

Low doses of alcohol substantially decrease glucose metabolism in the human brain

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Moderate doses of alcohol decrease glucose metabolism in the human brain, which has been interpreted to reflect alcohol-induced decreases in brain activity. Here, we measure the effects of two relatively low doses of alcohol (0.25 g/kg and 0.5 g/kg, or 5 to 10 mM in total body H₂O) on glucose metabolism in the human brain. Twenty healthy control subjects were tested using positron emission tomography (PET) and FDG after placebo and after acute oral administration of either 0.25 g/kg, or 0.5 g/kg of alcohol, administered over 40 min. Both doses of alcohol significantly decreased whole-brain glucose metabolism (10% and 23% respectively). The responses differed between doses; whereas the 0.25 g/kg dose predominantly reduced metabolism in cortical regions, the 0.5 g/kg dose reduced metabolism in cortical as well as subcortical regions (i.e. cerebellum, mesencephalon, basal ganglia and thalamus). These doses of alcohol did not significantly change the scores in cognitive performance, which contrasts with our previous results showing that a 13% reduction in brain metabolism by lorazepam was associated with significant impairment in performance on the same battery of cognitive tests. This seemingly paradoxical finding raises the possibility that the large brain metabolic decrements during alcohol intoxication could reflect a shift in the substrate for energy utilization, particularly in light of new evidence that blood-borne acetate, which is markedly increased during intoxication, is a substrate for energy production by the brain.
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Introduction

Among substances of abuse, alcohol is the one most widely consumed. It is estimated that 50% of Americans 12 years or older consume alcohol at least once a month (SAMHSA, 2003). Though 6.8% are heavy drinkers (5 or more drinks on at least 5 different days in the past 30 days), the majority of individuals use alcohol in moderation. Brain imaging studies have shown that acute alcohol administration results in decreased brain glucose utilization, which has been interpreted to reflect decreases in brain activity during intoxication. Most of the studies measuring effects of alcohol on glucose metabolism have used moderate to high doses of alcohol (0.5–1 g/kg administered over 15–45 min). Thus, the decrements in brain glucose metabolism are likely to reflect the CNS depressant effects of alcohol that occur at high doses (Pohorecky, 1977). However, in contrast to large doses, small doses of alcohol are stimulatory (Pohorecky, 1977). This biphasic effect of alcohol as a function of dose was corroborated for brain glucose metabolism in an autoradiographic study in rodents showing that, whereas a 1 g/kg dose of alcohol decreased metabolism, a 0.25 g/kg dose increased it (Williams-Hemby and Porrino, 1994). The extent to which a similar biphasic effect of alcohol on glucose metabolism occurs in the human brain has not been investigated. Here, we evaluate the effects of low to moderate doses of alcohol (0.25 g/kg and 0.5 g/kg respectively) on brain glucose metabolism and compare them to effects we had previously observed after administration of a high dose (0.75 g/kg) to assess if we could document the biphasic effects of alcohol on glucose metabolism in the human brain.

For this purpose, we measured the regional brain metabolic changes induced by a 0.25 g/kg and a 0.5 g/kg dose of alcohol

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using PET and FDG. Twenty healthy controls were studied with PET and FDG twice, once after placebo and once 40–50 min after acute alcohol administration. We chose a 40–50 min delay since this is the time when peak alcohol concentrations are reached in brain after oral administration (Sammi et al., 2000). We selected the 0.25 g/kg and 0.5 g/kg doses since these are typical doses consumed by social drinkers (Stinson et al., 1998), roughly equivalent to one and two drinks, respectively, for a 50 kg person. In parallel, we also measured the behavioral and cognitive effects of these low to moderate doses of alcohol. We hypothesized that, in contrast to previous findings showing that high doses of alcohol decreased brain glucose metabolism, low doses would increase brain metabolic activity.

