Gender Differences in Brain Metabolic and Plasma Catecholamine Responses to Alpha₂-Adrenoceptor Blockade

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α_2-Adrenergic receptors modulate the release of several neurotransmitters implicated in the treatment and pathophysiology of mood and anxiety disorders. Significant sex differences occur in the prevalence of both disorders. To test whether gender affects α_2 function, the plasma catecholamine and brain metabolic responses to α_2 blockade were measured in male and female volunteers. Ten female and thirteen male volunteers underwent [¹⁸F]-fluoro-deoxyglucose (FDG) positron emission tomography (PET) scans before and after infusion of idazoxan (200 µg/kg). Measures of plasma catecholamines, blood pressure, and anxiety were obtained. Norepinephrine responses were larger in males. Women showed global increases in metabolism, whereas males had no global changes and some regional decreases in FDG uptake following idazoxan administration. The differences in norepinephrine increases are consistent with previously reported effects of gender on sympathetic activation. The PET data suggest gender differences in responses to α_2-receptor blockade in brain as well.   [Neuropsychopharmacology 16:298–310, 1997] Published 1997 by Elsevier Science Inc.

Gender has long held a prominent position in psychological and social theories of human psychopathology. Whether gender may influence the biological underpinnings of mental illness is not well understood. Among the biological systems thought to affect the pathophysiology of psychiatric disorders, the adrenergic system has been reported to exhibit sex differences across species and at multiple levels.

One of the elements of the adrenergic system for which there is evidence of sexual differentiation is the α_2-adrenergic receptor. Activation of α_2-adrenoceptors on cell bodies in the locus ceruleus reduces the firing rate of central noradrenergic neurons, and activation of presynaptic receptors on noradrenergic nerve endings inhibits neurotransmitter release (Freedman and Aghajanian 1984; Dennis et al. 1987; van Veldhuizen et al. 1993), thus providing feedback control of the noradrenergic system. Although these autoinhibitory effects are the best known functions of α_2-receptors, most central α_2-adrenoceptors are postsynaptic receptors (Heal et al. 1993). Postsynaptic α_2-adrenoceptors have been identified on serotonergic nerve endings that inhibit neurotransmitter release when activated (Raiteri et al. 1990). Postsynaptic receptors also are abundant on cor-

tical neurons in primate brain, although their function is not known (Aoki et al. 1994).

Responses to α_2-adrenoceptor drugs can differ by sex and be influenced by estrogen concentration, although the nature of effects vary depending on the measure and system being studied. A preclinical study of central analgesia found male rats to exhibit greater analgesic responses to clonidine (Kiefel and Bodnar 1991). Estradiol treatment reduces high-affinity binding by α_2-agonists and attenuates inhibition of norepinephrine release mediated by α_2-receptors in rat hypothalamus (Karkanias and Etgen 1993, 1994). Augmentation of norepinephrine release from rat frontal cortex slices treated with yohimbine has been reported to vary across the estrous cycle, rising after estradiol levels fall during diestrus (Parada et al. 1991). Collectively, these studies suggest that central α_2-adrenoceptor function is attenuated by estrogen and as a consequence is relatively "blunted" in females. However, in contrast, norepinephrine release from cardiac sympathetic nerve endings following rauwolscine was found to be greater in female than in male rat hearts (Du et al. 1991).

In humans, clonidine produces greater vasoconstriction and growth hormone release in males, consistent with a relative attenuation of α_2 function in women (Freedman et al. 1987; Tulandi et al. 1987), although the same drug has been reported to result in greater inhibition of norepinephrine release in women (Del Rio et al. 1993). Whether α_2-receptor function is influenced by gender and/or estrogen concentration under physiological conditions in humans is not known. α_2-Adrenoceptor binding in platelets has been reported both to vary between the sexes and across the menstrual cycle and not to differ by sex or menstrual status at all (Jones et al. 1983; Sundaresan et al. 1985). Estrogen treatment increases platelet α_2-antagonist binding in males, although the functional consequences are not known, nor whether such an effect can be generalized to cyclical changes in estrogen levels in females (Reimann et al. 1987). Interestingly, sympathoneuronal responses to a variety of physiological stressors have consistently been found to differ between the sexes; males typically show larger responses (Frankenhauser et al. 1976; Sanchez et al. 1980; Diamond et al. 1993). Gender differences in the regulation of release of norepinephrine by α_2-adrenoceptors could account for some of the reported differences in sympathetic activation.

Blockade of α_2-receptors can be demonstrated *in vivo* by increases in plasma norepinephrine following a challenge with an α_2-antagonist (Elliot et al. 1984; Grossman et al. 1991). Moreover, the distribution of noradrenergic responses to such challenges suggests differences in the functional sensitivity of α_2-receptors in selected clinical populations (Charney et al. 1984; Siever and Davis 1985; Goldstein et al. 1991). Such differences have been proposed to be relevant to the pathophysiology of mood

and anxiety disorders, each of which differs by sex in prevalence and expression (Weissman and Klerman 1977; Eaton et al. 1994). It therefore is of interest to identify gender differences in α_2-adrenoceptor function.

We have adapted a method of serial [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) scans coupled with a pharmacological challenge to assess more directly central α_2 function (Brooks et al. 1987; Chang et al. 1987, 1989; Schmidt et al. 1995, 1996). FDG PET scans are acquired before and following an infusion of idazoxan, an α_2-adrenoceptor antagonist. Idazoxan is highly selective for α_2- over α_1-adrenoceptors (Doxey et al. 1983). Some data suggest that idazoxan has higher affinity for presynaptic receptors, although the drug blocks both pre- and postsynaptic α_2-receptors (Martire et al. 1988). Unlike yohimbine, idazoxan has no direct effect on serotonin or dopamine receptors (Scatton et al. 1980; Winter and Rabin 1992); although it does have high affinity for the recently defined I_2-imidazoline binding sites (Michel et al. 1989). Animal studies using [^{14}C]-2-deoxy-D-glucose autoradiography have demonstrated reductions in glucose metabolism in projection fields of the locus ceruleus following challenges with selective and nonselective α-adrenoceptor antagonists, including idazoxan (Savaki et al. 1982; French et al. 1995).

