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The Influence of Ketamine on Regional Brain Glucose Use

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The purpose of this study was to determine the effect of different doses of ketamine on cerebral function at the level of individual brain structures as reflected by glucose use. Rats received either 5 or 30 mg/kg ketamine intravenously as a loading dose, followed by an infusion to maintain a steady-state level of the drug. An additional group received 30 mg/kg as a single injection only, and was studied 20 min later, by which time they were recovering consciousness (withdrawal group). Regional brain energy metabolism was evaluated with [6-^{14}C]glucose and quantitative autoradiography during a 5-min experimental period. A subhypnotic, steady-state dose (5 mg/kg) of ketamine caused a stimulation of glucose use in most brain areas, with an average increase of 20%. At the larger steady-state dose (30 mg/kg, which is sufficient to cause anesthesia), there was no significant effect on most brain regions; some sensory nuclei were depressed (inferior colliculus, −29%; cerebellar dentate nucleus, −18%; vestibular nucleus, −16%), but glucose use in the ventral posterior hippocampus was increased by 33%. In contrast, during withdrawal from a 30-mg/kg bolus, there was a stimulation of glucose use throughout the brain (21–78%), at a time when plasma ketamine levels were similar to the levels in the 5 mg/kg group. At each steady-state dose, as well as during withdrawal, ketamine caused a notable stimulation of glucose use by the hippocampus. (Key words: Anesthetics, intravenous: ketamine. Brain: entorhinal cortex; hippocampus. Metabolism: glucose. Receptors: glutamate; NMDA; phencyclidine.)

KETAMINE (2-orthochlorophenyl, 2-methylamino-cyclohexanone HCl) is an intravenous anesthetic agent introduced into clinical practice in 1967.[1] Ketamine produces analgesia with less depression of cardiovascular and respiratory function than that caused by many commonly used anesthetics. While most anesthetics produce a state of unconsciousness, ketamine has been described as a dissociative anesthetic[2] producing a feeling of controlled confusion or a sense of being separated from one's extremities.[1] A drug that produces a state so different from that caused by most other anesthetics may also be expected to have a unique effect on brain function and energy metabolism. Several studies of the cerebral metabolic rate of glucose use (CMR_{Glc}) during ketamine anesthesia have produced differing conclusions.[3–5] Nelson *et al.*,[3] using qualitative techniques, found CMR_{Glc} unchanged in the cortex and increased in the hippocampus. Crosby *et al.*,[4] using a quantitative 2-deoxyglucose (2DG) method, found CMR_{Glc} decreased in the cortex, but increased in some limbic and extrapyramidal regions. Hawkins *et al.*,[5] using quantitative autoradiography and [2-^{14}C]glucose, found CMR_{Glc} was not significantly affected in 16 of 17 brain regions examined. Direct comparisons between the different studies are difficult, because of variations in the dose, route of administration, and level of anesthesia. Perhaps the most significant factor, however, is that none of the studies considered the short half-life of ketamine in circulation and, therefore, none was conducted in a steady-state condition. The present study was designed to evaluate the effect of ketamine on regional brain energy metabolism during steady-state conditions.

Materials and Methods

Three experiments were conducted. The purpose of the first experiment was to determine the effects of the ketamine doses to be used on physiological variables. Eight male Long Evans rats (250–350 g) were anesthetized with 2% halothane in O_2:N_2O (25:75, v/v) for 15 min while the left femoral artery and vein were cannulated. The rats were allowed to recover in restraining cages for 3 h. Fifteen minutes after intravenous injection of 200 I.U. of heparin, the experiment was begun by injecting an intravenous bolus of ketamine (5 mg/kg or 30 mg/kg); the catheter was then connected to a Sage infusion pump (Model 355). The infusion schedule, designed to maintain the blood levels established by the bolus injection, was constructed from data obtained in rats by Marietta *et al.*[6] The bolus was administered over a 1-min period whereupon the clock was started and the following infusion program was followed (rates are expressed as % of the initial dose/min): 14.1% min, 0–1 min; 6.8% min, 1–3 min; 5.8%/min, 3–5 min; 2.0%/min, 5–10 min; 1.2% min, 10–15 min; and 0.7%/min, 15–20 min. At 20 min, the infusion was stopped. It was calculated that the plasma concentration of ketamine would fall less than 4% over the subsequent 5-min experimental interval. Measurements of heart rate, mean arterial pressure, rectal temperature, Pa_{O_2}, Pa_{CO_2}, and *p*H were made immediately before beginning the infusion and at 5-min intervals thereafter.

