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Local Changes in Cerebral Glucose Utilization during Ketamine Anesthesia

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Ketamine produces both excitatory and depressant actions in the brain, but there have been conflicting results regarding which structures are affected and the magnitude of the alteration in cerebral metabolism produced. The authors applied the 2-[^{14}C]deoxyglucose method quantitatively to a study of ketamine anesthesia (10 or 30 mg/kg intravenously) in the rat. Ketamine caused both increases and decreases in local cerebral glucose utilization. The areas with altered glucose utilization could be grouped into functional systems. Some structures of the limbic system showed large increases in glucose utilization; indeed the 70 per cent increases in cingulate gyrus and hippocampus were the largest of all regions examined. The extrapyramidal motor system and corpus callosum showed significant but less dramatic (20–40 per cent) increases. On the other hand, decreased metabolism occurred in the somatosensory and auditory systems, with the greatest reduction (40 per cent) in the inferior colliculus. Within some structures, such as the caudate nucleus and visual cortex, a striking redistribution of metabolism which is characterized by a change in the autoradiographic pattern of activity was noted.

Reduced glucose utilization in the somatosensory and auditory systems suggests that a selective sensory deprivation occurs during ketamine anesthesia while the increased metabolism in the limbic system is consistent with neurophysiologic studies which have demonstrated seizure activity in this region. Compared with other anesthetics, which tend to produce a generalized decrease in metabolism, the cerebral metabolic effects of ketamine are unique and emphasize that it produces a state of "anesthesia" which is quite different from that of other commonly used drugs. (Key words: Anesthetics, intravenous: ketamine. Brain: glucose utilization; metabolism, regional.)

THE CONCEPT that the "anesthetic" state is not always associated with a functionally "quiet" brain with reduced neuronal activity has been advanced by Winters.[1] He proposed that whereas some anesthetic drugs depress activity in the central nervous system (CNS), others are predominantly excitatory agents.[1] Several neurophysiologic and metabolic studies have suggested that ketamine is, at least in part, a drug that belongs in the latter category. Although the results of studies on neuronal electrical or metabolic responses to ketamine have been confusing, even conflicting, they are in agreement that ketamine produces both excitatory and depressant effects in the CNS. Corssen and Domino,[2] for example, reported depressed neuronal firing in neocortex and thalamus while that in hippocampus was activated. Others have found that ketamine stimulated all parts of the brain studied and proposed that "anesthesia" was in fact the consequence of cortical seizure activity.[3] Recently, Sinclair and Tien[4] reported inconsistent and erratic firing patterns in some neuronal populations during ketamine anesthesia and suggested that a functional disorganization of the nervous system results from its action.

Autoradiographic studies of regional brain metabolism during ketamine anesthesia have yielded similarly equivocal results. Hawkins *et al.*,[5] using the [^{14}C]glucose technique, have reported essentially no effects of ketamine on regional brain glucose utilization. On the other hand, Nelson *et al.*[6] employed the 2-[^{14}C]deoxyglucose (2-[^{14}C]DG) method qualitatively and obtained autoradiographic evidence of substantial, region-specific alterations in glucose metabolism during ketamine anesthesia. Because of these discrepant findings on the extent of the metabolic changes and the regions of the CNS most affected by ketamine we have applied the quantitative 2-[^{14}C]DG technique[7] to study the local cerebral metabolic effects of ketamine anesthesia in the rat. The results of this study establish that ketamine does indeed produce significant, region-specific alterations in cerebral glucose utilization, especially in the limbic, extrapyramidal, auditory and sensory-motor systems. Some redistribution of metabolic activity within anatomical regions was also observed.

