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Regional Brain Glucose Utilization in Rats during Etomidate Anesthesia

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The influence of etomidate on regional cerebral function as reflected by regional cerebral glucose utilization ($rCMR_{Glc}$) was studied. Three experiments were performed. In the first, rats had both left femoral vessels cannulated and were placed in restraining cages. Etomidate was infused intravenously (12 mg/kg) at a rate of 6 $mg \cdot kg^{-1} \cdot min^{-1}$. This large dose had a modest effect on blood pressure and heart rate, which could be explained by the elimination of stress in restrained rats, and no effect on body temperature, Pa_{O_2}, Pa_{CO_2}, or pH. A second group of rats were used to determine the effect of etomidate on the ratio of brain glucose to plasma glucose, which is necessary for calculating $rCMR_{Glc}$. In the third experiment $rCMR_{Glc}$ was measured in unstressed rats. The rats were anesthetized with an intravenous dose of 1, 2, 6, or 12 mg/kg etomidate infused at a rate of 6 $mg \cdot kg^{-1} \cdot min^{-1}$. Etomidate had a marked effect on glucose consumption in many, but not all, cerebral structures. The forebrain (telencephalon and diencephalon) was most affected (−25% to −35%) while the hindbrain was minimally affected. There was no demonstrable dose dependency; 1 mg/kg depressed $rCMR_{Glc}$ as much as 12 mg/kg. The pattern of $rCMR_{Glc}$ depression is in accord with the minimal effects observed on physiologic variables and similar to that caused by the steroid anesthetic Althesin,® although the depression seen was not as severe. The pattern of metabolic depression produced by etomidate differs markedly from that produced by barbiturates, which affect all brain regions to a similar degree. The possibility is discussed that the anesthetic effect of etomidate may be mediated by receptors. (Key words: Anesthetics, intravenous: etomidate. Brain: function; glucose metabolism. Measurement techniques: autoradiography.)

ETOMIDATE IS A short-acting, nonbarbiturate intravenous hypnotic,[1] introduced into clinical practice as an anesthetic induction agent in 1972. It has a high therapeutic index and rapid onset of action, while causing no histamine release.[2] Etomidate is less cumulative than barbiturates. In rats it is removed by hepatic metabolism and by plasma esterase, whereas in humans the esterase does not play a role in its elimination.[3] Etomidate, like barbiturates, depresses cerebral blood flow and cerebral oxygen consumption.[4] However, etomidate does not seriously interfere with cardiac function, respiration, or temperature maintenance.[5,6] The lack of adverse effects on important physiologic variables has encouraged its use as a sedative for long periods in critically ill patients. However, this practice became controversial when there were reports of increased mortality, possibly related to lower circulating cortisol levels.[7] Another feature of etomidate's action is that many patients manifest purposeless and often violent movements (sometimes seizure-like) after induction.[8,9] In order to gain insight into the site of central action of etomidate, we studied its effect on local brain energy metabolism in rats through measurement of regional cerebral glucose utilization ($rCMR_{Glc}$).

Materials and Methods

EXPERIMENTS

Three experiments were performed. In the first, the effects of a large dose (12 mg/kg) of etomidate on physiologic variables were determined in five rats. This was necessary to ensure that the anesthetic would not compromise the animal to the extent that the use of our unrestrained rat model would be impractical. A second group of rats was anesthetized with etomidate (1 to 12 mg/kg) and the ratio of brain glucose to plasma glucose was determined. This ratio is necessary for calculating $rCMR_{Glc}$. In a third experiment $rCMR_{Glc}$ was determined in ten control rats and 23 rats given doses of etomidate ranging from 1 mg/kg to 12 mg/kg.

The doses of etomidate studied ranged from 1 mg/kg to 12 mg/kg. The smallest dose was chosen because it was reported to be the minimum necessary to cause unconsciousness in rats.[1] In our experience doses greater than 12 mg/kg infused at 6 $mg \cdot kg^{-1} \cdot min^{-1}$ resulted in some deaths. Therefore the 12 mg/kg dose, which has been reported to cause unconsciousness for about 40 min in rats, was the largest dose studied. The rate of infusion has an influence on the onset and duration of unconsciousness[1]; fast rates decrease the onset time and increase the duration. For this reason we chose a relatively rapid rate of infusion to ensure rapid induction and maximal maintenance of unconsciousness. All rats were unconscious throughout the experiment.

