

Regional Brain Metabolism During Alcohol Intoxication

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Background: Ethanol has a broad range of actions on many neurotransmitter systems. The depressant actions of ethanol in the brain are related in part to facilitation of γ -aminobutyric acid (GABA) neurotransmission via its interaction with the benzodiazepine/GABA receptor complex. The purpose of this study was to evaluate the effects of ethanol on regional brain metabolism in 10 healthy right-handed men. The results were compared with those we previously published in a different group of 16 normal male subjects who received intravenous lorazepam, a benzodiazepine drug that also enhances GABA neurotransmission.

Methods: The subjects were scanned with positron emission tomography and [F-18] fluorodeoxyglucose twice: 40 min after the end of placebo (diet soda) or ethanol (0.75 g/kg) oral administration. Image data sets were analyzed by using both the region of interest and the statistical parametric mapping (SPM) approach. SPM was used to generate a difference image between baseline and ethanol, which we compared to the difference image between baseline and lorazepam (30 μ g/kg).

Results: Ethanol significantly increased self-reports of "high" ($p \leq 0.0001$), dizziness ($p \leq 0.004$), and intoxication ($p \leq 0.0001$). Ethanol significantly decreased whole brain ($-25 \pm 6\%$, $p \leq 0.0001$) and regional metabolism. Normalization of the regional measures by whole brain metabolism (relative measures) showed that ethanol decreased relative metabolic activity in occipital cortex ($-4.9 \pm 4.1\%$, $p \leq 0.006$), whereas it increased relative metabolic activity in left temporal cortex ($+3.5 \pm 2.9\%$, $p \leq 0.006$) and left basal ganglia ($+9 \pm 6.3\%$, $p \leq 0.0009$). SPM analyses revealed the same pattern of responses as the relative measures, showing decreases in occipital cortex and increases in left temporal cortex. Comparison of the relative measures and the SPM analyses obtained with lorazepam data revealed a similar pattern of effects, with relative decreases in occipital cortex ($-7.8 \pm 4.8\%$) and relative increases in left temporal cortex ($+3.8 \pm 5.7\%$). Lorazepam, but not ethanol, also decreased thalamic metabolism ($-11.2 \pm 7.2\%$).

Conclusions: These results support similar though not identical mechanisms for the effects of alcohol and benzodiazepines on brain glucose metabolism. The fact that lorazepam, but not alcohol, reduced thalamic metabolism, an effect associated with sleepiness, could explain the higher sedative effects of lorazepam than of alcohol.

Key Words: Alcohol, Benzodiazepines, Cerebral Glucose Metabolism, [F-18] Fluorodeoxyglucose, Statistical Parametric Mapping.

IT IS BELIEVED that alcohol interacts with ethanol-sensitive elements within neuronal membranes and that this conveys the specificity of its neurochemical actions. The effects of ethanol are mediated by an activation of α -aminobutyric acid (GABA_A) receptors, release of opioid peptides, release of dopamine, inhibition of glutamate re-

ceptors, and interaction with serotonin systems (Anton, 1996). The depressant actions of ethanol in the brain are related to its interaction with *N*-methyl-D-aspartate and the benzodiazepine/GABA receptor complex (Weight et al., 1992). Acute ethanol facilitates GABAergic transmission by enhancing chloride conductance through the GABA_A receptor and inhibits glutamatergic function by decreasing cationic conductance through the *N*-methyl-D-aspartate receptor (Fitzgerald and Nestler, 1995).

Positron emission tomography (PET) with 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) is an imaging method that has been used to measure regional brain metabolism and that provides an index of brain function. This measurement has been applied to assess cerebral dysfunction and to evaluate the effects of acute and chronic drug administration on regional brain metabolism. The brain metabolic response to acute administration of ethanol has been investigated, and it has been shown that ethanol decreases regional brain glucose metabolism and that the pattern of

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decreases roughly parallels the regional distribution of benzodiazepine receptors in the human brain (Volkow et al., 1990).

Benzodiazepine agonists facilitate GABA-induced chloride flux at the GABA-benzodiazepine receptor complex (Morrow and Paul, 1988). PET studies that evaluated acute administration of benzodiazepine agonists in brain metabolism found that benzodiazepine agonists also decrease metabolism in the human brain (Buchsbbaum et al., 1987; De Wit et al., 1991; Volkow et al., 1993). These decrements are reversed by benzodiazepine antagonists, which indicates that they involve interaction with benzodiazepine receptors (Brogden et al., 1988).

