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Depression of Thalamic Metabolism by Lorazepam Is Associated with Sleepiness

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Though it is well recognized that the pharmacological actions of benzodiazepines are mediated by facilitation of GABAergic neurotransmission, the consequences of these changes in regional brain function are not well understood. This study measured regional brain glucose metabolism using Positron Emission Tomography and 2-deoxy-2[^{18}F]fluoro-D-glucose in normal controls (n = 21) investigated with and without lorazepam (30 μg/kg IV) and with flumazenil given after lorazepam (n = 9). Lorazepam markedly decreased metabolism in thalamus (23 ± 8%) and occipital cortex (19 ± 8%), and flumazenil partially reversed these changes. Changes in metabolic activity in thalamus were significantly correlated with lorazepam-induced sleepiness (r = .69, df 20, p < .0005) and there was a trend of an association between the reversal by flumazenil of lorazepam-induced change in thalamus and in sleepiness (r = .63, df 8, p = .07). Benzodiazepine-induced changes in thalamic activity may account for their sedative properties. ***[Neuropsychopharmacology 12:123–132, 1995]***

KEY WORDS: *Benzodiazepines; Positron emission tomography; Brain glucose metabolism; Sedation; Thalamus*

Benzodiazepines are among the most frequently prescribed therapeutic drugs (APA Task Force 1990; Woods et al. 1992). They are the drug of choice in the treatment of anxiety and are the most frequently prescribed drug for insomnia (Mendelson 1992). They are also used as muscle relaxants (Martin 1987), in alcohol detoxification (Ciraulo et al. 1988), in status epilepticus (Martin 1987), and as adjuncts in the treatment of schizophrenia (Wolkowitz and Pickar 1991). Benzodiazepines facilitate GABAergic neurotransmission by potentiating GABA-induced chloride flux at the $GABA_A$-benzodiazepine receptor complex (GBRC) (Haefely et al. 1975, 1985; Olsen 1981; Morrow and Paul 1988; Villar et al. 1990). The GBRC is an oligomeric complex consisting of subunits of different structural classes (alpha, beta, gamma, delta) coupled to chloride channels. The subunit composition of the GBRC gives it its unique pharmacological properties (Pritchett et al. 1989a) and its regional brain heterogeneity (Schofield et al. 1987; Pritchett et al. 1989a). Receptors composed of the alpha, beta, and gamma subunits elaborate a benzodiazepine binding site the pharmacology of which is largely determined by the alpha subunit (Pritchett et al. 1989b). Although there appears to be a close correlation between the affinities of various benzodiazepines at the GBRC and their potencies as anxiolytics, anticonvulsants, and muscle relaxants (Squires and Braestrup 1977), the relation to their sedative properties is not clear (Mendelson 1992), and the mechanisms by which benzodiazepines induce sleep remains poorly understood. Also, the consequences of benzodiazepine-induced changes in GBRC on regional brain function and its relation to its behavioral effects are poorly understood.

Positron-emission tomography is an imaging

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method that allows direct noninvasive measurement in the living human brain of metabolism, neurochemistry, pharmacology, and perfusion (Fowler et al. 1990). Brain glucose metabolism is the most frequently applied measurement with PET. Because brain glucose metabolism reflects brain activity, its measurement provides an index of regional brain function (Sokoloff et al. 1977). Measurements of the effects of drugs on brain glucose metabolism allow one to determine those areas of the brain that are most sensitive to the drug and may provide some direction in understanding the mechanisms of drug action. Furthermore, because the measurements are made in conscious human subjects, the relationship between specific behavioral and regional metabolic effects of drugs can be investigated.

The acute and chronic effects of benzodiazepine drugs on brain glucose metabolism in normal controls (DeWit et al. 1991), alcoholics (Volkow et al. 1993), and patients with anxiety disorders (Buchsbaum et al. 1987) have been evaluated with PET. Though all of the studies have shown reductions of brain glucose metabolism by benzodiazepines, they have been inconsistent with respect to the magnitude of these effects and their regional specificity. These discrepancies could reflect differences between benzodiazepine drugs, doses administered, subjects investigated, and/or conditions of study.

This study evaluates the effects of lorazepam on regional brain glucose metabolism and its relationship to its behavioral effects. Lorazepam was chosen because of its unique pharmacokinetics, which allow relatively stable drug concentrations in brain during the 30-minute FDG uptake period, and its kinetics in brain can be monitored because they parallel those in plasma (Greenblatt and Sethy 1990). A lorazepam dose (30 μg/kg), which had been shown to consistently induce behavioral and regional brain metabolic effects in normal controls (Volkow et al. 1993), was selected. We also evaluated if lorazepam-induced changes in regional metabolism could be reversed by a benzodiazepine antagonist, to assess the extent to which the regional changes were the result of lorazepam's actions on benzodiazepine receptors. For this purpose, flumazenil at a dose (0.6 mg) that has been found to be effective in reversing benzodiazepine-induced conscious sedation was used (Brogden and Goa 1988).