In the second experiment, eight rats were used to

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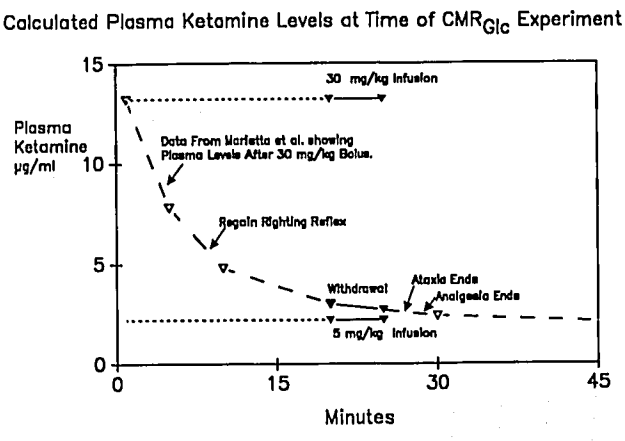

FIG. 1. Data from Marietta *et al.*[6] (dashed line) shows the plasma levels of ketamine and behavioral states in rats following a single injection of ketamine (30 mg/kg). The calculated plasma levels achieved by a single injection of either 5 or 30 mg/kg of ketamine followed by ketamine infusion are indicated by the horizontal dotted lines. The solid lines indicate the period when CMR_{Glc} was measured.

determine the brain-to-plasma glucose ratio during ketamine anesthesia. This ratio was used in the subsequent calculation of CMR_{Glc}. While anesthetized with pentobarbital 2 days before the experiment, two catheters were inserted in the internal jugular vein at the level of the right atrium. The catheters were led out through the skin in the mid-scapular area and through a soft spring guard to exit through a swivel at the top of an isolation box.[7] The rats wore a harness (Spaulding Medical Products, Arroyo Grande, CA) to prevent access to the catheter, but were otherwise free to move about the cage. After 2 days' recovery, the rats were anesthetized with either 5 mg/kg or 30 mg/kg ketamine by bolus injection, followed by infusion, as described above. After 25 min, arterial blood was sampled and the brain of each rat was rapidly removed and frozen by a "pneumatic decerebration" device.[8]

The third experiment, measurement of CMR_{Glc}, was conducted on four groups of rats using [6-^{14}C]glucose and a 5-min experimental period.[9,10] Catheters were inserted in the internal jugular vein as described above. The rats were allowed 2 days for recovery in individual isolation boxes, where they remained undisturbed until the end of the CMR_{Glc} experiment. On the day of CMR_{Glc} measurement, ketamine (5 or 30 mg/kg) was injected as a bolus followed by an infusion as described above. Control rats were treated identically, but received an equivalent volume of 0.154 M NaCl. The fourth group of rats received only the 30-mg/kg bolus of ketamine, and will be referred to as the withdrawal group. When these rats were studied (20–25 min after the bolus), the plasma ketamine concentration was expected to have fallen to a level only slightly greater than that of the 5-mg/kg plus infusion group (fig. 1).

Twenty-one minutes after beginning the ketamine infusion, 35 µCi of [6-^{14}C]glucose in 0.154 M NaCl was injected through one catheter used only for this purpose. Five samples of blood (0.1 ml each) were drawn during the next 5 min for determination of plasma glucose and specific radioactivity. At 25 min (5 min after receiving the [^{14}C]glucose), the rats were killed by a cardioplegic dose of pentobarbital. The brain was quickly removed and suspended in a 2-phase solution of 1-methylbutane and 2-bromobutane, chilled to −30°C in Freon-12®. Coronal sections, 40 µm thick, were cut, mounted onto glass slides, dried at 55°C, and exposed for 10–12 days to x-ray film (Lo-Dose Mammography Film, E.I. du Pont de Nemours, Wilmington, DE) along with a set of calibrated ^{14}C-methylmethacrylate standards. Optical densities were measured with a pinhole densitometer (Tobias, Ivyland, PA) for determination of CMR_{Glc} in 40 discrete regions. In addition, the film of a representative rat from each group was measured with the use of a computer-controlled scanning microdensitometer, which sampled the sections at 100 µm resolution, providing more than 1 million data points for each brain.[11]

ASSAYS

Glucose was measured spectrophotometrically with hexokinase and glucose-6-phosphate dehydrogenase in neutralized perchloric acid extracts of tissue.[12] Plasma radioactivity was determined by liquid scintillation counting.