Even though ethanol and benzodiazepine agonists have common actions at the GABA-benzodiazepine receptor complex, the effects of ethanol on other neurotransmitter systems are also likely to contribute to its effects on regional brain glucose metabolism. It is therefore of interest to compare regional metabolic response after acute intervention of ethanol with the response seen after a benzodiazepine agonist.

In this study we evaluated the effects of ethanol on regional brain metabolism in 10 healthy subjects. We compared the results with those we previously published (Wang et al., 1999) in a different group of 16 normal male subjects who were tested with FDG before and after intravenous injection of the benzodiazepine agonist lorazepam. Because the studies were done on scanners of different resolution, which yield different absolute metabolic values (Grady et al., 1989), we limited the comparisons to the regional patterns of metabolic changes rather than to the magnitude of the absolute metabolic changes within a given region.

MATERIALS AND METHODS

Subjects

Ten healthy, right-handed men (mean 41 ± 8 years, age range 25–53) who consumed less than five alcohol drinks per week were selected for the study. To exclude subjects with medical and/or neuropsychiatric illnesses, subjects received a complete physical, neurological, and psychiatric examination as well as routine laboratory test that included urine toxicology tests. Also excluded were those treated with any prescription drugs. Subjects were instructed to refrain from drinking alcohol and taking over-the-counter medication 1 week before the scan. Informed consent was obtained from each participant after the nature of the study was fully explained.

Experimental Design

Subjects received two PET scans with FDG on two separate days within 1 week of each other. In the first day, 40 to 50 min before FDG (baseline-FDG scan) administration, subjects drank a placebo (100 ml of diet noncaffeinated soda) over a 40 min period. On the second day, 40 to 50 min before FDG (alcohol-FDG scan), subjects drank a mixture of 95% ethanol (0.75 g/kg) with diet soda equal to 100 ml for 40 min. The subjects were blind to the drug received. To avoid circadian variability (Bartlett et al., 1988), the two scans for a given subject were done at the same time of day (± 1 hr). Blood alcohol concentration was measured before and 20, 40,

55, 80, 100, 140, and 160 min after the initiation of alcohol administration by using the enzymatic assay of Lloyd et al. (1978).

PET Scanning

Subjects were asked to refrain from smoking, drinking caffeine-containing beverages, and eating for at least 4 hr before the study. PET scans were performed with a Siemens (Siemens Medical Systems, Iselin, NJ) HR⁺ tomograph (resolution $4.5 \times 4.5 \times 4.5$ mm, full width half maximum, 63 slices). To ensure accurate repositioning of subjects in the Siemens HR⁺ tomograph for the repeated scans, an individually molded headholder was made for each subject. The subject's head was then positioned in the gantry with the aid of two orthogonal laser lines, one placed at the corner of the canthus and the other parallel to the sagittal plane. Procedures for scanning protocol, arterialized blood sampling, and conditions of study were as previously described (Wang et al., 1994). Briefly, a 20 min emission scan was obtained beginning 35 min after injection of 4 to 5 mCi of FDG. Arterialized venous blood samples were obtained after warming the hand with a hand-warming device and were used to measure plasma radioactivity and plasma glucose concentration. Metabolic images were computed as described previously (Lloyd et al., 1978).

Behavioral and Cognitive Evaluation

Before placebo or alcohol and at 20, 40, 55, 80, and 140 min after initiation of placebo or alcohol drinking, subjects were asked to evaluate on an analog scale (rated 0–10) their desire for more alcohol and their subjective perception of intoxication (feeling of drunkenness), sleepiness, dizziness, "high," anxiety, and tiredness. Subjects were also evaluated with the Stroop test, the Word Association test, the Symbol Digit Modality test, and arithmetic calculations (Woods et al., 1992a) before placebo or alcohol and at 55 and 140 min.

