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Multiphasic Consequences of the Acute Administration of Ethanol on Cerebral Glucose Metabolism in the Rat

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LYONS, D., C. T. WHITLOW AND L. J. PORRINO. *Multiphasic consequences of the acute administration of ethanol on cerebral glucose metabolism in the rat.* PHARMACOL BIOCHEM BEHAV **61**(2) 201–206, 1998.—The present study investigated the role of the postinjection interval in determining the functional consequences of acute ethanol administration in the CNS. Local cerebral metabolic rates for glucose (LCMRglc) were determined by the 2[^{14}C]deoxyglucose method in 48 brain structures of ethanol-naive Sprague–Dawley rats. Tracer was injected 1 or 45 min after a 0.8 g/kg intragastric dose of ethanol or water. At the early time point, LCMRglc was increased in a highly restricted portion of the basal ganglia that included the dorsal striatum, globus pallidus, and core of the nucleus accumbens, compared to water controls. No significant decreases were found at this early time point. At the later time point, by contrast, LCMRglc was decreased in a different set of brain structures. These sites were limbic in nature and included the infralimbic and anterior cingulate cortices, dentate gyrus, lateral septum, and the bed nucleus of the stria terminalis. These data indicate that there are multiple phases that can be detected during the time course of an acute dose of ethanol. They further demonstrate the involvement of different neural systems at the two time points. Increased activity in basal ganglia is consistent with stimulated motor activity, whereas diminished activity in limbic sites may correspond to changes in mood and motivation. © 1998 Elsevier Science Inc.

Functional activity Alcohol Pharmacokinetics Autoradiography

THE behavioral and subjective effects of an acute dose of ethanol are often biphasic with respect to time since ingestion (17,27). In humans, euphoria and increased verbal activity frequently occur during the period directly after ethanol intake when blood ethanol levels are rising (1,19). Later, sedation becomes a more prominent feature of the ethanol response. Rodent studies have similarly demonstrated time-dependent effects on locomotor activity, sensitivity to rewarding brain stimulation (18), and reinforcement (29). It was only during the early period following ethanol administration that behavioral activation and positive reinforcement were found (18,29). Because positive changes in mood and motivation are markedly more pronounced shortly after ethanol intake, this period may play an important role in ethanol-seeking behavior and alcoholism.

Acute tolerance is another important time-dependent phenomena, which occurs during the course of acute exposure to ethanol. It was originally described as a greater effect on the ascending limb of the blood alcohol curve than the one found on the descending limb at the same blood alcohol concentration (14,17,24,27). Subsequently, acute tolerance to the effects of ethanol has been demonstrated in a number of motor, sensory, and cognitive tasks (9,17).

Time-dependent biphasic actions of ethanol have been described not only in studies of behavior and subjective report, but also in the investigation of the neurobiological consequences of ethanol exposure. Ethanol-induced euphoria associated with the ascending limb of the blood alcohol curve has been linked to specific changes in human EEG activity (19,20). Furthermore, animal studies have implicated specific brain regions in the time-dependent effects of ethanol. Early time-dependent activation of functional activity as assessed by regional cerebral blood flow in rats was found 5 min after ethanol administration in portions of motor systems (e.g., motor cortex, caudate/putamen, and cerebellar gray matter) and limbic forebrain (e.g., agranular insular cortex and the olfac-

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tory tubercle.) By 15 min after administration this effect was no longer detectable, despite relevant blood alcohol levels, which is suggestive of acute tolerance (21).