PROCEDURE FOR EFFECTS OF ETOMIDATE ON PHYSIOLOGIC VARIABLES

Rats were anesthetized with halothane (induction: 4% halothane in air; maintenance: 1% halothane in O_2:N_2O,

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TABLE 1. Physiologic Effects of Etomidate

	Min			
	0	2	5	10
Blood pressure (mmHg)	124 ± 2	82 ± 7	93 ± 5.4	97 ± 5
Heart rate (beats/min)	431 ± 40	380 ± 31	416 ± 39	394 ± 32
Temperature (° C)	38.1 ± 0.4	37.6 ± 0.6	37.3 ± 0.6	37.4 ± 0.6
Pa_{CO_2} (mmHg)	31 ± 2	35 ± 2	34 ± 2	34 ± 3
Pa_{O_2}	78 ± 3	71 ± 2	74 ± 1	77 ± 2
*p*H	7.44 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.39 ± 0.02

Values are mean ± SEM of five rats given etomidate (12 mg/kg) at 0 min.

25:75 v/v) while catheters were placed in the femoral artery and vein. This procedure took about 15 min, after which the rats recovered in a restraining cage for 2 h. Etomidate, 12 $mg \cdot kg^{-1}$, was administered over a 2-min period. Heart rate, blood pressure, rectal temperature, arterial *p*H, Pa_{CO_2}, and Pa_{O_2} (see table 1) were monitored for 10 min.

Procedure for Brain Glucose/Plasma Glucose Determination

Rats were prepared, placed in isolation boxes and treated exactly as those for $rCMR_{Glc}$ measurements. However, after the rats were anesthetized with 1, 2, 6 or 12 mg/kg etomidate, they were removed from the isolation box and placed in a device that allows rapid sampling and fixation of brain tissue.[10] Immediately before sampling the brain, an arterial blood sample was withdrawn (1 ml) for determination of plasma glucose. At 5 min after receiving the etomidate the brain was removed and frozen to −196° C within 0.5 s. Brain glucose was measured in a perchloric acid extract of the tissue.

Procedure for $rCMR_{Glc}$

$rCMR_{Glc}$ was measured in unstressed rats prepared in a manner similar to that described elsewhere previously.[11,12] Briefly, rats were anesthetized with pentobarbital (50 mg/kg body weight) and two cannulas were placed into the jugular vein near the right atrium. After surgery each rat was housed in a box insulated against light and sound where it remained undisturbed until after the measurement of $rCMR_{Glc}$ 2 days later. About 15 min before the experiment, 200 μl of heparin (1000 U/ml) was infused into the jugular vein and 0.3 ml of blood was withdrawn for determination of plasma glucose. The experiment was begun with the administration of 1, 2, 6, or 12 $mg \cdot kg^{-1}$ of etomidate, infused at a rate of 6 $mg \cdot kg^{-1} \cdot min^{-1}$. Immediately on completion of the etomidate infusion, 35 μCi of [6-^{14}C]glucose (100 μCi/ml in 0.15 M NaCl) was injected through one of the cannulas. Blood samples (five samples of 0.05 ml) were taken for determination of glucose-specific radioactivity, and 5 min after the [6-^{14}C]glucose injection the rats were killed by a cardioplegic dose of pentobarbital. This short (3–5 s) exposure to pentobarbital does not affect the rates of metabolism measured during the preceding 5 min. Etomidate did not affect the blood glucose concentration during the experiment. Control rats were treated identically but received a saline infusion.