Methods

Local cerebral glucose utilization (LCGU) was measured by the 2-[^{14}C]DG technique[7] in eight control male Sprague-Dawley rats, six rats treated with 10 mg/kg of ketamine, and six treated with 30 mg/kg of the drug. Animals were allowed free access to food and water until the time of the surgical procedure for the insertion of femoral arterial and venous catheters; this was accomplished quickly under light halothane anesthesia. The

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TABLE 1. Physiological Variables in Ketamine Anesthetized Rats

	Control (8)	Ketamine (6) (10 mg/kg)	Ketamine (6) (30 mg/kg)
Hematocrit (Per cent)	51 ± 2	49 ± 1	50 ± 2
Rectal temp. (°C)	37.4 ± 0.1	37.0 ± 0.3	37.1 ± 0.3
Mean arterial blood pressure (mmHg)	123 ± 2	128 ± 6	118 ± 4
Arterial blood gases (mmHg)			
P_{O_2}	91 ± 2	98 ± 3	95 ± 2
P_{CO_2}	37 ± 1	39 ± 1	41 ± 1*
Arterial *p*H	7.41 ± 0.15	7.38 ± 0.15	7.38 ± 0.06

Data are means ± the standard error obtained in the number of animals indicated in parentheses.
The units for each physiologic variable are indicated in parentheses.
* Significantly different from control, $P < 0.05$.

animals were then restrained by means of a loose-fitting, pelvic plaster cast and allowed to recover from the effects of the halothane for a minimum of two hours. The ketamine was administered intravenously 2 to 5 min prior to the measurement of LCGU, which was initiated by an intravenous pulse of 50 μCi of 2-[^{14}C]DG (Spec. Act. = 50–55 mCi/mmol) (New England Nuclear, Boston, MA). Timed arterial blood samples were then drawn for the measurement of plasma 2-[^{14}C]DG concentrations (Beckman Scintillation Counter LS 255, Beckman Instruments, Fullerton, CA) and plasma glucose concentrations (Beckman Glucose Analyzer, Beckman Instruments, Fullerton, CA). Arterial blood-gas tensions, *p*H, blood pressure, and rectal temperature (which was maintained with a heat lamp) were monitored. Approximately 45 min after the 2-[^{14}C]DG was injected, the animals were killed with an overdose of pentobarbital, and the brain was removed and frozen in isopentane at −40° to −60° C as previously described.[7] Brain sections, 20 μm thick, were cut in a cryostat at −22° C and then autoradiographed on Kodak MR1 film (Eastman Kodak Co., Rochester, NY). The autoradiographs produced by this procedure were then analyzed with a densitometer (aperture 200 μm, Photovolt Corp., NY, NY); optical density readings for a given structure were made in a minimum of six brain sections. LCGU was calculated as described previously,[7] and statistical comparisons were carried out with Dunnett's *t* test for multiple comparisons.[8]

Results

Ketamine produced relatively few effects on the physiological variables that were measured (table 1). A transient decrease in blood pressure occurred immediately following the injection of the high dose of ketamine, but blood pressure spontaneously returned to normal before the 2-[^{14}C]DG was injected. The 30 mg/kg dose of ketamine also produced a small increase in arterial P_{CO_2} while arterial *p*H remained normal (table 1).

Animal behavior varied considerably during the 45 min of the experiment. There was generally at first a 5- to 10-min period of cataleptic-like unresponsiveness followed by a longer period of side-to-side head rocking, and eventually frantic, agitated hyperactivity. This latter behavior was quite unlike that of the normal control rats, who appeared to be calm and groomed or dozed.

LCGU was determined in 35 anatomic regions of the brain. Both doses of ketamine produced quantitatively similar alterations in LCGU (table 2). Those structures that were statistically significantly affected ($P < 0.05$) by ketamine are presented in figure 1. Of note are the widely diverse local effects of ketamine with some brain regions, such as hippocampus and cingulate, showing dramatic increases in LCGU, while some of the sensory systems and cerebellar white matter reveal sizable decreases. In control animals one sees substantial differences in metabolic rate between regions (table 2). During ketamine anesthesia this heterogeneity in metabolism between regions is accentuated. Furthermore, ketamine produces a redistribution of metabolism within some normally homogeneous anatomical regions, which is especially apparent as a change in the autoradiographic pattern of activity in the caudate nucleus and in the visual and auditory corticies (fig. 2). This variation in LCGU within regions may account for the large standard errors (table 2) which in some cases has prevented structures with a change in LCGU of as much as 20 per cent from reaching statistical significance.