There are other examples of the involvement of specific brain sites in alcohol's time-dependent actions. For instance, lesions of the median raphe delayed the development of acute tolerance to ethanol-induced motor impairment in rats on a moving belt (3). Acute ethanol exposure in rats initially stimulated dopamine synthesis, but later lead to a dose-dependent depression of synthesis (28). In addition, acute ethanol administration to anesthetized rats increased the discharge rate of cerebellar purkinje cells; however, acute tolerance to these effects occurred within a matter of minutes (35). Similarly, ethanol inhibited NMDA-mediated excitatory postsynaptic potentials in the CA1 region of the rat hippocampus in brain slices, but this effect was also markedly reduced after only 15 min of exposure to ethanol (10). In summary, the effects of ethanol on brain activity during a single exposure are highly dynamic, with specific stimulatory effects occurring shortly after administration. Furthermore, a variety of sites throughout the brain have been shown to respond to ethanol in a time-dependent fashion.

The purpose of the present study was to further clarify the precise neural substrates in which functional activity was altered during the time course of a single exposure to ethanol. This was accomplished by assessing local cerebral metabolic rates for glucose (LCMRglc) using the quantitative 2[^{14}C]deoxyglucose (2DG) method. The magnitude and regional distribution of LCMRglc was compared at two times during a single exposure to ethanol. This study extended our previous work by evaluating time points that were more temporally distinct, rather than clustered near the peak blood ethanol level, in an attempt to isolate different phases of the CNS response to ethanol better. Additional improvements also included the use of freely moving animals and ethanol administration via oral gavage to more closely parallel the pharmacokinetics of ingestion.

METHOD

Animals

Eighteen adult male Sprague–Dawley rats that weighed 250–300 g at the time of the experiment were used as subjects. Animals were housed under a 12 L:12 D cycle, lights on at 0700 h, with access to food (Purina Rat Chow) and water ad lib. All animals were handled for 10 days prior to treatment and habituated to the oral gavage by once daily administration of water over this period. All procedures were carried out in accordance with established practices as described in the NIH Guide for Care and Use of Laboratory Animals. In addition, all procedures were reviewed and approved by the Animal Care and Use Committee of Wake Forest University.

Experimental Procedure

This experiment evaluated the effects of an acute dose of ethanol on LCMRglc in ethanol-naive rats at two different time points following ethanol administration. The 2DG experiments were initiated 1 or 45 min after the administration of ethanol so that maximal tracer incorporation occurred when blood ethanol concentrations were either rising (1 min, EARLY group) or falling (45 min, LATE group). These times were chosen on the basis of pilot experiments in a separate group of rats that showed that at this dose of ethanol the average blood ethanol level achieved during the first 5 min of the experimental procedure (the time of greatest tracer incorporation) was roughly equivalent to the level at 45 min.

Ethanol was diluted with tap water and administered by oral gavage. A standard 16-gauge feeding needle was inserted into the esophagus, and ethanol was administered over 3–5 s. Rats received tap water as the control in an identical fashion. Approximately 2.0 ml of solution were administered. Three groups of rats received intragastric doses of water or ethanol diluted with water (0.8 g/kg ethanol, 20% v/v): ethanol/1 min ($n = 7$), ethanol/45 min ($n = 5$), and water/1 or 45 min ($n = 7$) as water controls. The water control group consisted of three animals that were tested 1 min after water treatment and four animals tested 45 min after treatment.

Measurement of Blood Alcohol Levels

Blood alcohol levels were determined in each animal during the course of the experimental procedure. Arterial blood levels were measured 2, 6, and 46 min after ethanol administration in the EARLY group, and 2, 46, 51, 60, and 90 min after ethanol in the LATE group to describe the blood alcohol curve, for a total of 90 min following the intragastric administration of 0.8 g/kg ethanol. Samples of arterial blood were taken for the measurement of blood ethanol levels, which were determined using an alcohol dehyrogenase assay (Sigma Chemical Co., St. Louis, MO). Blood plasma (10 μl) was added to a glycine buffer and incubated in a water bath for 10 min at 35°C. Absorbance at 340 nm was then determined on an Ultrospec II spectrophotometer.