Image Analysis

We selected regions by using a template of 423 nonoverlapping regions of interest (ROIs) based on Talairach and Tournoux's atlas (Talairach and Tournoux, 1988). Values for the cortical, subcortical, and cerebellar regions were computed by using the weighted average from the different slices where the regions were obtained and were grouped into 14 composite regions that included frontal, parietal, temporal, occipital cortices, basal ganglia bilaterally, thalamus, limbic system, midbrain, and cerebellum. Measurement of global brain metabolism was obtained by averaging the values from all of the ROIs.

Statistical Parametric Mapping (SPM)

We analyzed metabolic images by using the software package for Statistical Parametric Mapping SPM95 (MRC Cyclotron Unit, Hammer-smith Hospital, London, UK). Details on the procedures for SPM have been described previously (Wang et al., 1999). Briefly, four steps (spatial registration, anatomic geometric registration, functional registration, statistical analysis) were involved in the automatic image analysis. Statistical parametric maps were displayed in coronal, transverse, and sagittal views which showed only those pixels that reached a statistical significance of $p < 0.01$. The pixel with the highest Z-score within each isolated significant region was chosen to report its coordinates in Talairach and Tournoux's atlas reference space, which uses a middle-sagittal plane that contains the line between anterior and posterior commissures (AC-PC) as the y-z coordinate origin and its associated orthogonal transaxial plane to contain the x-y axes with the x and y coordinate origins in the anterior commissure.

Statistical Analysis

We compared differences in behavioral parameters, cognitive parameters, blood pressure, and pulse rate between placebo and ethanol condi-

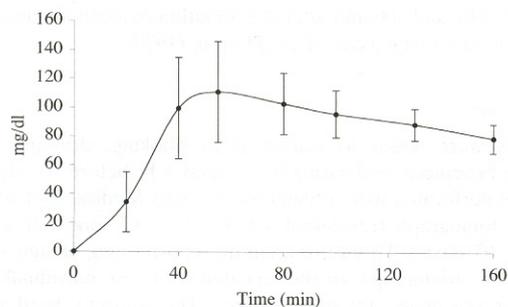


Fig. 1. Time course of blood alcohol concentration (mg/dl).

tions by using a paired *t* test (two-tailed). Pearson product moment correlation analysis was performed to evaluate changes between behavioral parameters, cognitive parameters, blood alcohol concentration, and regional brain metabolic (absolute and relative) values after ethanol as well as between blood alcohol concentration and changes in behavioral and cognitive parameters. We analyzed absolute and relative (ratios of regional to global brain metabolism) values by using a repeated-measures analysis of variance to evaluate statistical significance of the difference between baseline and postethanol condition. Laterality effects were tested with paired *t* tests by comparing the difference between placebo and alcohol for the left and the right region. To correct for multiple comparisons incurred by analyzing 14 brain regions, we set the level of significance at $p = 0.01$. We chose this criterion of significance as being intermediate between the $p < 0.05$ considered significant for an individual variable and the $p < 0.004$ 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 $0.01 < p < 0.05$ are reported as trends.

RESULTS

Figure 1 shows the mean levels for blood alcohol concentrations before and after ethanol drinking. The maximum level of alcohol concentration (110 ± 3.5 mg/dl) in blood was obtained between 40 and 100 min after the initiation of ethanol drinking.

Ethanol significantly increased the subjective perception (0–10) of intoxication at 40 min ($+5.4 \pm 2.4$, $p \leq 0.0001$) and 55 min ($+4.2 \pm 1$, $p \leq 0.0001$); of “high” at 40 min ($+4.3 \pm 2.5$, $p \leq 0.0001$), 55 min ($+3.8 \pm 1.8$, $p \leq 0.0001$), and 80 min ($+3.1 \pm 1.1$, $p \leq 0.003$); and of dizziness at 40 min ($+2.5 \pm 2.1$, $p \leq 0.004$) and 80 min ($+2 \pm 1.4$, $p \leq 0.03$) after drinking (Fig. 2). Ethanol also significantly decreased performance in the Word Association (-4.3 ± 1.3 , $p \leq 0.03$) at 55 min after drinking. Blood pressure did not change during the study, but pulse rate significantly increased at 80 min ($+17 \pm 19\%$, $p \leq 0.04$) and 95 min ($+23 \pm 23\%$, $p \leq 0.01$) after ethanol drinking (Fig. 3).