MATERIAL AND METHODS

Subjects

Twenty-one right-handed, healthy males 32.5 ± 10 years of age (age range 23 to 59) who were mild or moderate drinkers (not more than five drinks/week) were selected. Each subject had a routine physical, psychiatric, and neurologic examination. Routine laboratory tests were performed as well as a random urine test to exclude the use of psychoactive drugs. Subjects were excluded if they had present or past psychiatric and/or neurological illnesses in themselves or in a first degree relative, if they had medical illnesses, and/or if they were taking any medication. Subjects were instructed to discontinue any over-the-counter medication 2 weeks prior to the PET scan and to refrain from drinking alcohol the week prior to the PET scan. This study was approved by the Human Subjects Research Committees of Brookhaven National Laboratory and the Northport VA Medical Center. After explaining the procedure, written informal consent was obtained from each subject. Data on 10 of these subjects has been published (Volkow et al. 1993).

PET Studies

PET measurements were performed using a whole-body, high-resolution positron emission tomograph (6.5 mm × 5.9 mm Full Width Half Maximum at the center of the field of view, interslice distance 5.9 mm, 15 slices, Computer Technologies, Incorporated, CTI 931). Positioning of the subject in the gantry was accomplished using an individual headholder and two sets of weak laser fan beams that illuminated the head surface along the canthomeatal line (CM) and along the sagittal line, respectively. Prior to radiotracer injection, each subject underwent a transmission scan performed with a ring filled with germanium 68/gallium 68 to allow the subsequent emission image to be corrected for attenuation. A catheter was placed in the antecubital vein for radiotracer injection and in a dorsal hand vein for "arterialized" blood sampling. Arterialized blood was obtained to measure plasma concentration of F-18, glucose, PO_2, and PCO_2. The emission scans were taken 35 minutes following injection of 4 to 6 mCi of FDG for a total of 20 minutes. A description of procedures including calculation of metabolic "rates" has been published (Volkow et al. 1993). Each subject underwent two different PET procedures. For the first scan, subjects were injected with a placebo (3 cc of saline solution) given 40 to 50 minutes prior to FDG. For the second scan, subjects were injected with 30 μg/kg of lorazepam given 40 to 50 minutes prior to FDG. In addition, nine of the subjects received a third PET scan in which the benzodiazepine antagonist flumazenil (6 mg IV given over 6 minutes) was administered 30 minutes after administration of 30 μm/kg lorazepam and 10 to 15 minutes prior to FDG administration (lorazepam–flumazenil). The subjects were blind to the drugs received. To ensure that the subjects would not fall asleep, they were monitored throughout the procedure and were asked to keep their eyes open. Subjects were scanned with their ears unplugged in a dimly lit room with noise kept to a minimum. The only intervention was the periodic assessment of the behavioral and cog-

Table 1. Behavioral and Cognitive Measures Obtained after Placebo, Lorazepam, and Lorazepam Followed by Flumazenil (Lorazepam-Flumazenil)

	Two Scans (n = 21)		Three Scans (n = 9)		
Region	**Placebo**	**Lorazepam**	**Placebo**	**Lorazepam**	**Lorazepam–Flumazenil**
Desire	2.5 ± 7	3.5 ± 8	0	2.2 ± 7	0
Intoxication	0.5 ± 1	35.2 ± 26[b]	0	29.0 ± 10[a]	3.9 ± 7
Sleepiness	1.5 ± 5	57.0 ± 25[c]	3.3 ± 7	49.0 ± 29[b]	4.0 ± 9
Tiredness	14.0 ± 7	44.4 ± 29[a]	14.1 ± 8	45.3 ± 33[a]	10.0 ± 11
Stroop-read	102.6 ± 14	77.4 ± 14[c]	103.3 ± 19	72.9 ± 12[c]	103.0 ± 13
Stroop-XXX	74.0 ± 11	68.2 ± 17	76.2 ± 13	54.4 ± 13[b]	73.1 ± 13
Stroop-color	47.7 ± 9	40.7 ± 12[b]	48.9 ± 2	36.6 ± 9[b]	45.2 ± 10
SDMT	48.6 ± 4	36.2 ± 9[c]	50.1 ± 4	26.3 ± 3[b]	44.7 ± 4[a]
WA	15.1 ± 2	10.6 ± 5[b]	15.2 ± 3	7.4 ± 4[c]	9.6 ± 4[a]
Calculation	12.1 ± 1	10.6 ± 2[b]	14.0 ± 3.2	12.0 ± 1	13.5 ± 2

Subjects were asked to evaluate in an analog scale (0 to 100) their desire for more drug, sleepiness, tiredness, and subjective sense of intoxication. Cognitive tests involved the Stroops (separate values are reported for the three sections: reading color names [read], describing the color [XXX], and reading color names colored with discrepant colors [color]), symbol digit modality test (SDMT), word association (WA), and arithmetic calculations. Comparisons are with respect to placebo.