Autoradiography

The amount of ^{14}C that accumulated in cerebral tissue was determined by quantitative autoradiography as described elsewhere.[12] In summary, the brain was removed immediately after death and frozen in Freon-12® at −29.8° C, where it was kept until sectioning. Sections 40 μm thick were made, mounted on slides, dried, and exposed to x-ray film. The optical densities were measured in individual areas about 300 μm in diameter (to obtain the values given in table 2) or with the assistance of a computer (to obtain fig. 1). A set of precalibrated ^{14}C methylmethacrylate standards was incubated with each film, allowing the optical densities of the tissue autoradiographs to be related to ^{14}C.

Glucose Determinations

Glucose was measured spectrophotometrically with hexokinase and glucose-6-phosphate dehydrogenase.[13]

Chemicals

Etomidate, [R-(+)-ethyl-1-(α-methyl-benzyl)imidazole-5-carboxylate] 2 $mg \cdot ml^{-1}$ in 35% propylene glycol, was purchased from Abbott Laboratories, North Chicago, Illinois. Enzymes and coenzymes were from Boehringer Mannheim Corporation, New York, New York. [6-^{14}C]glucose (6.8 mCi/mmol) was from Amersham, Arlington Heights, Illinois. All other chemicals were of the best available grade.

TABLE 2. Regional Cerebral Glucose Utilization during Etomidate Anesthesia

	Control (10)	1 mg/kg (6)	2 mg/kg (6)	6 mg/kg (5)	12 mg/kg (6)
Telencephalon					
Frontal cortex	87 ± 3.7	64 ± 4.1*	59 ± 3.1*	57 ± 3.5*	64 ± 2.9*
Cingulate gyrus	98 ± 5.3	66 ± 3.9*	69 ± 6.8*	66 ± 1.9*	68 ± 2.6*
Parietal cortex	96 ± 4.2	65 ± 5.6*	62 ± 5.6*	64 ± 1.2*	67 ± 2.9*
Pyriform cortex	65 ± 4.2	37 ± 3.2*	35 ± 2.9*	40 ± 2.3*	50 ± 3.3*
Insular cortex	84 ± 4.0	59 ± 7.7*	60 ± 4.3*	56 ± 2.9*	66 ± 3.3*
Occipital cortex	94 ± 4.7	65 ± 3.7*	54 ± 2.8*	54 ± 0.7*	64 ± 2.4*
Caudate nucleus	88 ± 4.5	63 ± 3.0*	56 ± 4.2*	57 ± 2.3*	52 ± 1.5*
Globus pallidus	50 ± 3.0	35 ± 3.0*	28 ± 2.7*	35 ± 1.6*	41 ± 2.0
