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Effects of Moderate Ethanol Sedation on Brain Regional 2-Deoxyglucose Uptake in Alcohol-Sensitive and Alcohol-Insensitive Rat Lines

F. LINDROOS* AND E. R. KORPI†

**Department of Physiology, University of Helsinki, Helsinki, Finland*
†Research Laboratories of the Finnish State Alcohol Company, Alko Ltd., Helsinki, Finland

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LINDROOS, F. AND E. R. KORPI. *Effects of moderate ethanol sedation on brain regional 2-deoxyglucose uptake in alcohol-sensitive and alcohol-insensitive rat lines.* PHARMACOL BIOCHEM BEHAV **30**(3) 781–786, 1988.—Acute intraperitoneal ethanol administration (2 g/kg) decreased the accumulation of radioactivity after [^{14}C]2-deoxy-D-glucose injection into grossly dissected brain regions of alcohol-sensitive (ANT) and alcohol-insensitive (AT) rat lines. In autoradiography, the balance of radioactivity uptake between different functional systems (as judged from relative optical density ratios) was changed after ethanol: especially in the ANT rats, areas associated with sensory input were damped but motor relay nuclei were relatively active, suggesting a tendency to motor overactivity relative to sensory input. The ANT rats furthermore showed slight relative damping of cortical associative areas and differences in limbic structures compared to the AT rats, which, provided that changes in the balance between brain regions with a decreased overall activity are meaningful, suggests that the higher level of ethanol-induced motor impairment of the ANT rats may be related to defects in their integration of sensory and motor processes.

Acute ethanol 2-Deoxyglucose Autoradiography Brain Alcohol-sensitivity Selected rat lines

THE mechanisms by which ethanol acts to produce motor impairment are largely unknown, although a wide variety of biochemical or biophysical hypotheses have been offered (see [17] for review). Our laboratory has maintained two rat lines by selective breeding, avoiding sib-mating, for differences in ethanol-induced motor impairment as measured on a tilting plane test [10]. Although there are some differences between the alcohol-sensitive (ANT) and alcohol-insensitive (AT) rat lines in the concentrations of biogenic amines [19] and in the activities of membrane-bound enzymes [12] of the central nervous system, no clear explanation for the differential ethanol sensitivity has been established. Since the selection criterion for the breeder pairs has been based on the performance in the tilting plane test 30 min after 2 g/kg ethanol and the blood ethanol concentration at the testing time, it would be unlikely that only one basic mechanism would have been favored: instead a diverse set of physiological properties might be expected to differentiate the two rat lines. For instance, the ATs might be more activated and alert than the ANTs, which could enhance their processing of diverse sensory, associative and motor signals so that they would manage better on the tilting plane test after a moderately sedating dose of ethanol. It is as well possible that the selection has produced a rat line (ANT) that is very susceptible to ethanol-induced muscle relaxation.

2-Deoxyglucose (2-DG) autoradiography of the brains during the ethanol-withdrawal syndrome in the rat has indicated increased brain 2-DG uptake, especially by central motor and sensory regions [4,8], which agrees with the tremor and hyperreactivity the animals display during withdrawal. Little is known about the acute effects of ethanol on 2-DG uptake as studied by autoradiography. The aim of the present study was to find out the effects of acute ethanol on the balance of 2-DG uptake between smaller brain areas and nuclei, and whether the AT and ANT rat lines have specific differences in brain 2-DG uptake.

METHOD

Altogether, 39 adult male rats (250–350 g) from the F_{25} and F_{26} generations were used in the present study. The rats, 20 ATs and 19 ANTs, were maintained in stainless steel cages in groups of 4–5 animals. They had 12:12 hours dark:light cycles and free access to tap water and food pellets (Ewos). In the animal house, the temperature was 22±2°C and relative humidity 55±5%. Rats from these generations gave the following results in the tilting plane test 30 min after 2 g/kg ethanol intraperitoneally: for the ATs and ANTs the decline in the sliding angle was 10±9° (mean±SD, n=22) and 25±6° (n=22) with the blood ethanol levels of 48±7 mM and 45±8 mM, respectively.