Material and methods

Subjects

Twenty right-handed healthy subjects (37 ± 9 years of age, 12M, 8F) who drank in moderation (not more than 5 drinks/week) were selected. Each subject had a routine physical, psychiatric and neurologic examination. Routine laboratory tests were performed, as well as urine tests to exclude the use of psychoactive drugs. Subjects were excluded if they had a present or past psychiatric and/or neurological illness, if they had a present or past history of substance abuse or dependence (except nicotine), if they had medical illnesses and/or if they were taking any medication. Subjects were also excluded if they expressed they would have difficulty abstaining from drinking any alcohol for 1 week prior to the study. Four of the subjects were current smokers. Subjects were instructed to discontinue any over the counter medication 2 weeks prior to the PET scan and were asked to abstain from alcohol for 1 week prior to the PET scans whether it was the placebo or the alcohol scanning session. Self-reports were used to determine if they had used any alcohol during the week prior to the study. The study was approved by the Human Subjects Research Committee of Brookhaven National Laboratory. After explaining the procedure, written informed consent was obtained from each subject.

Scans

PET scans were acquired on a whole-body, high-resolution positron emission tomograph (SiemensTI ECAT HR+; with $4.6 \times 4.6 \times 4.2$ mm resolution at center of field of view and 63 slices) in 3D dynamic acquisition mode using FDG. Methods for positioning of subjects, catheterizations, transmission scans and blood sampling and analysis have been published (Wang et al., 1993). Briefly, a 20 min emission scan was started 35 min after injection of 4–6 mCi of FDG. Arterialized venous blood sampling was used to measure FDG and glucose concentration in plasma.

Subjects were scanned on 2 different days with FDG within 1 week of each other. On one of the days, subjects drank a placebo (100 ml of diet non-caffeinated soda) over a period of 40 min, given 40–50 min prior to FDG (baseline-FDG scan) administration. On the other day, subjects drank a mixture of 95% ethanol with diet soda added up to 100 ml over a period of 40 min, given 40–50 min prior to FDG (alcohol-FDG scan). The order was randomized so that for half of the subjects the first scan was with placebo, and for the other half, with alcohol. Thirteen subjects received the 0.25 g/kg dose (8M, 5F) and 7 received the 0.5 g/kg

dose (4 M, 3 F). Subjects were blind to whether placebo or alcohol was given. To avoid circadian variability (Bartlett et al., 1988), the two scans for a given subject were done at the same time of day (± 1 h). Plasma alcohol concentration was measured prior to and 20, 40, 55, 80, 100, 140 and 160 min after the initiation of alcohol administration using the enzymatic assay of Lloyd et al. (1978).

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 cognitive effects of alcohol or of placebo. For the females, the studies were done in the mid-luteal phase (16–23 days after the onset of menstruation).

Behavioral and cognitive evaluation

Before placebo or alcohol, and at 20, 40, 60, 80 and 135 min after placebo or alcohol administration, subjects were asked to evaluate on an analog scale (rated 0–10) their subjective sense of intoxication, sleepiness, high and anxiety. To assess the cognitive effects of alcohol, subjects were evaluated with the Stroop Test, the Word Association Test (WA), Symbol Digit Modality Test (SDMT) and arithmetic calculations (Lezak, 1995), which were obtained prior to placebo or alcohol and 80 min (just prior to FDG injection) and 140 min (end of PET scanning procedure) after initiation of placebo or alcohol administration.

Image analysis

Regions were selected using a template of 423 non-overlapping regions based on Talairach and Tournoux's atlas (Talairach and Tournoux, 1988). Values for the cortical, subcortical and cerebellar regions were computed using the weighted average from the different slices where the regions were obtained and grouped into 12 composite regions, which included frontal, parietal, temporal, occipital cortices, insula, anterior cingulate gyrus, orbitofrontal cortex, basal ganglia, thalamus, amygdala/hippocampus, mesencephalon and cerebellum. An estimate of whole-brain metabolism was obtained by averaging the values from all of the regions of interest.

Statistical analyses

Differences in measures of regional brain glucose metabolism during alcohol intoxication were evaluated using a factorial repeated ANOVA with dose as the between factor (0.25 g/kg versus 0.5 g/kg) and drug (placebo versus alcohol) and regions (12 different regions) as the repeated measures. For the behavioral measures, we used a factorial repeated ANOVA with dose as the between factor and drug and time as the repeated measures.

Pearson product moment correlations were used to quantify the relationship between the changes in regional brain glucose metabolism computed as percent change from placebo (placebo – alcohol / placebo \times 100) and the changes in the behavioral and cognitive measures that were significantly affected by alcohol. To compute the changes in self-reports of drug effects, we averaged the scores obtained between 40 and 80 min after alcohol from those obtained prior to alcohol administration. To compute the changes in cognitive measures, we subtracted the scores collected prior to those obtained 80 min after alcohol. In consideration of the “multiple”

correlations, we set the level of significance to $P \leq 0.01$, and values of $P < 0.05$ are reported as trends.