Amygdala	65 ± 4.0	41 ± 3.8*	39 ± 2.7*	47 ± 2.6*	48 ± 2.6
Hippocampus	64 ± 3.8	39 ± 3.9*	39 ± 2.5*	47 ± 1.8*	48 ± 3.2*
Lateral septal nucleus	57 ± 4.7	34 ± 4.0*	30 ± 1.9*	29 ± 5.4*	45 ± 2.9
Corpus callosum	52 ± 4.2	43 ± 3.4	42 ± 5.8	45 ± 1.8	58 ± 5.3
Internal capsule	49 ± 3.6	32 ± 2.2*	33 ± 4.0*	36 ± 2.3	46 ± 2.5
Diencephalon					
Habenula	98 ± 6.1	78 ± 4.2	71 ± 8.3*	74 ± 2.3*	78 ± 4.3
Hypothalamus	61 ± 4.5	44 ± 4.0*	43 ± 3.9*	47 ± 2.0	51 ± 3.6
Thalamus-anterior nucleus	99 ± 5.2	73 ± 5.9*	65 ± 6.6*	65 ± 3.2*	72 ± 5.0*
-ventral nucleus	90 ± 4.9	69 ± 7.4*	64 ± 3.2*	70 ± 4.1*	70 ± 4.7*
-medial geniculate	108 ± 7.3	75 ± 7.8*	61 ± 5.6*	70 ± 3.1*	72 ± 3.9*
-lateral geniculate	94 ± 4.5	61 ± 3.6*	59 ± 5.1*	61 ± 3.0*	68 ± 3.3*
Mesencephalon					
Substantia nigra	73 ± 4.0	50 ± 1.4*	44 ± 4.4*	52 ± 1.9*	59 ± 6.6
Red nucleus	84 ± 5.0	61 ± 1.8*	53 ± 3.1*	63 ± 3.1*	70 ± 5.7
Occulomotor complex	99 ± 6.2	83 ± 3.0	70 ± 7.0*	79 ± 3.1	89 ± 4.0
Interpenduncular nucleus	101 ± 6.1	104 ± 8.3	90 ± 4.7	91 ± 7.3	102 ± 6.1
Reticular formation	73 ± 4.1	51 ± 1.9*	49 ± 4.5*	53 ± 2.7*	65 ± 2.9
Superior colliculus	105 ± 6.1	87 ± 4.9	73 ± 3.2*	81 ± 1.6*	82 ± 3.0*
Inferior colliculus	170 ± 11.3	154 ± 1.9	125 ± 11.0*	141 ± 2.1	143 ± 8.6
Metencephalon					
Pons	78 ± 4.5	54 ± 5.6*	50 ± 3.6*	48 ± 2.6*	54 ± 2.3*
Cerebellar gray-molecular	78 ± 3.8	63 ± 4.2	59 ± 4.6*	66 ± 3.3	73 ± 5.2
-granular	88 ± 3.9	74 ± 2.4	71 ± 6.4	73 ± 5.3	81 ± 3.4
-vermis	95 ± 5.2	67 ± 3.2*	62 ± 6.5*	70 ± 2.2*	75 ± 3.7*
Dentate nucleus	102 ± 7.6	89 ± 5.7	77 ± 4.5*	81 ± 7.5	87 ± 4.6
Cerebellar white	48 ± 4.1	36 ± 2.5	39 ± 3.9	45 ± 2.3	52 ± 4.5
Myelencephalon					
Vestibular nucleus	123 ± 6.8	119 ± 4.3	102 ± 6.1*	119 ± 3.4	121 ± 5.4
Cochlear nucleus	124 ± 7.6	115 ± 3.0	111 ± 4.4	115 ± 4.0	122 ± 6.0
Superior olive	125 ± 11.9	148 ± 2.9	117 ± 7.2	141 ± 2.9	141 ± 7.7
Inferior olive	99 ± 10.7	80 ± 4.2	70 ± 5.5	79 ± 3.7	82 ± 5.8