Ethanol significantly decreased whole brain metabolism ($-25 \pm 6\%$, Fig. 4), and these decreases were significant in all of the brain regions analyzed. The largest decrease in absolute metabolism occurred in the occipital cortex ($-29.1 \pm 5.7\%$, $p < 0.0001$) followed by cerebellum ($-27.3 \pm 8.0\%$), limbic system ($-25.5 \pm 7.3\%$), parietal cortex ($-25.3 \pm 5.5\%$), frontal cortex ($-25.1 \pm 5.1\%$), cingulate gyrus ($-24.3 \pm 4.9\%$), temporal cortex ($-24.0 \pm 6.6\%$), thalamus ($-22.8 \pm 9.4\%$), and midbrain ($-22.2 \pm$

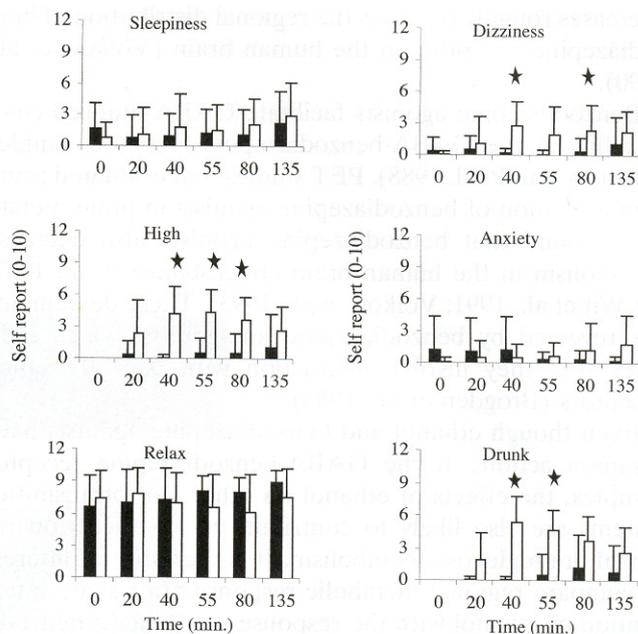


Fig. 2. Self-reports of drug effect after placebo (black column) and ethanol (white column). * $p \leq 0.05$.

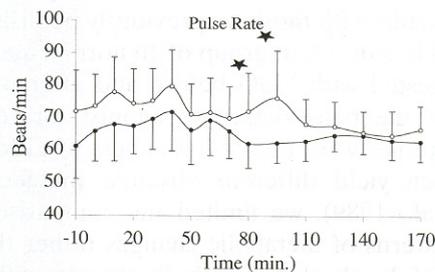


Fig. 3. Time course of pulse rate changes after placebo (●) and ethanol (○). * $p \leq 0.05$.

12.3%), and the smallest decrease occurred in the basal ganglia ($-19.8 \pm 8\%$, $p < 0.0001$; see Fig. 5). Normalization of the regional metabolic measures by whole brain metabolism showed that ethanol induced relative decreases in the occipital cortex (right: $-5 \pm 4.6\%$, $p \leq 0.009$; left: $-4.8 \pm 4.1\%$, $p \leq 0.007$) and relative increases in the left basal ganglia ($+9 \pm 6.3\%$, $p \leq 0.0009$) and left temporal cortex ($+5.5 \pm 3.5\%$, $p \leq 0.006$). The laterality effects were not significant for any of the absolute metabolic measures, and they showed a trend of an effect for the relative increase in basal ganglia, which were larger for the left than for the right ($p < 0.05$).

SPM analysis (Fig. 6) revealed that ethanol decreased relative metabolic activity in the right occipital region ($p \leq 0.01$) and increased the relative metabolic activity in the left temporal and left basal ganglia regions ($p \leq 0.0001$). Comparison of the SPM results obtained with ethanol with the results previously obtained (Wang et al., 1999) for lorazepam revealed a similar pattern of changes (Fig. 7). Lorazepam, like ethanol, significantly decreased metabolic activity in occipital cortex while it significantly increased left