A number of structures were clearly unaffected by ketamine; these include frontal and primary olfactory cortex, ventromedial and dorsolateral thalamus, hypothalamus, nucleus accumbens, vestibular and cochlear nuclei, superior olive, lateral lemniscus, pontine gray, and cerebellar cortex and dentate nucleus (table 2). Increased LCGU in entorhinal cortex and cortical Layers I and VI is apparent in the autoradiographs but has not been quantified (fig. 2). The optical density of the medial habenula (not shown) is consistently and markedly decreased although the magnitude of the change was not quantified.

Discussion

This study shows that ketamine produces marked and diverse effects on regional glucose utilization; the drug produces increases and decreases in LCGU and, at the same time, leaves some regions unaffected. Initially it may appear that ketamine affects brain regions in a random fashion. A system-specific effect becomes more apparent, however, when regions with altered LCGU are grouped into functional systems (table 2). For example,

TABLE 2. Regional Cerebral Glucose Utilization during Ketamine Anesthesia in Rats ($\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$)

	Control (8)	Ketamine (6) (10 mg/kg)	Ketamine (6) (30 mg/kg)
Auditory System			
Cortex	128 ± 4	105 ± 8*	94 ± 6†
Medial geniculate	100 ± 3	87 ± 8	87 ± 5
Inferior colliculus	166 ± 5	109 ± 9*	97 ± 5†
Superior olivary nucleus	132 ± 4	136 ± 8	131 ± 9
Cochlear nucleus	110 ± 5	100 ± 4	100 ± 6
Lateral lemniscus	100 ± 5	96 ± 7	90 ± 4
Visual System			
Cortex	94 ± 3	116 ± 10	114 ± 7
Lateral geniculate	78 ± 2	84 ± 7	79 ± 4
Superior colliculus	76 ± 3	78 ± 7	67 ± 5
Sensorimotor System			
Sensory motor cortex	97 ± 2	83 ± 6*	69 ± 3†
Cerebellar cortex	48 ± 1	47 ± 3	43 ± 2
Cerebellar nuclei	95 ± 7	83 ± 5	81 ± 5
Vestibular nucleus	101 ± 3	102 ± 7	97 ± 6
Pontine gray	56 ± 2	59 ± 4	56 ± 3
Thalamus: ventral nucleus	77 ± 2	75 ± 7	69 ± 5
Limbic System			
Cingulate gyrus	73 ± 7‡	127 ± 8†	122 ± 10†
Hippocampus	73 ± 2	119 ± 8†	122 ± 9†
Dentate gyrus	60 ± 2	65 ± 5	63 ± 3
Amygdala	46 ± 1	46 ± 4	40 ± 3
Septal nucleus	56 ± 3	46 ± 5	50 ± 4
Nucleus accumbens	74 ± 3	94 ± 11	85 ± 11
Hypothalamus	54 ± 1	55 ± 7	49 ± 4
Mamillary body	97 ± 3	140 ± 12*	133 ± 7†
Interpeduncular nucleus	89 ± 7‡	113 ± 3*	107 ± 9
Extrapyramidal System			
Globus pallidus	55 ± 3	76 ± 5*	79 ± 8†
Substantia nigra	63 ± 2	80 ± 5*	85 ± 9
Caudate nucleus	94 ± 2	113 ± 7	112 ± 8
Myelinated Fiber Tracts			
Corpus callosum	35 ± 1	46 ± 3*	48 ± 4*
Genu of corpus callosum	28 ± 2	28 ± 3	32 ± 2
Internal capsule	34 ± 2	29 ± 2	28 ± 2
Cerebellar white	36 ± 1	30 ± 3	29 ± 1*
Cerebral Association Areas			
Frontal cortex	93 ± 2	92 ± 8	79 ± 6
Parietal cortex	90 ± 2	90 ± 5	73 ± 4
Olfactory System			
Olfactory cortex	96 ± 5	102 ± 9	103 ± 7

Data are means ± standard errors obtained in numbers of animals in parentheses.