Our initial study using this method included only males (Schmidt et al. 1995). We have subsequently included healthy young women. In addition to developing reference data for clinical samples, we were interested in testing whether gender influenced the effects of α_2-adrenoceptor blockade in brain independent of clinical state. The present study compares the brain metabolic and peripheral responses to idazoxan in healthy young men to those in a group of healthy young women.

MATERIALS AND METHODS

Thirteen male (mean age $\pm$ SD: 25 $\pm$ 5.1 years) and ten female volunteers (25.4 $\pm$ 6.9 years) were studied following a complete clinical screening. The screening included a semistructured diagnostic interview by a board-certified psychiatrist (M.E.S.), physical examination, EKG, EEG, complete blood chemistries, and urine drug screens at the time of screening and the day before the PET experiment. All subjects gave written consent after an explanation of the purpose and risks associated with participation. Exclusionary criteria included confirmed or possible pregnancy, history of any significant medical illness, psychiatric illness or treatment with psychotropic medications, history of drug or alcohol abuse, or history of clinical mood or psychotic disorders in any first-degree relative. Subjects were free of all medications except contraceptives for 2 weeks prior to the scan. Five of the women were taking contraceptives at the time of the scan. Scans were not scheduled with re-

gard to menstrual cycle. Volunteers were placed on a low-monoamine diet for 3 days prior to the scan and were admitted to a research unit the night before the study.

Approximately 1 hour before the scans, a 20-gauge catheter was inserted into the radial artery in the right wrist under local anesthesia (1% lidocaine) for blood sampling, and a 22-gauge catheter was inserted into an antecubital vein in the left arm for infusion of drug and tracer. All studies were conducted using a Scanditronix PC-1024-7B camera (Scanditronix, Stockholm, Sweden) with the gantry aligned to the canthomeatal line. The first emission scan was obtained 30 minutes after a slow bolus injection of 3 mCi of FDG. This was followed by an infusion of idazoxan (200 μg/kg). At the completion of the infusion, 5 mCi of FDG was injected and emission data acquired 30 minutes later. Subjects performed an auditory continuous performance task (CPT) (Sunrise Systems CPT V2.20, Sunrise Systems, Pembroke, MA) described previously (Schmidt et al. 1995). Subjects had their eyes patched during the 30 minutes following each injection of FDG tracer. After positioning on the camera table subjects remained supine until completion of the study. Details of the scanning method and camera performance characteristics have been previously reported (Schmidt et al. 1995, 1996). The tracer injection for the second FDG scan occurred 90 minutes after the tracer injection for the first scan. As the half-life of FDG is 110 minutes, this requires subtracting residual activity of the first scan from the FDG uptake during the second scan. The model correction used was that developed by Brooks and others (1987). Plasma FDG activity immediately before the second tracer injection is measured, and estimates of tracer clearance and decay are used to subtract residual activity from the second scan. This method has been validated under resting conditions (Brooks et al. 1987), during cognitive tasks (Chang et al. 1987), and placebo challenges (Schmidt et al. 1996). The tracer dose ratio and timing of the emission scans were adjusted to minimize the error in the modeled estimates (Brooks et al. 1987). The plasma time activity curve of the tracer was determined from arterial samples drawn after tracer injection. Blood pressure and heart rate were measured via a pressure transducer in the arterial line used for blood sampling. Blood pressure and heart rate were recorded every 10 minutes for 30 minutes prior to infusion with idazoxan, every 10 minutes for 1 hour after starting the infusion, and 90 minutes after the start of the infusion. Arterial samples for drug and catecholamine concentrations were collected at those points. Samples were collected into glass tubes with EDTA and kept on ice until centrifugation to separate the plasma. A sample was collected from all female subjects before the first scan to determine estradiol concentration. The sample was collected into a glass tube with no preservatives and kept on ice until the se-

rum was decanted. Plasma and serum samples were then stored at −70°C until assayed. Following completion of the scans, subjects rated their level of anxiety during the entire experiment using the Spielberger State-Trait Anxiety Inventory (Spielberger et al. 1983).

Image Analysis

PET images were analyzed by two different methods: regions of interest (ROI) and pixel by pixel. ROIs were used to permit inspection of individual data, to test for between group differences, and to determine the direction of change of significant interactions between groups and has been described (Schmidt et al. 1995). Global CMRglu was defined as an average of values from all cortical ROIs. One of the image volumes from a male subject lacked a suitable A plane; therefore, the cortical regions from the B through E planes were used to calculate global CMRglu. The pixel-based method was used to facilitate within-group analyses. Preprocessing of image data prior to pixel-based analysis included the following: for each subject the original PET image volumes were linearly interpolated from 21 to 43 slices using ANALYZE (Biodynamic Research Unit, Mayo Clinic, Rochester, MN). The postinfusion image volume was registered with the preinfusion image volume using an algorithm described by Minoshima and others (1992). The intercommissural line was used to define a reference plane. The registered image volume pairs were stereotactically normalized to Talairach coordinates (Talairach and Tournoux 1988), and contrasts were performed (postinfusion minus preinfusion values) using statistical parametric mapping software (MRC Cyclotron Unit, Hammersmith Hospital; Friston et al. 1991). The contrast or "difference" images were thresholded to critical value intervals (z values corresponding to $p < .05, .01$, and $.001$, two-tailed) and the thresholded contrast images were mapped onto a reference set of MRI image templates stereotactically normalized to Talairach coordinates (MRC Cyclotron Unit, Hammersmith Hospital). Both the ROI and the pixel-based analyses were applied to the "absolute" metabolic data. Relative regional metabolic rates were analyzed by normalizing regional values to global CMRglu (Clark et al. 1985).

Plasma catecholamine and idazoxan concentrations were determined by high-performance liquid chromatography (HPLC) (Schmidt et al. 1995; Eisenhofer et al. 1986). Serum 17 β-estradiol was determined by radioimmunoassay (Corning Hazleton Laboratories, Vienna, VA).

