subjects arrived at the clinic at approximately 8 AM after an overnight diet limited to clear fluids. Sleep and eating were

not allowed throughout the 5-hr study period, during which the subjects remained at bedrest.

An indwelling intravenous (IV) catheter was placed in a forearm vein a minimum of 1 hr before drug administration. After at least 30 min of complete bedrest, baseline behavioral and endocrine measures were obtained. Between 9 and 10:30 AM, each subject received identical unmarked capsules of placebo, *m*-CPP, or caffeine. The *m*-CPP dose was 0.5 mg/kg (mean ± SD dose = 36.5 ± 4.1 mg). The theoretical rationale for using this dose and route of *m*-CPP administration have been discussed in detail elsewhere (Mueller et al 1985). Caffeine was given in a fixed dose of 480 mg according to a previously described protocol (Boulenger et al 1987; Uhde et al 1984). This dose has been shown in our laboratory to reliably discriminate between panic disorder patients and normal controls in that panic disorder patients have a differentially greater increase in anxiety and plasma levels of cortisol and lactate (Uhde and Boulenger 1989; Uhde 1990) than normal controls. To avoid any biasing effect on the *m*-CPP or placebo responses resulting from caffeine's anxiogenic effects, caffeine was always given as the last study drug, whereas *m*-CPP and placebo were randomly assigned. Though some criticism on this design may be justified, we thought that caffeine's robust anxiogenic effect might condition patients to respond with increased anxiety to the other challenges and thus bias their net effect.

Baseline blood samples were collected from the IV cannula into EDTA-treated tubes 15 minutes before and at +90, +120, +150, +180, and +210 min after drug administration. Blood samples were placed immediately on ice and centrifuged within half an hour of collection. The resulting plasma was separated and stored at −70°C until assay. Blood pressure and pulse were measured at 5-min intervals using an automated monitor (Dinamapp).

Behavioral ratings and ratings of side effects were obtained at baseline and at hourly intervals throughout the study. The scales that were used included Zung Anxiety rating scale (Zung 1971), Hamilton Depression rating scale (Hamilton 1960), NIMH panic attack inventory, and NIMH rating scales for anxiety, depression, and global impairment (range 1–15). Two rating scales have been described before (Zohar et al 1987; Uhde 1990). A semiquantitative self-rated scale (range 1–5) was used to assess the similarity of the drug-induced anxiety state to the patient's own natural panic attacks. A rating of 1 indicated that the chemically induced panic attack was "totally different" and a 5 indicated that the drug-induced panic attack was "identical" to the subject's spontaneous panic attack. Panic attacks were also assessed on the panic attack inventory according to DSM-III criteria. All ratings were performed by the same blind rater (MFG) prior to and at ±90, ±180, and ±210 min following drug or placebo administration.

Biochemical Methods

Plasma prolactin was measured using double antibody radioimmunoassay (RIA) kits purchased from Amersham (Arlington Heights, IL) with minor modifications of the procedure to optimize determinations of prolactin concentrations within the lower normal range. The sensitivity of the assay was 1.3 ng/ml. Plasma cortisol was measured using a double antibody RIA kit obtained from New England Nuclear (Boston, MA). The sensitivity of the assay was 0.3 μg/100 ml. The mean interassay correlation coefficient for those subjects for whom multiple assays were performed was 0.80 for cortisol and prolactin. All samples from an individual subject were measured in duplicate in a single

assay run, and were accepted for the analysis only if their interassay coefficient of variation was less than 10%.

Data Analysis

To assess the effects of *m*-CPP, caffeine, and placebo on behavioral ratings and on plasma concentrations of prolactin and cortisol, a two-way analysis of variance (ANOVA) with repeated measures was employed. In this analysis, the statistical significance of the main effects of drug (placebo versus *m*-CPP versus caffeine) and time (changes over several time points), and the drug × time interaction, were evaluated. In a separate analysis, one-way ANOVA with repeated measures was performed to assess the statistical significance of peak change from baseline. Significant results from the ANOVA were examined post hoc by Bonferroni *t*-tests.

Results

Effects of m-*CPP and Caffeine on the Frequency of Panic Attacks*

None of the patients experienced panic attacks following the administration of placebo. Following the administration of *m*-CPP, 5 of the 7 patients (70%) had panic attacks. Five patients also had panic attacks following caffeine ingestion. Thus, both *m*-CPP and caffeine showed similar potency in their ability to induce panic attacks, which was robustly different from that of placebo. Four patients had panic attacks following both challenges, 1 had a panic attack only after *m*-CPP, and 1 only after caffeine. All 4 of the patients who had panic attacks after both challenges reported them to be more severe at the time they had received caffeine. The patients described the attacks as remarkably similar in quality to their naturally occurring panic attacks.