Local Cerebral Metabolic Rates for Glucose

On the day before of the measurement of rates of local cerebral glucose metabolism rats were anesthetized with a mixture of halothane and nitrous oxide. Polyethylene catheters were inserted into a femoral vein and artery and run subcutaneously exiting at the nape of the neck. Such catheter placement allows for the intravenous administration of drug or tracer and permits animals to move freely throughout the experimental procedure (4). Animals were given approximately 18 h to recover from the catheter placement before the initiation of the 2DG procedure. During recovery, water but not food was available.

The 2DG experimental procedure was initiated by the injection of an intravenous pulse of 125 μCi/kg of 2-deoxy-D-(1-^{14}C)glucose (New England Nuclear, Boston, MA; specific activity 50–55 mCi/mmol) followed by a flush of heparinized saline. Timed arterial blood samples were drawn thereafter at a schedule sufficient to define the time course of the concentrations of arterial 2DG and plasma glucose. Arterial blood samples were centrifuged immediately. Plasma concentrations of 2DG were determined by liquid scintillation spectrophotometry (Beckman Instruments, Fullerton, CA) and plasma glucose concentrations assessed with a glucose analyzer (Beckman Instruments). Approximately 45 min after tracer injection, the animals were killed by an intravenous overdose of sodium pentobarbital (100 mg/kg, IV). Brains were rapidly removed, frozen in isopentane (−45°C) and stored at −70°C. Coronal sections (20 μm thick) were cut in a cryostat maintained at −22°C. Five of every 10 sections were thaw mounted on glass coverslips, dried on a hot plate, and autoradiographed with Kodak EMC or MINUTE-R X-ray film, along with a set of [^{14}C]methylmethacrylate standards (Amersham, Arlington Heights, IL) previously calibrated for their equivalent ^{14}C concentration in 20-μm brain sections.

Densitometry

Autoradiograms were analyzed by quantitative densitometry with a computer-assisted image processing system (Imaging Research Inc., St. Catharine's, Ontario). Optical density measurements of tissue ^{14}C concentrations for each structure were made in a minimum of five brain sections. Tissue ^{14}C concentrations were determined from the optical densities of tissue compared to calibration curves obtained by densitometric analysis of the autoradiograms of calibrated standards. Glucose utilization was calculated from the local tissue ^{14}C concentrations, the time course of the plasma [^{14}C]deoxyglucose, and glucose concentrations by the operational equation of the method (37).

Statistics

Standard statistics software (SigmStat for Windows, Jandel Corp.) was used for statistical analysis. Rates of local cerebral glucose utilization were determined in 48 discrete brain regions. Statistical analysis was carried out on each brain structure independently. To evaluate the effect of time after the administration of a single 0.8 g/kg dose of ethanol, regional rates of cerebral metabolism were compared by means of a Dunnett's test comparing the alcohol-treated rats to controls.

RESULTS

Blood Alcohol Levels

Blood ethanol levels are shown in Fig. 1. Levels reach peak at approximately 5 min postinfusion and slowly decline. Significant elevations in blood ethanol levels are still present at 90 min. These values are consistent with other published reports. Although the ascending limb was steeper than the descending limb, the average blood ethanol level during the 5 min following the infusion of tracer was roughly equivalent in the EARLY and LATE groups [1 min group, blood ethanol level = 54.8 ± 8 mg/dl (mean ± SEM); 45 min group, blood ethanol level = 53.3 ± 17 mg/dl; *t*-test, $t(9) = 0.205$, $p = 0.842$].