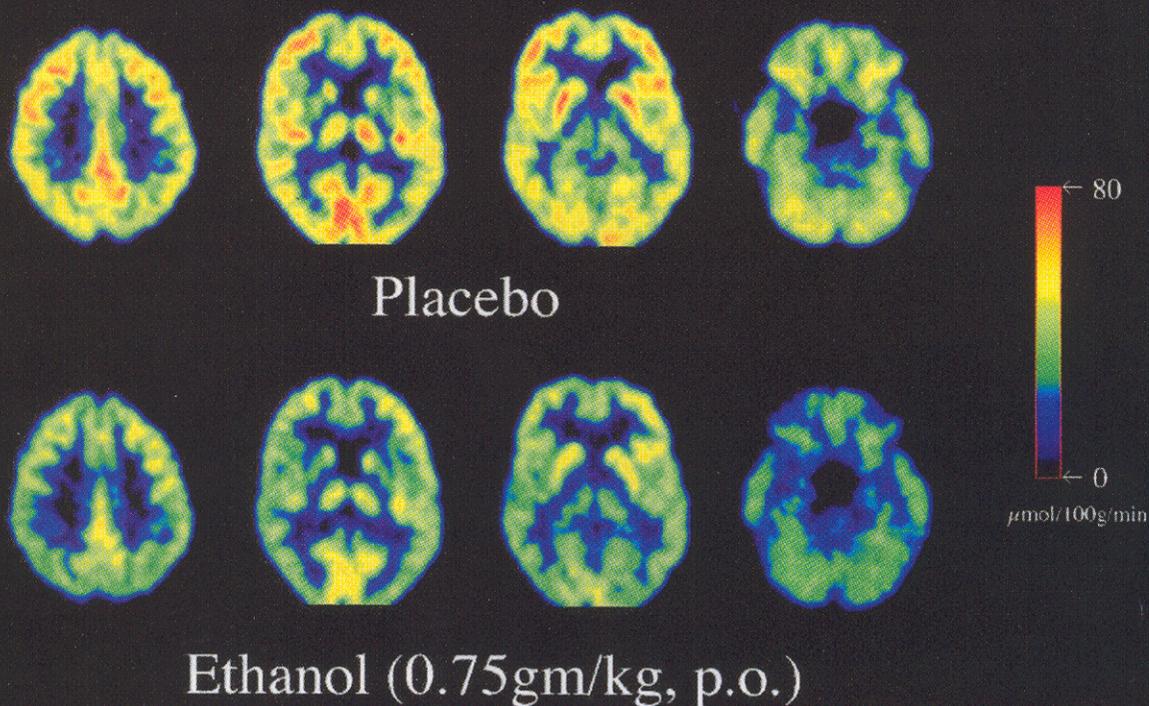


Fig. 4. FDG-PET images of normal subject after placebo (diet soda) and ethanol (0.75 g/kg).

temporal cortex. The magnitude of these effects as quantified with the relative measures corresponded for the occipital cortex to $-7.9 \pm 4.8\%$ ($p \leq 0.0001$) and for the left temporal cortex to $+3.8 \pm 5.7\%$ ($p \leq 0.02$). These two drugs differed in that although alcohol increased relative metabolic activity in left basal ganglia, lorazepam did not, and although lorazepam decreased metabolism in thalamus, alcohol did not.

Correlations between blood alcohol concentrations and regional brain metabolic response after ethanol drinking were significant only for the right temporal cortex ($p \leq 0.0004$). There were no significant correlations between regional changes in metabolism and self-report of drug effects or the cognitive measures.

DISCUSSION

This study shows significant reductions in absolute measures of regional brain glucose metabolism after acute alcohol administration. These effects were most accentuated in occipital cortex and cerebellum. These findings are similar in pattern to those previously reported for the effects of acute alcohol administration on brain glucose metabolism (De Wit et al., 1990; Volkow et al., 1990). However, the results differ in that the magnitude of the changes reported

in the current study is significantly larger than previously reported. A previous study from our center, which used a PET VI scanner, showed a 15% decrement in whole brain metabolism after ethanol administration (1 g/kg) (Volkow et al., 1990). Using a similar scanner, De Wit et al. (1990) reported a 9% decrement of whole brain metabolism after 0.8 g/kg ethanol. In the current study, whole brain metabolism decreased 25% after 0.75 mg/kg of ethanol. The reasons for this discrepancy are unclear and could reflect several factors: differences between the PET scanners, the fact that in the current study the measures were taken predominantly in the morning whereas those for our previous study were taken predominantly in the afternoon, age and gender differences in the composition of the samples, and/or differences in the data analyses (Lloyd et al., 1978).