CHEMICALS

Ketamine HCl (Ketalar®) was bought from Parke-Davis, Morris Plains, NJ. Enzymes and coenzymes were from Boehringer Mannheim Corp., New York. NY. [6-^{14}C]Glucose (6.8 mCi/mmol) was from Amersham, Arlington Heights, IL. All other chemicals were of the best available grade.

STATISTICAL ANALYSES

Programs from SAS Institute, Cary, NC, were used for all statistical analyses. Each cerebral structure in table 1 was considered to be an independent family consisting of four groups (control plus three ketamine-treated). Each family of observations was examined by analysis of variance (ANOVA) at $P \leq 0.05$ to identify whether differences existed. Only families with significant differences at this stage were analyzed further. Although there were six possible comparisons, only four were of interest; control compared with each ketamine-treated group, and the 5-mg/kg group compared with the withdrawal group. All individual comparisons were

TABLE 1. Regional Cerebral Glucose Use during Ketamine Anesthesia

	Control (5)	5 mg/kg (6)	Δ%	30 mg/kg (6)	Δ%	Withdrawal (6)	Δ%
Telencephalon							
Cortex							
Frontal	98 ± 4	125 ± 5	+28*	88 ± 4	−10	144 ± 6	+47*†
Insular	97 ± 4	120 ± 7	+24*	85 ± 4	−12	129 ± 6	+33*
Pyriform	63 ± 3	85 ± 4	+35*	58 ± 3	−8	87 ± 5	+38*
Cingulate	106 ± 1	142 ± 7	+34*	108 ± 4	+2	165 ± 10	+56*†
Parietal	103 ± 3	135 ± 6	+31*	96 ± 3	−7	159 ± 7	+54*†
Entorhinal	73 ± 4	101 ± 5	+38*	89 ± 5	+22	119 ± 13	+63*
Occipital	106 ± 6	142 ± 7	+34	97 ± 6	−8	156 ± 6	+47*
Caudate	94 ± 2	123 ± 8	+31	96 ± 3	+2	142 ± 5	+51*†
Globus pallidus	50 ± 2	72 ± 4	+44*	51 ± 3	+2	89 ± 4	+78*†
Amygdala	71 ± 3	91 ± 5	+28*	68 ± 3	−4	104 ± 4	+46*†
Hippocampus							
Anterior	68 ± 2	88 ± 4	+29*	71 ± 4	+4	100 ± 4	+47*†
Posterior	68 ± 3	88 ± 4	+29*	70 ± 2	+3	97 ± 3	+43*
Post.vent.	82 ± 4	118 ± 10	+44*	109 ± 6	+33*	128 ± 5	+56*
Septal n.							
Lateral	60 ± 6	72 ± 7	+20	54 ± 2	−10	77 ± 5	+28*
Medial	67 ± 2	67 ± 6	0	58 ± 3	−13	111 ± 5	+66*†
Diencephalon							
Habenula	100 ± 9	111 ± 6	+11	90 ± 4	−10	128 ± 7	+28*
Hypothalamus							
Anterior	70 ± 2	80 ± 4	+14	62 ± 3	−11	93 ± 3	+33*†
Thalamus							
Anterior n.	111 ± 4	137 ± 8	+23*	115 ± 3	+4	154 ± 7	+39*
Ventral n.	94 ± 5	113 ± 6	+20*	86 ± 3	−9	141 ± 9	+50*†
Medial geniculate	111 ± 4	110 ± 9	−1	97 ± 3	−13	127 ± 6	+14
Lateral geniculate	94 ± 3	118 ± 7	+26*	86 ± 3	−9	142 ± 7	+51*†
Mesencephalon							
Substantia nigra	70 ± 4	93 ± 6	+33*	74 ± 5	+6	109 ± 4	+56*†
Red nucleus	92 ± 2	113 ± 7	+23*	87 ± 4	−5	129 ± 5	+40*†
Oculomotor complex	102 ± 3	129 ± 7	+26*	97 ± 3	−5	146 ± 6	+43*†
Interpeduncular n.	120 ± 3	143 ± 13	+19	118 ± 3	−2	159 ± 6	+33*
Reticular formation	66 ± 2	85 ± 6	+29*	61 ± 3	−8	94 ± 4	+42*
Superior colliculus	101 ± 2	117 ± 8	+16	87 ± 3	−14	144 ± 5	+43*†
Inferior colliculus	187 ± 4	170 ± 11	−9	133 ± 6	−29*	182 ± 13	−3
Mesencephalon							
Pons	86 ± 4	118 ± 9	+37*	86 ± 3	0	133 ± 5	+55*
Cerebellar gray							
Molecular	96 ± 6	109 ± 10	+14	79 ± 2	−18	117 ± 4	+22*
Granular	104 ± 8	120 ± 8	+15	89 ± 3	−14	133 ± 4	+28*
Dentate n.	124 ± 5	133 ± 8	+7	102 ± 4	−18*	156 ± 7	+26*†
Vermis	92 ± 8	112 ± 8	+22*	82 ± 4	−11	114 ± 6	+24*†
Myelencephalon							
Vestibular	136 ± 3	146 ± 8	+7	114 ± 3	−16*	164 ± 8	+21*
Cochlear n.	151 ± 2	143 ± 10	−5	127 ± 4	−16	172 ± 11	+14†
Superior olive	141 ± 3	146 ± 11	+4	131 ± 2	−7	174 ± 7	+23*†
Inferior olive	105 ± 2	121 ± 3	+15*	91 ± 3	−13	150 ± 7	+43*†
Reticular formation	75 ± 3	95 ± 7	+27*	65 ± 2	−13	115 ± 6	+53*†
White matter							
Corpus callosum	63 ± 5	82 ± 4	+30*	63 ± 2	0	89 ± 5	+41*
Internal capsule	42 ± 2	59 ± 3	+40*	42 ± 3	0	69 ± 3	+64*†
Cerebellar white	53 ± 5	67 ± 5	+26*	46 ± 4	−13	72 ± 7	+36*