Statistical Analysis

Comparisons of image data within groups, either by region or by pixel, from pre- versus postidazoxan scans were evaluated by two-tailed paired t-tests with $p < .05$

set as the level for significance. Between-group comparisons were performed on the ROI data by two-factor (sex and time) ANOVA. Simple effects in regions with significant main effects or interactions also were tested by paired t-tests, using two-tailed distributions. Corrections for multiple comparisons were not employed in the analysis of image data, because of the exploratory nature of this study. Catecholamine and drug concentrations were log-transformed for data analysis to make the variance more homogeneous. Cardiovascular and catecholamine values were analyzed by two-factor ANOVA, with the response value as a repeated-measures factor. Differences in regional and global metabolic rates (pre- versus postidazoxan) were used to calculate Pearson's correlation coefficients with changes in peripheral measures and with mood and anxiety ratings. For correlation analysis, cardiovascular changes in response to idazoxan were calculated by subtracting the average of three baseline values recorded every 10 minutes prior to infusion from the average of three values recorded every 10 minutes after the infusion had been completed. Changes in catecholamine concentrations were calculated as the area under the curve (AUC) over the 30 minutes following completion of the infusion (and during the second tracer uptake period) minus the AUC over 30 minutes of baseline prior to the infusion.

RESULTS

Cardiovascular Effects

Diastolic blood pressure at baseline was lower in the female subjects (males: 73.7 ± 8.8 mm Hg; females: 64.1 ± 7.0 mm Hg; $t = 2.80, p < .01$, df $= 21$) (Figure 1). Systolic blood pressure increased during and following infusion with idazoxan in both groups (main effect of time: $F = 19.50, p < .0001$), men had slightly higher values at all time points (main effect of sex on systolic blood pressure $F = 3.05, p < .10$). Similarly, diastolic blood pressure showed a modest increase with drug (main effect of time $F = 2.75, p < .005$) and was higher in males throughout the study (main effect of sex: $F = 9.81, p < .005$). There were no significant changes in heart rate, and there were no significant interactions (time by sex) on either blood pressure parameters or heart rate. Because of the baseline differences, the data also were analyzed following normalization to the average of the baseline measurements. Normalized systolic and diastolic blood pressure increased following the infusion (main effect of time: $F = 19.45, p < .0001$ for systolic and $F = 2.05, p < .05$ for diastolic blood pressure), but gender no longer affected either measure (main effect for sex: $F = .097$ for systolic, $F = .24$ for diastolic blood pressure), nor were there interactions between the two factors.
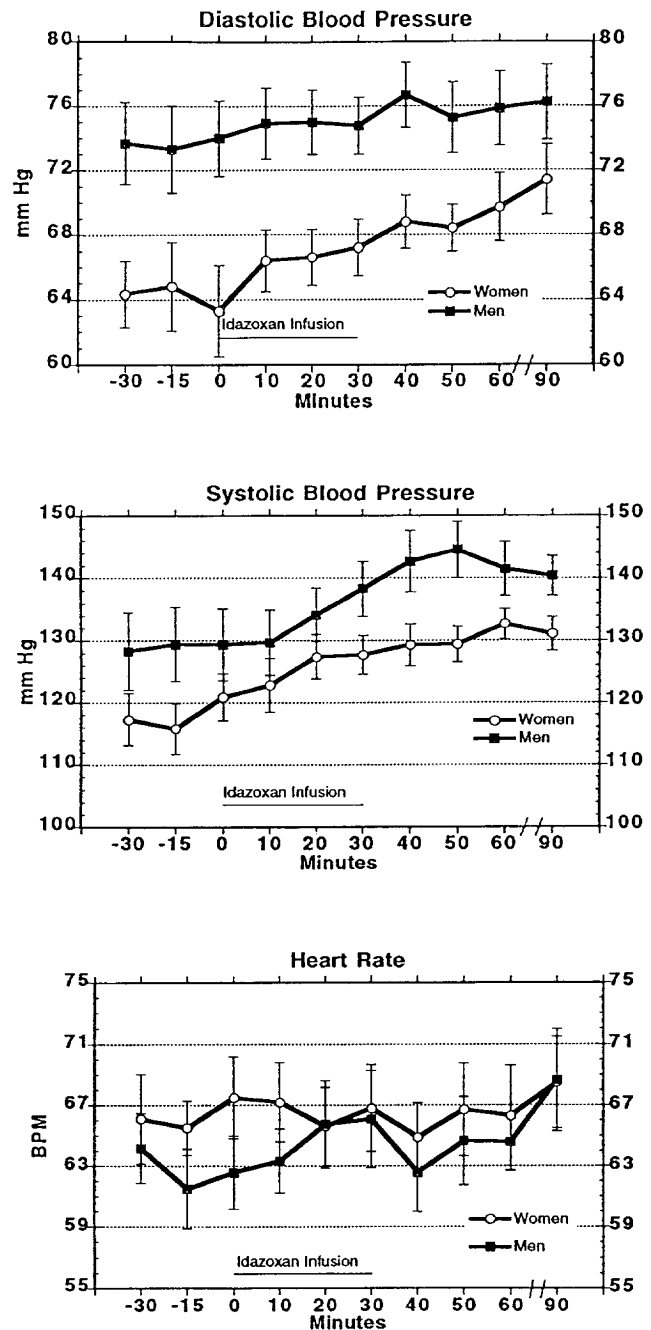
Figure 1. Cardiovascular measures. The mean ± SEM values are plotted for men ($n = 13$) and women ($n = 10$). The statistical analyses of the data (log-transformed) are presented in the Results section.

Plasma Measures

Norepinephrine and epinephrine levels increased during the infusion of idazoxan (main effect of time on norepinephrine (NE): $F = 21.94, p < .0001$; epinephrine: $F = 9.69, p < .0001$; Figure 2). There was a trend for an interaction of time by sex on norepinephrine ($F = 1.72, p < .10$). Idazoxan AUC (min*ng/ml) was significantly