This study also revealed significant effects of ethanol on the relative measures; ethanol decreased relative metabolic values in occipital cortex and increased relative metabolic values in the left basal ganglia and in the left temporal region. These regional effects resemble those observed after lorazepam, which also induced relative decreases in the occipital region and relative increases in the left temporal region (Wang et al., 1996, 1999). The similar pattern of metabolic changes after the administration of ethanol and lorazepam, at least for the occipital cortex, is likely to

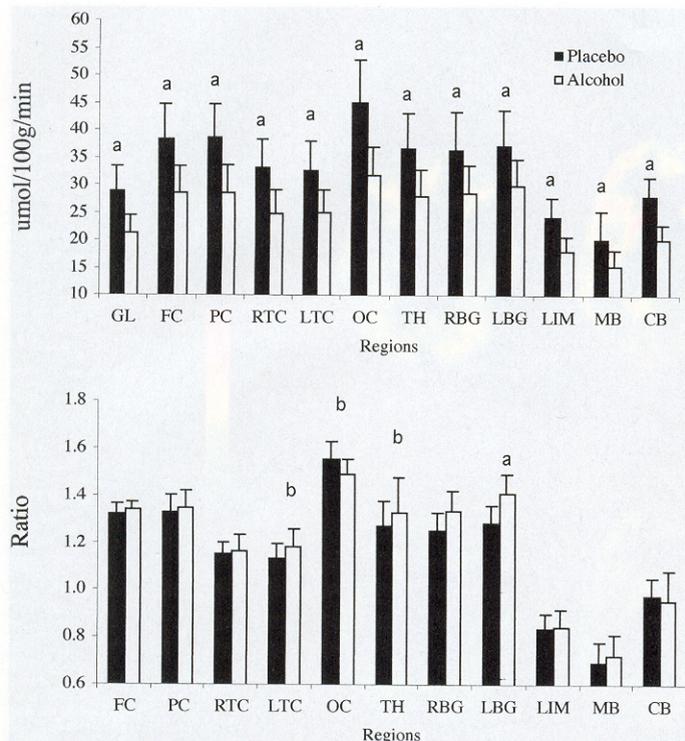


Fig. 5. Absolute and relative glucose metabolic rates after placebo and ethanol. Because there was no laterality effect for the frontal, parietal, and thalamus regions, the data for the right and the left were averaged in this figure. GL, global value; FC, frontal cortex; PC, parietal cortex; RTC, right temporal cortex; LTC, left temporal cortex; OC, occipital cortex; TH, thalamus; RBG, right basal ganglia; LBG, left basal ganglia; LIM, limbic system; MB, midbrain; CB, cerebellum. $^a p \leq 0.001$, $^b p < 0.01$.

reflect the activation of common GABA/benzodiazepine receptors because the occipital cortex is a brain region with a high density of various benzodiazepine receptors subtypes (Inoue et al., 1992; Mennini and Gobbi, 1990; Woods et al., 1992b). Moreover, the occipital cortex is highly sensitive to the actions of different benzodiazepine agonists (Abadie et al., 1996; De Wit et al., 1991). Also, the decrements in metabolism in occipital cortex after lorazepam are reversed by pretreatment with a benzodiazepine antagonist, which indicates that they are a direct effect of the interaction of the drug with GABA/benzodiazepine receptors (Volkow et al., 1995b).

The similar effects of alcohol and lorazepam in the left temporal cortex are harder to ascribe to the regional location of GABA/benzodiazepine receptors because there is no evidence, to our knowledge, of a laterality in the temporal cortex for the distribution of these receptors. Because the acute effects of a drug on metabolism are due not only to its direct effect on its target receptors but also to downstream effects, the relative increase in left temporal activity most likely reflects secondary responses. The temporal cortex is part of a corticolimbic circuit involved with emotion and mood changes (Beauregard et al., 1998; Sprengelmeyer et al., 1931). This is relevant in that moderate doses of alcohol increase overall affective expression (Ingvar et al., 1998) and lorazepam increases emotional reactivity (Garcia