Rates are reported as mean ± SEM ($\mu mol \cdot min^{-1} \cdot 100\ g^{-1}$) with the number of rats in parentheses. Those decreases that were significant at the 1% level compared with the control are indicated by *. There were no differences among the etomidate-treated groups except those values underlined, which are different from each other. See "Methods" for statistical methods.

RATS

Male Long-Evans rats (Charles River Laboratories, Wilmington, Massachusetts) weighing between 225 and 275 g were used. Rats had free access to food and water.

STATISTICAL ANALYSIS

Analysis of statistics was done as described in the following using SAS procedures (SAS Institute, Inc., Cary, North Carolina).

The data in Table 2 were evaluated to determine whether there were differences between the control and the drug-treated groups or among the drug-treated groups. The rates of $rCMR_{Glc}$ in the different groups were compared using a modified Bonferroni method of multiple comparisons as follows. Cerebral structures were considered to be independent families consisting of five groups (control plus four drug-treated) between which there were ten possible comparisons. The individual comparisons were made at the $P = 0.01$ level. Therefore,

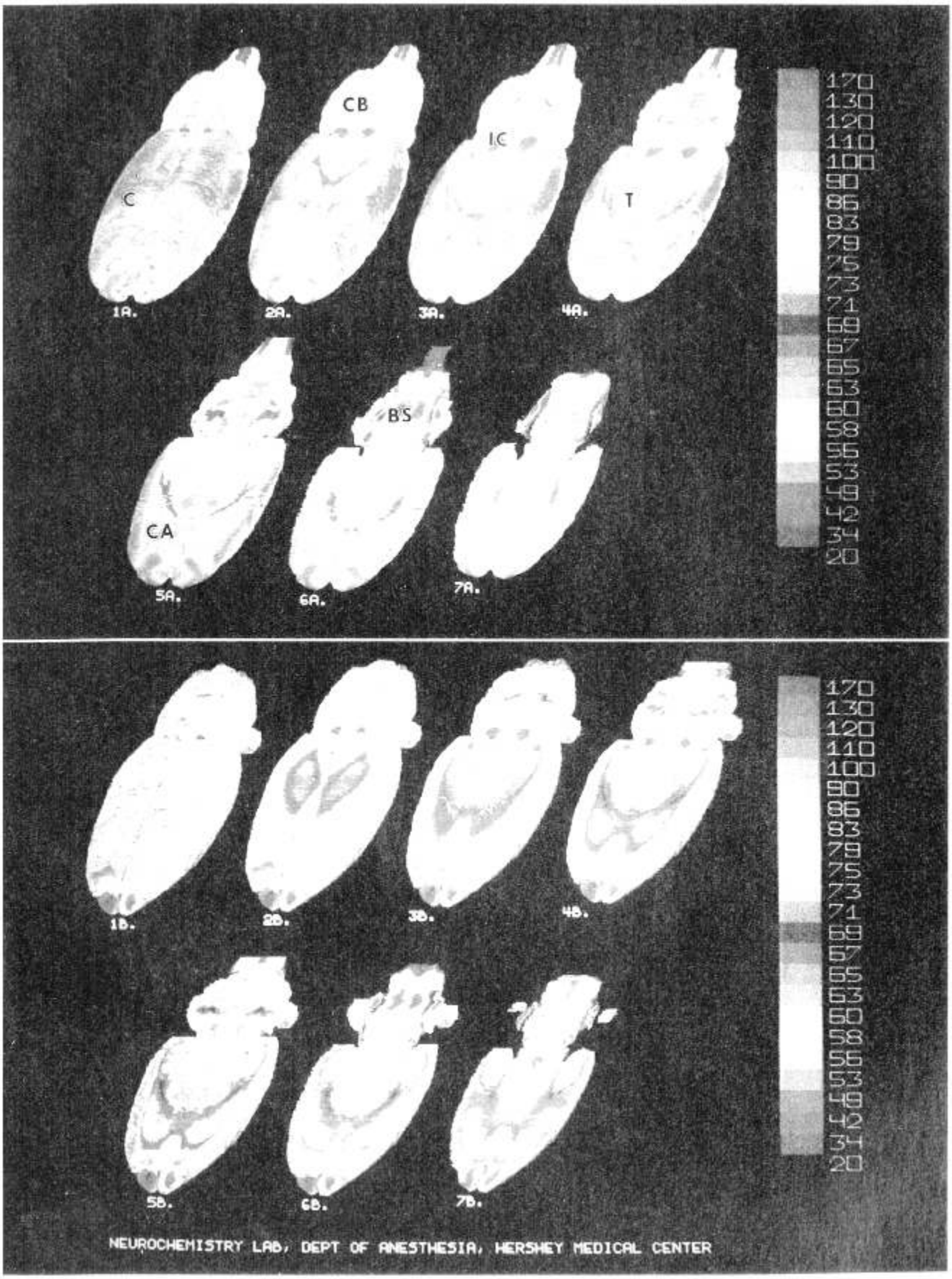

FIG. 1. Regional effects of etomidate on $rCMR_{Glc}$. The top panel (*1A–7A*) illustrates the metabolic rate of glucose utilization throughout the brain of a control rat. The whole brain (*1A*) was reconstructed from sequential coronal sections, stacked from front to back, *i.e.*, the front of the brain is at the lower end and the cerebellum and spinal cord (*blue*) at the upper. Images *2A* through *7A* show the same reconstructed brain, with successive 1-mm layers artifically removed from the top, exposing internal structures. The lower panel shows the corresponding images from a rat anesthetized with 6 $mg \cdot kg^{-1}$ etomidate. Whereas rates in the forebrain are markedly depressed, the lower areas of the brainstem are much less affected. Rates are expressed in $\mu mol \cdot min^{-1} \cdot 100\ g^{-1}$. Major structures are indicated by the following letters: C = cortex; Cb = cerebellum; Ca = caudate; IC = inferior colliculus; T = thalamic nuclei; Bs = brainstem.

the experimentwise error rate was kept to $P \leq 0.1$ for each family of comparisons.

