Effects of Ethanol on Glucose Utilization in Rat Brain[1] (35045)

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After ethanol is ingested, it enters the brain rapidly and accumulates in concentrations similar to those in blood (1, 2). The metabolites of ethanol, acetaldehyde and acetic acid, produced chiefly in the liver (3), accumulate in small amounts in blood and brain (4–7). Small amounts of these metabolites also may be produced in the brain because it contains some alcohol dehydrogenase and aldehyde dehydrogenase (8–10).

Ethanol and acetaldehyde (in much smaller amounts) inhibit K^+-stimulated respiration in brain cortex slices (11, 12); acetaldehyde inhibits brain mitochondrial respiration (12, 13). Ammon and co-workers (14, 15) found that, after intravenous injection of very large amounts of ethanol in mice, the concentration of glucose was doubled in the brain, and the concentrations of glycogen, lactate, and coenzyme A were all reduced. Roach and Williams (16, 17) administered glucose-U-^{14}C to ethanol-intoxicated hamsters and found a higher percentage of brain ^{14}C in glucose and less in amino acids than in control hamsters.

This paper reports additional studies of the effect of ethanol on glucose metabolism in cerebrum and hindbrain, and particularly on the conversion of glucose to amino acids, in fed and fasted rats given ethanol by stomach tube and in fed rats given ethanol by intraperitoneal injection. Glucose-U-^{14}C was injected 2¼ hr after the dose of ethanol; 15 min later, the brain was frozen *in situ*. Comparisons were made between fed and fasted control rats, between fed control and fed alcohol-treated rats, and between fasted control and fasted alcohol-treated rats.

Materials and Methods. Male rats of the Sprague-Dawley strain, weighing 240–345 g and maintained on Rockland rat diet, were used in this study. Some of the rats were fasted for 15 or 24 hr. With the rats under ether anesthesia, polyethylene tubing (PE no. 10) was inserted into the tail vein for intravenous injections; polyethylene tubing (PE no. 50) was inserted in the femoral artery for collection of blood. Zero time was the start of ethanol administration, immediately after insertion of the tubing. Ethanol (33% solution) was administered to fed rats by stomach tube (4.3 mg/g body weight) (4) or intraperitoneally (3.3 mg/g; 25% solution) and to fasted rats by stomach tube (3.3 mg/g). Even with the higher doses given to fed rats by stomach tube the blood ethanol concentrations were only about half as great as in the other two groups (2). Ethanol-treated rats and control rats were placed in restraining cages (18) and infused with physiologic saline (1.25 ml/hr) for 2½ hr. At 2¼ hr a single injection of glucose-U-^{14}C (New England Nuclear; 20 μCi; 0.24 mg of glucose) in 0.2 ml was given into the tail vein. The infusion of saline was resumed until pentobarbital sodium (20 mg) was injected intravenously exactly 30 sec before the rat was immersed, head first, in liquid nitrogen at 2½ hr (after injection of ethanol) for 2 min. Blood was obtained from the femoral artery immediately before the brain was frozen *in situ*.

Preparation of brain extracts. Precautions were taken to prevent thawing of brain during processing because this results in rapid destruction of brain glucose as shown by Lowry and co-workers (19). The frozen brain was chiseled out quickly and split into cerebrum and rhombencephalon or hindbrain (20) and replaced in liquid nitrogen. The frozen cerebrum and hindbrain were weighed

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quickly, dropped into ice-cold 0.1 *N* HCl, and homogenized immediately in the VirTis homogenizer. Aliquots of homogenate were deproteinized with picric acid for measurement of amino acids and with perchloric acid for measurement of glucose and lactate.

In some experiments, blood was collected from the femoral artery at half-hour intervals, during the 2½ hr infusion, for measurement of blood glucose concentration. In other experiments, glucose-U-^{14}C was administered 30 min before the end of the infusion, and blood was collected at 1–30 min for measurement of radioactivity and glucose concentration.