[a] $p < .01$
[b] $p < .005$
[c] $p < .001$

nitive effects of lorazepam, lorazepam–flumazenil, or of placebo.

Lorazepam concentration in blood was measured 20, 60, and 120 minutes after lorazepam injection with HPLC (National Psychopharmacology Laboratory).

Behavioral and Cognitive Evaluation

Before placebo or lorazepam and at 20 minutes, 60 minutes, and 2 hours after placebo or lorazepam administration, subjects were asked to evaluate on an analog scale (rated 0 to 100) their subjective sense of intoxication, desire for more drug, tiredness, and sleepiness and were also evaluated with the Stroop Test, the Word Association Test (WA), Symbol Digit Modality Test (SDMT), and arithmetic calculations (Woods et al. 1992). Differences in the behavioral and cognitive measures between placebo and lorazepam and between lorazepam and lorazepam–flumazenil were tested with paired t tests (two tail). For the correlation analysis, we computed a delta score for the behavioral and cognitive changes with lorazepam and with lorazepam–flumazenil by subtracting the scores collected 60 minutes after lorazepam administration from those obtained during placebo.

Image Analysis

Regions of interest (ROI) were drawn directly on the transaxial PET images using the Matsui/Hirano atlas as reference (Matsui and Hirano 1978). Seventy-two ROI were selected from 10 of the 15 images obtained with the tomograph. Weighted averages (to correct for difference in sizes) of the ROI from different slices corresponding to the same anatomical areas where computed to obtain metabolic values in 10 "composite" brain regions. The location of the ROI sampled and the ROI that were included to obtain the 10 "composite" brain regions have been published (Volkow et al. 1993). A measure of "whole brain" metabolism was obtained by averaging metabolism in the 15 brain slices. "Relative" measures of regional brain metabolism were obtained using the ratio of the metabolic value in the "composite" brain regions to the metabolic value for the whole brain.

Statistical Analyses

Differences in "absolute" and "relative" measures of regional brain glucose metabolism during lorazepam administration were evaluated with repeated measure ANOVA. Pearson product moment correlations were used to quantify the relationship between changes in regional brain glucose metabolism (placebo − lorazepam/placebo × 100, expressed as percentage change from placebo), plasma lorazepam concentration, and the delta scores for the behavioral and cognitive measures. Correlations were performed only on the absolute metabolic measures. Correlations that were found to be significant were retested with Spearman correlation analysis to rule out that significance was a result of outliers. Multiple regression analyses were also done

Table 2. Absolute Metabolic Values for the Different Brain Regions after Placebo, Lorazepam, and Lorazepam Followed by Flumazenil

	Two Scans (n = 21)		Three Scans (n = 9)		
Region	**Placebo**	**Lorazepam**	**Placebo**	**Lorazepam**	**Lorazepam–Flumazenil**
R frontal	51.5 ± 4	44.6 ± 5[c]	50.4 ± 3	44.3 ± 2[c]	45.0 ± 3[c]
L frontal	52.2 ± 4	44.8 ± 5[c]	51.0 ± 2	44.6 ± 2[c]	45.8 ± 3[c]
R parietal	51.2 ± 4	45.0 ± 4[c]	50.9 ± 3	44.7 ± 2[c]	44.9 ± 2[c]
L parietal	51.2 ± 2	44.8 ± 6[c]	50.2 ± 3	44.8 ± 3[b]	46.5 ± 4[b]
R temporal	50.1 ± 4	45.6 ± 4[c]	50.1 ± 3	44.1 ± 2[c]	44.9 ± 2[c]
L temporal	50.4 ± 5	45.3 ± 6[c]	49.5 ± 2	44.5 ± 2[b]	44.6 ± 2[b]
Occipital	54.9 ± 6	44.4 ± 5[c]	54.3 ± 4	43.3 ± 2[c]	46.0 ± 5[cd]
Thalamus	52.7 ± 5	40.3 ± 4[c]	52.6 ± 3	41.8 ± 4[c]	46.5 ± 5[cd]
Basal ganglia	52.0 ± 6	45.3 ± 6[c]	50.6 ± 2	45.6 ± 3[c]	46.2 ± 4[c]
Cerebellum	43.1 ± 4	36.6 ± 3[c]	42.0 ± 4	35.4 ± 2[c]	36.4 ± 4[c]

Values during placebo were compared against those obtained with lorazepam in 21 subjects. Nine subjects underwent a third scan with lorazepam followed by flumazenil. Independent comparisons were done in these nine subjects. Lorazepam significantly reduced brain glucose metabolism in all brain regions. Though metabolism was significantly lower during lorazepam–flumazenil than during placebo, it was significantly higher than during lorazepam (alone) in thalamus and occipital cortex. Comparisons with placebo are marked with superscripts *a–c*; those between lorazepam and lorazepam–flumazenil are marked with superscript *d*.