Results

Plasma alcohol concentration, behavioral and cognitive effects

Plasma alcohol concentrations differed across doses ($F = 32$, $P < 0.001$) and time of measurement ($F = 16$, $P < 0.001$) (Table 1). Peak alcohol plasma concentrations were achieved around 40 min after administration and were 32 ± 12 mg % for the 0.25 g/kg dose and 71 ± 18 mg % for the 0.5 g/kg dose. These values correspond to peak blood alcohol concentrations (plasma alcohol/1.16) of 27 mg % and 61 mg % respectively.

Peak behavioral effects for both doses of alcohol occurred around 40 min after alcohol administration (Fig. 1). Both doses increased self-reports for intoxication (df 5,85, $F = 14$, $P < 0.0001$), high ($F = 18$, $P < 0.0001$) and sleepiness ($F = 2.6$, $P < 0.05$) but did not change self-reports of anxiety. Though overall the effects of the 0.5 g/kg dose tended to be greater than those for the 0.25 g/kg dose, the differences were only significant for self-reports of high ($F = 2.8$, $P < 0.01$) (Fig. 1). Alcohol effects on cognitive performance were minimal and were not significant (Table 2). The cognitive effects did not differ between doses.

Effects on brain glucose metabolism

Alcohol significantly decreased whole-brain glucose metabolism (ANOVA, Drug effect, df 1,18; $F = 27$, $P < 0.0001$) (Fig. 2). The magnitude of the decrease in brain glucose metabolism differed between the doses (ANOVA, drug by dose interaction effect, df 1,18; $F = 5.7$, $P < 0.03$). Reductions in whole-brain glucose metabolism were significantly smaller for the 0.25 g/kg dose ($10 \pm 13\%$) than for the 0.5 g/kg dose ($23 \pm 11\%$). The smaller decrements in whole-brain glucose metabolism for the 0.25 g/kg dose than for the 0.5 g/kg dose were due to the fact that, while the 0.5 g/kg dose decreased whole-brain glucose metabolism in all subjects, the 0.25 g/kg decreased metabolism in some subjects but not in others (Fig. 3).

Alcohol-induced decrements in glucose metabolism were not homogeneous throughout the brain but differed among the 12 regions analyzed (ANOVA, region effect, df 1,11; $F = 2.1$; $P < 0.05$). The regional changes also differed between the doses (ANOVA, region by dose interaction effect, df 1,11; $F = 2.5$, $P < 0.007$) (Fig. 4). The regional differences between doses appeared to be accounted for mostly by the significantly smaller decrements in

subcortical regions and cerebellum for the 0.25 g/kg than for the 0.5 g/kg dose. The largest differences between the 0.25 and the 0.5 g/kg dose were in thalamus (5% versus 26% respectively), mesencephalon (4% versus 24%) and cerebellum (7% versus 24%) (Fig. 4).

Correlation with behavioral measures

Correlations between metabolism and self-reports of drug effects showed a trend for significance ($P < 0.05$) between the “high” and changes in mesencephalon. Correlations with intoxication and sleepiness were not significant.

Discussion

These results do not discern a biphasic response to the effects of alcohol on glucose metabolism in the human brain as has been reported in rodents. In contrast, we show that relatively low doses of alcohol, just as had been reported for larger doses of alcohol (Wang et al., 2003), significantly decreased glucose metabolism in the human brain. Indeed, the 0.25 g/kg dose, which is equivalent to one drink for a 50 kg person, induced a 10% reduction, and the 0.5 g/kg dose, equivalent to two drinks, induced a 23% reduction in whole-brain metabolism. These marked reductions in whole-brain metabolism are consistent with prior studies showing whole-brain metabolic reductions of 26% by 0.75 g/kg of alcohol (Volkow et al., 2000), 25% by 40 g iv (approximately 0.6 g/kg iv) (Schreckenberger et al., 2004) and 18% by 1 g/kg (Volkow et al., 1990). However, they are considerably larger than the 2.8% decreases in brain glucose metabolism reported with 0.5 g/kg alcohol (de Wit et al., 1990). The reason for the discrepancy with the study by De Wit et al. is unclear and may reflect differences in the times at which the FDG measurements were made, experimental conditions, PET scanners and/or subject characteristics.