CMR_{Glc} was measured in four groups of rats: control, NaCl infused; 5 mg/kg, an injection of 5 mg/kg followed by infusion; 30 mg/kg, an injection of 30 mg/kg followed by infusion; withdrawal, an injection of 30 mg/kg only. All values are reported as mean ± SEM expressed in $\mu mol \cdot min^{-1} \cdot hg^{-1}$ with the number of rats in parenthesis.

* Indicates $P \leq 0.05$ compared with the control group.

† Indicates $P \leq 0.05$ compared with the 5-mg/kg group. See text for further details.

TABLE 2. Physiological Effects of Ketamine

	0 Min	5 Min	10 Min	15 Min	20 Min	25 Min
5 mg/kg						
Temp. (°C)	37.6 ± 0.3	38.0 ± 0.2	38.3 ± 0.3	38.4 ± 0.2	38.5 ± 0.3	38.6 ± 0.3
Mean P_a (mmHg)	119 ± 2	145 ± 3	147 ± 2	151 ± 4	144 ± 3	146 ± 3
Heart rate (per min)	473 ± 22	543 ± 10	550 ± 8	545 ± 9	543 ± 10	535 ± 23
P_{CO_2} (mmHg)	41.4 ± 2.3	41.9 ± 1.0	40.3 ± 1.8	41.0 ± 1.0	40.8 ± 1.2	39.5 ± 0.7
P_{O_2} (mmHg)	84.0 ± 4.8	74.4 ± 4.4	78.8 ± 1.9	80.6 ± 3.3	82.0 ± 1.9	86.2 ± 2.4
*p*H	7.41 ± 0.01	7.42 ± 0.01	7.41 ± 0.01	7.42 ± 0.02	7.39 ± 0.01	7.39 ± 0.01
30 mg/kg						
Temp. (°C)	37.6 ± 0.2	37.2 ± 0.2	37.0 ± 0.3	36.9 ± 0.4	36.8 ± 0.5	36.8 ± 0.4
Mean P_a (mmHg)	125 ± 7	90 ± 5	102 ± 7	115 ± 7	118 ± 10	124 ± 10
Heart rate (per min)	495 ± 15	368 ± 10	393 ± 18	415 ± 22	430 ± 34	460 ± 41
P_{CO_2} (mmHg)	42.1 ± 0.3	52.3 ± 2.1	49.7 ± 1.8	51.5 ± 1.9	48.8 ± 1.8	44.2 ± 1.6
P_{O_2} (mmHg)	79.9 ± 2.2	71.6 ± 0.7	68.2 ± 5.3	65.9 ± 1.5	73.5 ± 4.3	82.5 ± 8.2
*p*H	7.42 ± 0.01	7.33 ± 0.01	7.35 ± 0.01	7.35 ± 0.01	7.36 ± 0.01	7.38 ± 0.01