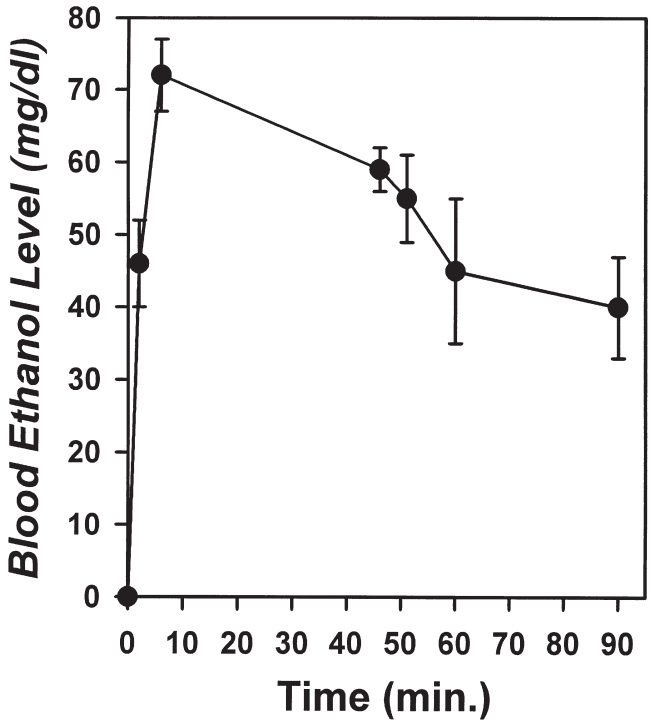

FIG. 1. Blood ethanol levels over 90 min after a 0.8 g/kg intragastric dose. The 2[^{14}C]deoxyglucose was injected at 1 or 45 min after the intragastric administration of 0.8 g/kg ethanol so that the maximal accumulation of tracer occurred during the ascending and descending portions of the blood ethanol curve, respectively.

Rates of Local Cerebral Glucose Utilization

Rates of local cerebral glucose utilization were determined in 48 brain structures and are shown in Tables 1 and 2. There were no significant differences in rates of glucose utilization of water-treated controls tested at either 1 or 45 min. Data from these two groups were, therefore, combined for further analysis.

In the EARLY group, cerebral metabolism was increased in 8 of 48 structures when compared to values of water controls. No decreases in metabolism were observed in this group at this time point. Although rates of metabolism were in general higher in the EARLY group than water controls, statistically significant increases in LCMRglc were concentrated in portions of the nigrostriatal system and included the dorsome-

TABLE 1

LOCAL CEREBRAL METABOLIC RATES FOR GLUCOSE IN BASAL GANGLIA, THALAMUS, AND HABENULA OF RATS THAT WERE INFUSED WITH TRACER 1 OR 45 MIN AFTER ETHANOL ADMINISTRATION (0.8 g/kg, IG)

	mean ± SEM		
		Ethanol 0.8 g/kg	
	Water 1 or 45 min	1 min	45 min
Structure	(*n* = 7)	(*n* = 5)	(*n* = 7)
Basal ganglia and related sites			
Caudate			
Dorsomedial	104 ± 2	120 ± 1*	102 ± 6
Dorsolateral	111 ± 3	126 ± 1*	113 ± 7
Ventral	102 ± 3	116 ± 1*	105 ± 6
Globus Pallidus	56 ± 1	62 ± 2*	52 ± 1
Entopenduncular n.	56 ± 1	58 ± 2	51 ± 2
Subthalamus	95 ± 3	104 ± 2	92 ± 3
Substantia nigra, compacta	73 ± 2	79 ± 1	71 ± 3
Substantia nigra, reticulata	58 ± 2	62 ± 3	54 ± 1
Thalamus			
Anteroventral nucleus	114 ± 5	133 ± 3	106 ± 3
Anteromedial nucleus	116 ± 6	135 ± 5	111 ± 5
Mediodorsal nucleus	95 ± 3	105 ± 3	90 ± 5
Lateral nucleus	92 ± 3	102 ± 3	87 ± 3
Medial geniculate	133 ± 3	149 ± 9	127 ± 4
Lateral geniculate	88 ± 3	95 ± 2	82 ± 3
Habenula			
Medial	77 ± 2	89 ± 2	71 ± 2
Medial lateral	91 ± 3	105 ± 2*	86 ± 1
Lateral lateral	107 ± 4	124 ± 7	104 ± 2
White matter			
Corpus callosum	37 ± 1	44 ± 1*	35 ± 2

