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Effects of Antiglucocorticoid Treatment on 5-HT_{1A} Function in Depressed Patients and Healthy Subjects

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Clinical studies suggest that 5-HT_{1A} receptor function may be blunted in depression, while 5-HT_{1A} agonists may possess antidepressant activity. Preclinical findings implicate changes in 5-HT_{1A} receptor sensitivity in the mechanism of antidepressant action. The hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in depression could be related to these observations, since 5-HT_{1A} receptors are inhibited by glucocorticoids. To evaluate the interaction of the HPA and 5-HT_{1A} systems, we pretreated 15 unipolar depressed patients and 12 healthy control subjects with the antiglucocorticoid ketoconazole (KTCZ) prior to administration of a test dose of the 5-HT_{1A} agonist ipsapirone (IPS). Neuroendocrine (ACTH, cortisol, growth hormone), physiological (hypothermia), and behavioral responses to IPS were assessed. As expected, KTCZ inhibited cortisol biosynthesis, but non-HPA responses to IPS were not enhanced. This study failed to show that glucocorticoid modulation of 5-HT_{1A} receptor function is altered in depression.

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KEY WORDS: *Antiglucocorticoids; Serotonin; Depression; Ketoconazole; 5-HT_{1A} receptor; HPA axis*

There is extensive evidence supporting the involvement of serotonin (5-hydroxytryptamine [5-HT]) function in the pathophysiology of depression (Meltzer and Lowy 1987; Maes and Meltzer 1995; Blier and de Montigny 1994; Delgado et al. 1990). Relevant findings include decreased plasma levels of the 5-HT precursor tryptophan; abnormalities of 5-HT metabolism and receptor binding in platelet, cerebrospinal fluid, and postmortem brain; abnormal neuroendocrine responses to 5-MT-selective pharmacologic probes; the facilitatory effects of antidepressant treatments on 5-HT function; and the reversal of antidepressant-induced remission by depletion of plasma tryptophan.

Equally compelling data document hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in depression (Stokes and Sikes 1987; Holsboer 1995; Dinan 1994). Depressed patients have been shown to have increased basal levels of cortisol and corticotropin-releasing hormone (CRH); increased frequency, duration, and magnitude of cortisol and corticotropin (ACTH) secretory episodes; resistance to suppression of cortisol and ACTH secretion by dexamethasone; abnormal HPA axis responses to exogenous ACTH and CRH; adrenal and

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pituitary gland enlargement; decreased glucocorticoid (GC) receptor binding in platelet and postmortem brain; and diminished GC negative feedback. Recent studies have suggested that conventional antidepressant drugs may exert their clinical effects through actions on the HPA axis (Barden et al. 1995). Moreover, some findings indicate antidepressant activity for antiglucocorticoids, drugs which act primarily to inhibit HPA function (Price et al. 1996).

The 5-HT and HPA systems interact extensively with each other. On the one hand, 5-HT exerts a stimulatory influence on HPA activity, particularly via the 5-HT$_{1A}$ and 5-HT$_{2A/2C}$ receptor subtypes (Fuller 1992). Conversely, the HPA axis acts as a modulatory influence on the 5-HT system, with permissive effects on 5-HT biosynthesis and dampening effects on neuronal sensitivity to 5-HT both occurring in the context of various stressful conditions (McEwen 1987; Chaouloff 1993). Again, the 5-HT$_{1A}$ receptor plays a key role in mediating these effects. Hippocampal 5-HT$_{1A}$ receptors are under tonic inhibitory control of GCs, with considerable evidence that GCs exert stress-related inhibitory effects as well (Chaouloff 1995). The clinical significance of these studies is underscored by evidence that neuroendocrine and physiological responses to 5-HT$_{1A}$ agonists may be blunted in depressed patients (Lesch et al. 1990a; Lesch et al. 1990b; Cowen et al. 1994; Moeller et al. 1994; Mobayed and Dinan 1990). Several 5-HT$_{1A}$ agonists have also shown efficacy as antidepressants and anxiolytics (Cutler et al. 1994; McGrath et al. 1994; Pecknold et al. 1993; Amsterdam 1992; Grof et al. 1993; Heller et al. 1990), and it has been proposed that many other antidepressants act by altering the sensitivity of hippocampal 5-HT$_{1A}$ receptors (Blier and de Montigny 1994; Stahl 1994).

The hyperactivity of the HPA axis in depression could decrease the sensitivity of 5-HT$_{1A}$ receptors, accounting for both the diminished responses to 5-HT$_{1A}$ agonists under laboratory conditions and for the therapeutic actions of these agents. This argument is strengthened by recent evidence that the gene encoding the 5-HT$_{1A}$ receptor itself is intact in depression (Xie et al. 1995). Removal of the inhibitory effects of GCs on 5-HT$_{1A}$ receptors could also be a mechanism underlying the antidepressant actions of antiglucocorticoids. To evaluate these possibilities, we pretreated depressed patients and healthy control subjects with the antiglucocorticoid ketoconazole (KTCZ) (Sonino 1987; Engelhardt and Weber 1994) prior to administration of a test dose of the 5-HT$_{1A}$ agonist ipsapirone HCl (IPS) (Lesch et al. 1989; Kahn et al. 1994). We hypothesized that 1) cortisol synthesis inhibition by KTCZ should attenuate the cortisol response to IPS, while enhancing the adrenocorticotropic hormone (ACTH) response due to diminished negative feedback; 2) non-HPA responses to IPS, particularly the growth hormone (GH) and hypothermia responses, should be enhanced by KTCZ pretreatment as a result of the decreased inhibitory effect of cortisol on 5-HT$_{1A}$ receptors; and 3) the magnitude of the enhancement of non-HPA responses by KTCZ pretreatment should differ between depressed patients and controls, due to the greater basal inhibition of 5-HT$_{1A}$ receptor function in the depressed patients resulting from HPA hyperactivity.

METHODS

Subjects

Voluntary written informed consent was obtained from 15 unipolar depressed patients (8 female, 7 male; mean ± SE; age, 41.8 ± 3.0 years; age range, 26–63) to participate in this study at the Clinical Neuroscience Research Unit of the Connecticut Mental Health Center, New Haven, CT. Serious medical illness was excluded on the basis of complete physical, neurological, and laboratory examinations. Diagnostic assessment was based on a semi-structured interview conducted by a research psychiatrist in conjunction with all other available medical records. All patients met DSM-III-R criteria for a principal diagnosis of unipolar major depression (melancholic = 4, nonmelancholic = 11; psychotic = 1, and nonpsychotic = 14). Patients with schizophrenic or other psychoses, organic mental disorders, obsessive compulsive disorder (OCD), substance dependence, or any other primary psychiatric disorder were excluded; comorbidity with anxiety disorders other than OCD was not exclusionary. Both outpatients (n = 8) and inpatients (n = 7) participated.