[a] $p < .01$.
[b] $p < .005$.
[c] $p < .001$.
[d] $p < .01$

to assess if the lorazepam-induced changes in regional metabolism that were found to be significantly correlated with behavioral measures were the result of the interaction with other variables. For this purpose, the regional metabolic change-induced by lorazepam was entered as the dependent variable, and the regional baseline metabolic measure, the change in behavioral rating, and the plasma lorazepam concentrations were entered as independent variables.

For the nine subjects who received the third scan after lorazepam–flumazenil, repeated measure ANOVA were done to assess differences in metabolism between the lorazepam (alone) and the lorazepam–flumazenil scans. Post hoc "*t* tests" (one tail) were done to assess significance between pairs of interventions. The relationship between flumazenil effects in lorazepam-induced behavioral (lorazepam − lorazepam–flumazenil) and metabolic effects (lorazepam − lorazepam–flumazenil/lorazepam × 100, expressed as percentage change from lorazepam) were assessed with Pearson product moment correlations.

In consideration of the "multiple comparison problem" incurred by analyzing values for 10 brain regions, we set the level of significance to $p \leq .01$. We chose this criterion of significance as being intermediate between the $p < .05$ value, considered significant for an individual variable and the $p < .005$ value required by the Bonferroni adjustment; the Bonferroni criterion assumes that variables are independent (Haiz 1973), but regional metabolic values are highly dependent on one another (Volkow et al. 1986). Values of $p < .05$ are reported as trends.

RESULTS

Plasma lorazepam concentrations corresponded to 41.3 ± 12 ng/ml at 20 minutes, 31.9 ± 10 at 60 minutes, and 28.1 ± at 2 hours. The behavioral and cognitive changes after lorazepam and after lorazepam followed by flumazenil are shown in Table 1. Lorazepam significantly induced sleepiness and tiredness and significantly affected cognitive performance in all tests except that of arithmetic calculations. When flumazenil was administered after lorazepam, it significantly reversed most of the behavioral and cognitive changes induced by lorazepam. The effects of lorazepam–flumazenil on cognitive performance were not significantly different from those with placebo, except for the symbol digit modality test and/or the word association test (WA) (Table 1). The effect of flumazenil appeared to be temporary because reversal of lorazepam-induced behavioral and cognitive changes was most significant immediately after flumazenil infusion (data shown in Table 1). At the end of the study, subjects reported higher levels of sleepiness and tiredness than during placebo ($p < .05$), and performance in cognitive tests was also worse than during placebo ($p < .11$) (data not shown).

Lorazepam significantly decreased whole brain (13 ± 6%) (F 100.2, df 1,20, $p < .0001$) and regional brain metabolism (Table 2). Figure 1 shows the percent change

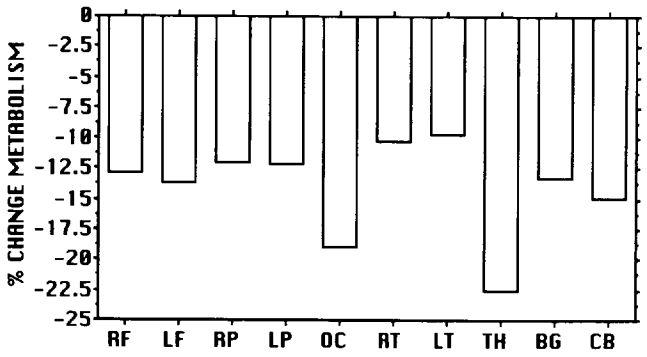

Figure 1. Percent change in regional brain glucose metabolism after lorazepam administration. All brain regions showed significant decreases ($p < .001$) in metabolism with lorazepam. Abbreviations: RF = right frontal, LF = left frontal, RP = right parietal, LP = left parietal, RT = right temporal, LT = left temporal, OC = occipital, TH = thalamus, BG = basal ganglia, CB = cerebellum.