*Indicates a significant Dunnett's *t*-test ($p < 0.05$) of treatment group compared to control.

dial, dorsolateral, and ventral portions of the caudate/putamen (+14–15%) and the globus pallidus (+11%). In addition, glucose metabolism was elevated in the core portions of the nucleus accumbens (+16%) (Table 2) when compared to water-control levels. In the thalamus, glucose utilization was elevated in the medial and lateral habenula as well as in the anteroventral nucleus (+17%). The corpus callosum was also found to have increased rates of glucose metabolism. There were no other statistically significant alterations in glucose utilization in the EARLY group.

In contrast to the increases seen in the EARLY group, rates of glucose utilization in the LATE group were decreased below water control values in 6 of 48 regions examined. These included the infralimbic cortex (−12%), anterior cingulate cortex (−9%), the lateral septum (−21%), and the bed nucleus of the stria terminalis (−18%). Furthermore, depressed rates of glucose utilization were also found in the dentate gyrus of the hippocampal formation (−10%) and in the dorsal raphe (−9%). Changes in cerebral metabolism were restricted to these sites; statistically significant alterations were not observed in any other brain region measured.

TABLE 2

RATES OF LOCAL CEREBRAL METABOLIC RATES FOR GLUCOSE IN NEOCORTICAL AND LIMBIC SITES OF RATS THAT WERE INFUSED WITH TRACER 1 OR 45 MIN AFTER ETHANOL ADMINISTRATION (0.8 g/kg, IG)

	mean ± SEM		
		Ethanol 0.8 g/kg	
	Water 1 or 45 min	1 min	45 min
Structure	(n = 7)	(n = 5)	(n=7)
Neocortical areas			
Prelimbic cortex	101 ± 3	104 ± 1	95 ± 5
Infralimbic cortex	80 ± 3	86 ± 1	70 ± 5*
Orbitofrontal cortex	124 ± 4	127 ± 4	126 ± 6
Agranular insula	91 ± 3	102 ± 3	88 ± 6
Anterior cingulate cortex	106 ± 3	112 ± 3	96 ± 4*
Motor cortex	101 ± 3	106 ± 2	96 ± 4
Entorhinal cortex	73 ± 2	81 ± 2	74 ± 2
Perirhinal cortex	72 ± 2	81 ± 2	74 ± 2
Auditory cortex	131 ± 4	148 ± 7	138 ± 7
Mesolimbic system			
Accumbens, anterior	90 ± 4	92 ± 4	84 ± 4
Accumbens, shell	86 ± 3	93 ± 2	82 ± 4
Accumbens, core	83 ± 3	96 ± 3*	81 ± 4
Olfactory tubercle	86 ± 5	91 ± 3	79 ± 3
Medial septum	87 ± 2	95 ± 2	80 ± 4
Lateral septum	62 ± 2	63 ± 2	49 ± 2*
Ventral pallidum	58 ± 2	63 ± 1	53 ± 2
BNST	50 ± 2	51 ± 2	41 ± 2*
Lateral preoptic area	82 ± 3	91 ± 4	78 ± 2
Medial preoptic area	87 ± 3	95 ± 2	80 ± 2
MFB	68 ± 2	69 ± 2	62 ± 2
Ventral tegmental area	66 ± 2	69 ± 1	62 ± 2
Limbic system			
Amygdala, central	50 ± 2	50 ± 3	45 ± 2
Amygdala, basolateral	87 ± 2	94 ± 3	84 ± 4
Hippocampus, CA1	65 ± 3	70 ± 2	63 ± 3
Hippocampus, CA3	78 ± 3	83 ± 3	72 ± 3
Hippocampus, DG	59 ± 2	62 ± 2	53 ± 2*
Hindbrain and brainstem			
Dorsal raphe	92 ± 2	91 ± 3	84 ± 2*
Median raphe	99 ± 2	103 ± 3	93 ± 3
Locus ceruleus	65 ± 2	66 ± 2	61 ± 3
Cerebellum	60 ± 2	63 ± 2	56 ± 2

BNST = Bed nucleus of the stria terminalis; MFB 5 medical forebrain bundle.