Twelve healthy controls (7 female, 5 male; mean age, 31.1 ± 2.7 years; age range, 20–48) were recruited by word-of-mouth and newspaper advertisement. In addition to the medical screening and consent procedures described for the patient group, controls were also screened for a personal and family (first-degree relative) history of mental disorder and substance dependence by a research psychiatrist using a semi-structured interview. Control subjects were paid for their participation.

Study Procedures

Testing of patients occurred during a placebo treatment period prior to initiation of a double-blind antidepressant drug trial. Before testing was begun, patients were given placebo treatment for at least 2 weeks and were kept free of major psychotropic drugs for at least 3 weeks (free of fluoxetine for at least 5 weeks). Low-dose benzodiazepines were available for severe agitation and insomnia. Healthy control subjects were medication-free and were requested to avoid use of any other psychoactive drugs for 2 weeks before testing.

Each subject underwent two IPS test days, one with KTCZ pretreatment and one with placebo pretreatment, scheduled at least one week apart. The test sequence was randomly determined. The pretreatment drug was given subacutely as one capsule 3 times during the day before each test, and acutely as two capsules the morning of the test, with each capsule containing either KTCZ 200 mg or placebo. The total cumulative dose of KTCZ was 1000 mg, with a maximum daily dose of 600 mg. Although pretreatment was given with either KTCZ or placebo, active IPS 0.3 mg/kg was given on both of the two test days. All research personnel and subjects were blind to the content of the capsules.

The test procedure began at 8:00 AM following an overnight fast. Test sessions were conducted in a specially equipped room in which subjects were kept semi-recumbent on a hospital bed, with ambulation to void only. To facilitate blood-drawing, an intravenous catheter was inserted into an arm vein and kept patent by a slow infusion of normal saline. After at least 60 minutes (time: −120 min), KTCZ 400 mg or placebo was given. Two hours after the KTCZ administration, IPS 0.3 mg/kg po was given (time 0). The test session ended 3 hours later (time: +180 min).

Blood samples for cortisol, ACTH, and GH were taken before the IPS test dose at −125 minutes (i.e., just prior to the test day dose of KTCZ) and −5 minutes (i.e., +115 min after the KTCZ), and again at +60, +90, +120 and +180 minutes after the IPS. Blood for IPS levels was obtained at the latter 5 time points. Samples were immediately placed on ice, centrifuged, and then stored at −70°C until the time of assay. Physiological measures (systolic and diastolic blood pressure, heart rate, and oral temperature by glass thermometer) were monitored and behavioral ratings were administered at selected time points throughout the test day. Clinician-rated instruments included a modified 19-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) and the Hamilton Anxiety Rating Scale (HARS) (Hamilton 1959). Subject-rated scales included the Beck Depression Inventory (BDI) (Beck et al. 1961), the 29-item Physical Symptoms Checklist (PSC) (Woods et al. 1986), and visual analog scales (VAS) (McCormack et al. 1988) describing 16 different mood states ("talkative," "happy," "drowsy," "nervous," "sad," "calm," "depressed," "anxious," "energetic," "fearful," "mellow," "high," "angry," "irritable," "hungry," and "tired").

Biochemical Methods

Plasma cortisol was measured with a competitive binding radioimmunoassay (RIA) kit from INCSTAR (Stillwater, MN), with intra- and interassay coefficients of variation (CVs) of 3% and 5%, respectively. ACTH and GH were determined with RIA kits from Nichols Institute Diagnostic (San Juan Capistrano, CA) employing a monoclonal/polyclonal antibody sandwich technique. Intra- and interassay CVs were 3% and 8% for ACTH and 3% and 4% for GH, respectively. Ipsapirone was assayed using high-performance liquid chromatography with UV detection. The laboratory staff was blind to the sequence of active and placebo test days.

Data Analysis

To determine the effects of subacute KTCZ pretreatment during the day preceding the test day, analyses of variance (ANOVAs) were applied to neuroendocrine and physiological measures at the −125 time point in a Drug (active vs. placebo) × Diagnosis (depressed vs. healthy) model. To determine the effects of acute KTCZ pretreatment on these variables the morning of the test day, multivariate ANOVAs were performed on the −125 and −5 time points in a Drug × Diagnosis × Time model. The effects of subacute + acute KTCZ pretreatment on behavioral variables were evaluated at the −60 time point. To determine the effects on all variables of the IPS test dose alone and interacting with KTCZ pretreatment, multivariate ANOVAs were performed on all time points subsequent to −5 minutes, which was used as the baseline, again in a Drug × Diagnosis × Time model. Late effects of KTCZ were also evaluated using these time points. Huynh-Feldt-corrected significance values are reported when the sphericity assumption was not met. Peak change for neuroendocrine and temperature responses, calculated as the absolute value of the largest difference between the −5 time point baseline and all time points after the IPS test dose, was also subjected to ANOVA. Area under the concentration time curve (AUC) was calculated for IPS levels using the trapezoidal rule. Significance was set at $p < .05$ (two-tailed).

Because depressed patients were significantly older than healthy controls ($t = 2.62$, $df = 25$, $p = .015$), all analyses were also conducted using age as a covariate. However, age did not correlate with any dependent variable in the analysis of covariance model.

RESULTS

Effects of KTCZ Pretreatment

Compared with placebo, subacute pretreatment with KTCZ during the day before testing resulted in increased plasma levels of ACTH ($F = 6.90$, $df = 1,21$, $p < .016$) at the −125 time point (i.e., just prior to the test day dose of KTCZ) (Figure 1), with no effect on cortisol (Figure 2), GH (Figure 3), or temperature (Figure 4). There were no significant main or interaction effects with diagnosis. KTCZ had no significant effects on blood pressure or heart rate.