Dose effects

The 0.5 g/kg dose had significantly greater effects on whole-brain and regional brain metabolism than the 0.25 g/kg dose. The differences appeared to be accounted for mostly by the fact that the 0.5 g/kg dose of alcohol decreased metabolism in all subjects, while the 0.25 g/kg dose decreased whole-brain metabolism in some subjects but not in others. This corroborates the intersubject variability previously reported for the effects of alcohol on brain metabolism as well as on its behavioral effects (de Wit et al., 1990). Since there was not a correlation between alcohol plasma concentration and the magnitude of the brain metabolic decrements, this suggests that the variability cannot be accounted solely by differences in blood alcohol concentration (BAC).

The largest differences in metabolism between the doses were in thalamus, mesencephalon and cerebellum, where the 0.25 g/kg dose had no effect, whereas the 0.5 dose produced large decrements in metabolism. The large decrements in metabolism observed for the 0.5 g/kg dose (BAC 60 mg %) in thalamus, a brain region in which drug-induced decrements in metabolism or cerebral blood flow are associated with sedation (Volkow et al., 1995; Fiset et al., 1999; Schlunzen et al., 2004), and in cerebellum, a brain region involved with motor coordination (Miall et al., 2001), could explain why the risks of being in a car crash for BAC

Table 1

Plasma alcohol concentrations (mg %) for the subjects who received 0.25 g/kg and those that received 0.5 g/kg alcohol doses

Time (min)	0.25 g/kg Mean	0.5 g/kg Mean
20	14 ± 11	17 ± 16
40	32 ± 12	71 ± 18
55	29 ± 7	50 ± 34
80	18 ± 8	46 ± 22
100	14 ± 10	46 ± 19
130	10 ± 6	35 ± 9
160	6 ± 5	28 ± 10

Values correspond to means and standard deviations.

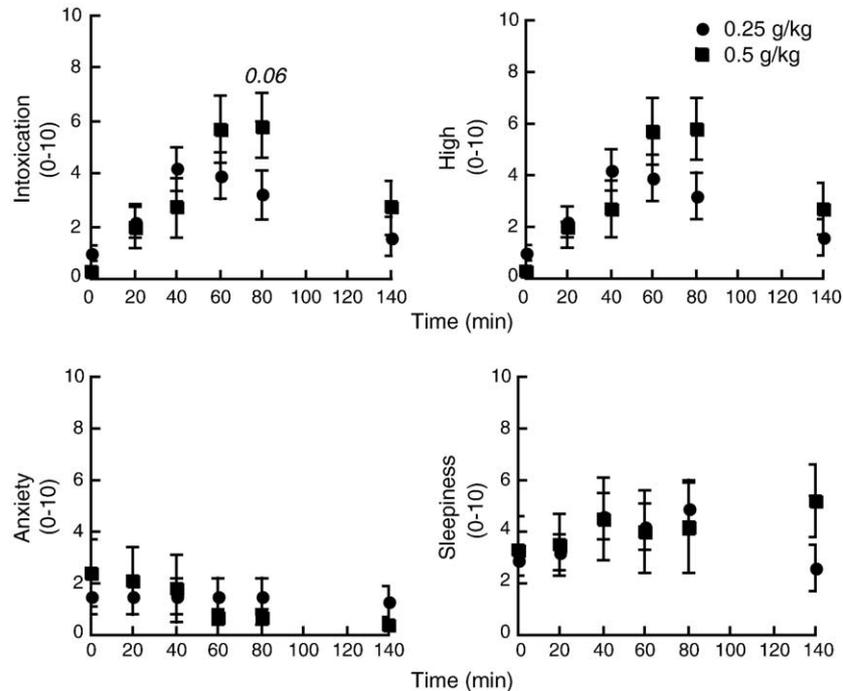


Fig. 1. Behavioral effects for the 0.25 g/kg and the 0.5 g/kg doses of alcohol. Measures correspond to mean and SE for the self-reports of drug effects, which were scored from 0–10. The only difference between doses was for self-reports of “high”, which were significantly higher for the 0.5 g/kg than for the 0.25 g/kg alcohol dose ($F = 2.8$, $P < 0.01$).

in the 50–90 mg % range are so large, at least nine times greater than for no alcohol in blood (Zador, 1991).