Effects of m-*CPP and Caffeine on Generalized Anxiety and Mood*

The behavioral responses to *m*-CPP, caffeine, and placebo are summarized in Figure 1. The statistical analysis of the various rating instruments revealed significant drug × time interactions on the Zung Anxiety ($F_{[6/30]} = 4.55$, $p < 0.007$); Hamilton Depression ($F_{[6/30]} = 4.21$, < 0.003); NIMH Anxiety ($F_{[6/30]} = 5.38$, $p < 0.006$); and NIMH Global Impairment ($F_{[6/30]} = 5.2$, < 0.004) scales. The one-way ANOVA, which examined peak changes from baseline in the three drug conditions (determined by the difference between time 0 and time 90 or 150 values) (Figure 2), was also significant for all aforementioned rating scales ($F_{[12/12]} = 12.8$, $p = 0.001$; $F_{[12/12]} = 4.95$, $p = 0.03$; $F_{[12/12]} = 15.8$, $p = 0.0006$; $F_{[12/12]} = 11.9$, $p = 0.002$, respectively). Post hoc analysis revealed that on the Zung, NIMH Anxiety, and NIMH Impairment ratings, both *m*-CPP and caffeine responses differed significantly from placebo ($p < 0.02$, in all cases). Caffeine ($p < 0.03$) and *m*-CPP ($p < 0.05$) also produced significant increases in Hamilton Depression ratings. No significant differences between *m*-CPP and caffeine were observed, although there were persistently higher ratings following caffeine on all rating scales. Subjectively, 4 patients described the overall experience with caffeine as worse than with *m*-CPP, 2 described them as similar, and 1 had a more robust response to *m*-CPP. Interestingly, this patient's response to caffeine was similar to his placebo response. A deviation from the overall similar behavioral response pattern to *m*-CPP and caffeine was