Chemical determinations. For glucose determination, protein-free extracts of blood were made immediately with Somogyi reagents and of brain, with perchloric acid; for column chromatography (amino acid analyzer), protein-free extracts of blood were made with sulfosalicylic acid and of brain, with picric acid. The amino acid analyzer was used for measurement of free amino acids in brain (21, 22). Enzymatic methods were used for determination of glucose (23), lactate (24), and alcohol (25). Additional details of the procedures have been presented previously (26, 27).

Radioactivity measurements. Radioactivity in blood and in protein-free extracts of blood and brain was measured in a 2:1 mix-

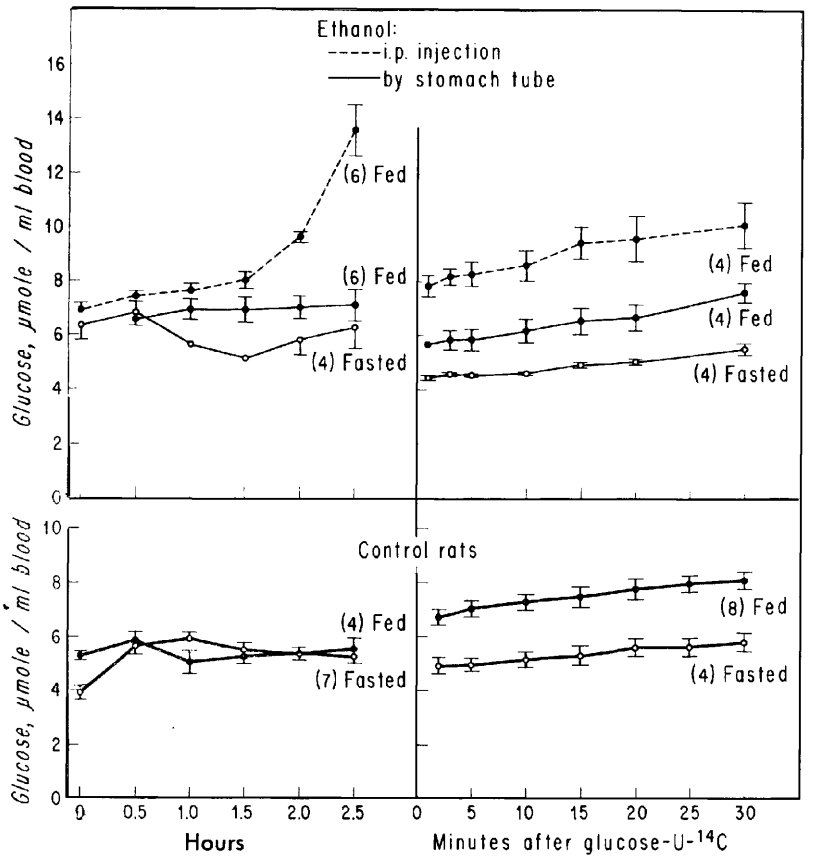

FIG. 1. Upper left. Concentration of glucose in femoral artery during 2½-hr infusion of physiologic saline begun immediately after ethanol was administered by stomach tube to fed or fasted rats or by intraperitoneal injection to fed rats. Means ± SE are shown (number of rats in parentheses). Lower left. Concentration of glucose in blood during infusion of saline in fed and fasted control rats. Upper right. Concentration of glucose in blood during last half hour of saline infusion in alcohol-treated rats (after intravenous injection of glucose-U-^{14}C). Lower right. Concentration of glucose in blood of control rats during last half hour.

ture of toluene–PPO–DMPOPOP and Triton X–100 (28) in a Packard scintillation spectrometer. Radioactivity in column effluents of extracts of blood and brain was measured in an anthracene-filled flow cell (vol 1 or 2.5 ml) in a scintillation spectrometer before the effluent entered the mixing manifold in the amino acid analyzer for reaction with ninhydrin.

Calculations. Brain amino acid specific activities were determined by comparison of the radioactive peaks with the ninhydrin peaks of the column effluent. Specific activities of glucose and lactate in brain were determined by comparison of radioactive peaks with concentrations measured enzymatically.

The specific activity of blood glucose (dpm/μmole) was obtained by dividing the total blood ^{14}C (dpm/ml) by the glucose concentration (μmole/ml). This simple calculation was used because over 90% of blood ^{14}C was found in glucose when protein-free extracts of blood were made promptly (Flock and associates, unpublished data).