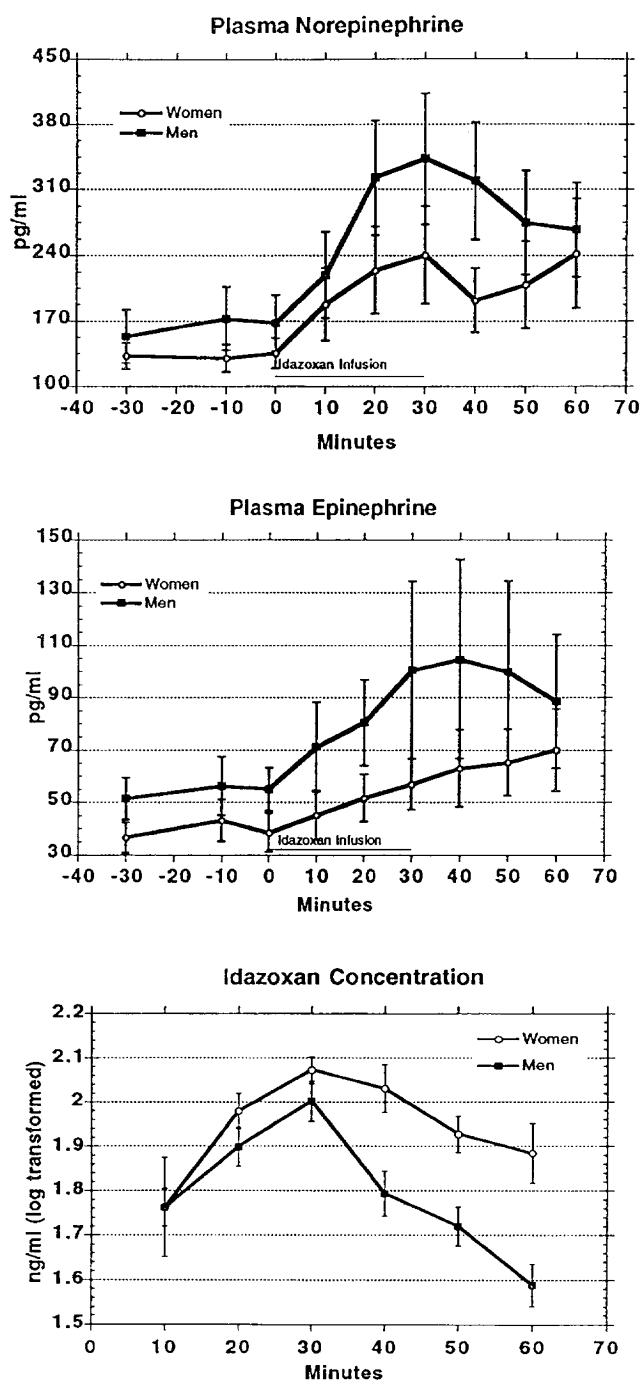**Figure 2.** Plasma measures. The mean ± SEM values are plotted for men (n = 10 for plasma catecholamines, 8 for plasma idazoxan) and women (n = 10 for plasma catecholamines, 8 for plasma idazoxan). The number of subjects for plasma measures varies, depending on the number of subjects for whom complete data were available. The statistical analyses of the data (log-transformed) are presented in the Results section.

higher in female subjects (females: 7183.1 ± 1647.5; males: 4510.5 ± 1464.3; t = 3.81, p < .01, df = 18); therefore, the norepinephrine concentrations were normalized to drug concentration (log[NE]/log[IDX]). Men

had an even larger increase in the ratio compared to women (main effect of time: F = 6.92, p < .0001, main effect of sex: F = 2.88, p < .10, interaction of time by sex: F = 4.24, p < .002).

Global Metabolic Effects

Global brain metabolism after the infusion increased in women while remaining the same in men resulting in a significant interaction of time and sex (F = 4.15, p < .05; post hoc test of postinfusion global metabolic rate minus preinfusion rate in women: t = 4.28, p < .01, in men: t = .46).

Regional Effects

Change in "absolute" metabolic rates after idazoxan significantly interacted with sex in 14 regions (Table 1, Figure 3). In most cases this was due to significant increases in metabolism following the infusion in women, but in some regions, particularly the right prefrontal regions, the interaction was a product of decreases in regional metabolism in the men. There was no main gender effect on any of the regions. Time produced a significant main effect for 12 regions, reflecting areas that increased significantly in both groups (the mesial occipital regions encompassing the primary visual cortex), regions that, with all subjects averaged, showed a significant increase (mesial occipital regions above the primary visual cortex, thalamic regions, and the left posterior frontal region, C plane) or regions that increased so much in women that the effect carried when the two groups were analyzed together (e.g., the cingulate region).

Effects on Metabolic Rates Normalized to Global CMRglu

Time had a significant effect on 17 regions, 10 of which also showed a significant effect on absolute metabolic rate (Table 1). Analysis of simple effects revealed significant increases in relative rates in mesial occipital regions in both groups (occipital region: C plane, and both primary visual cortex regions), additional significant increases in posterior midline regions in women (posterior medial cortex: A plane, superior occipital: B plane, cingulate cortex), the right thalamus in women, and the left posterior frontal region (C plane) in men. Relative rates decreased in medial and right frontal regions in both men and women; however, significant decreases occurred in three regions only in men (right anterior frontal: B and C plane, anterior medial frontal: D plane). An interaction between gender and time occurred in a single region: the left sylvian region, C plane.

Table 1. Analysis of Regional Cerebral Glucose Metabolism Pre and Post Idazoxan: Absolute CMRglu and as a Fraction of Global CMRglu (Normalized)