Table 3 was analyzed to determine whether differences existed at the level of major anatomic divisions between the drug-treated groups and the control group or among the drug-treated groups. Brain areas were segregated into the major divisions (telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon; see table 2) and the averages of $rCMR_{Glc}$ in each division were determined for each rat. The means for each group were determined and the data analyzed by the Bonferroni method as described previously except that divisions were considered as families.

Finally, data were evaluated to determine whether a particular dose of etomidate had the same effect on each brain division. Brain areas were segregated into major divisions as described previously and the ratios were calculated (for each rat) for all ten possible combinations and converted to logarithms (*e.g.*, ln [telencephalon/diencephalon], ln [telencephalon/mesencephalon], *etc.*). The means of the ratios were compared to the corresponding mean of ratios in each drug-treated group by the Bonferroni method as described earlier.

Results

Etomidate at the largest dose used (12 mg/kg) had an effect on blood pressure that could be explained by the elimination of stress in restrained rats.[11] There was no demonstrable effect on body temperature, blood gases, and *p*H (table 1).

Calculation of $rCMR_{Glc}$ using [^{14}C]glucose requires knowledge of the brain-to-plasma glucose concentration ratio. This ratio was determined in four rats at each dose. There were no differences between the groups given different doses when examined by analysis of variance; therefore, the drug-treated groups were combined. The average brain-to-plasma ratio for etomidate-anesthetized rats (0.32 ± 0.07 SD; n = 16) was significantly higher than in the controls (0.22 ± 0.03 SD; n = 5).

Etomidate caused a marked depression, which seemed to be independent of the dose, in the rate of glucose utilization in many individual cerebral structures (table 2). The overall pattern suggested that there was less effect of etomidate on lower brain structures (metencephalon and myelencephalon). The trends can be seen more clearly when the data are grouped into major anatomic divisions (table 3). Here also it is evident that there is no demonstrable dose dependency. Statistical analysis of the grouped results suggests the following order of etomidate action: telencephalon = diencephalon > mesencephalon = metencephalon > myelencephalon.

Discussion

Etomidate causes unconsciousness without seriously compromising respiratory or cardiovascular function. This suggests that selected brain regions may be affected while those involved with maintenance of vital physiologic function are spared. We examined the effect of etomidate directly by measurement of $rCMR_{Glc}$. The major findings were that there was no demonstrable dose dependency and that etomidate had a pronounced effect on glucose consumption in many, but not all, cerebral structures.

The results in table 1 confirmed other reports that etomidate has little effect on common physiologic variables.[6,14] The changes in heart rate and blood pressure were similar to those reported by Bryan *et al.*, who compared stressed and unstressed rats.[11] The negligible effect on physiologic variables enabled the measurement of $rCMR_{Glc}$ in the unstressed rat model because artificial ventilation and temperature control were not necessary. This was an advantage because $rCMR_{Glc}$ is abnormally high in brains of stressed rats.[11]

It may be calculated from the results of others[3] that etomidate metabolism in rats occurs at approximately 0.2

TABLE 3. Glucose Utilization in Major Brain Divisions

	Control Rates	% Change Caused by Etomidate			
		1 mg/kg	2 mg/kg	6 mg/kg	12 mg/kg
Telencephalon	73 ± 3.4	−31*	−35*	−33*	−25*
Diencephalon	85 ± 4.9	−27*	−35*	−29*	−23*
Mesencephalon	100 ± 5.6	−16	−29*	−20*	−14
Metencephalon	82 ± 4.4	−22*	−28*	−22*	−15
Myelencephalon	97 ± 5.3	+2	−13	1	+6

Individual areas of each rat were segregated into major brain divisions as indicated in table 2, and the average rate was calculated. Control rates are reported as mean ± SEM ($\mu mol \cdot min^{-1} \cdot 100\ g^{-1}$). The symbol * indicates statistical significance compared with the control. There were no differences among the etomidate-treated groups.