et al., 1997). Though the laterality effect was not significant for the left and right temporal cortex, which indicates that they have similar sensitivity to alcohol's effects, alcohol disrupted the overall pattern of brain activity such that it led to a pattern that highlights the activation of the left temporal cortex. This is relevant, because there is evidence that changes in relative activity of left versus right brain are associated with changes in affective states (Davidson, 1992). Thus, it is possible that this effect may contribute to the use of these drugs as mood modifiers (Glazer, 1997; Zarate et al., 1998) and as anxiolytics (Davidson et al., 1992; Streater et al., 1998). Although in this study we did not find an association between metabolic changes and behavioral effects, this may reflect the fact that the behavioral effects of alcohol vary as a function of the dynamic changes in the concentration of alcohol in plasma (Lewis, 1996). Hence, imaging methods with better temporal resolution such as functional magnetic resonance imaging may be better suited to map the relationship between drug-induced changes in brain regional activation or deactivation and their behavioral effects.

There were also significant differences in the regional metabolic effects of alcohol and lorazepam. More specifically, lorazepam significantly decreased relative metabolic activity in the thalamus, whereas alcohol did not. Lorazepam-induced decreases in thalamic metabolism have been reported consistently in controls (Abadie et al., 1996), alcoholics (Volkow et al., 1993), subjects at risk for alcoholism (Volkow et al., 1995a), and cocaine abusers (Volkow et al., 1998). Decreases in thalamic metabolism after lorazepam are associated with lorazepam-induced changes in sleepiness; the larger the decrements in metabolism, the more intense the sleepiness (Abadie et al., 1996). Because the thalamus maintains and regulates the level of alertness through widespread influences on the activity of cerebral cortex (Newman, 1995; Pare and Llinas, 1995), it is likely that the high sensitivity of the thalamus to lorazepam's effects may be responsible for its sedative effects. The higher sensitivity of the thalamus to lorazepam than to alcohol could account for the greater self-report of sleepiness observed after lorazepam ($+3.1 \pm 2.5$) than after alcohol ($+0.7 \pm 2.7$, $p \leq 0.04$). It is also possible that doses of alcohol large enough to have sedative effects will decrease thalamic metabolism. In fact, in rodents, 3.2 g/kg doses of alcohol, which induced sedation, decreased thalamic metabolism by 30% (Grunwald et al., 1993).

Another difference in the metabolic changes after the administration of ethanol and lorazepam was the relative increase in the basal ganglia induced by ethanol but not by lorazepam. This is intriguing in that the basal ganglia is the main target for the nigrostriatal and ventro tegmental dopamine pathways and that the nucleus accumbens, which is located in the ventral region of the basal ganglia, is considered to be crucial in drug reinforcement (Amalric and Koob, 1993; Robbins and Everitt, 1996). Moreover, ethanol-induced activation of mesolimbic dopamine pathways, directly or indi-

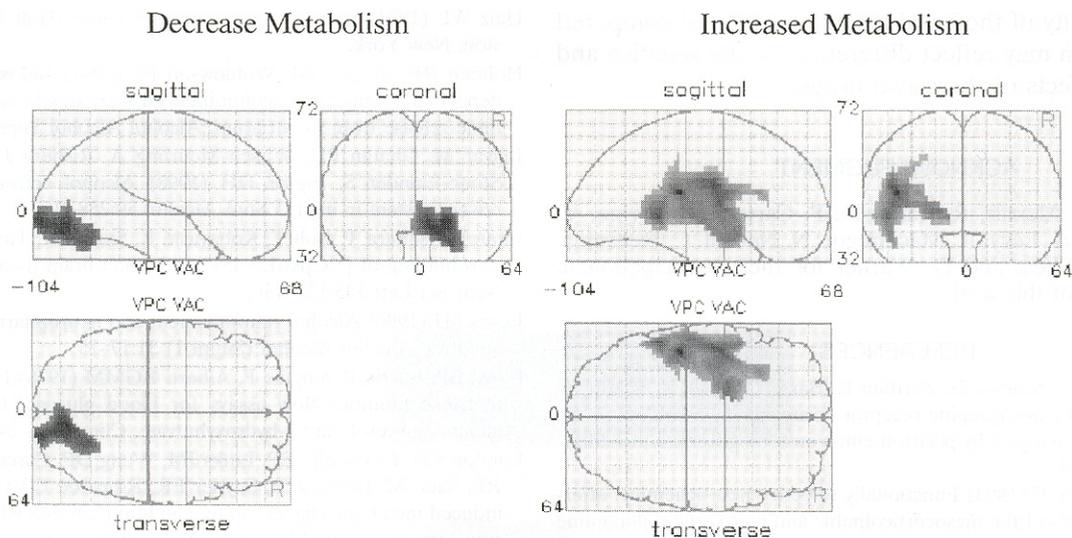


Fig. 6. SPM analysis for the differences between placebo and alcohol (0.75 g/kg).

