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Regional Cerebral Glucose Utilization during Althesin® Anesthesia

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The effect of Althesin®, an anesthetic comprising two steroids, on regional cerebral function was determined by measurement of regional cerebral glucose utilization. Rats were anesthetized with an intravenous dose of 4, 8, or 20 mg total steroid/kg. These doses produced anesthesia for 12, 18, and 37 min, respectively. There were no physiologically significant effects of Althesin® (20 mg/kg) on body temperature, blood pH, or blood gases. Blood pressure and heart rate decreased slightly after administration of Althesin®. Althesin® had a profound effect on glucose consumption in many, but not all, cerebral structures. The forebrain (especially cerebral cortex) was affected most, while the hindbrain was much less so or not at all. This pattern of functional depression is in accord with the minimal effects observed on physiologic variables. The effects of Althesin® differ from those of other known anesthetics and suggest a unique mechanism. The possibility of action through naturally occurring steroid receptors is considered. (Key words: Anesthetics, intravenous: althesin. Brain: metabolism, glucose.)

ALTHESIN®, a steroid anesthetic comprising alphaxalone and alphadolone acetate, is used for the induction and maintenance of anesthesia in several countries. Its favorable qualities include the following: rapid induction, short duration of action, minimal accumulation in body tissues, and a wide margin of safety.[1,2] Because the constituent steroids of Althesin® are not soluble in water they are dissolved in an aqueous medium containing polyoxyethylated castor oil. Allergic reactions (*e.g.*, flush or rash, marked hypotension, bronchospasm, facial edema) have been observed in 0.05–0.3% of patients; whether these effects are due to the steroid or the vehicle is not yet clear.[1–3] Nevertheless, the appreciable incidence of allergic reactions has limited the popularity of Althesin®.

Althesin® can cause a marked decrease in cerebral blood flow (CBF), cerebral O_2 consumption ($CMRO_2$), and intracranial pressure,[4–11] similar to the changes caused by high doses of barbiturates.[12–17] Even at large doses, however, Althesin® has only a moderate effect on blood pressure, respiration and the maintenance of body temperature.[2,7,8,10,18–20] These observations raise the question whether Althesin® has a different effect upon the function of the various cerebral structures. Measurements of CBF in humans showed that Althesin® reduces flow almost homogeneously in all cortical zones.[21,22] The techniques used were, however, not satisfactory for analysis of subcortical or lower brain structures.[23,24] In order to better define the site of action, we studied the effect of Althesin® on regional cerebral metabolism as indicated by measurements of cerebral glucose utilization (CMRglc) in many individual brain structures using a quantitative autoradiographic technique.[17,25] The results show that Althesin® is unique among anesthetics studied to date; it decreases the metabolism of forebrain to a much greater extent than hindbrain.

Methods

Rats

Male Long-Evans rats (Charles River Breeding Laboratories, Wilmington, Massachusetts) weighing 250–350 g were used. Food, but not water, was withheld the night before the experiment.

Chemicals

Enzymes and coenzymes were from Boehringer Mannheim Corporation, New York, NY. [2-^{14}C]Glucose (6.7 mCi/mmol) was from New England Nuclear, Boston, Massachusetts. Althesin® (Alfathesin) was from Glaxo-Allenburys, Wadeville, Transvaal, South Africa. This anesthetic is a solution of two steroids, alphaxalone (3α-hydroxy-5α-pregnane-11,20-dione), 9 mg/ml, and alphadolone acetate (21-acetoxy-3α-hydroxy-5α-pregnane-11,20-dione) 3 mg/ml in polyoxyethylated castor oil and water (1:4). All other chemicals were of the best available grade.

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Enzymatic Determinations

Glucose was measured with hexokinase and glucose-6-phosphate dehydrogenase.[26] β-Hydroxybutyrate and acetoacetate were measured with β-hydroxybutyrate dehydrogenase.[26]

Experimental Procedures

Before measuring regional CMRglc, experiments were conducted to determine the relationship between dose of Althesin® and unconsciousness; the effect of Althesin® on blood pressure, heart rate, and temperature; and the effect of Althesin® on the brain-to-plasma ratio of glucose.

To determine sleeping time as a function of dose, Althesin® was given through the tail vein (4, 8, or 20 mg total combined steroid/kg, four rats with each dose) and the time required to regain a righting reflex recorded. In order to allow similar volumes to be injected in all rats, Althesin® was diluted in 0.154 M NaCl for the 4- and 8-mg groups. The 20 mg/kg group received undiluted Althesin.® Control rats received an equal volume of 0.154 M NaCl.

For all the other experiments, catheters were placed in a femoral artery and vein during halothane anesthesia (induction 4% in O_2, maintenance 2.5% in O_2). The period of anesthesia was 20–35 min. The rats then were placed in restraining cages and allowed to recover for 2 h. Heparin (200 units) was given through the femoral vein cathether 15 min before the end of the recovery period.

Physiological measurements were made on eight rats given the largest dose of Althesin® (20 mg steroid/kg) through the femoral vein catheter. Blood pressure and heart rate were recorded continuously through the femoral artery catheter. Immediately after loss of consciousness, a rectal probe was inserted to monitor body temperature.