Region	CMRglu Men Pre	Men Post	Women Pre	Women Post	ANOVA Time Absolute	Time Normal	Time × Sex Absolute	Time × Sex Normal
Global CMRglu	11.71 (1.14)	11.56 (1.39)	11.01 (1.36)	11.75 (1.23)			4.81*	
A plane								
Anterior medial frontal	11.82 (1.36)	11.60 (1.44)	11.36 (1.73)	11.63 (1.53)				
Middle medial cortex	11.59 (1.30)	11.68 (1.63)	11.71 (1.51)	12.72 (1.15)				
Posterior medial cortex	13.05 (1.71)	13.45 (1.96)	11.68 (2.32)	13.45 (2.22)	13.35‡	6.64*	5.33*	
Left anterior frontal	12.48 (1.43)	12.52 (1.27)	11.77 (1.76)	12.26 (1.77)				
Right anterior frontal	12.62 (1.59)	12.13 (1.63)	11.79 (1.46)	12.22 (1.32)		4.59*		
Left posterior frontal	12.47 (1.36)	12.36 (1.58)	11.29 (1.43)	11.97 (1.23)				
Right posterior frontal	12.65 (1.37)	12.17 (1.04)	11.78 (1.40)	12.28 (1.25)				
Left parietal	11.74 (1.27)	12.00 (1.79)	11.03 (1.71)	12.35 (1.66)	6.91‡	4.48*		
Right parietal	12.62 (1.51)	12.33 (1.64)	11.38 (1.40)	11.74 (1.68)				
B plane								
Anterior medial frontal	11.83 (1.36)	11.45 (1.26)	10.99 (1.85)	11.56 (1.89)			6.83*	
Superior occipital	12.07 (1.49)	12.28 (1.62)	10.72 (1.88)	12.25 (1.75)	11.92‡	12.08‡	6.80*	
Left anterior frontal	12.45 (1.61)	12.11 (1.60)	11.44 (1.79)	12.38 (1.71)			6.63*	
Right anterior frontal	12.73 (1.50)	11.93 (1.17)	11.77 (1.77)	12.14 (1.63)		6.34*	8.86†	
Left posterior frontal	12.78 (1.61)	12.68 (1.59)	11.76 (1.92)	12.89 (1.22)			4.32*	
Right posterior frontal	13.43 (1.60)	13.10 (1.71)	12.16 (1.50)	12.59 (1.59)		4.30*		
Left rolandic	11.18 (1.14)	11.08 (1.40)	10.31 (1.37)	11.28 (1.10)				
Right rolandic	11.16 (1.45)	11.03 (1.46)	10.40 (1.18)	10.95 (1.30)				
Left parietal	11.32 (1.71)	11.50 (1.73)	10.83 (1.71)	11.71 (1.65)				
Right parietal	11.85 (1.33)	11.41 (1.31)	11.08 (1.98)	11.17 (1.68)		5.85*		
Middle cingulate	11.59 (1.34)	11.49 (1.52)	10.22 (1.42)	12.04 (1.09)	6.46*	4.91*	8.09†	
C plane								
Anterior medial frontal	11.69 (1.32)	11.42 (1.32)	11.14 (1.52)	12.16 (1.39)			5.51*	
Occipital	11.91 (1.19)	12.62 (1.63)	11.02 (1.45)	13.05 (1.94)	15.37‡	18.81‡		
Left anterior frontal	12.57 (1.14)	12.33 (1.64)	11.67 (1.73)	12.47 (2.03)				
Right anterior frontal	12.58 (1.20)	11.78 (1.59)	12.30 (1.83)	12.65 (1.41)		6.70†	4.18*	
Left posterior frontal	12.10 (1.71)	12.76 (1.78)	11.72 (1.74)	12.69 (1.63)	6.67*	7.10†		
Right posterior frontal	12.90 (1.66)	12.93 (1.30)	12.38 (1.35)	13.18 (1.66)				
Left sylvian	11.45 (1.53)	11.36 (1.75)	11.12 (1.58)	11.21 (1.57)				6.05*
Right sylvian	11.69 (1.67)	11.20 (1.48)	10.87 (1.51)	11.62 (1.32)				
Left parietal	11.21 (1.35)	11.38 (1.88)	10.40 (1.48)	11.49 (1.38)		4.59*		
Right parietal	11.35 (1.26)	10.99 (1.65)	10.42 (0.99)	10.93 (1.47)			5.20*	
Left parietal/occipital	9.41 (1.65)	9.39 (1.69)	8.69 (0.85)	9.30 (1.03)				
Right parietal/occipital	9.74 (1.31)	9.48 (1.44)	8.55 (0.84)	9.24 (1.28)			4.82*	
C minus 1 plane								
Left visual cortex	10.95 (1.13)	12.63 (2.06)	10.14 (1.61)	11.81 (1.50)	18.39‡	17.99‡		
Right visual cortex	11.50 (1.71)	12.36 (1.64)	10.29 (1.62)	12.31 (1.46)	19.85‡	30.96‡		
D plane								
Anterior medial frontal	11.89 (1.24)	10.99 (1.71)	10.88 (1.39)	11.29 (1.20)		8.71†	5.00*	
Left anterior frontal	12.54 (1.55)	12.76 (1.84)	11.47 (2.20)	12.50 (1.57)	5.51*			
Right anterior frontal	13.00 (1.96)	12.50 (2.16)	11.63 (1.58)	12.74 (1.76)			4.65*	
Left posterior frontal	12.05 (1.70)	11.91 (2.32)	11.23 (1.85)	11.84 (1.36)	4.57*			
Right posterior frontal	11.82 (1.87)	12.25 (2.36)	11.06 (1.05)	11.99 (1.44)				
Left anterior temporal	11.69 (1.32)	11.41 (1.70)	10.58 (1.18)	11.32 (1.24)				
Right anterior temporal	11.79 (1.40)	11.36 (1.76)	11.03 (1.26)	11.67 (1.22)				
Left middle temporal	11.41 (1.09)	11.68 (2.05)	10.69 (1.55)	11.41 (1.53)				
Right middle temporal	12.07 (1.48)	11.85 (2.32)	10.89 (1.38)	11.34 (1.31)				
Left posterior temporal	10.09 (1.24)	10.34 (1.40)	9.85 (1.38)	10.35 (1.93)				
Right posterior temporal	10.03 (1.70)	10.38 (1.86)	8.98 (1.61)	9.87 (1.80)				

(continued)

Table 1. *(continued)*

| | CMRglu | | | | ANOVA | | | |
| | Men | | Women | | Time | | Time × Sex | |
Region	Pre	Post	Pre	Post	Absolute	Normal	Absolute	Normal
Left thalamus	11.62 (2.10)	12.12 (2.23)	10.83 (1.21)	11.83 (2.08)	4.51*			
Right thalamus	11.37 (2.25)	11.97 (2.45)	10.77 (0.93)	12.67 (1.77)	7.87†	11.38†		
Basal Ganglia								
Left caudate (head)	11.45 (1.88)	11.57 (2.86)	10.77 (1.55)	12.09 (1.09)				
Right caudate (head)	11.11 (2.03)	11.28 (2.80)	10.73 (1.12)	11.41 (1.23)				
Left anterior putamen	11.41 (2.03)	11.09 (3.04)	10.51 (1.57)	11.13 (1.09)				
Right anterior putamen	11.39 (2.08)	10.11 (2.13)	10.32 (1.36)	11.00 (1.44)			4.31*	
Left posterior putamen	11.34 (1.78)	10.75 (2.54)	10.34 (1.66)	10.84 (1.26)				
Right posterior putamen	10.69 (1.45)	10.26 (2.05)	9.69 (1.59)	10.18 (0.98)				
E plane								
Anterior medial frontal	11.57 (1.34)	11.14 (1.26)	10. 85 (1.71)	11.05 (1.47)		8.09†		
Left anterior frontal	12.21 (1.42)	12.09 (1.31)	11.53 (1.56)	11.91 (1.34)				
Right anterior frontal	12.59 (1.49)	11.86 (1.46)	11.77 (1.07)	12.19 (1.36)			4.46*	
Left posterior frontal	11.11 (1.63)	11.07 (1.32)	10.83 (1.59)	11.30 (1.10)				
Right posterior frontal	11.74 (1.62)	11.43 (1.83)	10.85 (1.50)	11.90 (1.54)			5.75*	
Left temporal	10.42 (1.35)	10.52 (1.63)	9.92 (1.42)	10.68 (1.34)				
Right temporal	10.93 (1.34)	10.54 (1.74)	10.02 (1.19)	10.64 (1.21)				
Left hippocampus	8.54 (1.31)	8.54 (1.04)	8.09 (0.96)	8.58 (0.99)				
Right hippocampus	8.82 (1.36)	8.42 (1.27)	7.82 (1.04)	8.77 (0.78)			5.50*	