[1]Requests for reprints should be addressed to E. R. Korpi, Research Laboratories, Alko Ltd., P.O.B. 350, SF-00101 Helsinki, Finland.

For the 2-DG injections, the right external jugular veins were cannulated with polyethylene tubing (PE-50, Clay Adams) under halothane anesthesia. The cannulae were filled with diluted heparin in saline, and taken subcutaneously to the scalp, where they were fastened with two stiches. After the surgery, the animals received two daily injections of penicillin G procaine (15,000 I.U./kg body weight, SC). The cannulae were cleared daily by injection of diluted heparin in saline. After cannulations, the rats were housed in individual cages until the experiments on the second or third postoperative day.

Twenty cannulated rats (10 each line) were divided into four groups, injected with either saline or ethanol [2 g/kg as 12% (w/v) solution in saline] intraperitoneally. Fifteen minutes later the rats were injected intravenously with 2-deoxy-D[^{14}C]glucose (specific radioactivity 282 mCi/mmol, New England Nuclear) 25 μCi/kg (1.5 ml/kg) followed by 300 μl of heparin-saline to wash all the radioactivity through the cannulae. The animals were left in their cages undisturbed. Forty-two min after 2-DG, the animals received intraperitoneally pentobarbital (Mebunat®, Orion) 120 mg/rat, and samples of tail blood were taken for radioactivity, ethanol and D-glucose measurements. The animals were decapitated at 45 min; the brains quickly removed from the skull and dissected into a number of structurally and functionally different regions. In addition, cervical spinal cords, adrenal glands, and samples from liver and testes were dissected out, and frozen on solid carbon dioxide together with the brain samples. Tissue samples were weighed, and all tissue and blood samples were deproteinized with 0.6 M perchloric acid and centrifuged. Samples of the clear supernates were mixed with Aquasol scintillation cocktail (New England Nuclear), and the radioactivities counted with an LKB Wallac liquid scintillation counter (model 1210 Ultrobeta). Blood D-glucose concentration was analyzed with a glucose-oxidase kit (Boehringer Mannheim GmbH). Blood ethanol concentrations were determined using head-space gas chromatography [9]. The statistical analysis of the results was carried out using two-tailed Student's t-test.

A group of 19 rats (10 ATs, 9 ANTs) were treated with ethanol or saline, and injected with [^{14}C]2-DG (40 μCi/kg) as described above. After decapitation, the brains were gently removed and frozen inside Tissue-Tek® embedding medium (Miles Scientific) blocks in a bath of isopentane and solid CO_2. Coronal sections 30 μm thick were cut throughout the brain in a cryostat. The sections were thawmounted onto slides and immediately dried on a hot plate at +70°C. The sections were autoradiographed using an X-ray film (CEA reflex 15). The exposure time for each brain was adjusted to give the most efficient linearity for absorbance measurement [21]. After exposure, the slides were stained with ACEB-Nissl stain [22], and the films measured using a laser-densitometer (Scanoptics). The optical densities (OD) of 32 different brain regions were measured and divided with the mean OD of all regions in individual brains (relative OD values) to show the regional balance in 2-DG uptake. Our theoretical and methodological approach thus resembled that in a study by Dunn and Hurd [7]: Could a change in the functional balance between various brain regions explain the differential sensitivity to ethanol in these rat lines? Normalization of 2-DG uptake values by a mean of the values of selected brain areas within each brain (without calibration on an absolute scale) should reveal rather sensitively changes in the balance between afferent, efferent and integrative systems of the brain, although it is not equally objective as a normalization by integrated whole brain values [7]. It should, however, compensate for unduly great influence of the differences in anatomical size (e.g., striatum versus locus coeruleus). The four experimental groups were compared using a two-way analysis of variance to give separately the influence of rat line, ethanol treatment and their interaction (i.e., the differential response of the lines to ethanol administration). The p-values were not adjusted for multiple comparisons, and therefore some of the differences associated with p-values slightly below 0.05 may be fallacious. Student's two-tailed t-test was used in post hoc comparisons of various groups.