The reductions in whole-brain metabolism observed after 0.5 g/kg (23%) did not differ in magnitude from those we had previously reported using the same experimental protocol and PET instrument after 0.75 g/kg of alcohol (26%) (Volkow et al., 2000). Furthermore, using a PET instrument with a much more limited spatial resolution (PET VI camera) but the same experimental protocol, we had reported that 1 g/kg reduced metabolism by 18% (Volkow et al., 1990). These results would appear to indicate a ceiling effect for the depressant effects of alcohol on glucose metabolism in the human brain.

Our findings of decreases in metabolism after low, moderate and high doses of alcohol differ from the results obtained by an autoradiographic study in rodents (Williams-Hemby and Porrino, 1994), which reported regional increases in brain glucose metabolism with 0.25 g/kg of alcohol, minimal effects with 0.5 g/kg and decreases with 1 g/kg. On the other hand, our findings in

humans are consistent with those of another autoradiographic study done in low alcohol drinking (LAD) rats that reported decreases in brain glucose metabolism both after a 0.25 g/kg and a 1 g/kg dose of alcohol (Learn et al., 2003). However, in that study, the 0.25 g/kg and 1 g/kg doses of alcohol had minimal effects in high alcohol drinking (HAD) rats despite having equivalent BAC to those in LAD. These discrepancies are therefore likely to reflect, in part, differences in response to alcohol between strains. Other variables known to influence the effects of alcohol on brain glucose metabolism such as the timing of measurements after alcohol (Lyons et al., 1998), past alcohol history of the animals (Porrino et al., 1998), whether alcohol is self-administered versus given by the investigator (Williams-Hemby et al., 1996) and dose and route of administration (Williams-Hemby and Porrino, 1997) are also likely to contribute to some of the discrepancies. In humans, imaging studies have shown that alcohol-induced changes in brain glucose metabolism are also sensitive to prior histories of chronic alcohol use (Volkow et al., 1990) and to gender (Wang et al., 2003). In the

Table 2

Scores on neuropsychological tests obtained prior to and 80 and 140 min after initiation of alcohol intake

	0.25 g/kg			0.5 g/kg		
	Placebo	ETOH 80 min	ETOH 140 min	Placebo	ETOH 80 min	ETOH 140 min
Stroop—read	93 ± 9	86 ± 21	95 ± 15	108 ± 17	99 ± 23	101 ± 15
Stroop—color	72 ± 14	67 ± 18	71 ± 12	78 ± 9	72 ± 12	76 ± 8
Stroop—interference	42 ± 9	39 ± 13	45 ± 10	47 ± 10	49 ± 11	51 ± 8
SDMT	51 ± 9	47 ± 9	50 ± 7	50 ± 14	43 ± 8	42 ± 21
WA	13 ± 4	12 ± 5	13 ± 5	14 ± 3	12 ± 3	12 ± 5
Calculation	11 ± 2	10 ± 3	11 ± 2	12 ± 2	11 ± 1	10 ± 5

There were no differences in the scores before or after alcohol administration nor between subjects that received 0.25 g/kg and those that received 0.5 g/kg of alcohol. Values correspond to means and standard deviations.

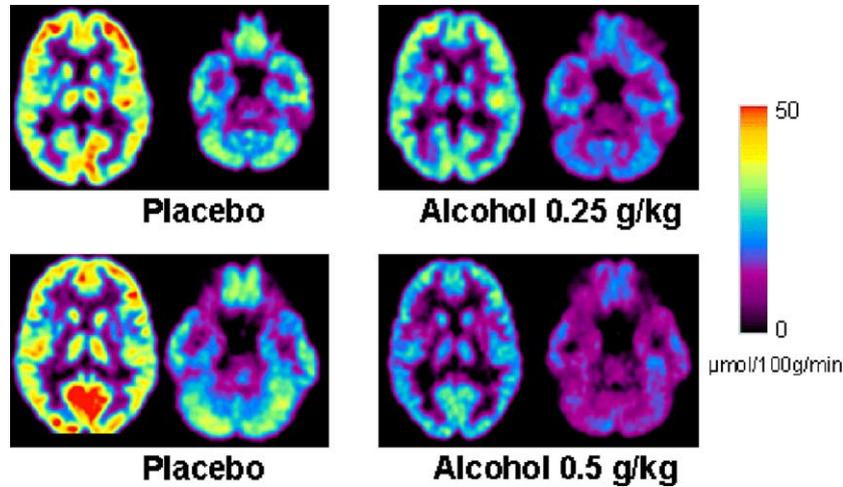


Fig. 2. Images of brain glucose metabolism for a subject tested at baseline (placebo) and after 0.25 g/kg alcohol and for a subject tested at baseline and after 0.5 g/kg alcohol. Axial planes shown are at the thalamic and cerebellar levels.

current study, we did not have a large enough sample to assess the gender effects on the responses to alcohol.