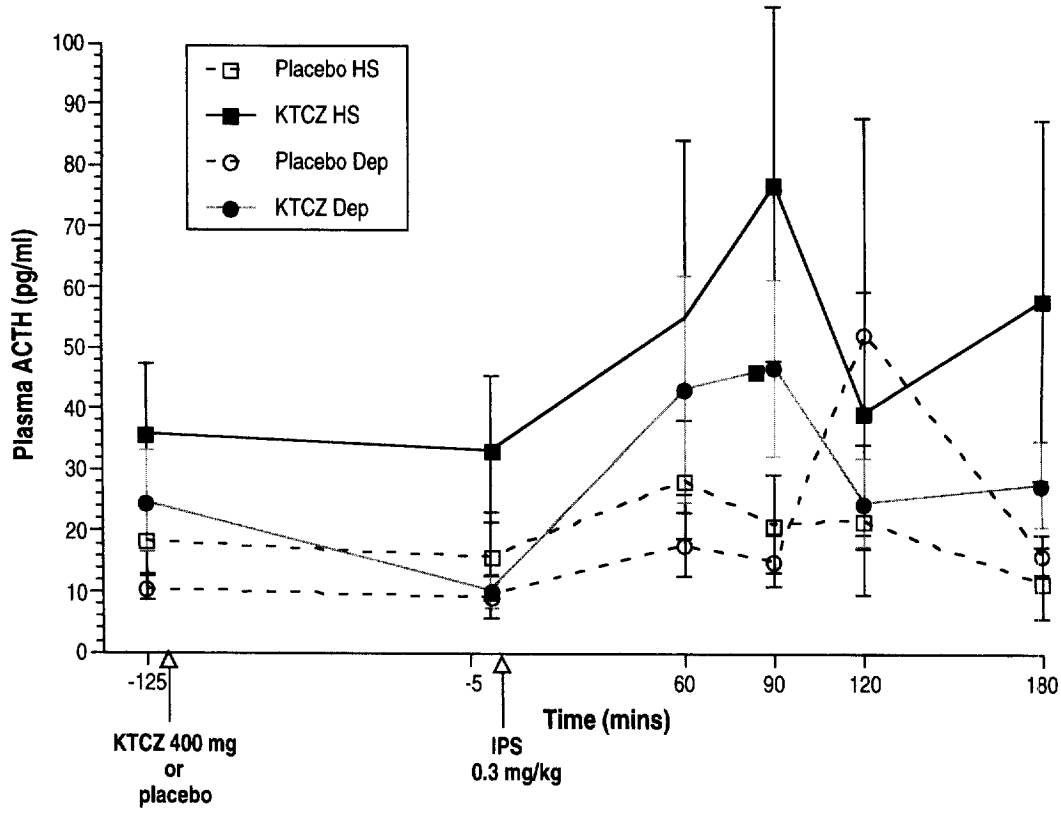

Figure 1. Mean ± SE plasma adrenocorticotropic hormone (ACTH) response to ipsapirone (IPS) following pretreatment with active ketoconazole (KTCZ) or placebo in depressed (Dep) and healthy subjects (HS).

Acute pretreatment with KTCZ on the morning of the test day significantly affected plasma GH levels (F = 5.18, df = 1,24, $p < .032$), which increased in controls but remained unchanged in patients (F = 5.38, df = 1,24, $p <$ .029) between the −125 and −5 time points (Fig. 3).

Subacute + acute pretreatment with KTCZ resulted in decreased VAS ratings of "sad" (F = 7.27, df = 1,25, $p <$ .012) and "irritable," (F = 4.56, df = 1,25, $p < .043$) at the −60 time point (Table 1). These decreases were only evident in the depressed subjects ("sad," F = 8.04), df = 1,25, $p < .009$; "irritable," F = 3.47, df = 1,25, $p < .074$), who predictably were more symptomatic than healthy controls at baseline ("sad," F = 64.03, df = 1,25, $p < .001$; "irritable," F = 17.18, df = 1,25, $p < .001$). KTCZ pretreatment had no effects on HDRS, HARS, BDI, or PSC scores.

Late effects of KTCZ included decreased VAS ratings of "happy" (F = 5.53, df, 1,25 $p < .027$) and "calm" (F = 6.19, df = 1,25, $p < .02$) (Table 1). There were increased ratings of "drowsy" (F = 6.19, df 1,25, $p < .02$). Decreases in ratings of "happy" (F = 9.32, df = 1,25 $p <$ .005) were greater in healthy controls than in patients; there were no other interactions with diagnosis. Late effects of KTCZ also included increased PSC scores (F = 5.60, df = 1,25, $p < .026$).

Effects of IPS

IPS caused a robust increase in cortisol (F = 12.31, df = 4,100, $p < .001$) (Figure 2) and GH (F = 4.92, df = 4,96, $p <$ .007) (Fig. 3) levels, and a decrease in temperature (F = 5.83, df = 8,200, $p < .001$) (Figure 4). The increase in ACTH was not significant (F = 2.16, df = 4,84, $p < .105$) (Figure 1). The cortisol increase was greater in depressed patients than in controls (F = 2.73, df = 4,100, $p < .05$), as was the peak change in cortisol (after placebo KTCZ: depressed patients, 14.9 ± 2.1 μg/dl; controls, 8.5 ± 1.3 μg/dl) (F = 9.42, df = 1,25, p < .005). The decrease in temperature tended to be greater in depressed patients than in controls (F = 1.83, df = 8,200, $p < .074$), and the peak decrease was significantly greater (after placebo KTCZ: depressed patients, −.038 ± .007° C; controls, −.024 ± .007° C) (F = 6.95, df = 1,25, $p < .014$). IPS caused heart rate to decrease (F = 2,68, df = 8,200, $p <$ .023), with no effect on blood pressure. IPS decreased VAS ratings of "talkative" (F = 10.83, df = 4,92, $p <$ .001), "calm" (F = 6.20, df = 4,100, $p < .001$), "hungry" (F = 5.56, df = 4,92, $p < .002$), "happy" (F = 12.77, df = 4,100, $p < .001$), "energetic" (F = 14.53, df = 4,92, $p <$ .001), and "mellow" (F = 3.78, df 4,96, $p < .002$), and increased ratings of "high" (F = 5.19, df 4,100, $p < .007$), "anxious" (F = 4.39, df = 4,100, $p < .007$), "drowsy" (F =