Regional metabolic rates before and after infusion and results of two-way (time and sex) ANOVA of FDG uptake in regions of interest, with repeated measures for drug condition. Metabolic values are group (n = 13 males, n = 10 females) mean glucose metabolic rate (mg glucose/100 gm tissue/min) (SD). Only the significant F values are listed for effects on absolute metabolic rates and following ratio normalization to global CMRglu.
*$p < .05$; †$p < .01$; ‡$p < .001$. Main effect of time: df = 1,21; interaction: df = 1,21.

Behavioral Effects

CPT performance tended to improve following the infusion (percent correct: 73% ± 25% during the preinfusion scan, 84% ± 12% during the postinfusion scan; main effect for time: F = 2.76, $p < .10$). There was no difference between the sexes, nor was there an interaction between sex and time. Spielberger state anxiety ratings were not significantly different from reference values for either group (Spielberger et al. 1983), although there was a trend for males to rate themselves as more anxious (males, mean ± SD = 36.3 ± 11.8; females = 29.2 ± 4.7. t = 1.79, $p < .10$, df = 20).

Relationships among Responses

No significant correlations occurred between the peripheral response measures: drug concentration, blood pressure response, or catecholamine increase following the infusion. Norepinephrine levels at baseline were highly correlated with levels at the completion of the infusion in both groups (r = 0.78, $p < .01$, df = 8 for the males; r = 0.91, $p < .0001$, df = 8 for the females). Estradiol concentrations positively correlated with increases in plasma norepinephrine (r = 0.67, $p < .05$, df = 8). In testing for correlations between peripheral measures

and regional absolute metabolic changes in brain, only those regions that significantly differed between the two scans were considered. Drug AUC correlated with metabolic increases in the occipital (r = 0.71, $p < .05$, df = 6) and the right parietal occipital regions (r = 0.93, $p < .001$, df = 6), C plane, in women. Increases in systolic pressure positively correlated with metabolic increases in the left posterior frontal region, A plane (r = 0.66, $p < .05$, df = 8), and the right posterior frontal region, D plane (r = 0.65, $p < .05$, df = 8), in females. Increases in plasma norepinephrine negatively correlated with increases in the primary visual regions in both groups (C minus 1 plane), significantly so on the left in women (r = −0.63, $p < .05$, df = 8) and on the right in men (r = −0.75, $p < .01$, df = 8). Estradiol concentrations did not significantly correlate with any of the regional changes in women.

DISCUSSION

Brain metabolic responses to idazoxan differed substantially between young male and female volunteers. We observed gender differences in noradrenergic and pressure responses as well, consistent with several studies that report that males exhibit a more robust activation
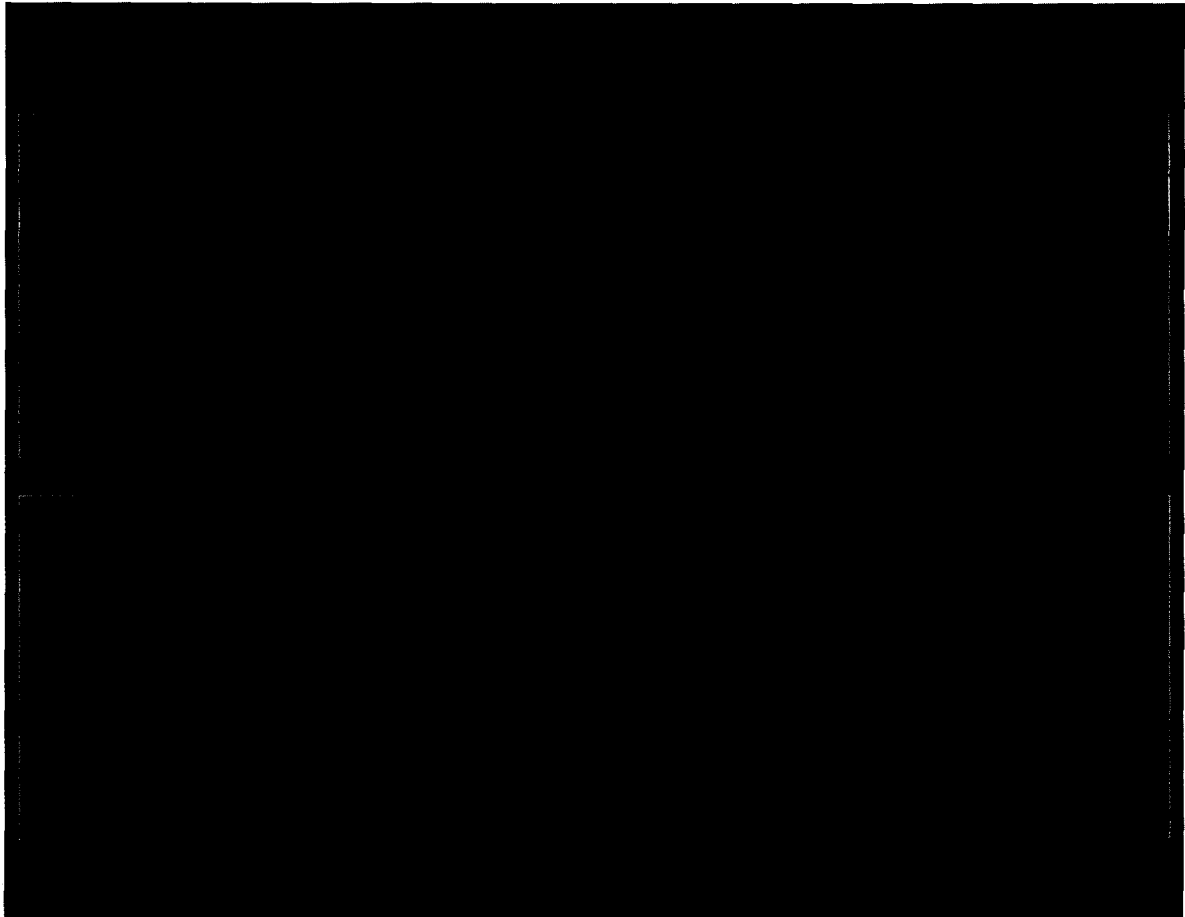
Figure 3. Brain glucose metabolism changes following idazoxan administration. Pixels in the stereotactically normalized FDG PET images (see Methods) that significantly differ between the scan pairs (postinfusion scan minus preinfusion scan) have been mapped onto transaxial planes from an MRI that has been stereotactically normalized to Talairach coordinates. The planes are arranged from left to right, the inferior most plane is on the bottom left. Left and right are the viewer's left and right. *Top*, pixels that significantly change in the males ($n = 13$); *bottom*, pixels that significantly change in the females ($n = 10$). Postinfusion > preinfusion: white $= p < .001$ ($z > 3.30$), red $= p < .01$ ($z > 2.57$), orange $= p < .05$ ($z > 1.96$). Postinfusion < preinfusion: blue $= p < .05$ ($z > 1.96$).