Comparison with effects of sedative drugs and with anesthetics

The marked reduction in whole-brain glucose metabolism caused by low doses of alcohol contrasts with its relatively mild behavioral effects and the minimal impairment of cognitive performance. It also contrasts with the much smaller decrements in brain glucose metabolism that we had previously reported in healthy controls induced by the benzodiazepine drug lorazepam at doses that had more pronounced behavioral and cognitive effects. Lorazepam (30 μg/kg iv) decreased whole-brain glucose metabolism 13% and induced marked sedation and disruption in the neuropsychological measures for which alcohol, at the doses given in this study, did not induce impairment (Volkow et al., 1993). However, despite the modest decreases in cortical metabolism, lorazepam induced relatively large decreases in thalamus (25% ± 9), which were associated with its sedative effects (Volkow et al., 1995).

On the other hand, the anesthetic agents, when given at doses that produce anesthesia, induce larger whole-brain metabolic decrements than those reported here for alcohol. The magnitude of the decrements varies for the various anesthetics. At doses titrated to induce participant unresponsiveness, halothane reduced whole-brain glucose metabolism by 40% (Alkire et al., 1999), isoflurane by 46% (Alkire et al., 1997) and propofol by 55% (Alkire et al., 1995). Decrements in glucose metabolism by

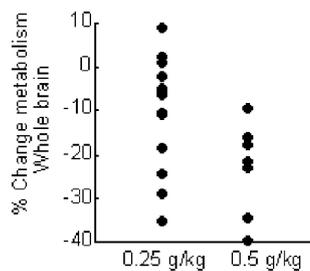


Fig. 3. Individual values for percent changes in whole-brain glucose metabolism after 0.25 g/kg and after 0.5 g/kg alcohol. Notice that while the 0.5 g/kg alcohol doses decreased metabolism in all subjects the response to 0.25 g/kg alcohol was quite variable.

halothane and isoflurane tend to be uniform throughout the brain, whereas propofol appears to affect cortical metabolism to a greater extent than subcortical metabolism.

Effects of alcohol on energy utilization

We were surprised by the large decrements in whole-brain glucose metabolism, particularly with the 0.5 g/kg dose, which induced much larger decrements than those induced by lorazepam at a dose that produced greater sedation and cognitive impairment than this dose of alcohol (Volkow et al., 1995). Moreover, in two of the subjects in the current study, whole-brain glucose metabolism was reduced by 30%, which is close to the levels encountered by doses of anesthetics that induce unconsciousness. Yet, these subjects were alert and only moderately intoxicated. This leads us to question the possibility that, during acute alcohol intoxication, there could be a shift in substrate utilization by the brain. In fact, it has been suggested that acetate, which serves as an energy substrate for astrocytes (Cruz et al., 2005), could become available as an energy

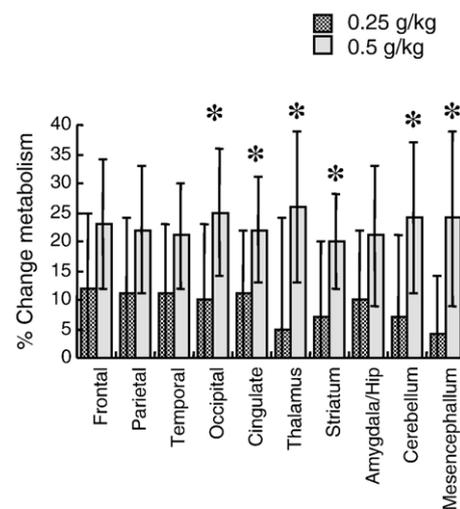


Fig. 4. Regional changes in brain glucose metabolism expressed as percent change from placebo. *Significant differences between doses. Values correspond to means and SE.