TABLE 1

EFFECT OF ACUTE ETHANOL ON BRAIN 2-DG ACCUMULATION

Brain Region	Radioactivity Counts (cpm/mg tissue) Control (saline)	Ethanol	Percent From Control
Hypothalamus	46 ± 5	34 ± 8†	74
Striatum	60 ± 2	46 ± 9†	77
Septum-hippocampus	92 ± 8	67 ± 14†	73
Thalamus-midbrain	107 ± 16	84 ± 23*	79
Frontal cortex	137 ± 42	98 ± 40*	72
Rest of the forebrain	117 ± 9	85 ± 18†	73
Pons-medulla	96 ± 31	82 ± 37	85
Cerebellum	94 ± 8	66 ± 14‡	70
Cervical spinal cord	56 ± 5	47 ± 9*	84

Results are means ± SD for 10 rats in both groups. The AT and ANT rats were combined since there was no statistically significant difference in any brain area between the lines. Significance of the differences between controls and ethanol-treated groups (Student's t-test): *$p<0.05$, †$p<0.01$, ‡$p<0.001$.

RESULTS

Accumulation of 2-DG Into Gross Brain Regions and Peripheral Tissues

Ethanol administration significantly decreased the accumulation of radioactivity into all areas of the central nervous system studied, except the pons-medulla area (Table 1). The decrease in cerebellum was particularly pronounced. In liver, adrenal glands and blood the radioactivity was increased by ethanol, but in the testes it was decreased (Table 2).

At the level of gross brain regions, no statistically significant differences could be found in the 2-DG accumulation between the AT and ANT lines (data not shown). Nor were there any significant line differences in radioactivities of liver, adrenal glands, blood and testes or in blood glucose concentration. Ethanol concentrations after the experiments were 45±9 mM (mean±SD, n=5) and 47±3 mM (n=5) for the AT and ANT rats, respectively.

Brain Regional 2-DG Uptake

Table 3 shows all the brain regions analyzed from autoradiograms and summerizes the statistical analysis of that data. The results are given as relative OD-values, not as absolute radioactivity values like the radioactivity accumulation data in Table 1. The relative OD-values are valid and sensitive for uptake comparisons between animal groups

TABLE 2

ACCUMULATION OF RADIOACTIVITY IN PERIPHERAL TISSUES AFTER 2-DG INJECTION

Tissue	Radioactivity Control (saline)	Ethanol	Percent From Control
Liver (cpm/mg)	20 ± 4	24 ± 6*	120
Testis (cpm/mg)	35 ± 6	29 ± 6*	83
Adrenal glands (cpm/mg)	54 ± 17	97 ± 25†	180
Blood (cpm/μl)	22 ± 6	31 ± 11*	141
	Glucose Concentration (mM)		
Blood glucose	5.9 ± 0.8	6.8 ± 0.6*	115

Results are means ± SD for 10 rats in both groups. The AT and ANT rats were combined since there were no statistically significant differences between the lines in these measures. Significance of the difference between the controls and ethanol-treated rats (Student's t-test): * $p<0.05$, † $p<0.001$.

having roughly similar physiological states when the calibration of the film is adequately performed [21, 26, 31]. Cerebral cortical and thalamic areas had higher relative OD-values than many subcortical limbic structures, which agrees with the radioactivity accumulation data.