of the sympathoadrenal system after a variety of physiological stressors (Frankenhauser et al. 1976; Sanchez et al. 1980; Diamond et al. 1993). When contrasted with the larger plasma catecholamine response to idazoxan found in men, the much greater increase in brain glucose metabolism observed in women is particularly interesting. It is worth considering mechanisms by which such differences in metabolic responses to idazoxan could occur.

A critical methodological issue is whether the changes in brain metabolism reflect an order effect of the scans. In a recent study of test–retest reliability of serial FDG PET scans, we found global metabolism to increase slightly but not significantly in two independent samples that received single-blind placebo challenges (Schmidt et al. 1996). Modest global increases have been observed by others comparing consecutive measure-

ments of brain glucose metabolism (Bartlett et al. 1988; Sachs et al. 1986) and brain blood flow (Matthew et al. 1993). Such increases may reflect diurnal changes in brain activity or increases in arousal over the course of an experiment. Under the same conditions used in the present study, absolute CMRglu in 6 out of 62 regions significantly increased after a placebo infusion, and no regions showed decreases. Relative regional CMRglu significantly differed in 2 out of 62 regions, but no more than would be expected by chance (Schmidt et al. 1996). The sample that received placebo infusions consisted of 5 male and 5 female volunteers. We reanalyzed those data testing gender as a factor and found no effect or interaction with gender (unpublished data). Although a portion of the increases in brain metabolism that occurred in women in the present study may reflect nonspecific increases in brain metabolism, the average global

increase we saw in women after idazoxan administration (7%) was nearly twice that seen after placebo (4.2%). A further implication of the slight increases we observed following placebo is that slight metabolic decreases caused by drug may be obscured by this method, and the regional decreases that occurred in men may represent greater relative changes in metabolism.

The regional changes in metabolic rate are not likely a function of the changes in blood pressure or cerebral blood flow. Blood flow is not rate-limiting for uptake of FDG, and the magnitude and time course of effect on arterial pressure are well within the range of buffering by vascular autoregulation in the brain (Baumbach and Heistad 1965). Moreover, baseline differences in blood pressure were present between the two groups, but there was no interaction between gender and blood pressure following the infusion, as occurred for CMRglu in many brain regions.

Apparent gender differences in drug responses could arise from pharmacokinetic differences, as women achieved a higher drug AUC. In a separate dose–response study of peripheral responses, we found the AUCs of plasma venous concentrations following the same dose of IV idazoxan used in the present study to be virtually identical in men and women (Schmidt et al. in press). Hence, the present study may reflect a random difference in drug AUCs and does not necessarily indicate a gender difference in the early plasma clearance of idazoxan. Variability in AUC did not account for a significant portion of the variance in any of the peripheral responses. When norepinephrine responses were analyzed as a function of drug concentration to "correct" for pharmacokinetic differences, men demonstrated even larger increases than women.

Although drug AUC did correlate with metabolic increases in two brain regions in women, this was only one more region than would be expected by chance. Moreover, in a dose–response study of idazoxan in rats, increasing drug doses were associated with larger and more regional *decreases* in CMRglu (French et al. 1995). Indeed, the only woman who had an overall reduction in her global brain metabolism following idazoxan had one of the higher plasma drug AUCs. This finding and the paucity of regional correlations suggest that the greater likelihood of metabolic increases in women does not reflect a simple dose–response effect. Instead, the more robust noradrenergic responses in men after controlling for drug concentration suggest that pharmacodynamic factors play a role in response differences.

After the idazoxan infusion, brain metabolism decreased in most regions in men and increased in all regions in women, giving rise to multiple significant regional interactions between CMRglu changes and gender, mostly in the prefrontal cortex (Table 1). Given the diffuse nature of these changes, it follows that normalization of regional values to global CMRglu re-

sulted in the virtual absence of any regional interactions in normalized data. Nonetheless, the simple effects on relative metabolic rates were similar to the pattern seen in absolute changes, namely, more significant regional increases in women (seven versus four in men) and significant decreases occurring in men (three prefrontal regions).