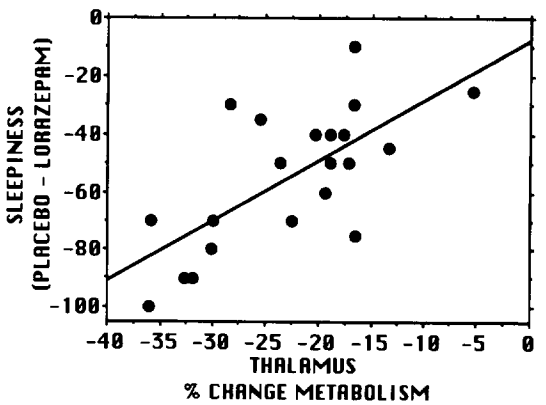

Figure 3. Correlation analyses between lorazepam-induced sleepiness (placebo-lorazepam) and lorazepam-induced changes in thalamic metabolism (% change in metabolism from placebo) ($r = 0.69$, $p < .001$).

in regional brain glucose metabolism after lorazepam administration. The largest metabolic changes with lorazepam were in the thalamus (23 ± 8%) (F 138.8, $p < .0001$) and in the occipital cortex (19 ± 8%) (F 95.7, $p < .0001$). The higher sensitivity of these two brain regions is apparent after normalization of regional metabolic values by whole brain metabolism ("relative measures"), which revealed significant decreases after lorazepam only in occipital cortex (F 31.9, $p < .0001$) and thalamus (F 59.9, $p < .0001$) (Figure 2). Lorazepam also led to a significant increase in relative metabolism in left (F 9.1, $p < .01$) and right temporal cortex (F = 13.9, $p < .002$). There were no significant correlations between the magnitude of the metabolic changes induced by lorazepam and plasma lorazepam concentration.

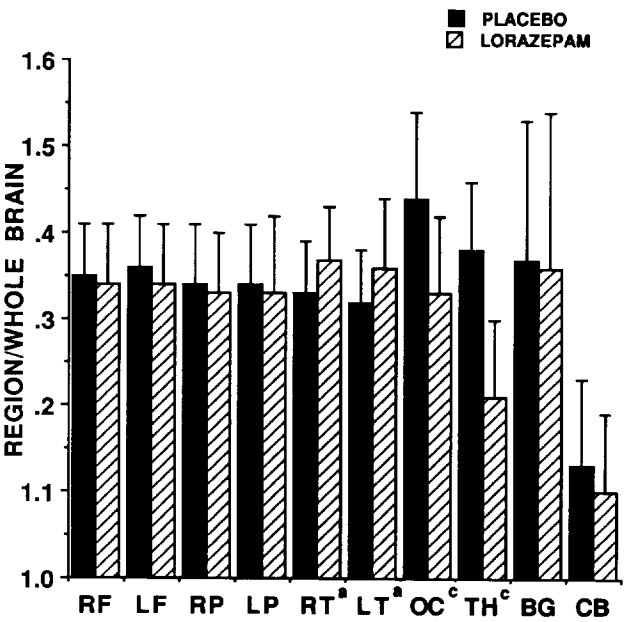

Figure 2. Relative metabolic measures during placebo and during lorazepam ($n = 21$). Relative measure correspond to the ratio of regional metabolic values by whole brain metabolism. Lorazepam significantly decreased relative metabolism in occipital cortex and thalamus while it increased metabolism in left and right temporal cortex. (Significance [a] $p < .01$, [b] $p < .005$, [c] $p < .001$). Abbreviation(s) as for Figure 1.

Correlation analyses between behavioral and metabolic changes with lorazepam were significant for changes in thalamic metabolism and sleepiness ($r = .69$, $p < .001$) and tiredness ($r = .65$, $p < .01$) and between cerebellar metabolism and tiredness ($r = .60$, $p < .01$) and a trend of a correlation with sleepiness ($r = .50$, $p < .03$) (Table 3). The strongest of the correlations, that between lorazepam-induced changes in thalamic metabolism and sleepiness, is shown in Figure 3. Results from the Spearman correlation analysis showed significant correlations only between sleepiness and changes in thalamic ($z = -2.8$, $p < .005$) and cerebellar metabolism ($z = -2.6$, $p < .01$). Changes in thalamic metabolism were significantly correlated with changes in cerebellar metabolism ($r = .71$, $p < .0003$).

Multiple regression analysis revealed that in addition to lorazepam-induced sleepiness ($t = 4.6$; $p < .001$), baseline thalamic metabolism ($t = -3.0$; $p < .01$) predicted lorazepam-induced changes in thalamic metabolism. When baseline cerebellar metabolism in addition to the plasma lorazepam concentration were entered in the multiple regression to predict lorazepam-induced changes in cerebellar metabolism, there was only a trend of significance with lorazepam-induced sleepiness ($t = 2.1$; $p < .05$). Plasma lorazepam concentration did not predict lorazepam-induced changes in thalamic or cerebellar metabolism.