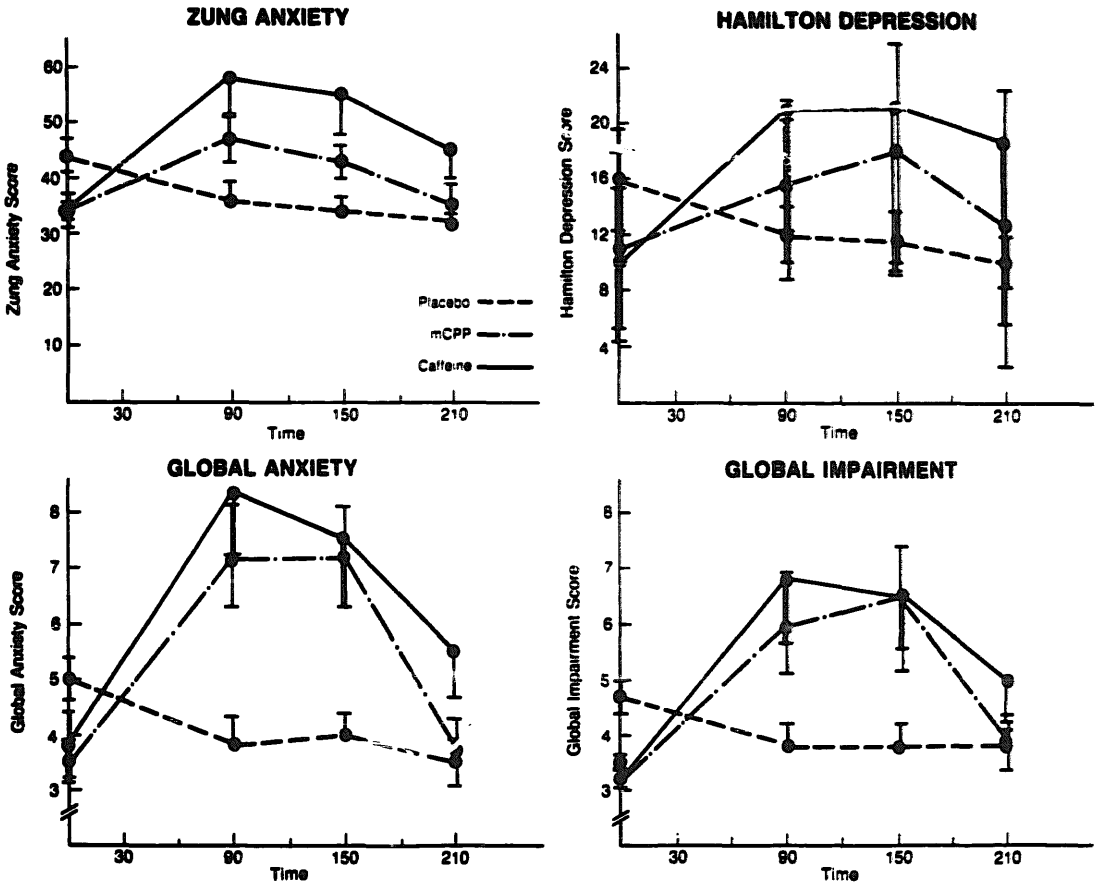

Figure 1. Mean ± SEM changes in Zung Anxiety, Hamilton Depression, Global Anxiety, and Global Impairment after oral placebo, *m*-CPP (0.5 mg/kg) and caffeine (480 mg) in patients with panic disorder.

observed on a score of activation derived from an NIMH Self-rating scale, where caffeine produced a significantly higher degree of activation than both *m*-CPP and placebo (data not shown).

Aside from these effects on anxiety and mood, both drugs were well tolerated physically by all patients. Patients could leave the clinic soon after the completion of the procedures. One patient reported a late onset headache (10–12 hr) following *m*-CPP; this patient had previously suffered from migraine.

Effects of m-CPP *and Caffeine on Plasma Prolactin and Cortisol*

The prolactin response over time and as peak changes from baseline in the three drug conditions are presented in Figure 3. The two-way ANOVA with repeated measures (factors: drug and time) revealed significant main effects for both factors and a significant drug × time interaction ($F_{[10/40]} = 4.74, p = 0.01$). The ANOVA for the peak changes from baseline was also significant ($F_{[2/12]} = 20.28, p = 0.001$). Post hoc analysis revealed that this significance was accounted for by a significantly greater increase in prolactin following *m*-CPP ($p < 0.005$) whereas caffeine's effect on the change in prolactin levels did not differ significantly from placebo.

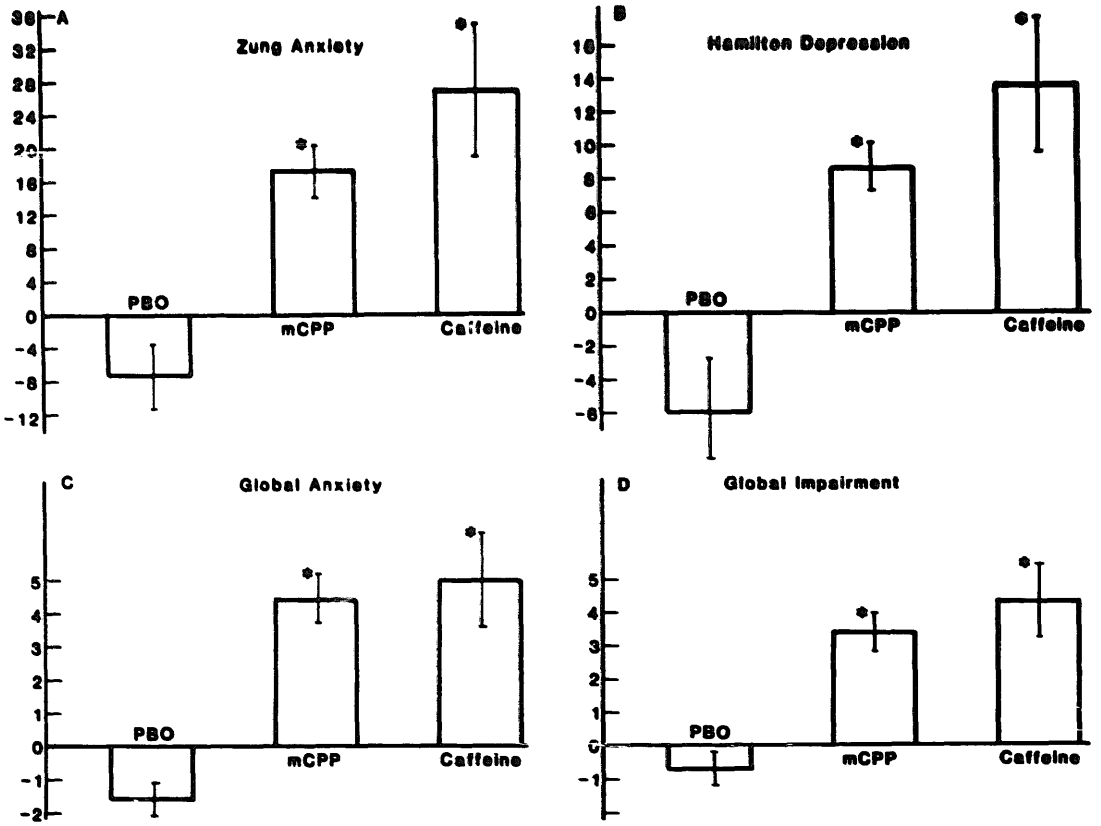

Figure 2. Panic disorder patients demonstrate a significantly greater anxiogenic response to oral *m*-CPP and caffeine compared with placebo. There were no statistically significant differences between the behavioral responses to *m*-CPP and caffeine, although there tended to be a consistent pattern of increased anxiogenic responses to caffeine. Error bars reflect SEM.