The balance of 2-DG accumulation was significantly altered between the brain regions. In brain areas associated with relaying of motor functions, vestibular nuclei, globus pallidus and nuclei pontis had slightly higher OD-values than the rest of the brain after ethanol (Table 3), but there were no significant line differences in these areas and post-hoc comparisons the effect of ethanol was significant ($p<0.01$) only in vestibular nuclei of the ANT's. In the cerebellar cortex no alterations in the OD-values were observed. Especially in the AT line, the greatest decreases in the OD-values occurred after ethanol in the auditory system. A great decrease of the OD-values was also found in the primary somatosensory cortex of the ANT rats. The ANT rats had higher relative activities in the visual associative cortex, lateral geniculate body and superior colliculus than the AT rats after saline injections. These line differences disappeared during ethanol. Ethanol-line interactions tended to become significant in the visual and multisensory associative cortices. Corpus callosum had higher relative activity after ethanol, which may have been due to a low, but stable OD-value in this structure regardless of the physiological state of the animals. The values for the cortical amygdaloid nucleus were slightly greater in the ANT rats than in the AT rats. There was also an indication of significant interactions between the rat line and the treatment in the periventricular gray matter and the interpeduncular nucleus. There were no changes during ethanol or line differences in the hippocampal OD-values.

DISCUSSION

In the present study, ethanol exerted an overall reduction in brain 2-DG accumulation in both AT and ANT rats as measured using direct liquid scintillation counting. Ethanol is known to increase significantly the brain glucose concentration [34,35], which is in keeping with diminished glucose utilization. Ethanol also increased the blood glucose concentration, which might have diluted the label in relation to unlabelled D-glucose. Although the radioactivity of plasma (liver and adrenal glands) at the end of the experiments was also increased in ethanol-treated animals, and although an acute increase in blood glucose concentration does not alter the brain regional glucose utilization [6], but ethanol at sedating doses decreases it (C. A. Marietta, poster communication [25] when studied with the Sokoloff's technique [33], it is difficult to rule out the effect of decreased specific radioactivity of the plasma in explaining the ethanol effects in the present study, because timed plasma samples were not collected. The reason for decreased radioactivity in the testes after ethanol is unknown.

Ethanol produces hypothermia that is measurable even at doses below 2 g/kg [13] and at least hypothermia strong enough to lower the rectal temperature to about 31°C decreases the cerebral 2-DG uptake [24]. Thus, the decreased 2-DG uptake in the present study may have partly reflected, in addition to direct CNS effects of ethanol, also hypothermia in freely-moving animals. This should not, however, be a confounding factor in the comparison of the AT and ANT lines, since their hypothermic responses to ethanol have been reported to be essentially the same [11].

Decreased 2-DG uptake into the CNS has been observed after acute treatments with other sedative drugs, such as barbiturates and benzodiazepines [1, 2, 5, 23], as well as with GABA receptor agonists muscimol and THIP (4,5,6,7-tetrahydroisoxazolo[5,4-C]pyridine-3-ol) [15, 18, 27], while the GABA receptor antagonists tend to increase 2-DG uptake [27,28]. Although the GABA-benzodiazepine-chloride channel complex has been suggested to be the predominant site of action of barbiturates, benzodiazepines and possibly also of ethanol [3, 14, 30], it remains to be established that all of these sedative compounds decrease brain 2-DG uptake by directly enhancing the inhibitory GABAergic neuronal activity. It should be noted, however, that both lorazepam and sodium barbital can differentiate the AT and ANT rat lines in the tilting plane test [16] in the same way that ethanol does.

Ethanol decreased the 2-DG uptake particularly in the brain areas associated with somatosensory and auditory functions (opposite to ethanol withdrawal [4,8]), but slightly increased it in some areas associated with relaying of motor functions. Such an altered balance between brain regions may modify functionally a general suppressing effect of ethanol. There were also ethanol-line interactions in associative cortical areas and limbic structures. It is thus tempting to postulate that moderate ethanol sedation partly disconnects the motor output, as it damps down the activity in the sensory and integrative systems, especially in the more sensitive ANT rat line. However, such a strong interpretation must be confirmed in other studies.