Metabolic values after lorazepam (alone) and after lorazepam–flumazenil for the nine subjects undergo-

Table 3. Correlation Coefficients (*r*) between Percent Changes in Regional Brain Metabolism and Plasma Lorazepam Concentration (50 Minutes post Lorazepam) and the Changes in Behavioral and Cognitive Measures (Placebo − Lorazepam)

	Frontal		Parietal		Temporal					
Test	**R**	**L**	**R**	**L**	**R**	**L**	**OCC**	**THL**	**BG**	**CBL**
Plasma LZP	.09	.01	.18	.11	.10	.06	.01	.13	.21	.35
Desire	.01	.12	.05	.02	.01	.04	.09	.01	.25	.04
Motor	.39	.26	.47	.31	.48	.38	.34	.22	.37	.62[b]
Intoxication	.40	.34	.31	.38	.01	.04	.1	.29	.39	.03
Sleepiness	.28	.36	.32	.43	.21	.39	.26	.69[c]	.12	.50[a]
Tiredness	.01	.20	.31	.05	.06	.21	.17	.65[b]	.50	.60[b]
Stroop	.09	.09	.04	.04	.01	.02	.01	.03	.21	.11
SDMT	.01	.03	.08	.10	.06	.15	.15	.29	.39	.03
WA	.05	.12	.12	.01	.03	.32	.20	.05	.21	.01

L = left, R = right.
[a] $p \leq .05$.
[b] $p \leq .01$.
[c] $p \leq .001$

ing the three scans are given in Table 2. Administration of flumazenil after lorazepam significantly reversed lorazepam-induced decreases in metabolism only in occipital cortex (F 64.6, df 2,16, $p < .0001$) and thalamus (F 24.8, $p < .0001$) (Figure 4). Post hoc "*t* tests" revealed that whereas both thalamic and occipital metabolism with lorazepam-flumazenil were significantly lower than placebo, they were higher than when lorazepam was given alone (t 2.9, df 8, $p < .01$). Effects of flumazenil on reversal of lorazepam-induced changes in relative metabolism were only significant in thalamus (F 7.2, df 2,16, $p < .006$) (Figure 5). Relative metabolic values in thalamus were significantly higher with lorazepam-flumazenil than with lorazepam alone (t = 4.7, df 8, $p < .005$). There was a trend of a correlation between flumazenil reversal of lorazepam-induced sleepiness and reversal of lorazepam-induced changes in thalamic metabolism (r = .63, $p < .07$).

DISCUSSION

This study demonstrates marked decreases in brain glucose metabolism after a moderate dose of lorazepam in occipital cortex and thalamus. Lorazepam also reduced, though to a lesser extent, metabolism in other cortical and subcortical regions. Except for the decreases in thalamic metabolism, the pattern of metabolic changes in response to this dose of lorazepam was almost identical, though larger in magnitude, than that observed after a low dose of lorazepam (1 mg/kg IV) (Volkow et al. 1991) and similar to those observed after diazepam (0.07 and 0.14 mg/kg IV) (De Wit et al. 1991). At the doses given in the latter studies, benzodiazepines were reported to have only modest behavioral effects, and the regional metabolic changes ranged between 5 and 12%. Autoradiographic studies at moderate to high doses of benzodiazepines (diazepam 0. to 1.0 mg/kg; Clonazepam 0.01 to 5.0 mg/kg) have reported regional metabolic decrements, including thalamic decrements, in the range of 10 to 40% (Kelly et al. 1986; Ishizuka et al. 1989).

The reversal by flumazenil of lorazepam-induced decrements in thalamic and occipital metabolism suggests that these metabolic changes reflect the actions of lorazepam on benzodiazepine receptors. The lack of a significant effect of flumazenil in reversing lorazepam-induced decrements in brain metabolism in other areas may reflect a dose effect, the short duration of action of flumazenil, and/or the small sample size of our studies. In animals, flumazenil (5 mg/kg) at doses

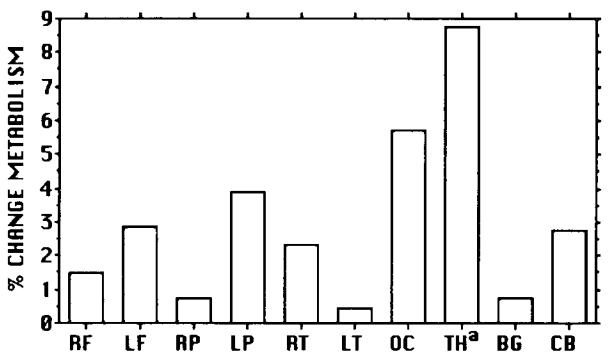

Figure 4. Percent change in regional brain glucose metabolism after lorazepam-flumazenil from that obtained during administration of lorazepam (alone). Administration of flumazenil after lorazepam significantly reversed lorazepam-induced decrements in metabolism only in occipital cortex and thalamus (Significance [a] $p < .01$, n = 9). Abbreviation(s) as for Figure 1.