The cortisol response over time and peak changes from baseline in the different drug conditions are illustrated in Figure 4. The two-way ANOVA with repeated measures (factors: drug and time) revealed a significant main effect for drug and a significant drug × time interaction ($F_{[10/40]} = 2.44$, $p = 0.004$). The ANOVA for the peak changes from baseline was significant ($F_{[2/12]} = 9.95$, $p = 0.004$), as reflected by significant increases in cortisol after both *m*-CPP ($p < 0.03$ post hoc), and caffeine ($p < 0.01$ post hoc) compared with placebo.

Discussion

Oral administration of *m*-CPP to panic disorder patients induced panic attacks and increased ratings of anxiety compared with placebo. These effects were found to be markedly similar to those of caffeine, which was used as a "reference challenge" in this study. Along with its behavioral effects, *m*-CPP caused a robust and significant increase in prolactin levels, unlike caffeine or placebo. However, both active drugs produced significant and a similar increases in cortisol levels compared with placebo. These results suggest that activation of the serotonergic system via *m*-CPP is associated with induction of panic attacks and increased anxiety in patients with panic disorder.

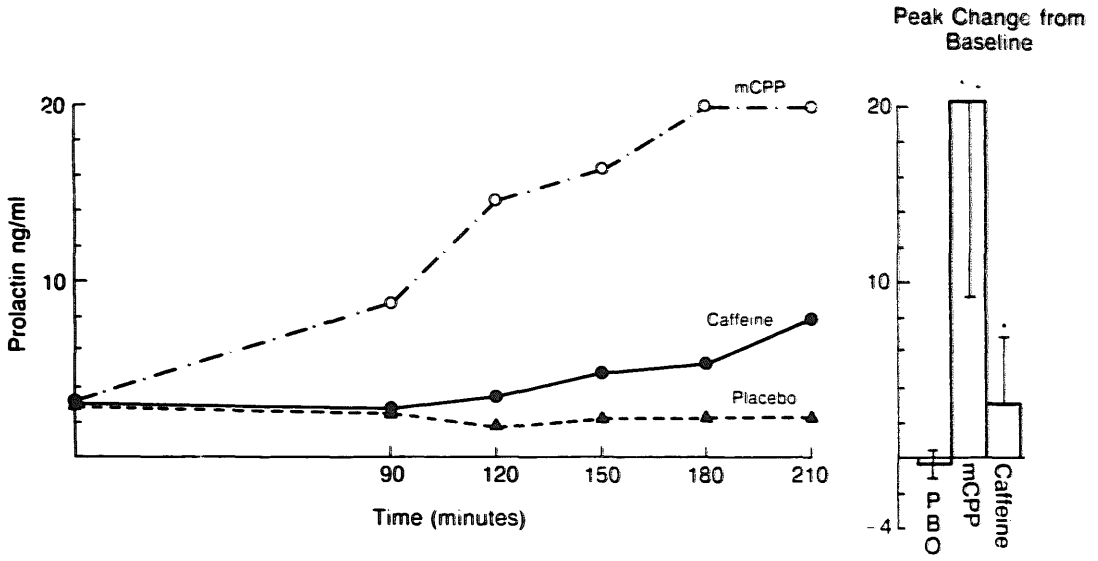

Figure 3. *m*-CPP produced a significantly greater increase in plasma prolactin levels compared with caffeine and placebo. The prolactin response to caffeine did not differ from placebo. Error bars reflect SEM.