$mg \cdot kg^{-1} \cdot min^{-1}$. On this basis it would be expected that rats given only 1 mg/kg would have been near wakening at the end of the 5-min interval necessary for measurement of $rCMR_{Glc}$, whereas at the larger doses they would remain unconscious for much longer periods of time. It could be argued that only at the largest doses would a near steady-state condition be maintained over the 5-min experimental period. But it is evident that this is irrelevant; all doses caused the same pattern and degree of metabolic suppression, implying that a steady-state situation did occur in brain. These results suggest that the mechanism through which etomidate causes anesthesia is saturated at doses close to the minimum anesthetic dose; the dose is important primarily in determining how long the effect will last.

The question whether etomidate had a significantly greater effect on certain brain divisions within each dose group was subjected to statistical analysis (see "Materials and Methods"). It was found that, at every dose, etomidate had a greater effect on the forebrain than the hindbrain.

The regional effect of etomidate can be appreciated in more detail from figure 1, which shows the reconstructed metabolic pattern in a normal rat brain compared with one anesthetized with 6 mg/kg etomidate. To produce this figure, autoradiographs of coronal sections were scanned by a computer-driven microdensitometer, converted to rates, reassembled as previously described,[15] and artificially sectioned at various levels in the axial (horizontal) direction. The reconstructed brains show that etomidate decreased $rCMR_{Glc}$ in most regions of the rat brain, although the effect on forebrain structures was greater. This pattern of depression, in which the brainstem and cerebellar nuclei are not affected, is similar to the pattern observed with another anesthetic, Althesin®.[16] Althesin® likewise had little effect on cardiorespiratory function or temperature maintenance.

The most frequent adverse effect of etomidate is muscular twitching, which occurs in as many as 80% of unpremedicated patients. These episodes have been referred to as "epileptic-like,"[17] and recently, epileptogenic recordings were observed in two patients.[18] In our study only one rat responded to the anesthetic (6 mg/kg) with myoclonic movements throughout the 5-min experiment. Electroencephalographic recordings were not obtained to confirm seizure activity. The $rCMR_{Glc}$ values in this rat were higher than in any other rat that received 6 mg/kg etomidate, but not higher than control rats. Thus if seizure activity was present, it was not severe. This animal was not included in calculating mean rates.

The specific regional variation in the effect of etomidate suggests that the mechanism of action may be complex, perhaps involving a receptor-ligand interaction. Recently, it was shown that etomidate enhances the binding of γ-aminobutyric acid (GABA) and diazepam at the benzodiazepine-GABA receptor-ionophore complex, and that the enhancement was not uniform; binding was increased by about 60% in the cortex while it increased only about 20% in the cerebellum.[19] Ashton *et al.*[20] showed that the stimulation of diazepam binding by etomidate was stereospecific; only the isomer with anesthetic properties increased diazepam binding. Furthermore, the effect was more pronounced in the forebrain than in the cerebellum, which was almost unaffected. Our findings show a pattern of metabolic depression that is similar to the pattern of enhanced receptor binding.

Some evidence for the existence of steroid receptors that bind naturally occurring steroids in the brain has been demonstrated,[21] and it has been suggested that Althesin®, a steroid anesthetic, may specifically bind to these sites.[16] Etomidate could similarly decrease $rCMR_{Glc}$ through selective enhancement of GABA binding to the GABA receptor complex, preferentially altering sites in the cortex, while allowing brainstem and cerebellar nuclei to remain unaffected.

The modest effect of etomidate on brainstem CMR_{Glc} is consonant with the observation that vital physiologic functions are not impaired. This feature, which is also found with Althesin®,[16] may be advantageous, especially in the management of critically ill or head-injury patients when it is desirable to decrease cerebral metabolism and intracranial pressure without interfering with vital functions. Barbiturates, by contrast, attain the same desirable results at the expense of marked interference with cardiovascular stability. A second useful feature of etomidate is its rapid reversibility. These qualities must be continuously reevaluated as further understanding of the basis of reported side effects of etomidate develops.