The specific activities of blood glucose during the first 30 min after injection of glucose-U-^{14}C were plotted on linear graph paper and extrapolated visually to zero. The specific activities read from the curves at 1-min intervals were averaged for the first 15 min and this average specific activity divided by the specific activity at 15 min gave a factor by which the average specific activity of blood glucose could be calculated when blood was taken only at the end of the experiment. Glucose incorporation or uptake in brain was calculated by dividing the total ^{14}C in brain (dpm/g) 15 min after injection of glucose-U-^{14}C by the average specific activity of blood glucose (dpm/μmole) during this interval; this was expressed as the equivalent of blood glucose (μmole/g). Similarly, the amount of glucose converted to metabolites in the brain was obtained by multiplying the percentage of brain ^{14}C in the metabolites of glucose by the glucose uptake in brain, and this also was expressed as the equivalent of blood glucose (μmoles/g). The amount of glucose converted to metabolites was also calculated by dividing the ^{14}C in each metabolite (dpm/g) by the specific activity of brain glucose, and this was expressed as the equivalent of brain glucose (μmoles/g).

Results. Concentrations of blood glucose. The blood glucose concentrations in fed rats given alcohol by stomach tube were relatively constant (6.59–7.15 μmoles/ml) during the first 2½ hr after alcohol ingestion; but in fed rats given alcohol by intraperitoneal injection, the blood glucose concentrations sometimes increased sharply during the last hour of the period (Fig. 1). The glucose concentration decreased somewhat in fasted rats given alcohol by stomach tube.

Steady but small increases in blood glucose concentration were found in all three groups

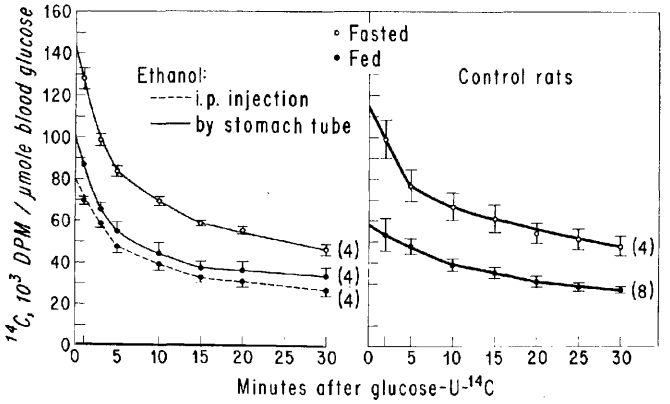

FIG. 2. Specific activity of blood glucose in femoral arterial blood during 30 min after injection of glucose-U-^{14}C. Means ± SE are shown. Lines were extrapolated to zero time visually. Left. Rats after ethanol administration. Right Control rats without ethanol.

TABLE I. Glucose and Lactate Concentrations in Cerebrum and Hindbrain of Rats.[a]

Measurement	Control rats		Ethanol-treated rats		
			Stomach tube		Intraperitoneal
	Fed (8)	Fasted (4)	Fed (6)	Fasted (4)	Fed (5)
Blood ethanol (mg/100 ml)	0	0	139 ± 27	292 ± 7	283 ± 13
Blood glucose (μmole/ml)	6.40 ± 0.23	5.40 ± 0.42[b]	5.49 ± 0.38[b]	4.39 ± 0.56	7.24 ± 0.38[b]
Cerebrum glucose (μmole/g)	0.58 ± 0.23	0.66 ± 0.16	1.00 ± 0.03	1.21 ± 0.09[c]	1.30 ± 0.05[b]
Hindbrain glucose (μmole/g)	0.72 ± 0.07	0.85 ± 0.14	1.43 ± 0.19[d]	1.12 ± 0.04	1.63 ± 0.08[e]
Glucose ratio					
Cerebrum/blood	0.09 ± 0.01	0.12 ± 0.02	0.19 ± 0.02[e]	0.28 ± 0.02[f]	0.18 ± 0.01[e]
Hindbrain/blood	0.11 ± 0.01	0.16 ± 0.02[b]	0.28 ± 0.06[d]	0.27 ± 0.03[e]	0.23 ± 0.01[e]
Cerebrum lactate (μmole/g)	4.80 ± 0.31	3.81 ± 0.13[b]	3.53 ± 0.20[d]	3.41, 3.28 (2)	2.58 ± 0.36[e]
Hindbrain lactate (μmole/g)	6.91 ± 0.57	4.50 ± 0.23[b]	4.73 ± 0.40[d]	5.25, 5.78 (2)	5.00 ± 0.70[b]