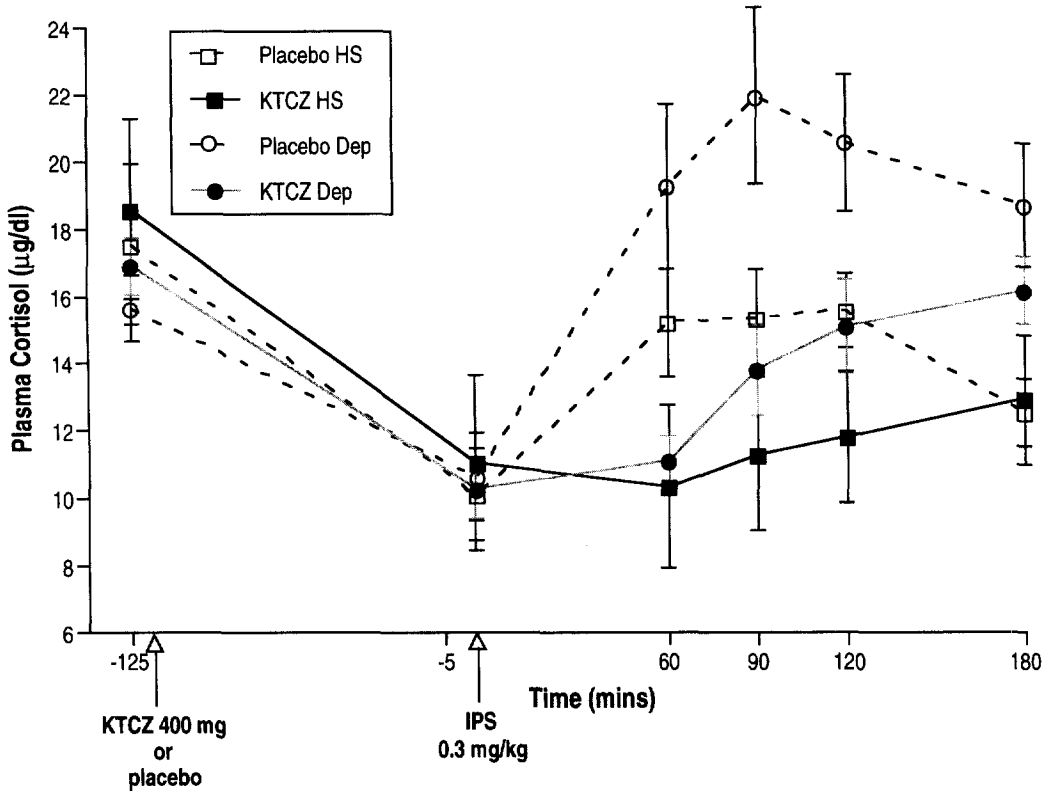

Figure 2. Mean ± SE plasma cortisol response to ipsapirone (IPS) following pretreatment with active ketoconazole (KTCZ) or placebo in depressed (Dep) and healthy subjects (HS).

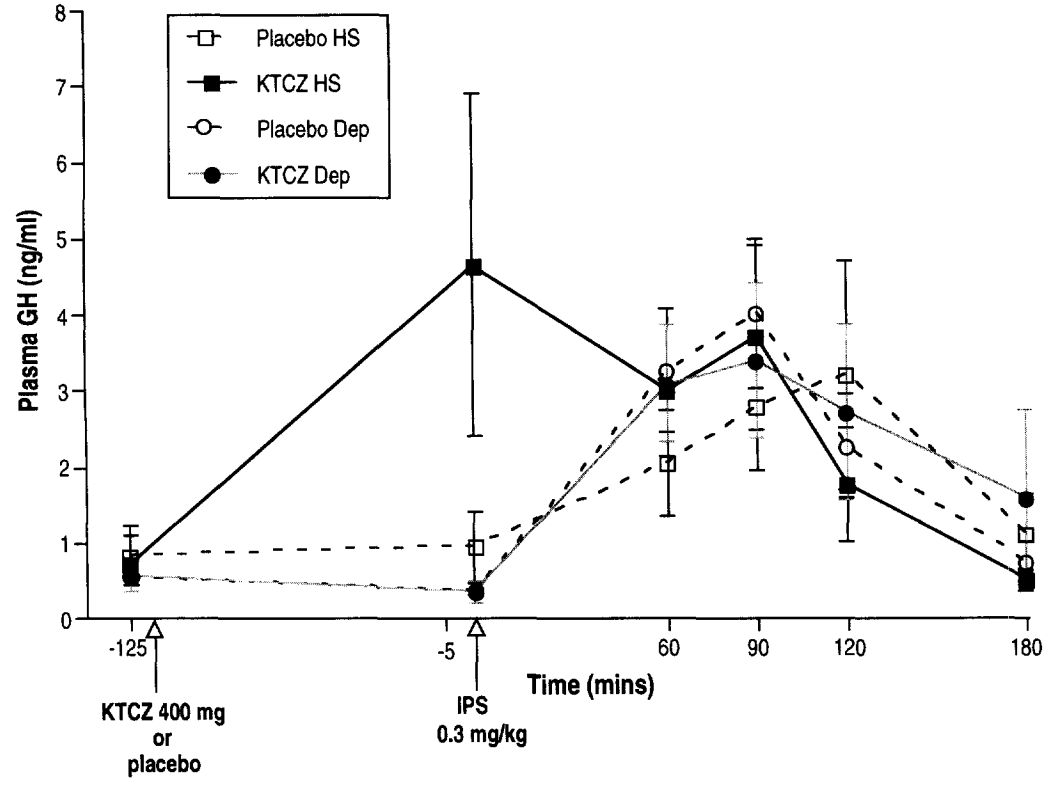

Figure 3. Mean ± SE plasma growth hormone (GH) response to ipsapirone (IPS) following pretreatment with active ketoconazole (KTCZ) or placebo in depressed (Dep) and healthy subjects (HS).