rectly by interaction with opiate receptors (Di Chiara et al., 1996; Holman et al., 1987), is thought to participate in the rewarding effect of alcohol (Ingvar et al., 1998) and to be responsible for the increase in arousal, euphoria, and motor stimulation (Glazer, 1997; Phillips and Shen, 1996). Thus, the larger sensitivity of the basal ganglia to alcohol than to lorazepam may reflect differences in the levels of activation of the nigrostriatal and ventro tegmental dopamine pathways. This could account for the differences in the reinforcing effects of alcohol and lorazepam for the doses tested; whereas alcohol induced significant increases in self-reports of "high," lorazepam did not (De Wit et al., 1990; Tyrer, 1993). Although we did not find a correlation between the "high" and the metabolic changes, this may reflect (as described before) the poor temporal resolution of the FDG-PET measurements vis-à-vis the dynamic changes in the behavioral effects of alcohol. The difficulty in identifying the relationship between reinforcing

effects of drugs and metabolism has been reported for alcohol (Volkow et al., 1986) and for morphine (London et al., 1990).

A limitation of this study is that the effects of alcohol and lorazepam were not tested in the same subject, and hence the comparisons are limited to the analyses of patterns of brain activation. Future studies in which both of these drugs are tested on the same subject under similar conditions will allow researchers to assess if there are differences in the magnitude of the regional brain metabolic changes that are induced.

CONCLUSION

The decrease in metabolic activity in occipital cortex and the relative increase in left temporal cortex induced by ethanol and lorazepam are likely to reflect direct and secondary effects of activation of GABA/benzodiazepine receptors. The lower sensitivity of the thalamus and the

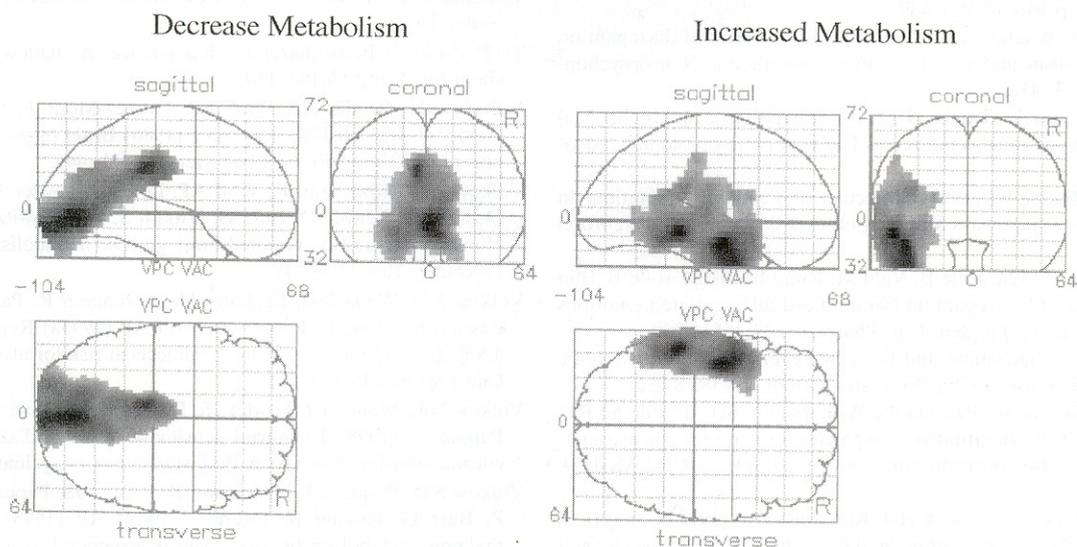


Fig. 7. SPM analysis for the differences between placebo and intravenous lorazepam (30 µg/kg).

higher sensitivity of the basal ganglia to ethanol compared with lorazepam may reflect differences in the sedative and reinforcing effects of these two drugs.

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