*Indicates a significant Dunnett's t-test ($p < 0.05$) of treatment group compared to control.

DISCUSSION

The present study demonstrates that the regional pattern of changes in functional brain activity in the rat following a single dose of ethanol depends upon the length of time that has elapsed since its administration. The intragastric administration of a 0.8 g/kg dose of ethanol elevated rates of glucose utilization in portions of the basal ganglia and the nucleus accumbens, as well as portions of the limbic thalamus, when assessed immediately following administration. At longer intervals after administration, however, when blood ethanol levels were declining, glucose utilization was decreased in a distinctly different topography that included portions of the limbic cortex and hippocampus, as well as the bed nucleus of the stria terminalis and lateral septum. These findings support a biphasic response to ethanol in the CNS with respect to time since administration.

Hadji-Dimo and co-workers (12) were among the first to demonstrate that ethanol administration increased cerebral blood flow in animals. In this study, whole-brain rates of blood flow were found to be increased in cats following the first of several intravenous infusions of ethanol. Later infusions produced decreased rates of cerebral blood flow. The authors attributed these increases to the low blood ethanol levels achieved (ca. 0.05 g ethanol/100 ml blood) after the first dose in comparison to subsequent doses (ca. 0.13 g/100 ml). More recently, increased cerebral blood flow following low doses of ethanol has also been effectively demonstrated to occur in humans (22,25,32,33,38,40). Furthermore, low doses of ethanol (<0.5 g/kg) in rats have also been shown to produce discrete elevations in glucose metabolism within the mesocorticolimbic and nigrostriatal systems (43). Low doses of ethanol, however, are not the only doses capable of stimulating brain activity. More moderate doses of ethanol (0.5–2.0 g/kg) have also been shown to increase rates of cerebral metabolism when assessed immediately following administration (21,42).

The highly localized increases in LCRMglc found in the EARLY group were restricted to portions of the basal ganglia including the dorsal striatum, globus pallidus, as well as the nucleus accumbens. The discrete pattern of changes in LCMRglc in the basal ganglia suggests that 0.8 g/kg ethanol has an early stimulating effect on subcortical motor systems in adult rats. Increased motor activity leads to commensurate changes in cerebral metabolism in the dorsal striatum and in motor and somatosensory cortex of rats (2,5). Furthermore, increased LCMRglc in the basal ganglia found shortly after ethanol intake is consistent with the behavioral observation that ethanol can stimulate motor activity for a brief period after administration (7,16,18,36,41).

The specific decrements in LCMRglc found at the LATE time point in mesoprefrontal cortex are paralleled by research indicating that acute ethanol administration alters the neurochemistry of this brain region. Ethanol alters mesoprefrontal dopaminergic activity, and is thought to play a role in ethanol reinforcement (8,13), as well as in the anxiolytic effects of eth-

anol (23). Ethanol-induced changes in prefrontal cortex have also been reported for norepinephrine (30), serotonin (34), and glutamate (15,26,31,34). The brain regions in which glucose utilizaton was reduced in the LATE group also included hippocampus, anterior cingulate, and dorsal raphe. These structures form a constellation of anatomically interrelated brain regions, along with the bed nucleus of the stria terminalis, that may act as substrates of the later effects of ethanol that have been characterized as more depressive or aversive in nature. This suggestion is supported by behavioral evidence that ethanol is less rewarding or aversive at times after administration of 30 min or greater in rodents (18,29). Moreover, the involvement of areas like the hippocampus in memory function suggests that ethanol's effects on memory may be concentrated at later times after ingestion.