[a] Data are shown as means ± SE (in parentheses: number of rats). In this and subsequent tables, in fasted control rats, the mean of four analyses done on eight rats is shown, two brains being combined for each analysis.

[b] For difference from fed control, $p < .05$; [d] $p < .01$; [e] $p < .001$.

[c] For difference from fasted control, $p < .05$; [f] $p < .001$.

of alcohol-treated rats and in fed and fasted control rats during the 30 min after the injection of glucose-U-^{14}C. This may have been due in part to the frequent sampling of blood even though it was collected from the polyethylene tubing in the femoral artery with minimal apparent disturbance to the rat.

Radioactivity in blood. The specific activity of blood glucose in all the rats decreased rapidly during the first 5 min after injection of glucose-U-^{14}C and then more slowly (Fig. 2). The blood glucose concentration was less in fasted than in fed rats and the specific activity was greater.

Concentrations of glucose and lactate in brain. The administration of ethanol by stomach tube doubled the concentration of glucose in the hindbrain of fed rats and in the cerebrum of fasted rats (Table I). Intraperitoneal injection of ethanol doubled it in both hindbrain and cerebrum. The glucose concentration ratios cerebrum/blood and

TABLE II. Effect of Fasting on Amino Acids and Taurine in Cerebrum and Hindbrain of Normal Rats.

Amino acids	Concentrations, mean ± SE (μmole/g wet wt)			
	Fed (8 rats)[a]		Fasted (4 analyses, 8 rats)	
	Cerebrum	Hindbrain	Cerebrum	Hindbrain
Alanine	0.38 ± 0.02	0.28 ± 0.02	0.37 ± 0.01	0.24 ± 0.02[d]
Glutamate	11.9 ± 0.4	9.14 ± 0.14	11.1 ± 0.12	8.93 ± 0.12[d]
Glutamine	6.31 ± 0.14	4.68 ± 0.13	5.91 ± 0.14	5.20 ± 0.11[b,c]
Aspartate	2.93 ± 0.11	2.50 ± 0.08	2.67 ± 0.05	2.27 ± 0.06[b]
GABA	2.06 ± 0.03	1.28 ± 0.03	1.51 ± 0.06[f]	1.07 ± 0.01[d,f]
Threonine	0.52 ± 0.04	0.54 ± 0.15	0.48 ± 0.03	0.49 ± 0.04
Glycine	0.74 ± 0.02	1.76 ± 0.08	0.75 ± 0.02	1.33 ± 0.08[d,e]
Taurine	4.50 ± 0.15	2.90 ± 0.15	4.31 ± 0.13	3.11 ± 0.08[d]

[a] These values have been published by Flock, Tyce, and Owen (2).

[b] For difference between hindbrain and cerebrum in comparable rats, $p < .01$; [d] $p < .001$.

[c] For difference between fasted and fed rats for comparable location, $p < .02$; [e] $p < .01$; [f] $p < .001$.

hindbrain/blood were significantly greater in all three groups of alcohol-treated rats than in comparable control rats. Differences in glucose concentration between hindbrain and cerebrum were found: there was more glucose in the hindbrain in fed rats given ethanol by stomach tube ($p < .05$) or intraperitoneally ($p < .01$).

The concentrations of lactate in both cerebrum and hindbrain were significantly decreased in all three groups of alcohol-treated rats compared to fed control rats, but there was no difference between fasted alcohol-treated rats and fasted control rats (Table I). The concentration of lactate was higher in the hindbrain than in the cerebrum in all groups ($p < .01$–$< .05$).