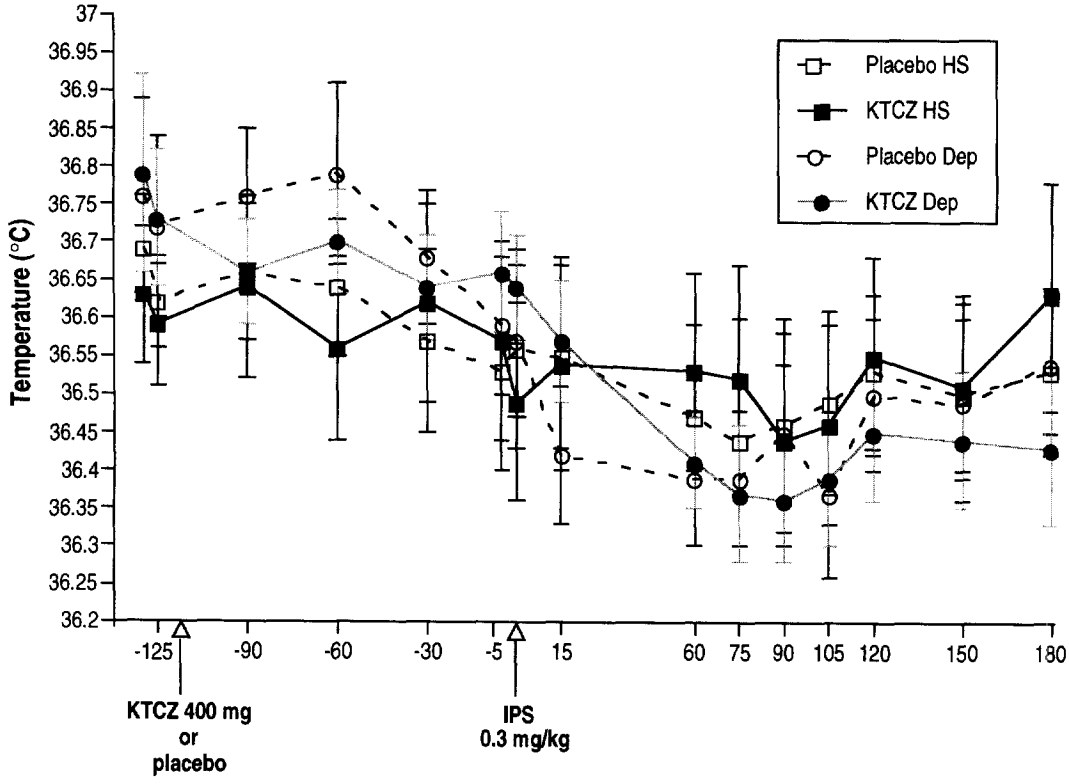

Figure 4. Mean ± SE temperature response to ipsapirone (IPS) following pretreatment with active ketoconazole (KTCZ) or placebo in depressed (Dep) and healthy subjects (HS).

11.75, df = 4,100, $p < .001$), "tired" (F = 20.16, df 4,100, $p < .001$), and "fearful" (F = 6.94, df = 4,100, $p < .002$) (Table 1). The decreases in "energetic" (F = 2.72, df = 4,92, $p < .042$) and "happy" (F = 3.64, df = 4,100, $p < .021$), and increases in "high" (F = 5.31, df = 4,100, $p < .006$), were more marked in the healthy controls. IPS slightly increased HDRS (F = 6.85, df = 1,25, $p < .015$) and PSC scores (F = 10.02, df = 4,100, $p < .001$), with no significant effects on the BDI or HARS.

Effects of KTCZ on Responses to IPS

KTCZ pretreatment markedly attenuated the cortisol response to IPS (F = 9.89, df = 4,100, $p < .001$) (Figure 2) and enhanced the ACTH response (F = 2.89, df = 4,84, $p < .041$) (Figure 1). KTCZ attenuated the GH response to IPS in controls, but not in patients (F = 2.76, df 4,96, $p < .038$) (Figure 3). KTCZ did not alter the hypothermic response to IPS (Figure 4). IPS-induced effects on "talkative" were enhanced by pretreatment with KTCZ (F = 3.51, df = 4,92, $p < .026$), with effects on "tired" (F = 2.71, df = 4,100 $p < .058$) and "anxious" (F = 2,51, df = 4,100, $p < .061$) showing a similar trend (Table 1). There was a tendency for KTCZ pretreatment to enhance the effects of IPS on ratings of "fearful" (F = 2.35, df = 4,100, $p < .089$) more in healthy subjects than in depressed patients.

Relationships Between Neurobiological and Other Variables

Peak neuroendocrine and hypothermic responses to IPS did not differ between melancholic and nonmelancholic patients, and there were no differences between inpatients and outpatients. Stratification of neuroendocrine and hypothermic responses by sex revealed that the peak GH response to IPS was greater in male patients compared with male controls (after placebo KTCZ: depressed patients, 6.8 ± 1.4 ng/ml; controls, 3.7 ± 2.3 ng/ml) (F = 6.12, df = 1,9, p < .035), but not in females. Peak cortisol response to IPS was greater in female patients compared with female controls (after placebo KTCZ: depressed patients, 14.7 ± 3.9 μg/dl; controls, 8.3 ± 2.1 μg/dl) (F = 5.10, df = 1,9, $p < .042$), which tended to be true in males also (after placebo KTCZ: depressed patients, 15.2 ± 1.6 μg/dl; controls, 8.9 ± 1.4 μg/dl) (F = 3.67, df = 10,1, $p < .084$). Peak hypothermia response to IPS was greater in male patients compared with male controls (after placebo KTCZ: depressed patients, −0.43 ± 0.11° C; controls, −0.31 ± 0.14° C) (F = 6.69, df = 10,1, $p < .027$), but not in females. There were

Table 1. Selected Mean ± SE Physiological and Behavioral Responses to Ipsapirone (IPS) Following Pretreatment with Active Ketoconazole (Act) or Placebo (Pla) in Depressed (DEP) and Healthy Subjects (HS)