* $P < 0.05$ and † $P < 0.01$, in comparison with control.
‡ n = 4

LCGU in some sensory regions, especially auditory (cortex, medial geniculate and inferior colliculus) and sensory-motor areas is decreased. In the visual cortex, on the other hand, the changes in glucose utilization suggest a trend toward increased activity while subcortical visual relay nuclei (superior colliculus and lateral geniculate) are unaffected. A few limbic system structures, namely the hippocampus and cingulate, have the largest increases in LCGU of all brain regions studied while the basal ganglia, including substantia nigra, globus pallidus, and possibly caudate nucleus, show significant, but less dramatic increases. Finally, the increased LCGU in corpus callosum was surprising; LCGU in other myelinated tracts was either unchanged or, in the case of cerebellar white matter, decreased. Perhaps more striking than the extent of the metabolic alteration is the heterogeneity of the changes within selected anatomical regions, especially caudate-putamen, and visual and auditory cortices (fig. 2). Insofar as metabolism reflects functional activity within the CNS,[9] inferences about the functional state

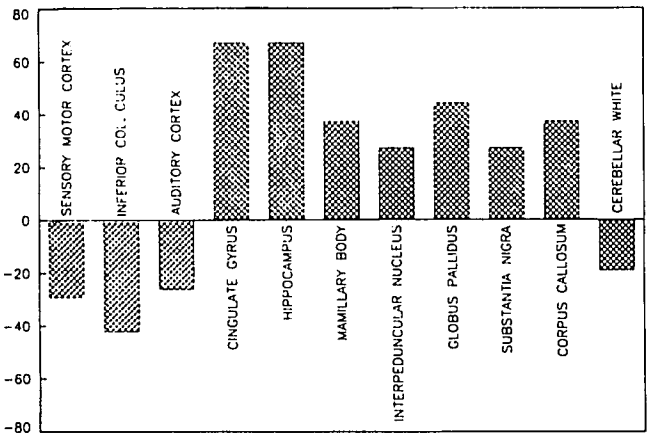

FIG. 1. Chart listing only those structures with a statistically significant change in glucose utilization during ketamine anesthesia. Bars show percent increase (upward) or decrease (downward) in LCGU for structures indicated. Percentage differences are between high-dose ketamine and control, except in the case of the substantia nigra and interpeduncular nucleus where comparison is based on the low dose result.

of the system can be made from our data. In the present study then, the reduced LCGU in auditory and sensorymotor areas implies that a state of relatively selective sensory deprivation occurs during ketamine anesthesia. Likewise, increased LCGU in the corpus callosum produced by ketamine is consistent with increased neuronal traffic between cortices; the glucose utilization of descending white matter tracts suggests little alteration in the interaction between cortical and subcortical structures. The limbic seizure activity reported to occur during ketamine anesthesia[1] would explain the large increases in LCGU noted in cingulate and hippocampus. From the increased LCGU in the extrapyramidal motor system, one might infer that ketamine activated this region. Movement was an independent variable in these experiments, however, and the metabolic effects seen in this functional system could, therefore, be secondary to peripheral motor activity rather than the cause of it. The substantial redistribution of metabolism within some anatomic regions (*e.g.*, caudate, visual cortex) and the activation of cortical layers (I, VI) which are normally rather quiescent metabolically (fig. 2), suggest that a disorganization of normal function has occurred in these regions secondary to ketamine's action. It is of some interest that a phencyclidine (PCP) receptor, which also binds ketamine, has recently been isolated[10,11] and is found in high concentration in areas of rat brain where substantial changes in LCGU occur during ketamine anesthesia. To conclude that this receptor is the molecular locus of ketamine's action is attractive, but premature inasmuch as Snyder[12] has questioned its existence.