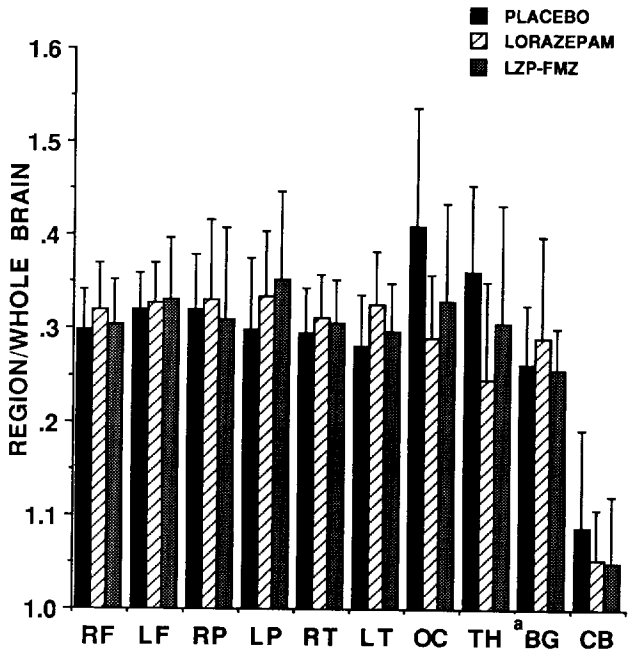

Figure 5. Relative metabolic measures during placebo, lorazepam, and lorazepam with flumazenil (LZP-FMZ) (n = 9). Lorazepam significantly decreased relative metabolism in occipital cortex and thalamus when compared with placebo, whereas lorazepam-flumazenil increased relative metabolism in thalamus when compared with lorazepam (alone). (Significance [a] $p < .01$, [b] $p < .005$, [c] $p < .001$.) Abbreviation(s) as for Figure 1.

higher than the one used for this study almost completely reversed the decreases in metabolism induced by clonazepam (Ishizuka et al. 1989). Similarly, a PET study investigating flumazenil reversal of lorazepam-induced decrements in cerebral blood flow (CBF) showed significant changes for most brain regions (S. Paul presented at a meeting organized by NIDA on "The Neurobiology Of Substance Abuse," Washington DC, May 1992). Because CBF measures reflect activity over 60 seconds and FDG activity over 30 minutes, it is probably more sensitive to detect changes caused by the short duration of action of flumazenil. The short duration of action of flumazenil could also explain the lack of a significant correlation between its effects in reversing lorazepam-induced changes in metabolism and the behavioral changes.

The lack of a correlation between plasma lorazepam concentration and the metabolic and sedative effects of lorazepam is probably not a result of a discrepancy between plasma concentration and brain receptor occupancy because plasma lorazepam concentration has been shown to be correlated with benzodiazepine receptor occupancy (Greenblatt and Sethy 1990). This discrepancy may reflect benzodiazepine "receptor reserve" by which only a fraction of all receptors need to be occupied by lorazepam to achieve maximal pharmacological response (Wieland et al. 1992). In fact, autoradiographic studies have documented a ceiling effect for benzodiazepine-induced decrements in brain glucose metabolism that is achieved prior to full receptor occupancy (Ishizuka et al. 1989). From the cerebral cortex, the maximum effect of clonazepam in glucose metabolism occurred with 30 to 40% receptor occupancy (Ishizuka et al. 1989). With the availability of PET and SPECT benzodiazepine receptor ligands, future work may enable us to determine the relation between changes in regional metabolism and percent receptor occupancy for the different brain regions in humans. These results disagree with a previous study in which changes in regional brain glucose metabolism in response to lorazepam in normals and alcoholics were found to be significantly correlated with plasma lorazepam concentration (Volkow et al. 1993). A separate analyses of the data revealed that the correlation was significant only in the alcoholics but not in the controls (Volkow et al., unpublished data). The reason for the discrepancy between normals and alcoholics requires further investigation.