Response	Subjects/ Drug	Time[a] −125 min	−60 min	+60 min	+90 min	+120 min	+180 min
Heart Rate (bpm)	DEP/Act	77.7 ± 2.8	72.4 ± 2.6	75.3 ± 3.1	70.0 ± 2.9	69.3 ± 2.8	68.6 ± 2.4
	HS/Act	71.5 ± 3.0	70.7 ± 3.2	69.5 ± 3.3	65.6 ± 3.3	66.0 ± 2.6	66.7 ± 3.2
	DEP/Pla	75.3 ± 2.5	73.3 ± 2.9	69.0 ± 2.5	69.9 ± 2.3	70.7 ± 2.2	71.1 ± 2.5
	HS/Pla	71.3 ± 3.7	66.8 ± 2.8	69.1 ± 2.6	68.2 ± 3.4	67.5 ± 3.1	66.9 ± 1.8
Sad	DEP/Act	–	55.3 ± 7.0	60.3 ± 8.2	57.5 ± 7.9	59.3 ± 7.8	59.7 ± 8.2
	HS/Act	–	0.3 ± 0.2	0.3 ± 0.2	0.3 ± .02	0.2 ± 0.2	0.2 ± 0.2
	DEP/Pla	–	65.3 ± 6.7	62.9 ± 6.9	61.6 ± 7.3	59.3 ± 7.5	57.5 ± 7.5
	HS/Pla	–	0.0 ± 0.0	0.8 ± 0.7	0.4 ± 0.4	0.0 ± 0.0	0.0 ± 0.0
Irritable	DEP/Act	–	24.3 ± 6.3	28.1 ± 7.5	26.8 ± 6.2	26.1 ± 7.0	28.3 ± 7.2
	HS/Act	–	1.0 ± 0.7	5.5 ± 2.9	4.0 ± 2.3	1.8 ± 1.7	2.5 ± 1.6
	DEP/Pla	–	37.8 ± 7.6	35.0± 6.6	35.0 ± 5.3	35.5 ± 6.0	33.9 ± 7.9
	HS/Pla	–	1.9 ± 1.3	7.3 ± 4.3	8.3 ± 4.2	2.3 ± 1.5	0.7 ± 0.5
Happy	DEP/Act	–	5.3 ± 2.3	1.7 ± 0.9	3.9 ± 1.9	3.1 ± 1.7	5.7 ± 2.2
	HS/Act	–	54.4 ± 4.9	39.6 ± 5.8	41.0 ± 5.9	44.9 ± 6.6	46.1 ± 6.0
	DEP/Pla	–	10.3 ± 2.7	7.3 ± 2.8	6.9 ± 2.6	6.7 ± 2.5	9.7 ± 2.7
	HS/Pla	–	55.3 ± 5.7	47.6 ± 5.7	48.8 ± 6.2	48.9 ± 5.6	55.2 ± 6.4
Calm	DEP/Act	–	30.1 ± 6.1	16.4 ± 4.4	22.9 ± 5.4	28.0 ± 6.8	24.1 ± 5.6
	HS/Act	–	65.1 ± 3.9	47.3 ± 7.3	54.9 ± 5.3	63.7 ± 5.1	66.8 ± 4.7
	DEP/Pla	–	38.7 ± 6.2	34.7 ± 6.8	40.1 ± 6.1	36.4 ± 5.8	40.9 ± 6.6
	HS/Pla	–	69.6 ± 3.8	62.3 ± 5.7	61.6 ± 5.2	67.3 ± 4.4	68.7 ± 4.5
Energetic	DEP/Act	–	10.2 ± 4.5	0.4 ± 0.4	5.8 ± 4.2	5.0 ± 2.6	7.8 ± 4.1
	HS/Act	–	44.9 ± 5.5	19.0 ± 4.1	18.3 ± 3.9	24.6 ± 5.7	25.8 ± 3.6
	DEP/Pla	–	12.4 ± 2.9	0.7 ± 0.5	3.3 ± 2.1	9.1 ± 3.5	13.7 ± 4.1
	HS/Pla	–	41.8 ± 5.2	27.5 ± 6.6	27.5 ± 5.8	31.3 ± 5.6	37.2 ± 5.8
Drowsy	DEP/Act	–	45.4 ± 8.3	63.1 ± 6.4	63.8 ± 5.4	59.6 ± 8.9	49.3 ± 8.3
	HS/Act	–	17.8 ± 5.2	51.9 ± 7.7	50.1 ± 5.7	46.9 ± 6.7	34.6 ± 7.8
	DEP/Pla	–	44.0 ± 7.5	52.7 ± 7.7	49.4 ± 8.8	38.1 ± 7.2	29.9 ± 6.1
	HS/Pla	–	19.3 ± 5.6	41.8 ± 7.4	46.8 ± 5.7	32.0 ± 7.0	20.3 ± 5.7
Tired	DEP/Act	–	48.1 ± 6.9	62.4 ± 7.5	72.1 ± 6.5	70.3 ± 6.9	63.7 ± 7.1
	HS/Act	–	26.3 ± 4.1	55.1 ± 6.7	56.3 ± 5.9	50.7 ± 5.1	36.1 ± 5.4
	DEP/Pla	–	53.3 ± 4.3	65.5 ± 6.4	64.9 ± 6.7	53.3 ± 6.9	46.5 ± 6.1
	HS/Pla	–	23.7 ± 4.6	42.6 ± 6.0	45.4 ± 6.3	32.9 ± 5.3	23.5 ± 4.9
Talkative	DEP/Act	–	22.8 ± 5.6	11.2 ± 4.3	12.1 ± 4.3	14.2 ± 5.2	14.3 ± 4.8
	HS/Act	–	39.8 ± 5.4	15.7 ± 3.7	18.2 ± 3.7	21.3 ± 3.9	29.4 ± 4.1
	DEP/Pla	–	16.1 ± 3.3	9.1 ± 3.1	7.8 ± 2.8	18.4 ± 5.4	25.3 ± 7.2
	HS/Pla	–	36.2 ± 6.3	28.0 ± 5.9	28.8 ± 5.0	31.8 ± 6.1	34.8 ± 7.3
Hungry	DEP/Act	–	43.0 ± 8.1	27.5 ± 8.2	32.8 ± 8.3	45.8 ± 7.8	55.5 ± 8.9
	HS/Act	–	32.1 ± 7.0	20.2 ± 6.2	25.8 ± 6.6	36.9 ± 8.1	39.3 ± 7.1
	DEP/Pla	–	47.1 ± 9.6	40.6 ± 7.7	46.0 ± 9.0	49.8 ± 10.8	66.8 ± 9.8
	HS/Pla	–	30.1 ± 5.8	29.7 ± 7.1	31.0 ± 5.8	34.3 ± 6.9	38.8 ± 8.4
Mellow	DEP/Act	–	28.3 ± 8.6	12.3 ± 7.1	20.6 ± 9.3	11.8 ± 3.9	13.9 ± 4.8
	HS/Act	–	47.6 ± 6.4	37.7 ± 7.5	42.8 ± 6.5	42.1 ± 5.6	43.5 ± 5.8
	DEP/Pla	–	22.6 ± 8.9	7.6 ± 3.0	11.1 ± 4.8	9.9 ± 4.6	13.9 ± 6.4
	HS/Pla	–	53.7 ± 3.7	51.8 ± 4.7	49.1 ± 3.5	50.1 ± 3.9	51.5 ± 4.0
High	DEP/Act	–	4.0 ± 1.8	1.9 ± 0.8	2.7 ± 1.7	3.1 ± 2.0	3.3 ± 2.2
	HS/Act	–	0.1 ± 0.1	12.3 ± 6.0	7.3 ± 2.6	1.9 ± 1.3	1.6 ± 1.1
	DEP/Pla	–	2.6 ± 1.7	4.3 ± 2.2	3.2 ± 1.8	2.9 ± 1.7	2.5 ± 1.7
	HS/Pla	–	6.3 ± 6.3	21.7 ± 7.5	20.1 ± 8.0	15.8 ± 7.3	7.9 ± 6.1
Anxious	DEP/Act	–	37.2 ± 6.3	50.9 ± 8.0	47.1 ± 6.6	41.9 ± 6.6	38.3 ± 7.4
	HS/Act	–	1.3 ± 0.9	16.7 ± 8.2	8.7 ± 3.3	6.3 ± 2.3	3.5 ± 1.9
	DEP/Pla	–	44.9 ± 6.5	45.6 ± 4.7	41.7 ± 4.6	35.7 ± 4.9	32.9 ± 7.3
	HS/Pla	–	1.0 ± 1.0	5.7 ± 2.7	5.6 ± 3.0	1.3 ± 1.1	0.2 ± 0.2
Fearful	DEP/Act	–	23.7 ± 5.9	32.6 ± 7.1	28.9 ± 7.3	28.5 ± 7.6	28.2 ± 7.4
	HS/Act	–	0.6 ± 0.4	12.9 ± 8.0	2.8 ± 2.1	0.3 ± 0.2	0.2 ± 0.2
	DEP/Pla	–	26.5 ± 7.7	29.2 ± 7.6	25.7 ± 7.4	20.0 ± 7.2	19.9 ± 7.2
	HS/Pla	–	0.4 ± 0.4	1.5 ± 1.0	0.2 ± 0.2	0.3 ± 0.2	0.1 ± 0.1