Concentrations of amino acids and taurine in control rats. Concentration of alanine, glutamate, glutamine, aspartate, and taurine were lower in the hindbrain than in the cerebrum in fasted control rats (Table II); the concentration of glycine was higher. Similar differences have been described previously in

TABLE III. Percentage Distribution of ^{14}C in Glucose and Metabolites in Cerebrum and Hindbrain.[a]

	Control rats		Ethanol-treated rats		
			By stomach tube		Intraperitoneal
	Fed (8)	Fasted (4)	Fed (6)	Fasted (4)	Fed (5)
Peak I[b]					
Cerebrum	4.8 ± 0.3	3.7 ± 0.2	5.1 ± 0.3	5.5 ± 0.4	5.1 ± 0.4
Hindbrain	4.2 ± 0.4	4.2 ± 0.2	4.8 ± 0.4	5.0 ± 0.7	5.7 ± 0.3
Glucose					
Cerebrum	7.6 ± 0.6	10.8 ± 2.3	13.4 ± 0.8[c]	19.1 ± 1.7[c]	27.4 ± 1.9[c]
Hindbrain	10.6 ± 0.4	13.8 ± 2.1	17.7 ± 1.6[c]	18.9 ± 1.8	30.2 ± 3.6[c]
Lactate					
Cerebrum	20.0 ± 0.9	16.9 ± 1.1	15.6 ± 0.5	14.0 ± 1.2	12.8 ± 1.5[c]
Hindbrain	20.7 ± 1.3	17.0 ± 1.0	18.3 ± 1.1	18.5 ± 1.0	16.2 ± 2.0
Aspartate					
Cerebrum	9.3 ± 0.4	9.6 ± 0.03	9.5 ± 0.2	8.6 ± 0.9	7.0 ± 6.0[c]
Hindbrain	8.6 ± 0.3	8.5 ± 0.08	8.0 ± 0.2	8.0 ± 0.5	6.0 ± 0.5[c]
Serine					
Cerebrum	0.94 ± 0.08	0.75 ± 0.13	0.8 (3)	0.6 (2)	0.8 (2)
Hindbrain	0.85 ± 0.03	0.63 (3)	0.7 (3)	1.2 (2)	1.2 (2)
Glutamine					
Cerebrum	9.7 ± 0.4	10.1 ± 0.2	8.9 ± 0.1	9.0 ± 0.7	8.2 ± 0.4[c]
Hindbrain	11.0 ± 0.4	9.9 ± 0.2	8.8 ± 0.3	8.2 ± 0.4[d]	7.6 ± 0.4[c]
Glutamate					
Cerebrum	39.2 ± 0.5	39.8 ± 0.8	39.3 ± 0.3	35.6 ± 1.6[c]	31.7 ± 0.6[c]
Hindbrain	35.3 ± 0.9	36.5 ± 1.0	33.6 ± 0.6	32.3 ± 1.4[c]	26.2 ± 1.0[c]
Alanine					
Cerebrum	2.4 ± 0.5	1.9 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	1.8 ± 0.06
Hindbrain	1.3 ± 0.1	1.4 ± 0.1	1.3 ± 0.1	1.4 ± 0.1	1.2 ± 0.04
GABA					
Cerebrum	4.8 ± 0.1	4.8 ± 0.2	4.7 ± 0.2	4.5 ± 0.2	3.7 ± 0.1[e]
Hindbrain	5.6 ± 0.2	5.6 ± 0.4	5.4 ± 0.2	5.3 ± 0.2	4.3 ± 0.5[c]

[a] Data, shown as means ± SE, are percentage of total ^{14}C in that portion of brain.

[b] Peak 1 contains glycogen and other compounds.

[c] For difference between alcohol-treated and control rats (fed vs fed; fasted vs fasted), $p < .05$; [d] $p < .01$; [e] $p < .001$.