As shown by Sharp *et al.* [31], optical density ratios should be valid measures for comparing relative brain regional glucose utilization between animals (here AT's and ANT's) having a similar physiological state. We found effects of the rat line alone only on sensory input (visual) and limbic (motivational) structures. These differences might be connected to sober behavioral differences between naive AT and ANT rats, e.g., the observed differences in the activity on the forced swimming test [32]. It is not, however, known whether the sober activity differences between the lines are resulting from the same genetic factors as the differences in alcohol sensitivity.

TABLE 3

RELATIVE 2-DG UPTAKE (RELATIVE OD-VALUES) IN VARIOUS BRAIN REGIONS OF AT AND ANT RATS AFTER SALINE OR ETHANOL ADMINISTRATION

Brain Region	Rat Line: ANT Saline	ANT Ethanol	AT Saline	AT Ethanol	Analysis of Variance[1]
Motor, Sensory-Motor and Extrapyramidal Regions					
Vermis cerebelli, lobus IX, stratum moleculare	0.74 ± 0.35	0.95 ± 0.12	0.97 ± 0.03	0.91 ± 0.13	—
Vermis cerebelli, lobus IX, stratum granulosum	1.24 ± 0.16	1.12 ± 0.10	1.12 ± 0.07	1.11 ± 0.16	—
Crus I lobulus ansiformis cerebelli, str. moleculare	0.92 ± 0.08	0.83 ± 0.05	0.83 ± 0.09	0.87 ± 0.08	—
Crus I lobulus ansiformis cerebelli, str. granulosum	0.84 ± 0.07	0.72 ± 0.02	0.78 ± 0.06	0.78 ± 0.09	—
N. vestibularis med. and sup. (combined)	1.27 ± 0.06	1.47 ± 0.11[b]	1.27 ± 0.03	1.29 ± 0.18	E*
Nuclei pontis	0.77 ± 0.09	0.89 ± 0.09	0.79 ± 0.05	0.87 ± 0.08	E*
Substantia nigra zona reticularis	0.68 ± 0.02	0.76 ± 0.11	0.69 ± 0.06	0.73 ± 0.10	—
Globus pallidus	0.65 ± 0.04	0.72 ± 0.09	0.66 ± 0.03	0.70 ± 0.05	E*
N. caudatus	1.05 ± 0.05	1.13 ± 0.16	1.15 ± 0.07	1.15 ± 0.11	—
Cortical area 10 (motor)	1.12 ± 0.09	1.26 ± 0.23	1.26 ± 0.19	1.17 ± 0.12	—
Sensory Regions					
Cortical area 17 (primary visual)	1.24 ± 0.07	1.18 ± 0.13	1.12 ± 0.09	1.20 ± 0.13	—
Cortical area 18 (visual associative)	1.19 ± 0.07	1.07 ± 0.08	1.07 ± 0.06[c]	1.14 ± 0.11	E-L*
Corpus geniculatum laterale	1.20 ± 0.11	1.19 ± 0.05	0.98 ± 0.10[c]	1.11 ± 0.06[a]	L†
Stratum griseum superficiale colliculi superioris	1.16 ± 0.09	1.13 ± 0.11	0.97 ± 0.10[c]	1.11 ± 0.10	L*
Cortical area 41 (primary auditory)	1.33 ± 0.10	1.16 ± 0.16	1.32 ± 0.05	1.23 ± 0.05[a]	E†
Corpus geniculatum mediale	1.11 ± 0.18	0.99 ± 0.12	1.18 ± 0.04	1.06 ± 0.09[a]	E*
Colliculus inferior	1.45 ± 0.17	1.21 ± 0.10[a]	1.54 ± 0.12	1.29 ± 0.07[b]	E‡
Cortical area 2 (primary somatosensory)	1.23 ± 0.06	1.04 ± 0.05[b]	1.25 ± 0.09	1.17 ± 0.04[d]	L*, E‡
Cortical area 39 (multisensory associative)	1.12 ± 0.07	1.02 ± 0.07	1.06 ± 0.04	1.10 ± 0.02[c]	E-L*
N. ventralis thalami	0.94 ± 0.10	0.95 ± 0.08	1.01 ± 0.07	1.07 ± 0.09	—
Limbic and Functionally Nonspecific Regions					
Locus coeruleus	1.14 ± 0.16	1.10 ± 0.06	1.11 ± 0.19	1.16 ± 0.20	—
N. reticularis pontis oralis	0.74 ± 0.04	0.79 ± 0.05	0.78 ± 0.06	0.76 ± 0.08	—
Substantia grisea periventricularis	0.67 ± 0.12	0.82 ± 0.06	0.81 ± 0.08	0.78 ± 0.06	E-L*
N. interpeduncularis	1.13 ± 0.05	1.03 ± 0.05[a]	1.07 ± 0.08	1.11 ± 0.08	E-L*
N. amygdaloideus corticalis	0.73 ± 0.07	0.75 ± 0.04	0.64 ± 0.06	0.69 ± 0.06	L*
Hippocampus, cornu Ammonis	0.82 ± 0.04	0.80 ± 0.08	0.77 ± 0.06	0.79 ± 0.03	—
Sulcus hippocampi	0.95 ± 0.07	1.01 ± 0.07	0.96 ± 0.07	0.96 ± 0.06	—
N. habenulae lateralis	1.21 ± 0.12	1.30 ± 0.12	1.21 ± 0.08	1.15 ± 0.10	—
N. anterior dorsalis thalami	1.11 ± 0.12	0.99 ± 0.10	1.07 ± 0.08	1.07 ± 0.09	—