Values are means ± SEM of four rats given an injection of ketamine (either 5 or 30 mg/kg) followed by an infusion of ketamine thereafter to maintain steady state. See text for other details.

made using the modified *t* statistic at the level of $P \leq 0.05$.

Results

Administration of different doses of ketamine to rats produced distinctly different behavior. After receiving the 5-mg/kg plus infusion dose, the rats circled slowly and continuously, often staggering. Stereotypic, side-to-side head movements occurred about every 2–3 s. This behavior was in marked contrast to that receiving 30 mg/kg plus infusion, in which every rat remained motionless throughout the entire 25-min period. The rats in the withdrawal group showed a succession of behavioral states, beginning with a 5–10-min period of motionless behavior similar to that of those receiving 30 mg/kg plus infusion. This motionless period was followed by a short interval (2–3 min) during which occasional head or limb movements were observed. These occasional movements progressed to head-swaying and crawling, though never quite reaching the level of activity observed in the 5 mg/kg plus infusion.

Ketamine had little effect on physiological variables (table 2). At a dose of 5 mg/kg, there was an increase in heart rate (about 15%) and blood pressure (about 20%). All values of arterial blood gases and *p*H were within normal ranges. Following the 30 mg/kg dose, there were only transient changes in heart rate, blood pressure, and blood gases, and all variables returned to preanesthetic values by 20–25 min. There appeared to be a increase in temperature (≈1°C) in the 5-mg/kg group and a decrease (≈0.8°C) in the 30-mg/kg group. These differences were considered to be too small to account fully for the changes in CMR_{Glc} described below.

The ratio of brain-to-plasma glucose concentration was not affected by ketamine. The values obtained (0.22 ± 0.01 [mean ± SEM, n = 6] for 5 mg/kg and 0.24 ± 0.02 [n = 7] for 30 mg/kg) were neither significantly different from each other, nor from the previously determined normal control value of 0.22 ± 0.01 (n = 5).[10]

The effect of ketamine on CMR_{Glc} is reported in table 1 and illustrated in figure 2. At a dose of 5 mg/kg, about half the brain areas examined showed increased CMR_{Glc}. The greatest effect was in the forebrain. In the telencephalon, all regions examined except the septal nuclei showed increased activity. The only structures affected in the diencephalon were the thalamic nuclei and the lateral geniculate. Several structures in the mesencephalon showed elevated CMR_{Glc}, while only the pons in the metencephalon and reticular formation of the myelencephalon were increased. The rate of glucose use in white matter (corpus callosum and internal capsule) was increased.

The metabolic picture was very different following the 30-mg/kg plus infusion dose of ketamine. In most areas, CMR_{Glc} was not different from control values (table 1). Of the four regions in which CMR_{Glc} was significantly changed, three regions had decreased consumption (inferior colliculus, cerebellar denate nucleus, and the vestibular nucleus); the ventral portion of the posterior hippocampus had a CMR_{Glc} 33% greater than control. Although it did not achieve statistical significance, CMR_{Glc} in the entorhinal cortex was likewise stimulated (fig. 2).