TABLE IV. Glucose Uptake and Metabolism in Cerebrum and Hindbrain of Rats.[a]

	Control rats		Ethanol-treated rats		
			By stomach tube		Intraperitoneal
	Fed (8)	Fasted (4)	Fed (6)	Fasted (4)	Fed (5)
Blood ethanol (mg/100 ml)	0	0	139 ± 27	292 ± 7	283 ± 13
^{14}C at 15 min (10^3 dpm/g)					
In cerebrum	448 ± 29	531 ± 39	427 ± 32	472 ± 25	321 ± 26[c]
In hindbrain	388 ± 30	494 ± 28[b]	376 ± 28	365 ± 45	308 ± 25
Blood glucose spec act (10^3 dpm/μmole)					
At 15 min	48.6 ± 5.0	67.4 ± 5.2[b]	50.1 ± 6.0	68.3 ± 6.0	33.3 ± 2.9[b]
Average, 0–15 min	61.7 ± 6.0	85.6 ± 6.6	73.6 ± 8.9	87.4 ± 7.6	47.6 ± 4.1
Factor, 0–15 min/15 min	1.27	1.27	1.47	1.28	1.43
Blood glucose equivalent (μmole/g)					
Of cerebrum ^{14}C	7.49 ± 0.38	6.21 ± 0.17	5.96 ± 0.28[c]	5.46 ± 0.32	6.78 ± 0.36
Of hindbrain ^{14}C	6.44 ± 0.26	5.81 ± 0.18	5.24 ± 0.26[c]	4.13 ± 0.17[d]	6.55 ± 0.54
^{14}C in glucose metabolites (%)					
In cerebrum	92.4 ± 0.6	89.2 ± 2.3	86.6 ± 0.8[d]	80.9 ± 1.7[b]	72.6 ± 1.9[d]
In hindbrain	89.4 ± 0.5	86.2 ± 2.1[b]	82.3 ± 1.6[d]	81.2 ± 1.8	70.2 ± 3.8[d]
Blood glucose equivalent in glucose metabolites (μmoles/g)					
In cerebrum	6.92 ± 0.36	5.54 ± 0.23	5.16 ± 0.22[c]	4.41 ± 0.17[c]	4.91 ± 0.18[d]
In hindbrain	5.76 ± 0.25	5.00 ± 0.15	4.31 ± 0.21[d]	3.36 ± 0.21[d]	4.52 ± 0.16[c]

[a] Data shown as means ± SE (in parentheses: number of rats—except for fasted controls there were four analyses on eight rats).

[b] For difference from appropriate controls, $p < .05$; [c] $p < .01$; [d] $p < .001$.

fed control rats (2). The only effects of fasting on the concentrations of amino acids in the cerebrum were a 27% decrease in γ-aminobutyric acid (GABA) and in the hindbrain, a 16% decrease in GABA, a 24% decrease in glycine, and an 11% increase in glutamine.

Radioactive compounds in brain. Fifteen min after injection of glucose-U-^{14}C, more than 90% of the radioactivity in extracts of cerebrum of fed control rats was present in eight compounds; more than half was in glutamate and lactate (Table III). A similar distribution of radioactivity was found in the fasted control rats. The percentage of cerebral ^{14}C found in glucose was greater in all three groups of ethanol-treated rats than in the control rats. This increase was greatest in rats given alcohol by intraperitoneal injection and, in these rats only, there were significant decreases in the percentage of ^{14}C in each of the five metabolites of glucose: lactate, aspartate, glutamine, glutamate, and GABA.

The distribution of ^{14}C in the hindbrain was generally similar to that in the cerebrum.

Blood glucose equivalents of radioactivity in brain. Glucose uptake by brain, as indicated by the blood glucose equivalent at 15 min after injection of glucose-U-^{14}C, was 7.49 μmoles/g in cerebrum and 6.44 μmoles/g in hindbrain of fed control rats but was decreased in fed rats given ethanol by stomach tube (to 5.96 and 5.24 μmoles/g). No decrease in glucose uptake was noted in fed rats after intraperitoneal injection of ethanol. There was a decreased uptake of glucose in hindbrain of fasted rats (Table IV). The

TABLE V. Brain Glucose Equivalents in Metabolites of Glucose.[a]