There are some similarities between the results of our study and previous reports of changes in regional glucose utilization caused by ketamine or its parent compound, PCP. In a qualitative study of the effects of PCP in the rat with the 2-[^{14}C]DG technique, Meibach *et al.*[13] reported increased optical density in hippocampus, anteroventral thalamus, cingulate gyrus, caudate nucleus and frontal cortex while the inferior colliculus showed a large decrease in optical density. Shapiro *et al.*[14] have quantified regional metabolic changes in the monkey following PCP and report increased LCGU in 19 gray matter structures and decreases or no change in the remaining six examined. Studies of regional metabolism during ketamine anesthesia are few. In a 2-[^{14}C]DG study of ketamine anesthesia in the rat in which only five brain regions were examined, Nelson *et al.*[6] reported increased LCGU in hippocampus, decreases in medial geniculate and inferior colliculus and no change in the one cortical area studied. The dose (25 to 75 mg/kg) and route of administration (intramuscular) of ketamine, as well as the qualitative nature of the analysis used by Nelson *et al.*,[6] precludes direct comparison with the present study. Our finding of increased LCGU in corpus callosum further complicates the interpretation of the data of Nelson *et al.*[6] inasmuch as they used the corpus callosum as a reference against which the optical densities of other structures were compared. Despite these differences, our results confirm that ketamine has substantial but opposing metabolic effects on the auditory and limbic systems with decreases in metabolism of the former and increases in the latter. The present observations of statistically significant changes in metabolism of the extrapyramidal system, corpus callosum, and auditory and sensory motor cortices during ketamine anesthesia include some previously unrecognized effects of this drug.

The findings of the present study are not consistent with all studies of regional metabolism during ketamine anesthesia, however. Hawkins *et al.*,[5] using the [^{14}C]glucose method, which requires a shorter experimental period, studied regional glucose utilization in rats in the first 10 to 15 min following ketamine (35 mg/kg) given intravenously. Quite unlike our results or the others mentioned previously, Hawkins *et al.*[5] report essentially no change in LCGU during ketamine. Methodological differences probably explain their unique results. They used the [2-^{14}C]glucose method which is susceptible to several serious sources of error. To determine the rate of glucose utilization it is necessary to determine accurately the amount of product formed. [^{14}C]Glucose is, however, very rapidly metabolized to $^{14}CO_2$, which is lost from the brain via the circulation. The amount of product formed is then underestimated. Correction for the loss of $^{14}CO_2$ is virtually impossible because of the