The lack of a normal control group limits the conclusions that can be drawn from this study. One might raise the question as to whether controls would develop panic attacks in response to the same *m*-CPP challenge. This would appear extremely unlikely, as we have previously demonstrated that under identical conditions, oral doses of 0.5 mg/kg *m*-CPP administered to normal controls yielded only minimal behavioral effects. That is, none of our previously studied normal controls developed panic attacks and only minor,

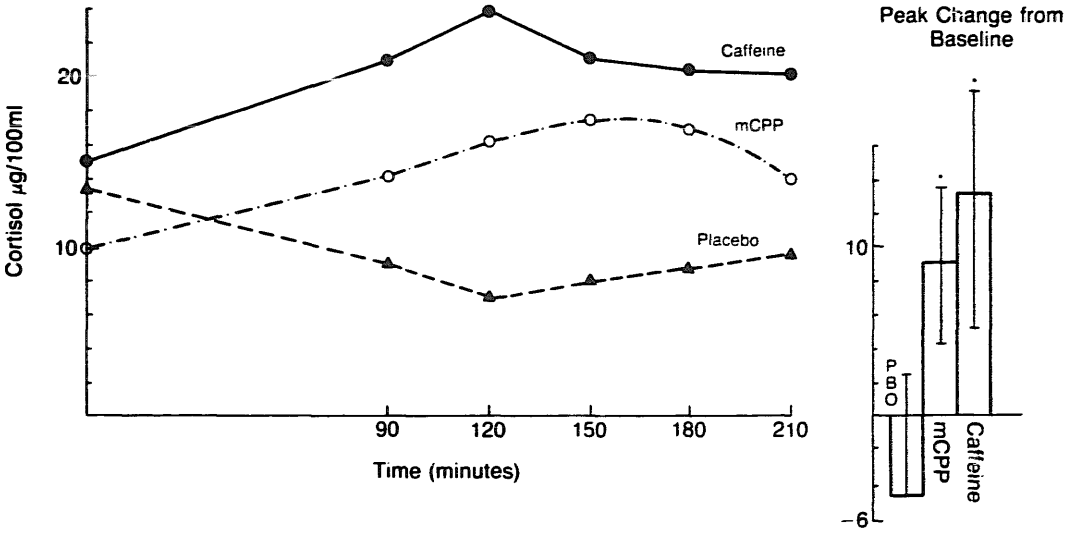

Figure 4. Caffeine and *m*-CPP produced significant increases in cortisol compared with placebo in panic disorder patients. Error bars reflect SEM.

clinically insignificant increases in anxiety were observed (Mueller et al 1985). Furthermore, the response to caffeine, which has been extensively studied in patients with panic disorder and in normal controls (Uhde et al 1984; Charney et al 1985; Boulenger et al 1987; Uhde 1990), is highly characteristic of these patients who display marked sensitivity to the anxiogenic effects of this compound. In this study it has been shown that the orally administered *m*-CPP, like caffeine, was anxiogenic in patients with panic disorder.

The similarities in the response pattern of our patients to *m*-CPP and caffeine are of interest. Four of the 5 patients who had panic attacks on each challenge developed them after both *m*-CPP and caffeine, and anxiety-related ratings were significantly increased following both *m*-CPP and caffeine compared with placebo. However, Hamilton Depression ratings were significantly increased compared with placebo only following caffeine. A marked depressive response to caffeine in panic disorder patients was seen also in earlier studies (Uhde, unpublished observations).

The mechanism by which these two drugs elicit panic attacks and increased anxiety might involve different pathways. Caffeine is known to be a potent adenosine blocker (Boulenger et al 1984). Adenosine, which is abundant in brain tissue, is known to be an inhibitory neuromodulator (Boulenger et al 1986). Caffeine's anxiogenic effects are thus believed to be mediated via its adenosine antagonistic activity.

The anxiogenic effects of *m*-CPP are most likely mediated via its selective serotonin agonistic activity, possibly via $5HT_{1c}$ receptors, as has been suggested by Kenneth and Curzon (1988). The involvement of serotonergic pathways in the mediation and manifestation of anxiety behaviors is also suggested from animal studies, which indicate that increased serotonergic activity is associated with increases in behaviors like the depressant effects of punishment (Geller and Blum 1970; Schoenfeld 1976; Tye et al 1979; Brady and Barrett 1985a, 1985b).

Though markedly similar in their behavioral effects, the two drugs elicit a different endocrine response as far as prolactin is concerned. The ability of serotonin and serotonin agonists to cause increased prolactin secretion from the pituitary is well documented (Fuller 1981) and *m*-CPP's ability to increase prolactin levels in our patients is thus consistent with its serotonin agonistic activity. Caffeine, on the other hand, despite its robust anxiogenic effects, did not cause a significant increase in prolactin secretion. Thus, it can be concluded, despite similar behavioral effects, that the two drugs differ in the prolactin response they elicit and that the increase in prolactin levels is not a result of the increase in anxiety.