	Control rats		Ethanol-treated rats		
			By stomach tube		Intraperitoneal
	Fed (8)	Fasted (4)	Fed (6)	Fasted (4)	Fed (5)
Lactate					
Cerebrum	1.51 ± 0.05	1.04 ± 0.10	1.20 ± 0.10[c]	0.88 ± 0.03	0.63 ± 0.11[d]
Hindbrain	1.37 ± 0.08	1.04 ± 0.08	1.64 ± 0.39	1.11 ± 0.07	0.93 ± 0.17[b]
Alanine					
Cerebrum	0.14 ± 0.01	0.12 ± 0.01	0.15 ± 0.01	0.13 ± 0.01	0.09 ± 0.005[d]
Hindbrain	0.09 ± 0.01	0.09 ± 0.01	0.12 ± 0.03	0.09 ± 0.01	0.07 ± 0.004
Glutamate					
Cerebrum	3.01 ± 0.20	2.45 ± 0.14	3.01 ± 0.23	2.29 ± 0.23	1.52 ± 0.09[d]
Hindbrain	2.42 ± 0.21	2.23 ± 0.12	2.86 ± 0.52	1.98 ± 0.26	1.47 ± 0.13[c]
GABA					
Cerebrum	0.37 ± 0.02	0.30 ± 0.02	0.36 ± 0.04	0.29 ± 0.03	0.18 ± 0.01[d]
Hindbrain	0.38 ± 0.03	0.34 ± 0.01	0.47 ± 0.10	0.33 ± 0.04	0.24 ± 0.03[c]
Glutamine					
Cerebrum	0.75 ± 0.06	0.62 ± 0.04	0.68 ± 0.04	0.58 ± 0.07	0.39 ± 0.01[d]
Hindbrain	0.75 ± 0.07	0.61 ± 0.04	0.76 ± 0.15	0.50 ± 0.04	0.43 ± 0.04[c]
Aspartate					
Cerebrum	0.72 ± 0.06	0.59 ± 0.03	0.73 ± 0.07	0.56 ± 0.08	0.33 ± 0.01[d]
Hindbrain	0.59 ± 0.06	0.52 ± 0.03	0.69 ± 0.14	0.50 ± 0.07	0.34 ± 0.04[c]

[a] Data, shown as means ± SE (number of rats in parentheses), are μmoles/g. The radioactivity (10^3 dpm/g) of each glucose metabolite at 15 min after injection of glucose-U-^{14}C was divided by the specific activity of brain glucose (10^3 dpm/μmole) at the same time for individual rats and then averaged.

[b] For difference from appropriate controls, $p < .05$; [c] $p < .01$; [d] $p < .001$.

percentage of cerebrum ^{14}C and hindbrain ^{14}C in glucose metabolites was significantly lower in fed rats given ethanol by stomach tube and was decreased further after intraperitoneal injection of ethanol. In the fasted rats treated with ethanol a significant decrease was found only in the cerebrum.

However, on the basis of the blood glucose equivalent of the metabolites, glucose utilization in brain was significantly decreased in both cerebrum and hindbrain of all three groups of ethanol-treated rats.

Comparisons of fed and fasted control rats showed small decreases in blood glucose equivalents of cerebrum ^{14}C (7.49 to 6.21 μmoles/g, $p < .05$) in the fasted rats and in the blood glucose equivalents of the glucose metabolites in cerebrum (6.92 to 5.54 μmoles/g, $p < .05$). Differences in hindbrain were not significant.

Brain glucose equivalents of radioactivity in glucose metabolites. The brain glucose equivalents in alanine, glutamate, GABA, glutamine, and aspartate at 15 min after injection of glucose-U-^{14}C in fed rats were not altered by alcohol given by stomach tube (Table V). After intraperitoneal injection of alcohol in fed rats, the brain glucose equivalents of all the metabolites in both cerebrum and hindbrain (with the exception of alanine in hindbrain) were significantly lower than in normal rats.

Comment. The effects of ethanol on glucose metabolism in brain were evident at 2½ hr after ethanol ingestion and, thus, at least an hour after the acute effects of intoxication had worn off. In fed and fasted rats with mean blood ethanol concentrations of 139 or 292 mg/100 ml, respectively (after ethanol administrations by stomach tube), glucose concentrations in cerebrum or hindbrain were greater than in control rats; in fed rats with

mean blood ethanol concentrations of 283 mg/100 ml (after intraperitoneal injection of ethanol), the glucose concentrations were greater in both parts of the brain than in control rats. The ratios of cerebrum and hindbrain glucose to blood glucose were greater in all three groups of ethanol-treated rats than in control rats. Previously, Ammon and Estler (14) showed that the brain glucose concentration was doubled in mice at 10 and 60 min after intravenous injection of doses of ethanol which produced blood ethanol concentrations of 6.9 and 5.2%. They also found decreased brain lactate concentrations. We found decreased lactate concentrations in fed rats after ethanol ingestion. In fasted rats, which had lower concentrations of brain lactate than fed rats, we observed no effect of ethanol.