During recovery from a single 30-mg/kg bolus injection of ketamine, CMR_{Glc} was 20–70% greater than control in almost every brain region examined. The medial geniculate, inferior colliculus, and cochlear nucleus were the only structures not affected. Unlike the rats receiving 5 mg/kg plus infusion, in the group recovering from 30 mg/kg ketamine, most areas of the

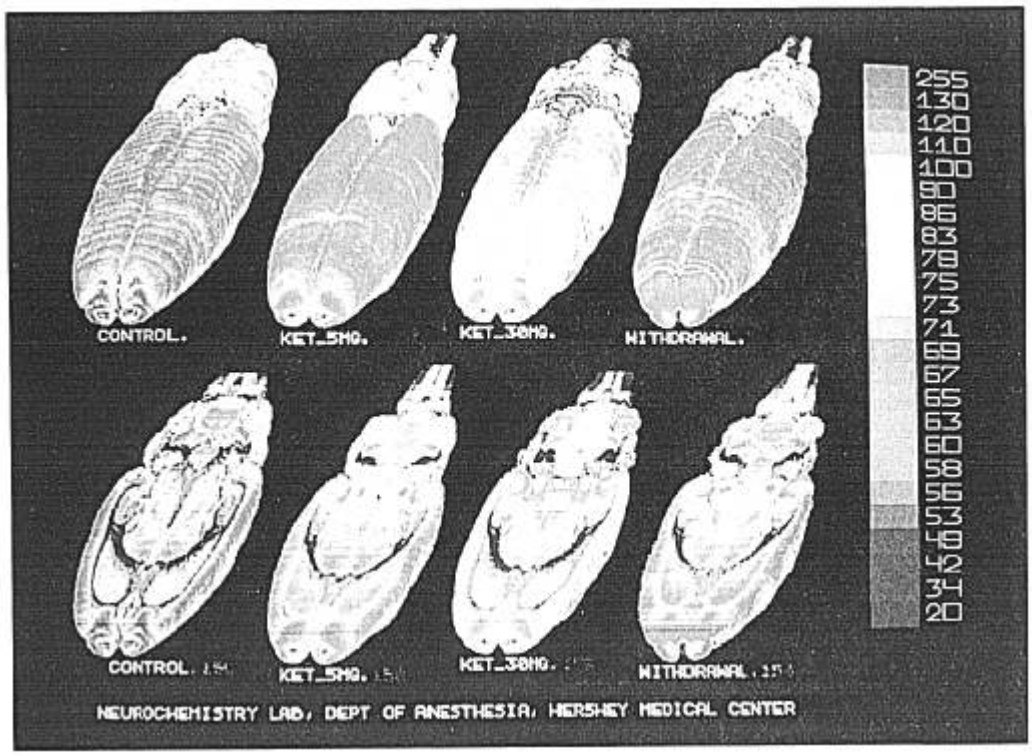

FIG. 2. Brain metabolism during ketamine anesthesia. Stereograms of brain metabolism were reconstructed with the aid of a computer from individual coronal sections as described by Hibbard *et al.*[11] The top row shows, from left to right, whole brains from control, 5 mg/kg, 30 mg/kg, and withdrawal rats, respectively. The bottom row shows the same brains with the top half removed to reveal the internal detail. The color key allows quantitative interpretation of CMR_{Glc} (μmol/min/hg).

cerebellum, myelencephalon, medial septal nucleus, habenula, hypothalamus, ventral thalamus, and interpenduncular nucleus were also stimulated.

Figure 2 graphically demonstrates the metabolic effects of ketamine. These perspective stereograms of the brain were produced by reassembly of the individual coronal images.[11] The top row shows whole brains representative of the control, 5 mg/kg, 30 mg/kg, and the withdrawal groups. Below each whole brain is a view of the same image with the top half removed by computer to reveal the internal structures. The 5 mg/kg image demonstrates the hypermetabolic state that existed in most areas. The 30 mg/kg image presents a notable contrast. CMR_{Glc} in most regions is indistinguishable from the control values; the hippocampus and entorhinal cortex are the exceptions. In the image of ketamine withdrawal, it is apparent that the metabolic condition more closely resembles the 5-mg/kg state than that produced by the steady-state, 30 mg/kg dose.