The possibility that etomidate acts through a receptor mechanism that is not homogeneously distributed requires further study. Knowledge of the distribution and properties of such a system would be an important consideration in the design of more specific agents.

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References

1. Janssen PAJ, Neimegeers CJE, Schellekens KHL, Lenaerts FM: Etomidate, R-(+)-ethyl-1-(α-methyl-benzyl)imidazole-5-carboxylate (R 16659) a potent, short-acting and relatively atoxic intravenous hypnotic agent in rats. Arzneimittelforsch 8:1234–1243, 1971
2. Doenicke A, Lorenz W, Beigl R, Bezecny H, Uhlig G, Kalmar L, Praetorius B, Mann G: Histamine release after intravenous application of short-acting hypnotics. Br J Anaesth 45:1097–1104, 1973
3. Van Hamme MJ, Ghoneim MM, Ambre JJ: Pharmacokinetics of

etomidate, a new intravenous anesthetic. ANESTHESIOLOGY 49:274–277, 1978
4. Renou AM, Vernhiet J, Macrez P, Constant P, Billerey J, Khadaroo MY, Caille JM: Cerebral blood flow and metabolism during etomidate anaesthesia in man. Br J Anaesth 50:1047–1051, 1978
5. Giese JL, Stanley TH: Etomidate: A new intravenous induction agent. Pharmacotherapy 3:251–258, 1983
6. Morgan M, Lumley J, Whitwam JG: Etomidate, a new water-soluble non-barbiturate intravenous induction agent. Lancet i:955–956, 1975
7. Longnecker DE: Stress free: To be or not to be? ANESTHESIOLOGY 61:643–644, 1984
8. Zacharias M, Clark RSJ, Dundee JW, Johnston SB: Evaluation of three preparations of etomidate. Br J Anaesth 50:925–929, 1978
9. Ghoneim MM, Yamada T: Etomidate: A clinical and electroencephalographic comparison with thiopental. Anesth Analg 56: 479–485, 1977
10. Veech RL, Harris RL, Veloso D, Veech EH: Freeze-blowing: A new technique for the study of brain *in vivo*. J Neurochem 20: 183–188, 1973
11. Bryan RM, Hawkins RA, Mans AM, Davis DW, Page RB: Cerebral glucose utilization in awake unstressed rats. Am J Physiol 244: C270–C275, 1983
12. Hawkins RA, Mans AM, Davis DW, Viña JR, Hibbard LS: Cerebral glucose use measured with [^{14}C]glucose labeled in the 1, 2 or 6 position. Am J Physiol 248:C170–C176, 1985
13. Bergmeyer HE: Methods in Enzymatic Analysis. New York, Academic Press, 1974
14. Newby DM, Edbrooke DL, Mather SJ, Bird TM, Hebron BS: Etomidate as a sedative agent in intensive care: Observations on its cardiovascular effects. Acta Anaesthesiol Scand 27:218–221, 1983
15. Hibbard LS, Hawkins RA: Three-dimensional reconstruction of autoradiographic data. J Cereb Blood Flow Metab 3(Suppl 1): S91–S92, 1983
16. Davis DW, Hawkins RA, Mans AM, Hibbard LS, Biebuyck JF: Regional cerebral glucose utilization during Althesin anesthesia. ANESTHESIOLOGY 61:362–368, 1984
17. Grant IS, Hutchison G: Epileptiform seizures during prolonged etomidate sedation. Lancet ii:511–512, 1983
18. Gancher S, Laxer KD, Krieger W: Activation of epileptogenic activity by etomidate. ANESTHESIOLOGY 61:616–618, 1984
19. Thyagarajan R, Ramanjaneyulu R, Ticku MK: Enhancement of diazepam and γ-aminobutyric acid binding by (+) etomidate and pentobarbital. J Neurochem 41:578–585, 1983
20. Ashton D, Geerts R, Waterkeyn C, Leysen JE: Etomidate stereospecifically stimulates forebrain, but not cerebellar, ^{3}H-diazepam binding. Life Sci 29:2631–2636, 1981
21. Holzbauer M: Physiological aspects of steroids with anesthetic properties. Med Biol 54:227–242, 1976