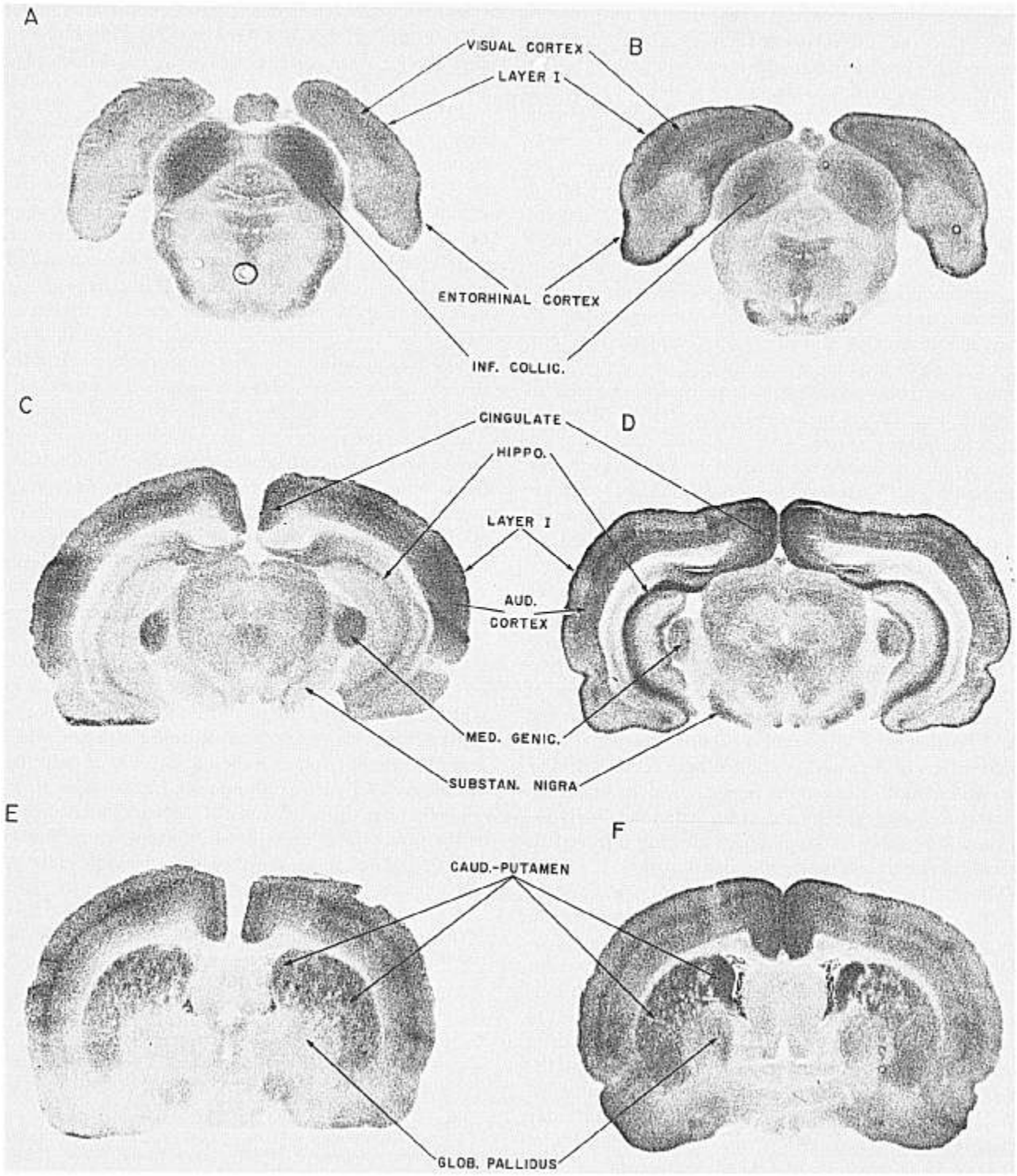

FIG. 2. Autoradiographic sections from control (*left*) and high-dose ketamine treated (*right*) rats. Reduced optical density (OD) is apparent in the auditory system (inferior colliculus, medial geniculate and auditory cortex) of treated animals (*B, D*). Increased OD is seen in a few limbic system structures (cingulate, hippocampus) (*D*) and in the basal ganglia (caudate-putamen, globus pallidus and substantia nigra) (*D, F*). The cortex of control animals (*A, C, E*) shows the normal metabolic heterogeneity and the typically dark band of activity in Layer IV. In treated animals, cortical heterogeneity is accentuated (*B, D*) and activation of cortical Layers I and VI, in addition to Layer IV, gives the cortex a laminated appearance (*B, D, F*). Another activated limbic system structure, the entorhinal cortex, is illustrated (*B*), but the changes have not been quantified.