Discussion

The objective of this study was to examine the influence of ketamine on cerebral function by measuring CMR_{Glc} at the level of individual brain structures, using an experimental design that took into account ketamine pharmacokinetics. Ketamine is water soluble, but it is also about ten times more lipid soluble than thiopental.[13] Therefore, it is rapidly taken up by brain after a single injection and then removed by redistribution and hepatic metabolism[1] in a manner similar to barbiturates. In rats, following a single intravenous injection, the redistribution half-life of ketamine is 10 min in plasma and 8 min in brain.[6] During that period, the plasma and brain levels of ketamine are in a dynamic state, making measurement of CMR_{Glc}, which requires that steady-state conditions exist, difficult. Marietta *et al.*[6] demonstrated that the duration of hypnosis following a single intravenous injection of 30 mg/kg was only 8 min, while ataxia and analgesia lasted 27 and 29 min, respectively. In order to measure CMR_{Glc} during an unchanging anesthetic state, a loading dose of ketamine was given followed by an infusion designed to replace drug lost to the various body compartments and thereby maintaining the plasma level near constant. The infusion program was continued for 20 min. The calculated change in plasma level was less than 4% during the 5 min measurement period (fig. 1).

The principal findings were as follows. First, after injection of a subhypnotic dose of ketamine (5 mg/kg) followed by ketamine infusion, CMR_{Glc} was increased throughout the brain. Second, after an hypnotic dose of ketamine (30 mg/kg) followed by ketamine infusion, CMR_{Glc} was near normal except in the hippocampus and entorhinal cortex. In these structures, there was a striking rise in CMR_{Glc}. This increased CMR_{Glc} produced a distinctive pattern on the autoradiographs that were seen in every rat and at all doses studied. And,

third, between 20 and 25 min after a single injection of an hypnotic dose of ketamine (30 mg/kg), when plasma levels of ketamine were low but probably still sufficient to produce ataxia and analgesia, there was a pronounced increase in metabolic activity throughout the brain.

There have been several other studies of the action of ketamine on cerebral energy metabolism, but none has been done under steady-state conditions; this has complicated the interpretation of data.[3-5] Hawkins *et al.*,[5] in a 10-min experiment using [^{14}C]glucose, found that a single intravenous injection of 35 mg/kg given 5 min before measuring CMR_{Glc} had no detectable effect on CMR_{Glc}. The rats were unconscious throughout the experiment, but the plasma level of ketamine was calculated to be changing from 15.4 to 5.6 μg/ml during the 10-min experiment (see figure 1 for calculated ketamine levels in the present study). The results of Hawkins *et al.*[5] were similar to the current observations made on anesthetized rats (30 mg/kg), with the exception that, in the previous study, no increase in CMR_{Glc} was reported in the hippocampus or entorhinal cortex. Nelson *et al.*,[3] with a qualitative technique using deoxyglucose, reported that CMR_{Glc} increased in the hippocampus and decreased in medial geniculate and inferior colliculus following 25–75 mg ketamine given intramuscularly. They reported all values of CMR_{Glc} as a ratio of gray-to-white matter (corpus callosum). Our results, as well as other quantitative studies, report increases in CMR_{Glc} for the corpus callosum; thus, the use of white matter as a standard of reference is of dubious value.

Crosby *et al.*,[4] using the deoxyglucose technique, measured CMR_{Glc} over 45 min following a single intravenous injection of either 10 or 30 mg/kg. They reported increased CMR_{Glc} in limbic structures (hippocampus, cingulate, mammilary body, and interpeduncular nucleus) and extrapyramidal structures (globus pallidus and substantia nigra), as well as corpus callosum, and decreased CMR_{Glc} in auditory cortex, inferior colliculus, and sensory motor cortex with both doses. In contrast to our study, they found no difference between the two doses of ketamine; both doses produced changes in about one-third of the regions examined. However, because of the short half-life of ketamine in circulation and the 45-min experimental period required with the deoxyglucose method,[14] a steady-state situation did not exist. Crosby *et al.* reported: "Animal behavior varied considerably during the 45 min of the experiment. There was generally at first a 5–10 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 control rats, who appeared calm and groomed and dozed."[4] Thus, it is obvious from their own description, as well as the calculated plasma levels (fig. 1), that Crosby *et al.* were not studying only ketamine anesthesia, but also various stages of recovery.