(*continued*)

Table 1. Continued

Response	Subjects/ Drug	Time[a] −125 min	−60 min	+60 min	+90 min	+120 min	+180 min
PSC[b]	DEP/Act	–	14.9 ± 2.5	22.3 ± 4.0	20.4 ± 2.8	15.1 ± 3.2	15.3 ± 2.6
	HS/Act	–	1.2 ± 0.3	7.8 ± 1.5	6.8 ± 1.2	5.2 ± 0.9	3.9 ± 1.1
	DEP/Pla	–	9.1 ± 3.0	13.4 ± 3.2	14.6 ± 2.9	13.0 ± 2.6	11.5 ± 3.3
	HS/Pla	–	1.1 ± 0.5	5.1 ± 0.9	3.8 ± 1.0	2.7 ± 0.7	1.4 ± 0.7
HDRS[c]	DEP/Act	–	17.3 ± 1.4	–	–	–	20.2 ± 1.5
	HS/Act	–	0.0 ± 0.0	–	–	–	1.6 ± 0.4
	DEP/Pla	–	18.6 ± 1.8	–	–	–	17.8 ± 2.0
	HS/Pla	–	0.0 ± 0.0	–	–	–	0.5 ± 0.3

[a]Ketoconazole or placebo given at −120 min; IPS given at 0 min.
[b]Physical Symptoms Checklist.
[c]Hamilton Depression Rating Scale.

no substantive effects of diagnostic subtype, hospitalization status, or sex on the interaction between KTCZ and IPS.

Effects of KTCZ on IPS Plasma Levels

IPS levels were significantly higher following KTCZ pretreatment ($F = 32.72$, $df = 1,25$, $p < .0001$) (Figure 5). There was no significant main effect of diagnosis, although the KTCZ-induced increase in IPS levels tended to be greater in depressed patients ($F = 3.94$, $df = 1,25$, $p < .58$).

DISCUSSION

As predicted by our first hypothesis, pretreatment with KTCZ markedly diminished the cortisol response to IPS, confirming that the dosage of KTCZ used had the intended effect of inhibiting cortisol synthesis. The increase in the ACTH response to IPS after KTCZ pretreatment, presumably reflecting decreased negative feedback of cortisol at the pituitary and above, further showed that the degree of cortisol synthesis inhibition achieved was of physiological significance. Interestingly, the effects of KTCZ on cortisol were not evident until cortisol release was stimulated, but its effects on ACTH were manifested even without stimulation. This may have reflected the GC receptor antagonist properties of KTCZ (Sonino 1987), which could have decreased negative feedback of cortisol even without biosynthesis inhibition.

Other effects of KTCZ included an increase in GH levels in control subjects, while patients showed a slight decrease. The increase in controls is consistent with evidence that GCs inhibit GH secretion, via enhanced somatostatin tone (Giustina et al. 1995; Thompson et al. 1995). Cortisol synthesis inhibition with metyrapone has also been shown to increase GH release in healthy subjects (Dinan et al. 1994). The failure of the depressed patients in this study to show a similar increase in GH may reflect increased basal HPA activity which was insufficiently attenuated by the KTCZ .

KTCZ had some behavioral effects as well, most notably decreases in subjective ratings of dysphoric mood states (e.g., "sad," "irritable,") in the depressed patients. This is consistent with reports that antiglucocorticoids may have antidepressant properties (Price et al. 1996), although the effects observed here were not clinically significant. KTCZ also increased ratings of drowsiness and somatic symptoms as a late effect in both subject groups.

The major predictions from our second and third hypotheses, that non-HPA responses to IPS would be enhanced by KTCZ and that the magnitude of the enhancement would differ between patients and controls, were generally not confirmed. The hypothermia response was unaffected, while the GH response was actually diminished in the control subjects. The apparent blunting of the GH response resulted from the increase in baseline GH caused by KTCZ alone. Weak support for the enhancement hypothesis comes from the behavioral responses, of which several ("talkative," "tired," "anxious") showed slight increases, although without significant differences between patients and controls. If HPA function had been diminished by KTCZ to the same extent in both subject groups, we would have expected greater enhancement of non-HPA responses to IPS in the patients, since the inhibitory effects of the HPA axis on 5-HT_{1A} receptors would have been greater to start with. If, as actually seems the case, KTCZ's effects were relatively less in the patients owing to the intrinsically increased drive of the HPA axis, we would have expected them to show lesser enhancement of responses to IPS than the controls.

Our failure to observe prominent effects of antiglucocorticoid treatment on responses to IPS is surprising given the extensive preclinical literature suggesting inhibitory effects of the HPA axis on 5-HT_{1A} receptors.

Adrenalectomy in rats has been shown to increase hippocampal 5-HT_{1A} receptor binding (Biegon et al. 1985; Mendelson and McEwen 1992) and mRNA expression (Chalmers et al. 1993), effects which are reversed by GC administration. These actions have been observed as early as one hour postoperatively (De Kloet et al. 1986). While these studies have been interpreted as supporting tonic inhibitory effects of GCs on 5-HT_{1A} receptors, other work has indicated that exogenous GCs in intact animals decrease 5-HT_{1A} receptor binding (Mendelson and McEwen 1992), and attenuate 5-HT_{1A}-mediated behavioral and neuroendocrine responses (Bagdy et al. 1989; Haleem 1992). However, some investigators have failed to detect effects of adrenalectomy on 5-HT_{1A} mRNA expression (Holmes et al. 1995) or behavior (Young et al. 1993), cortisol synthesis inhibition on behavior (Kennett et al. 1985), or GC administration on 5-HT_{1A} receptor binding (Chalmers et al. 1994).