uncertainties about the sizes and turnover rates of the pools of all the intermediates between glucose and the sites of CO_2 production in the metabolic pathways. To minimize the effects of loss of $^{14}CO_2$ the experimental period must be confined to only a few minutes following the administration of the labeled tracer. In the early period following the dose, it is difficult to determine the precursor specific activity in the tissues because of the lag between tissue and blood. Hawkins *et al.*[5] avoided this problem by assuming that the glucose pool in the tissue turned over so rapidly that it was in instantaneous and continuous equilibration with that of the plasma. This assumption is invalid because the glucose pool in brain has an average half-life of approximately 1.5 min, long enough to produce significant lags in the equilibration of the tissue pool with that of the plasma and to produce large errors in the early times after the pulse of labeled tracer.[15] The [^{14}C]deoxyglucose method avoids these problems because the product of [^{14}C]deoxyglucose metabolism, [^{14}C]deoxyglucose-6-phosphate, remains trapped in the cells for at least 45 min.[15] Because there is no loss of product, it is, therefore, possible to extend the experimental period to 45 min when the influence of the lag in the equilibration of the tissue with the plasma becomes essentially negligible.

The doses of ketamine used in this study, though relatively larger than those used in man, produce only a light (10 mg/kg) and moderate (30 mg/kg) depth of anesthesia, as measured by the righting reflex, in the rat.[16] Furthermore, it is unlikely that the regional metabolic effects of ketamine presented here reflect selective distribution of the drug to the regions involved inasmuch as measurements of regional brain ketamine levels indicate that as early as one minute following intravenous injection ketamine is uniformly distributed.[16]

The ability of the 2-[^{14}C]DG method to map the brain for regions of altered functional activity on the basis of changes in energy metabolism is a useful tool for identifying the neural sites of action of agents with neuropharmacological effects. The method has important limitations, however. It does not, for example, allow one to discriminate between direct and indirect actions of a drug since an entire pathway may be affected even though the direct action of the agent is at the origin of the pathway. Similarly, excitatory and inhibitory neuronal events may consume energy equally, thus making it impossible to attribute an increase in LCGU to one functional population of neurons. On the other hand, reduced neuronal activity, such as would occur throughout a pathway subjected to reduced input, is always followed by reduced energy consumption.[9] These limitations in the interpretation of regional metabolic data do not detract from the importance of the finding of large, bi-directional, and at times quite heterogeneous, region-specific alterations in glucose utilization. To the contrary, the metabolic findings localize areas where more specific experimental tools may be applied.

Data on the regional metabolic effects of other common, clinically used anesthetics have only recently become available. Nitrous oxide appears to have little effect[17,18] or perhaps produces a small decrease§ in regional cerebral energy metabolism. Pentobarbital produces large (30–50 per cent) decreases in glucose utilization and reduces the metabolic heterogeneity that normally exists between structures.[7] Halothane also produces a fairly uniform but less marked decrease in LCGU.[19] The LCGU reductions during enflurane anesthesia are quantitatively similar to those during halothane; notable exceptions were some limbic system structures where metabolic rate increased 20 to 30 per cent.[20] That ketamine produces a state of anesthesia quite different from the other agents mentioned is emphasized by its unique metabolic effects. There are dramatic increases and decreases in LCGU which are not only region specific, but are to a large extent selective for certain functional systems in the CNS. The data are consistent with a state of "anesthesia" characterized by auditory and somatosensory deprivation superimposed on a metabolically disorganized but still quite active CNS. The largest increases in LCGU during ketamine anesthesia occur in regions of the limbic system, and are consistent with previous observations of limbic seizure activity resulting from this drug.[1] The existence of a receptor for ketamine could explain some of its regional selectivity, but the data for such a receptor are inconclusive at present. Whatever the mechanism of its action, ketamine may be the prototypical example of an agent where the "anesthetic" state is associated with a metabolically very active brain.

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Erratum

Due to an unfortunate oversight, the article, "Air Embolism Associated with Pulmonary Artery Catheter Introducer Kit," was published in both the April (pp 307–309) and May (pp 389–391) issues of the Journal.