The present data indicate that the neural systems that mediate the early activating effects of ethanol are different from those that mediate the later effects. Separate networks of structures appear to be involved at different times after administration. Acute tolerance to the effects of ethanol may explain, for example, why the initial increases in LCMRglc were no longer detectable in the LATE group, even though significant blood ethanol levels were still evident. Although adaptation to the initial effects of ethanol may occur on the cellular or systems level, the present data also indicate that a distinct constellation of changes in functional activity develop following longer postingestion times that do not overlap with those responsible for the earlier effects. The recruitment of activity in a distinct set of structures at later times suggests that different neural substrates are responsible for the effects of ethanol that emerge late in the time course of a single dose than those that arise immediately after administration. Thus, the early and late effects of ethanol appear to be separable not only on a behavioral level, but on neuroanatomical level, as well.

Although moderate doses of ethanol have been shown to increase rates of metabolism under certain conditions, the administration of doses in this range has more generally been associated with decrements in metabolic rates. A number of previous 2DG studies examining the effects of moderate ethanol doses have shown that rates of LCMRglc were, in fact, decreased in brain regions associated with the memory, sensory, and motor processing including the hippocampus, auditory cortex, and caudate nucleus (11,39). These studies, however, were carried out at times when blood alcohol levels were near peak or declining. Lower doses (0.25 g/kg) assessed at these time points, stimulate rates of functional activity in a nonoverlapping pattern set of brain structures (6,43). This dose-dependent distinction in the brain regions involved in ethanol's effects closely parallels the time-dependent differences seen in the present study in which increases in glucose metabolism within nigrostriatal and mesolimbic regions were associated with early effects of ethanol, while changes in hippocampus were associated with later effects.

In a recent study of the time-dependent effects of ethanol on regional cerebral blood flow conducted in this laboratory (21) it was found that local rates of blood flow were increased 5 min after ethanol administration when blood ethanol levels were near peak. The effects on blood flow were no longer evident, however, 15 min after administration, as the blood ethanol levels began to decline. The present data differ from this earlier work in that the present study found decreased functional activity in several brain sites at the later time point. There are several potential explanations for this disparity. It may be due to the fact that LCMRglc was determined 45 min after ethanol administration, whereas blood flow was determined only 15 min after administration. Decrements in functional activity may be greater after the longer 45-min period. Alternatively, differences in route of ethanol administration and environment may have contributed to these differences as well.

The apparent discrepancies among studies conducted with different methods and at different times after ethanol administration may result from a number of factors, but when the data are taken together, they suggest that the effects of ethanol are highly dynamic and comprised of multiple phases. Functional mapping methods have been likened to a camera taking a snapshot of brain activity over the time course of the experimental period. During the first 10 to 15 min following the injection of 2[^{14}C]deoxyglucose the vast majority of the available tracer is taken up into cells and trapped for the remainder of the experiment. Therefore, the present study essentially compared LCMRglc during the first 10–15 min after ethanol administration to glucose metabolism during the period 45–60 min after ethanol treatment. These data show that following alcohol administration, the picture may change quite rapidly and involve a variety of different structures. The effects of acute ethanol, then, are likely to be the product of the complex interaction of dose and time, along with other factors such as route of administration, rate of change of blood ethanol levels, genetics, and behavioral context. The delineation of the sets of structures involved at any one time or dose undoubtedly depends on all of these factors.

In summary, a 0.8 g/kg intragastric dose of ethanol produces a biphasic response in the CNS of rats. Levels of functional activity were elevated in portions of the basal ganglia immediately following drug administration. In contrast, a set of limbic sites including mesoprefrontal cortex, hippocampus, and others were depressed 45 min after administration. These data indicate that the neural systems responsible for the early stimulating action of ethanol at this dose are motor in nature, and the later suppression may be responsible for diminished motivation and reinforcement associated with sedation. This report highlights the importance of recognizing that the actions of ethanol on brain activity and behavior are diverse and blended across variables such as dose and time, and future studies of this pharmacologically complex agent in the brain will require careful attention to these factors.

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