Both drugs caused increases in cortisol levels. Increased cortisol levels following both *m*-CPP and caffeine have also been reported in normal controls (Mueller et al 1985, 1986; Uhde and Boulenger 1989; Kahn et al 1988a, 1988b), and given the small number of patients, it cannot be concluded whether this response pattern might correlate with the anxiety state. Other investigations, however, have reported that lactate-induced panic attacks (Liebowitz et al 1984, 1985; Hollander et al 1989) and exposure-induced situational panic attacks (Curtis et al 1976; Woods et al 1987) are associated with unimpressive changes in plasma cortisol concentrations. Thus, increases in cortisol might be related to some anxiety states, but not necessarily to all cases of increased anxiety.

It has been reported by Charney et al (1987) that *m*-CPP administered intravenously provoked panic attacks and increased anxiety in 52% (12 of 23) of patients with panic disorder and 32% (6 of 19) of normal controls. Intravenous administration of *m*-CPP (2.1 mg/kg) in normal controls induces markedly exaggerated behavioral responses compared

with oral administration (0.5 mg/kg), with significantly greater anxiety, dysphoria, and impairment ratings (Murphy et al 1989). These differences in normal controls may help to explain the apparent discrepancy between the findings reported by Charney et al (1987) to those of the earlier NIMH study using oral *m*-CPP (Mueller et al 1986). This difference may be the result of higher blood levels achieved by the IV administration of *m*-CPP, which may suggest that the difference between panic disorder patients and normal controls in their response to *m*-CPP is a threshold phenomenon. This concept of threshold specificity is supported by the recent work of Kahn et al (1988a, 1988b) who found that panic disorder patients had a greater anxiogenic response than normal controls to an oral dose (0.25 mg/kg) of *m*-CPP that was half our oral dose. This type of "threshold specificity" has also been demonstrated with caffeine, where high doses (720 mg) are associated with increased anxiety and panic attacks in normal controls (Uhde and Tancer, 1988; Uhde and Boulenger 1989; Uhde 1990) whereas at lower doses (480 mg) there are marked increases in anxiety and panic attacks in panic disorder patients but not normal controls (Uhde and Boulenger 1989; Uhde 1990).

The marked behavioral response to *m*-CPP is not unique to panic disorder patients. Zohar et al (1988) demonstrated that patients with obsessive-compulsive disorder respond to *m*-CPP with marked exacerbation of obsessive-compulsive symptomatology and increased anxiety. The behavioral response profile to *m*-CPP is unique in that other challenges that induce panic attacks in panic disorder patients [e.g., yohimbine (Charney et al 1984; Uhde et al 1984; Uhde and Tancer 1988; Gurguis and Uhde 1990), caffeine (Charney et al 1985; Uhde and Tancer 1988; Uhde 1990), and lactate (Liebowitz et al 1984, 1985)] are not associated with increased anxiety or exacerbation of obsessive-compulsive symptomatology in obsessive-compulsive disorder patients (Gorman et al 1985; Rasmussen et al 1987). *m*-CPP is the only pharmacological challenge so far that induces increased anxiety and exacerbation of core symptomatology in both panic disorder and in obsessive-compulsive symptoms in obsessive-compulsive disorder patients. These findings might suggest some common serotonergic involvement in these two disorders and might provide a biochemical basis for the symptomatic overlap between these two disorders (Mellman and Uhde 1987).

In conclusion, we have demonstrated in this study that patients with panic disorder responded to *m*-CPP and caffeine with increased anxiety and panic attacks. The biochemical events mediating the effects of these two drugs probably involve different neurochemical pathways (e.g., serotonergic and purinergic) and support the possibility of more than a single neurochemical system being involved in pathological anxiety states.

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References

Boulenger J-P, Uhde TW, Wolff EA, Post RM (1984): Increased sensitivity to caffeine in patients with panic disorders: Preliminary evidence. *Arch Gen Psychiatry* 41:1067–1071.

Boulenger J-P, Marangos PJ, Zander KJ, Hanson J (1986): Stress and caffeine: Effects on central adenosine receptors. *Clin Neuropharmacol* 9:79–83.

Boulenger J-P, Salem N Jr, Marangos PJ, Uhde TW (1987): Plasma adenosine levels: Measurement in humans and relationship to the anxiogenic effects of caffeine. *Psychiatry Res* 21:247–255.

Brady LS, Barrett JE (1985a): Effects of serotonin receptor antagonists on punished responding maintained by stimulus-shock termination or food presentation in squirrel monkeys. *J Pharmacol Exp Ther* 234:106–122.

Brady LS, Barrett JE (1985b): Effects of serotonin receptor agonists and antagonists on schedule-controlled behavior of squirrel monkeys. *J Pharmacol Exp Ther* 235:436–441.

Caccia S, Ballabio M, Samanin R (1981): m-Chlorophenylpiperazine, a central 5-hydroxytryptamine agonist, is a metabolite of trazodone. *J Pharm Pharmacol* 33:477.