One limitation of the present study may have been use of the pyrimidinylpiperazine IPS as a probe of 5-HT_{1A} function. Agents of this class (including buspirone, gepirone, and tandospirone) are better characterized as *partial* agonists (or mixed agonists/antagonists) at the 5-HT_{1A} receptor, in contrast to such full agonists as 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (De Vry 1995) or the substituted benzamide flesinoxan (Schipper et al. 1991). Consistent with previous studies in humans, we obtained robust cortisol (Lesch et al. 1989; Kahn et al. 1994) and hypothermia responses (Lesch et al. 1990; Kahn et al. 1994). While we elicited a reliable GH response, our ACTH response was weak; previous findings with these neuroendocrine responses have also been inconsistent (Lesch et al. 1989; Kahn et al. 1994). Because of the non-5-HT_{1A}-mediated effects of KTCZ on cortisol, ACTH, and GH, our most sensitive response for evaluating 5-HT_{1A} function was hypothermia. This response was not altered by KTCZ pretreatment.

Another limitation stemmed from the fact that both KTCZ and IPS were given orally, undoubtedly resulting in additional variance owing to differences in absorption between subjects. We are not aware of any antiglucocorticoid that can be given parenterally, and access of independent investigators to parenteral 5-HT_{1A} agonists has been extremely limited (Seletti et al. 1995). The use of an oral 5-HT_{1A} agonist in the present study was particularly problematic, since plasma levels of IPS were significantly elevated as a result of KTCZ pretreatment. This effect is not surprising given KTCZ's inhibitory effects on degradative hepatic enzyme systems (Sonino, 1987). The increased IPS levels following KTCZ

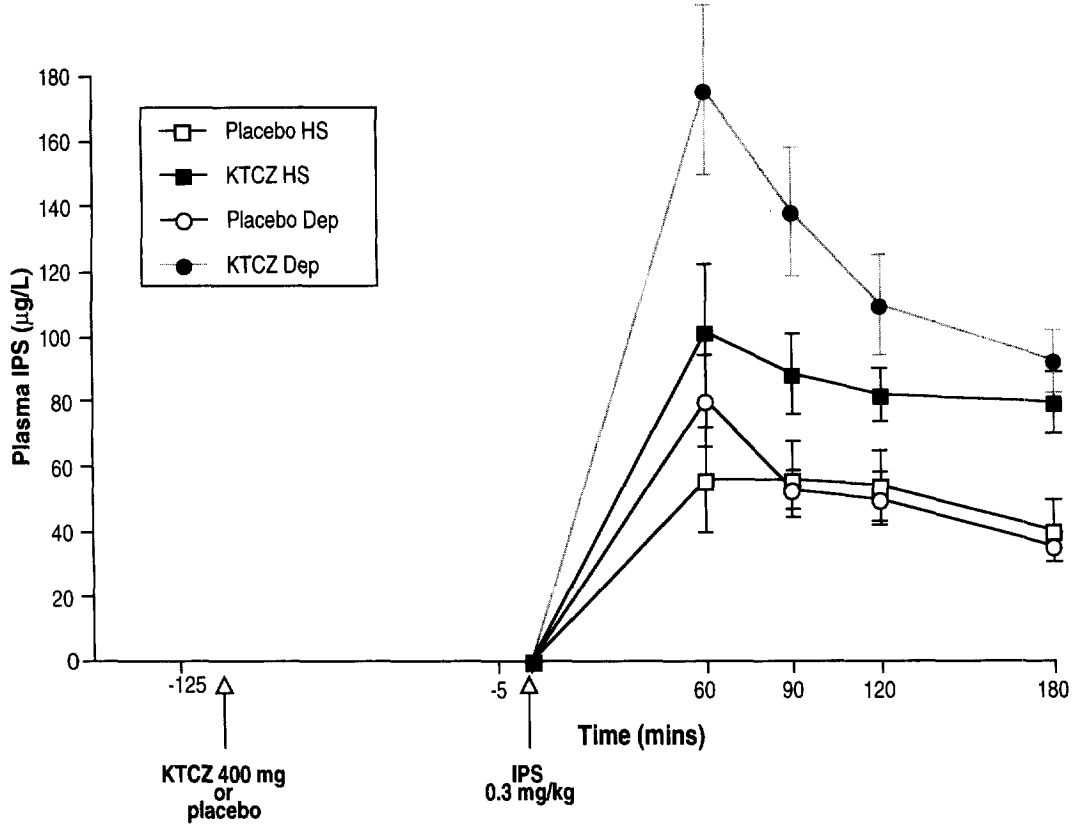

Figure 5. Mean ± SE plasma ipsapirone (IPS) levels following pretreatment with active ketoconazole (KTCZ) or placebo in depressed (Dep) and healthy subjects (HS).

might have been expected to cause enhanced cortisol, ACTH, GH, and hypothermia responses on pharmacokinetic grounds, while our pharmacodynamic hypotheses (based on decreased cortisol synthesis by KTCZ and consequent decreased inhibition of 5-HT_{1A} receptors by cortisol) predicted diminished cortisol and enhanced ACTH, GH, and hypothermia responses. In fact, we observed diminished cortisol and enhanced ACTH responses, while hypothermia responses were unchanged, and GH responses were diminished in control subjects. This pattern of findings does not suggest that pharmacokinetic factors played a major role in the outcome of the study. The fact that IPS levels tended to increase more after KTCZ pretreatment in patients than in controls was not reflected in differential responses to IPS between the two groups, nor did ANCOVA using IPS levels as a covariate alter these findings.

We did not replicate previous reports of blunted cortisol/ACTH (Lesch et al. 1990b) and hypothermia (Lesch et al. 1990a) responses to IPS in depressed patients compared with controls. In the present study, net cortisol response and peak change in cortisol were actually greater in patients than in controls, and the hypothermia response tended to be greater. Other investigators have also failed to detect differences in 5-HT_{1A}-mediated responses between depressed and healthy subjects (Meltzer and Maes 1994; Gillin et al. 1996). Careful review shows that positive studies have generally involved patient samples that were substantially inpatient or melancholic (Lesch et al. 1990a; Lesch et al. 1990b; Cowen et al. 1994; Moeller et al. 1994; Mobayed and Dinan 1990). In contrast, the present study comprised primarily outpatient nonmelancholics. This, plus the absence of a placebo IPS condition in our design, could account for the discrepant findings.

This study demonstrates the feasibility of using acute antiglucocorticoid treatment to investigate HPA/5-HT interactions in humans, although we failed to show that GC modulation of 5-HT_{1A} receptor function is altered in depression. However, even though physiological effects were obtained with both KTCZ and IPS, more potent and selective agents that could be administered parenterally (e.g., flesinoxan as a 5-HT_{1A} probe) (Seletti et al. 1995) would permit a stronger test. Given the extensive preclinical evidence of 5-HT_{1A} involvement in mediating HPA axis and antidepressant effects on the 5-HT system, as well as the clinical promise of 5-HT_{1A}-selective agents, further work in this area seems worth pursuing.

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