Despite conflicting results for many brain regions, there are points of agreement between different studies regardless of the dose, route of administration, or metabolic tracer used. There is general agreement that ketamine stimulates CMR_{Glc} in the hippocampus. When rats are deeply anesthetized throughout the experiment, quantitative experiments have shown only a modest change in CMR_{Glc} in other brain areas. In contrast, when rats are no longer anesthetized, but still ataxic, there is an indication of stimulated CMR_{Glc} throughout the brain.

The pattern of energy metabolism, and, presumably, neuronal function, caused by ketamine is markedly different from other intravenous anesthetics. For instance, at anesthetic doses, barbiturates produce a profound decrease in cerebral energy metabolism throughout the entire brain.[5] All cerebral structures are affected. In addition, barbiturates cause a decrease in blood pressure, body temperature, and respiration.[5] Anesthetics such as Althesin (a steroid anesthetic) or etomidate (an imidazole derivative) have little effect on temperature regulation, blood pressure, or respiration.[15,16] These latter two anesthetics depress cerebral glucose use rather markedly in the forebrain, but hindbrain structures are affected to a much lesser degree.[15,16] The very different effects of each of these anesthetics on both physiological variables, as well as cerebral energy metabolism, suggest that they work by different mechanisms.

The stimulation of CMR_{Glc} by ketamine in the posterior hippocampus and entorhinal cortex is intriguing. This stimulation was observed in all animals regardless of dose, being almost a signature of ketamine anesthesia. Nelson *et al.*[3] suggested that ketamine produced hippocampal seizures (although no electroencephalographic evidence was presented), which, in turn, inhibited input to auditory and visual pathway nuclei. They suggested the resulting sensory deprivation was a possible cause of ketamine anesthesia.[3] Whether ketamine actually causes seizures in the hippocampus is an open question, but the metabolic stimulation of this area that we observed was not as great as would be expected from an area showing seizure activity. On the other hand, it is tempting to speculate that the enhanced rate of energy consumption represents a disturbance in the normal neuronal function of these structures.

Ketamine is a non-competitive antagonist of the NMDA subtype of glutamate receptor.[17] There are few data relative to the mapping of ketamine interaction with brain receptors, but data do exist concerning a

closely related analog, phencyclidine, which may bind to the same receptor site as ketamine. Like ketamine, phencyclidine seems to stimulates CMR_{Glc} in the hippocampus in rats treated with phencyclidine. Gundlach *et al.*[19] and Contreras *et al.*[20] mapped phencyclidine receptors in rat brain using yet another analog 1-(1-(2-thienyl)cyclohexyl)piperidine (TCP). In both studies, the greatest density of receptors was found in the hippocampus and superficial layers of the cerebral cortex. This localization corresponds approximately to the areas where CMR_{Glc} is stimulated by both ketamine and phencyclidine. As mentioned, ketamine, PCP, and TCP are all non-competitive antagonists of the NMDA subset of the glutamate receptor family,¶ and these receptors have also been dense in the hippocampus. Although no direct evidence exists, it is reasonable to speculate that at least some of the effects of ketamine may be mediated by the NMDA-sensitive receptors; perhaps resulting in an increase in cellular activity leading to disorganization of normal neurotransmission and the resulting dissociative anesthetic state.

In summary, ketamine stimulated energy consumption in the hippocampus and entorhinal cortex at all doses, but the effect on the rest of the brain was biphasic. At low circulating ketamine concentrations, there was a marked stimulation of CMR_{Glc} that was especially pronounced during recovery. At an anesthetic ketamine concentration, CMR_{Glc} was near normal or slightly depressed except, as mentioned, in the hippocampus and entorhinal cortex. It appears, therefore, that a hypermetabolic state will invariably occur during the natural anesthesia-recovery cycle, and this may be of some practical importance. Although the mechanism of action of ketamine remains to be elucidated, it is interesting that several regions manifesting increased CMR_{Glc} in response to ketamine correspond to the regions with the greatest density of NMDA-sensitive glutamate receptors, suggesting a potential site of ketamine action.

¶ Kemp JA, Foster AC, Wong EHF. Non-competitive antagonists of excitatory amino acid receptors. Trends in Neurosciences 10:295–299, 1987.

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