substrate after alcohol administration (Waniewski and Martin, 1998). Acetate is readily taken up into the brain, crossing the blood–brain barrier via the monocarboxylate transporter. Although acetate concentration in blood is constitutively low (about 0.2 to 0.3 mM), it rises significantly during alcohol intoxication (Waniewski and Martin, 1998). A single intravenous dose of 0.5 g/kg alcohol in human results in acetate plasma levels of up to 1 mM (Orrego et al., 1988). The use of acetate by the brain is reportedly limited by its availability. Plasma acetate levels during intoxication (around 1 mM) might be associated with a cerebral metabolic rate for acetate of around 10–20% of total brain metabolic rate. This would require a high K_m for acetate utilization. Indeed, at least one paper (Waniewski and Martin, 1998) reports a K_m of 9 mM for acetate transport by astrocytes that is consistent with this view.

A shift from glucose to acetate as an energy substrate during alcohol intoxication could provide a potential explanation for our previously reported, seemingly paradoxical finding showing greater decreases in brain glucose metabolism during alcohol intoxication in alcoholic subjects when compared with controls, despite not having reduced behavioral, cognitive and motoric responses (Volkow et al., 1990). Alcoholics have significantly higher blood acetate concentrations after acute alcohol than controls, which is an effect that appears to reflect increased ethanol elimination (Nuutinen et al., 1985). We reported a similar, though opposite, dissociation in healthy female controls who showed significantly lower decreases in brain glucose metabolism after alcohol than males despite demonstrating much greater levels of intoxication (Wang et al., 2003). This would also be consistent with the significantly lower concentrations of blood acetate after acute alcohol administration reported for females when compared with males (Hannak et al., 1985).

If indeed there is an increase in brain acetate utilization as an energy source during alcohol intoxication, this could also provide an explanation of why alcohol increases cerebral blood flow even though it decreases brain glucose metabolism (Newlin et al., 1982; Mathew and Wilson, 1986; Volkow et al., 1988; Sano et al., 1993; Schwartz et al., 1993; Tiihonen et al., 1994). Similarly, the variability in the effects of alcohol on brain glucose metabolism among strains of rodents and between human subjects could reflect, in part, differences in the rate of metabolism of alcohol to acetate or, alternatively, differences in the ability to utilize acetate as a substrate for energy in brain. However, future studies are required to determine if indeed there is an increase in brain acetate metabolism as an energy source during alcohol intoxication.

Study limitations

This study evaluated the two alcohol doses in different groups of subjects, so the dose effects are confounded by the variability in responses to alcohol between subjects. Despite the intersubject variability, significant dose effects, mostly in subcortical structures, were revealed. However, studies done in the same subjects are required to properly address dose effects.

Measures of brain metabolism were made mostly during the influx phase of alcohol, but PET FDG studies have shown that the regional metabolic effects differ between the influx and elimination phases (Schreckenberger et al., 2004). Thus, these findings may differ for the clearance phase.

Because of technical constraints imposed by the PET procedure, the cognitive tests were only done at 80 min after initiation of alcohol (just prior or FDG injection) and at 140 min (end of PET

scanning). Thus, while we cannot rule out the possibility that there may have been some cognitive disruption during the early ascending curve of the alcohol phase, the point is that at the time when we observed the large brain metabolic decrements there was no evidence of significant cognitive disruption.

Though we are speculating that the large decreases in whole-brain metabolism could reflect metabolism of acetate as an alternative energy source, we did not measure acetate concentration in plasma, which could have allowed us to assess if indeed there was an association with alcohol-induced decrements in brain glucose metabolism.

Furthermore, we do not have a detailed description of the drinking histories from the subjects, and thus we could not ascertain if the amount of alcohol intake affected the brain metabolic decrements induced by alcohol.

Summary

We did not document a biphasic effect of alcohol on brain glucose metabolism in the human brain but instead showed decreases in metabolism after low and moderated doses of alcohol. The apparent paradoxical results between the large decrements in brain glucose metabolism induced by alcohol at doses that induced minimal cognitive impairment have led us to hypothesize that the large decrements may reflect changes in substrate utilization by the brain during alcohol intoxication (i.e. acetate). This possibility is relevant, not only for understanding the effects of alcohol in brain physiology, but also for the basic understanding of brain metabolism.

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