Caccia S, Fong MH, Garattini S, Zanini MG (1982): Plasma concentrations of trazodone and 1-(3-chlorophenyl)piperazine in man after a single oral dose of trazodone. *J Pharm Pharmacol* 34:605.

Charney DS, Heninger GR, Breier A (1984): Noradrenergic function in panic anxiety: Effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 41:751–763.

Charney DS, Heninger GR, Jatlow PI (1985): Increased anxiogenic effects of caffeine in panic disorder. *Arch Gen Psychiatry* 42:233–243.

Charney DS, Woods SW, Goodman WK, Heninger GR (1987): Serotonin function in anxiety. II. Effects of the serotonin agonist *m*-CPP in panic disorder patients and healthy subjects. *Psychopharmacology* 92:14–24.

Curtis G, Buxton M, Lippman D, Nesse R, Wright J (1976): "Flooding *in vivo*" during circadian phase of minimal cortisol secretion: Anxiety and therapeutic success without adrenal cortical activation. *Biol Psychiatry* 11:101–104.

Diagnostic and Statistical Manual of Mental Disorders (ed 3) [DSM-III]. American Psychiatric Association, 1980.

Engel JA, Hjorth S, Svensson K, Carlsson A, Liljequist S (1984): Anti-conflict effect of the putative serotonin receptor agonist 8-hydroxy-2-(DI-n-propyl-amino) Tetralin (8-OH-DPAT). *Eur J Pharmacol* 105:365–368.

Fuller RW (1981): Serotonergic stimulation of pituitary adrenocortical function in rats. *Neuroendocrinology* 32:118.

Fuller RW, Mason NR, Molloy BP (1980): Structural relationships in the inhibition of [^{3}H]-serotonin binding to rat brain membranes *in vitro* by 1-phenylpiprazines. *Biochem Pharmacol* 29:833.

Geller I, Blum K (1970): The effects of 5-HTP on para-chlorophenylalanine (p-CPA) attenuation of "conflict" behavior. *Eur J Pharmacol* 9:319–324.

Glaser T, Traber J (1983): Buspirone: Action on serotonin receptors in calf hippocampus. *Eur J Pharmacol* 88S:137–138.

Gloger S, Grunhaus L, Birmacher B (1981): Treatment of spontaneous panic attacks with chlorimipramine. *Am J Psychiatry* 138:1215–1217.

Gorman JM, Liebowitz MR, Fyer AJ, et al (1985): Lactate infusion in obsessive compulsive disorder. *Am J Psychiatry* 142:864–866.

Gurguis GNM, Uhde TW (1990): Effect of yohimbine on plasma homovanillic acid in panic disorder patients and normal controls. *Biol Psychiatry* 28:292–296.

Hamik A, Peroutka SJ (1989): l-(m-chlorphenyl)Piperazine (*m*-CPP) interactions with neurotransmitter receptors in the human brain. *Biol Psychiatry* 25:569–575.

Hamilton A (1960): A psychiatric rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.

Hollander E, Liebowitz MR, Gorman JM, Cohen B, Fryer A, Klein DF (1989): Cortisol and sodium lactate-induced panic. *Arch Gen Psychiatry* 46:135–140.

Kahn RS, Westenberg HGM: (1985): L-5-Hydroxytryptophan in the treatment of anxiety disorders. *J Affective Disord* 8:197–200.

Kahn RS, Asnis GM, Wetzler S, von Praag HM (1988a): Neuroendocrine evidence for serotonin receptor hypersensitivity in panic disorder. *Psychopharmacology* 96:360–364.

Kahn RS, Wetzler S, von Praag HM, Asnis GM, Strauman T (1988b): Behavioral indications for serotonin receptor or hypersensitivity in panic disorder. *Psychiatry Res.* 25:101–109.

Kenneth GA, Curzon G (1988): Evidence that *m*-CPP may have behavioral effects medicated by central 5-HT_{1c} receptors. *Br J Pharmacol* 94:137–147.

Liebowitz MR, Fyer AJ, Gorman JM, et al (1984): Lactate provocation of panic attacks. I. Clinical and behavioral findings. *Arch Gen Psychiatry* 41:764–770.

Liebowitz MR, Gorman JM, Fyer AJ, et al (1985): Lactate provocation of panic attacks. II. Biochemical and physiological findings. *Arch Gen Psychiatry* 42:709–719.

Mellman TA, Uhde TW (1987): obsessive-compulsive symptoms in panic disorder. *Am J Psychiatry* 144:1573–1576.

Mueller EA, Murphy DL, Sunderland T (1985): Neuroendocrine effects of m-chlorophenylpiperazine, a serotonin agonist, in humans. *J Clin Endocrinol Metab* 61:1–6.