Unanswered is why both regional increases and decreases should occur. Interpretation of the brain metabolic effects of idazoxan is confounded by the multiple potential consequences of α_2-blockade in brain. Besides acting as inhibitory autoreceptors on noradrenergic neurons, α_2-receptors also can modulate the release of other neurotransmitters through postsynaptic α_2-heteroceptors on their respective nerve terminals (Raiteri et al. 1990; Vizi 1980). Postsynaptic α_2-receptors on cortical cells also are present and presumed to have modulating effects on intraneuronal pathways (Aoki et al. 1994). Imidazoline binding sites, for which idazoxan has high affinity, have been identified in human brain as well (Sastre and Garcia-Sevilla 1993; De Vos et al. 1991). Although no gender differences have been reported in receptor density of either α_2-receptors or imidazoline binding sites (Probst et al. 1984; Biegon et al. 1992; Pascual et al. 1992; Sastre and Garcia-Sevilla 1993; De Vos et al. 1991, 1992) differences could exist in binding affinity. Moreover, gender differences could occur in the activity of any of the various neurotransmitter systems regulated by α_2-receptors.

If consideration is limited to the noradrenergic system, then a tentative hypothesis about the pattern of brain metabolic responses can be derived from preclinical studies involving pharmacological manipulation of brain noradrenergic pathways. α_2-antagonists can theoretically increase norepinephrine release in brain by blockade of presynaptic α_2-autoreceptors on noradrenergic nerve terminals and/or by increasing the activity of the locus ceruleus by blocking somatodendritic autoreceptors on cell bodies. Systemic administration of either idazoxan or yohimbine to rats results in an enhancement of norepinephrine release from cortex (Dennis et al. 1987; van Veldhuizen et al. 1993) that coincides with an increase in activity in the locus ceruleus (Freedman and Aghajanian 1984). Both drugs given acutely produce a reduction in cortical glucose metabolism, and in the case of idazoxan, this reduction coincides with a doubling of norepinephrine overflow in the cortex (Savaki et al. 1982; French et al. 1995). Interestingly, although idazoxan has been reported to increase norepinephrine release via autoreceptors on noradrenergic terminals in the cortex and by increasing the firing rate in the locus, yohimbine has not been found to affect cortical autoreceptors (van Veldhuizen et al. 1993). This phenomenon suggests that it is the increased firing of the locus ceruleus that results in reductions in brain glucose metabolism. In contrast, acutely increasing the

concentration of norepinephrine around nerve terminals and cell bodies by reuptake blockade with desmethylimipramine has been shown to decrease the activity of the locus ceruleus (Nyback et al. 1975) and to increase glucose metabolism throughout the cortex and subcortical areas (Gerber et al. 1983). Moreover, idazoxan increases activity in the locus ceruleus only after a threshold concentration has been achieved, although below the threshold amount, α_2-blockade can be demonstrated (Freedman and Aghajanian 1984). The regional increases we observed in brain metabolism could therefore reflect an effect of idazoxan on receptors in the cortex. Such an interpretation is supported by the fact that the largest metabolic increase in both groups occurred in the primary visual cortex, a region that has been reported to have the highest density of α_2-receptors of any region in the human cortex (Probst et al. 1984). The regional decreases in brain metabolism in men could reflect a greater effect of idazoxan on locus ceruleus activity. The larger catecholamine responses in men and the slightly higher level of anxiety they reported could both be consistent with this hypothesis, although the peripheral increases likely reflect both central α_2- and nerve terminal effects (Grossman et al. 1991). The absence of baseline assessments of anxiety limits interpretation of this measure.

An implication of the larger catecholamine responses in men is that they should have a higher rate of catecholamine release than women. As a result, more presynaptic α_2-receptors would be activated by endogenous catecholamines. Blockade of those "activated" receptors would produce a larger increment in plasma norepinephrine in men than in women. This interpretation is supported by the high correlations we observed between the baseline concentration and the norepinephrine level achieved after idazoxan administration ($r = 0.78$ in males, $r = 0.91$ in females). Resting plasma norepinephrine and epinephrine levels were lower in our female subjects, but not significantly so. Previous studies have generally found no gender differences in resting catecholamines levels, although some have reported that women have lower resting plasma epinephrine (Davidson et al. 1984; Williams et al. 1993; Eisenhofer et al. 1995). Plasma concentrations of catecholamines, however, are a function of both release and clearance rates. As estradiol inhibits monoamine oxidase and norepinephrine uptake (Endersby and Wilson 1974; Luine and McEwen 1977), a reduced clearance of catecholamines could obscure a lower release rate in women and indeed could account for the correlation ($r = 0.67$) between estradiol levels and increases in norepinephrine.

Gender differences in the basal state of sympathetic activity might or might not involve differences in affinity or density of α_2-receptors. For G-protein–coupled receptors, the degree of receptor coupling to the intracellular G-protein subunits is a critical determinant of both the affinity of the receptor for agonist and the functional effects of receptor activation (Manji 1992). In animal models, the regional expression of the G-protein alpha subunits coupled to dopamine and norepinephrine autoreceptors has been shown to be altered by estradiol treatment and to vary with the estrous cycle (Bouvier et al. 1991). Estradiol treatment of ovariectomized rats results in a reduction of the high-affinity form of the α_2-receptor in the brain (Karkanias and Etgen 1994). Whether estrogens can affect α_2-adrenoceptor affinity or density in human brain, or whether hormonal cycles produce change is not known. Moreover, animal studies demonstrate that cyclical changes in estradiol may influence α_2 function, but gender differences in sympathetic responses have been reported to occur in prepubertal children (Delamarche et al. 1994). This suggests that in humans, factors other than circulating sex steroids contribute to gender effects on adrenergic activity. To address these questions would require controlling the testing of female subjects for time in the menstrual cycle and contraceptive use and to include comprehensive measurements of reproductive hormones, which was not feasible because of logistical constraints and the exploratory nature of the study.

In summary, given the numerous previous reports of gender differences in sympathetic responses, our finding that gender influences the effect of idazoxan on plasma catecholamines is not unexpected. The significance of the differences in peripheral responses in the present study is that they occurred concurrently with differences in the brain metabolic responses. Two conclusions emerge. First, gender influences the central response to acute idazoxan. Second, measurement of brain metabolic activity following idazoxan fusion with FDG PET is sensitive enough to detect differences in response to α_2-blockade. These findings may be particularly relevant for the study and treatment of depression and panic disorder, given the gender ratio in prevalence for these disorders. A more general implication is that imaging of brain metabolism in conjunction with a receptor-selective drug challenge may be a useful method for assessing not only the distribution but also differences in central adrenergic receptor function.

ACKNOWLEDGMENTS

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