Glucose accumulation in brain can occur due to increased transport of glucose from the blood, as in diabetic rats (29), or to decreased utilization of brain glucose, as in anesthetized mice (30, 31), hyperglycemic eviscerated rats (27, 32), mice receiving chronic administration of hydrocortisone (33), and rats after injection of dihydroxyphenylalanine with the monoamine oxidase inhibitor, β-phenylisoprophylhydrazine [JB 516] (34). It also can occur as a result of both increased transport and decreased utilization.

Injections of glucose-U-^{14}C are useful in determining how glucose accumulates in brain, particularly when the radioactivity in brain is expressed in terms of blood glucose equivalents, a calculation based on blood glucose specific activity.

The effects of ethanol on glucose uptake by the brain were influenced by the mode of ethanol administration and by the state of nutrition of the animal. Fasting overnight alone was sufficient to lower glucose uptake by the cerebrum, as measured by the blood glucose equivalent of brain ^{14}C, probably due to decreased blood glucose concentration. There was a reduction in this index of glucose uptake in the hindbrain when ethanol was administered by stomach tube to fasted rats. In fed rats, ethanol produced a decrease in this index in both parts of the brain when given by stomach tube but not when given by intraperitoneal injection.

The effects of ethanol on glucose utilization in brain included the accumulation of glucose without an increase in glucose uptake and an altered distribution of radioactivity in brain after administration of glucose-U-^{14}C. Higher percentages of brain ^{14}C were found in glucose and less in the amino acids, as shown previously in severely intoxicated hamsters by Roach and Williams (16, 17). Calculations of radioactivity which compensated for differences in glucose pool sizes in blood and brain supported the hypothesis that brain glucose utilization was impaired. Thus, the blood glucose equivalent of brain ^{14}C present in glucose metabolites was reduced in all the alcohol-treated rats. However, the brain glucose equivalents in the individual amino acids that are synthesized via the tricarboxylic acid cycle were reduced particularly in rats after intraperitoneal injection of ethanol. In these rats the blood glucose concentrations were greater and the blood ethanol concentrations during the first hour after ethanol administration were greater than in the other alcohol-treated rats (2).

The impairment in glucose metabolism found in the brain at 2½ hr after ethanol administration was much smaller than that in rats at 2½ hr after evisceration (27) or at 30 min after injection of dihydroxyphenylalanine in rats treated with the monoamine oxidase inhibitor, JB 516 (34).

The concentration of GABA was smaller in both parts of the brain in control rats fasted 15 hr than in fed rats.

Summary. Signs of impairment of utiliztion of glucose in rat brains at 2½ hr after administration of ethanol included increased glucose ratios for cerebrum/blood and hindbrain/blood in fed and fasted rats, decreased concentrations of lactate in cerebrum and hindbrain in fed rats, higher percentages of brain ^{14}C in glucose at 15 min after injection of glucose-U-^{14}C, and decreases in blood glucose equivalents in the combined glucose metabolites in cerebrum and hindbrain of fed and fasted rats.

Glucose uptake in cerebrum and hindbrain was lower in rats given ethanol by stomach tube (fed or fasted) than in control rats. Glucose uptake was normal in fed rats given ethanol intraperitoneally, but they had increased blood glucose concentrations. However, in these rats with the greater supply of blood glucose the greatest decreases in blood glucose equivalents of brain glucose metabolites were found. Significant decreases were found in aspartate, glutamate, glutamine, and γ-aminobutyrate (GABA).

Effects of fasting in control rats included decreased concentrations of glucose in blood, of lactate and GABA in both cerebrum and hindbrain, and of glycine in hindbrain.

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