(continued on next page)

TABLE 3

(Continued)

Brain Region	Rat Line: ANT Saline	ANT Ethanol	AT Saline	AT Ethanol	Analysis of Variance
Corpus callosum	0.40 ± 0.03	0.55 ± 0.05[b]	0.46 ± 0.03	0.55 ± 0.03[b]	E‡
N. proprius striae terminalis	0.65 ± 0.06	0.72 ± 0.16	0.79 ± 0.06	0.71 ± 0.09	—
Cortical area 32	1.21 ± 0.10	1.34 ± 0.21	1.32 ± 0.19	1.22 ± 0.04	—

The values are means (±S.D.) of regional optical density/mean of all measured regions. The number of rats was five in each group, except the ANT ethanol-treated group, where it was four. Cortical areas were numbered according to Krieg [20].

[1]Statistical comparisons are from two-way analysis of variance, with a post hoc Student's t-test: E, ethanol effects; L, line effects; E-L, ethanol-line interactions; *$p<0.05$, †$p<0.01$, ‡$p<0.001$. [a]$p<0.05$; [b]$p<0.01$ for a difference from the corresponding control of the same line. [c]$p<0.05$; [d]$p<0.01$ for a difference from the corresponding value of the ANT line.

The results of the present study do not directly illuminate the differences in brain activity between the AT and ANT lines that may actually occur when the animals are reacting to the tilting plane test. Since the tilting plane test is a short test, taking less than one minute, the slow 2-DG method (45 min [33]) may not be the method of choice for determining the differences in functional activity during the test. Thus further studies are warranted with quicker methods for measuring regional brain blood flow or glucose utilization, e.g., the autoradiographic method using a quick tracer [^{14}C]octanoate [29], to determine the activity changes in the specific brain nuclei during motor performance as affected by ethanol. On the other hand, to the extent that our results are relevant to the tilting plane situation, they tend to suggest that AT and ANT rats may differ primarily in their sensitivity to disruption of the coordination of sensory and motor activities by ethanol and other sedative substances.

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