Mueller EA, Murphy DL, Sunderland T (1986): Further studies of the putative serotonin agonist, m-chlorophenylpiperazine: Evidence for a serotonin receptor-mediated mechanism of action in humans. *Psychopharmacology* 89:388–391.

Murphy DL, Mueller EA, Hill JL, Tolliver TJ, Jacobsen FM (1989): Comparative anxiogenic, neuroendocrine and other physiologic effects of *m*-CPP given intravenously or orally to healthy volunteers. *Psychopharmacology* 98:275–289.

Rasmussen SA, Goodman WK, Woods SW, Heninger GR, Charney DS (1987): Effects of yohimbine in obsessive-compulsive disorder. *Psychopharmacology* 93:308–313.

Samanin R, Mennini T, Ferraris A (1979): m-Chlorophenylpiperazine: A central serotonin agonist causing powerful anorexia in rats. *Naunyn Schmiedebergs Arch Pharmacol* 308:159.

Schoenfeld RI (1976): Lysteric acid diethylamide- and mescaline-induced attenuation of the effect of punishment in the rat. *Science* 192:801–803.

Simon P, Soubrie P (1979): Behavioral studies to differentiate anxiolytic and sedative activity of the tranquilizing drugs. In Boissier JR (ed), *Modern Problems in Pharmacopsychiatry*, Basel, New York: Karger, Vol 14, pp 99–143.

Stein L, Wise CD, Berger BD (1973): Anti-anxiety action of benzodiazepines: Decrease in activity of serotonin neurons in the punishment system. In Costa E, Greengard P (eds), *The Benzodiazepines*. New York: Raven Press, pp 299–326.

Stein L, Belluzzi JD, Wise CD (1977): Benzodiazepines: Behavioral and neurochemical mechanisms. *Am J Psychiatry* 134:665–669.

Thiebot MH, Hamon M, Soubrie P (1982): Attenuation of induced anxiety in rats by chlordiazepoxide: Role of raphe dorsalis benzodiazepine binding sites and serotoninergic neurons. *Neuroscience* 7:2287–2294.

Traber J, Davies MA, Dompert WU, Glaser T, Schurman T, Seidel P-R (1984): Brain serotonin receptors as a target for the putative anxiolytic TVX Q 7821. *Brain Res Bull* 12:741–744.

Tye NC, Iversen SD, Green AR (1979): The effects of benzodiazepines and serotonergic manipulations on punished responding. *Neuropharmacology* 18:689–695.

Uhde TW (1990): Caffeine provocation of panic: A focus on biological mechanisms. In Ballenger JC (ed), *Neurobiological Aspects of Panic Disorder*. New York: Alan Liss, pp 219–242.

Uhde TW, Boulenger J-P (1989): Caffeine model of panic, 1989. In Lerer B, Gershon S (eds), *New Directions in Affective Disorders*. New York: Springer-Verlag, pp 410–413.

Uhde TW, Tancer M (1988): Chemical models of panic: A review and critique. In Tyser P (ed), *Psychopharmacology of Anxiety*. Oxford: Oxford University Press, pp 110–131.

Uhde TW, Boulenger J-P, Jimerson DC, Post RM (1984): Caffeine: Relationship to human anxiety, plasma MHPG and cortisol. *Psychopharmacol Bull* 20: 426–430.

Uhde TW, Boulenger J-P, Roy-Byrne PP, Vittone BJ, Post RM (1985): Longitudinal course of panic disorder: Clinical and biological considerations. *Prog Neuropsychopharmacol Biol Psychiatry* 9:39–51.

Wise CD, Berger BD, Stein L (1972): Benzodiazepines: Anxiety-reducing activity by reduction of serotonin turnover in the brain. *Science* 177:180–183.

Woods SW, Charney DS, McPherson CA, Gradman AH, Heninger GR (1987): Situational panic attacks: Behavioral, physiologic and biochemical characterization. *Arch Gen Psychiatry* 44:365–375.

Zohar J, Mueller EA, Insel TR, Zohar-Kadouch R, Murphy DL (1987): Serotonergic responsivity in obsessive-compulsive disorder: Comparison of patients and healthy controls. *Arch Gen Psychiatry* 44:946–951.

Zohar J, Insel TR, Zohar-Kadouch RC, Hill JL, Murphy DL (1988): Serotonergic responsivity in obsessive-compulsive disorder effects of chronic clomipramine treatment. *Arch Gen Psychiatry* 45:167–172.

Zung WWK (1971): A rating instrument for anxiety disorders. *Psychosomatics* 12:371–379.