It was interesting that lorazepam-induced metabolic changes in thalamus were associated with "sleepiness" because the thalamus helps to maintain and regulate levels of alertness through widespread influences on the activity of the cerebral cortex (Carpenter and Sutin 1983). In fact, stimulation of the medial thalamus produces inattention, drowsiness, and sleep (Hess 1944), and hypersomnia has been reported after thalamic lesions (Akert 1965). The thalamus also receives direct projections from the mesencephalic reticular formation, the function of which has been linked with the regulation and maintenance of sleep and arousal (for review, see Brodal 1981). The effects of benzodiazepines on thalamic activity could be one of the mechanisms by which they induce sedation. Decrements of thalamic activity by benzodiazepines may require relatively large doses of benzodiazepines (Ableitner et al. 1985), and nonsedative doses of benzodiazepines do not decrease thalamic metabolism (DeWit et al. 1991; Volkow et al. 1991).

It has been postulated that the array of therapeutic effects of benzodiazepines is in part a result of the interaction with discrete benzodiazepine receptor subtypes (Wieland et al. 1992), which are heterogeneously distributed in brain (Montpied et al. 1988). In fact, Kds for various benzodiazepine ligands have been shown to be heterogeneous among brain regions (Mans et al. 1992). Thus, the unique regional metabolic response to lorazepam could reflect this heterogeneity. The occipital cortex is a brain region with a high density of various benzodiazepine receptors subtypes (Braestrup et al. 1977; Inoue et al. 1992; Mennini and Gobbi 1992), which could explain its high sensitivity to the actions of different benzodiazepine agonists (Buchsbaum et al.

1987; DeWit et al. 1991) as well as its sensitivity to other GABAergic enhancing drugs such as ethanol (Volkow et al. 1990). Even though most receptor binding studies have documented a relative low concentration of benzodiazepine receptors in the thalamus (Braestrup et al. 1977), the expression of the alpha 4 subunit mRNA in rat brain is most abundant in thalamus (Wieland et al. 1992). It has been reported that receptor subtypes containing the alpha 4 subunit lack the high affinity binding of classical benzodiazepine agonists, but they retain high affinity for benzodiazepine antagonists and for inverse agonists (Wisden et al. 1991). Thus, one could speculate that this unique profile could explain the lack of an effect of low doses of benzodiazepines on thalamic metabolism (DeWit et al. 1991; Volkow et al. 1991) and its sensitivity to flumazenil. Evidently, much more work is required to assess the possible role of thalamic interneurons containing the alpha 4 subunit in the sedating properties of benzodiazepines.

Because energy metabolism in a given region represents metabolic activity of nerve terminals and synaptic elements (Schwartz et al. 1979), the decreases in thalamic metabolism could also reflect changes in activity from GABAergic projections into the thalamus. One of the main GABAergic projections into the thalamus is that originating in the cerebellum (Scheel-Kruger 1986). In this respect, it is interesting that cerebellar metabolism at baseline is uniquely associated with the magnitude of lorazepam-induced changes in thalamic metabolism (Volkow et al. 1993). For the current study, lorazepam-induced sleepiness was associated with changes in metabolism both in thalamus and in cerebellum. Though a link between cerebellar activity and benzodiazepine-induced sedation has not been described, such an association has been reported for the sedative actions of ethanol, a drug that also facilitates GABAergic neurotransmission at the GBRC. The sensitivity of cerebellar Purkinje cells to ethanol was associated with its sedative effects (Spuhler et al. 1982), and neonatal cerebellectomy altered ethanol-induced sleep time in short-sleep mice (Palmer et al. 1984). Also, involvement of the cerebellum in regulating electrocortical activity via the reticular formation has been documented (Brodal 1981). Thus, benzodiazepine effects in cerebellum could participate in sedation via cerebellar projections into the reticular formation (Brodal 1981) and/or thalamus (Scheel-Kruger 1986).

In contrast to other PET studies using ligands such as ^{11}C Ro15-1788 (Halldin et al. 1988), ^{11}C suriclone (Frost et al. 1986), and ^{11}C RO 15-4513 (Inoue et al. 1992) to measure benzodiazepine receptors, this study measures the regional brain metabolic consequences of the interaction of a benzodiazepine drug with these receptors. The regional sensitivity of the brain to lorazepam-induced changes in metabolism did not parallel the distribution of benzodiazepine receptors. This discrepancy probably reflects not only the different affinities of lorazepam for the various benzodiazepine receptor subtypes but also secondary effects. These secondary effects may account for some of the pharmacological actions of the drug and for the variability in metabolic and behavioral responses to benzodiazepine drugs among individuals.

This study documents marked changes in thalamic and occipital metabolism after lorazepam administration. The partial reversal by flumazenil administration suggest that they represent, in part, direct interactions with benzodiazepine receptors. Lorazepam-induced decrements in thalamic metabolism were associated with sleepiness and were reversed by flumazenil, suggesting that the effects of benzodiazepines on thalamic activity may be one of the mechanisms by which they induce sedation.

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