Knowledge of the brain-to-plasma glucose ratio is necessary for the measurement of regional CMRglc. Measurement of brain glucose on the same rats used for regional CMRglc is not possible, since the brain must be removed carefully for autoradiography, introducing a period of time during which glucose is converted to lactate. Therefore, the brain-to-plasma glucose ratio was determined in a separate group using four rats at each dose. Althesin® was injected, and 12 min later the rats were killed by focused microwave irradiation in order to prevent post mortem metabolism of glucose.[27]

Regional CMRglc was determined with [2-^{14}C]glucose as previously described.[25] First, 0.5 ml of blood was drawn for the determination of plasma glucose and ketone body concentrations. Two minutes before injection of [2-^{14}C]glucose, Althesin® was administered. [2-^{14}C]Glucose (35 μCi) was injected into the femoral vein, and arterial blood samples (0.05 ml) were taken at frequent intervals thereafter. At 7.5 min, 0.2 ml was taken for determination of blood gases. The rats were killed humanely at 10 minutes by a means of a cardioplegic dose of pentobarbital (150 mg in 1.0 ml of 0.154 M NaCl). This stopped the heart in about 3 s, thereby preventing further delivery of [2-^{14}C]glucose to the brain. (Any decrease in CMRglc that pentobarbital may have caused could be ignored since pentobarbital was active for only about 3 s of a 10-min experiment.) The brain was removed rapidly, frozen in Freon-12 at −29.8°C, and sectioned at −20°C with a precision microtome. The radioactivity in each brain region was determined using quantitative autoradiography. Analysis of the autoradiographs was done manually[25] or with the assistance of a computer.[28] Regional CMRglc was calculated from the amount of label accumulated in each brain region and the plasma specific activity measured over the 10-min period.[25]

As stated above, rats were starved the night before experimentation. This was done to deplete liver glycogen, lower blood glucose, and decrease the variation in blood glucose that may occur in normally fed rats. The mean blood glucose of all rats used for regional CMRglc experiments (N = 19) was 4.48 ± 0.56 μmol/ml (SD). The plasma concentrations of the ketone bodies acetoacetate and β-hydroxybutyrate were 1.50 ± 0.28 and 0.78 ± 0.06 μmol/ml (SD), respectively. Ketone bodies can supplement glucose as a fuel of brain energy metabolism. At the extant concentrations, their contribution to the total cerebral energy requirement is modest, about 5–10% in conscious rats and 10–20% in deeply anesthetized rats.[29] Thus, glucose was the primary fuel of cerebral oxidative metabolism in the rats used.

Statistics

The physiologic data (table 1) were analyzed by analysis of variance, followed by paired *t* tests between the 0 and 1 min values and analysis of trend.[30] All other data (tables 2 and 3) were analyzed using the Least Significant Difference Test, which consists of two steps.[31] First, the probability of type I errors was reduced by performing an analysis of variance. The null hypothesis was accepted for all members of those sets in which F was nonsignificant at the 5% level. Second, the sets of data in which F was significant were examined by making all possible comparisons, using the modified *t* test with the critical limit set at $P < 0.05$.

Results

The minimum anesthetic dose of Althesin® has been reported to be 2 mg/kg in mice.[32] Reversal of anesthesia occurs as the steroids are metabolized by the liver,[32,33]

TABLE 1. Physiologic Effects of Althesin®

	Minutes				
	0	1	3	5	10
Blood pressure (mmHg)	119 ± 6	84 ± 11	96 ± 9	97 ± 9	100 ± 10
Heart rate (beats/min)	466 ± 47	396 ± 40	386 ± 39	382 ± 40	388 ± 35
Temperature (°C)	37.8 ± 0.5	37.6 ± 0.6	37.5 ± 0.7	37.4 ± 0.8	37.1 ± 0.8

Values are mean ± SD of eight rats given an intravenous dose of 20 mg/kg. Two-way analysis of variance showed a significant difference over time for all three variables. Upon further analysis, in the case of blood pressure and heart rate, the 1-min value was significantly different from the 0-min group (paired *t* test). There was no significant trend over time between 1 and 10 min, as indicated by trend analysis, for blood pressure and heart rate. Temperature was not significantly changed at 1 min, but there was a significant trend over time between 0 and 10 min. The temperature values could be fitted to a straight line with the formula $y = 0.075 \times \text{min} + 37.7$. In all tests, a level of $P < 0.05$ was taken to indicate statistical significance.

and the half-life in circulation of rats is about 7 min. In agreement, we observed that anesthesia was induced seconds after injection of Althesin® and the anesthetic time was proportional to the dose, 12 ± 3 (SD), 18 ± 2.7 and 37 ± 3.2 min in rats given 4, 8, or 20 mg/kg, respectively. Awakening was often abrupt, whereupon the rats took an immediate interest in their surroundings (*e.g.*, grooming, exploring, sniffing, eating, *etc.*).

Althesin® (20 mg/kg) produced a slight decrease in body temperature (table 1), lowering temperature at a rate of 0.075°C/min for the 10 min. Heart rate and blood pressure decreased somewhat during the first minute, but there was no significant trend thereafter (table 1). Additional data, collected on rats in which regional CMRglc was being measured, showed that Althesin® had no effect on *p*H or Pa_{O_2}, regardless of the dose, and only a small effect on Pa_{CO_2}. Immobilization of rats causes some stress,[34] including increased plasma glucose and catecholamines, as well as tachycardia and hyperventilation. The decreases in heart rate and blood pressure observed may reflect in part the alleviation of stress. The brain-to-plasma glucose ratio (needed for calculation of regional CMRglc) was determined on four rats at each dose (0, 4, 8, 20 mg steroid/kg) and found to be 0.22 ± 0.06, 0.27 ± 0.05, 0.32 ± 0.05 and 0.39 ± 0.02 (mean ± SD), respectively.

TABLE 2. Arterial Blood Gases and *p*H

	*p*H	Pa_{O_2} mmHg	Pa_{CO_2} mmHg
0 mg/kg (5)	7.47 ± 0.01	88 ± 2	35.6 ± 1.1
4 mg/kg (4)	7.44 ± 0.02	87 ± 3	39.0 ± 0.4
8 mg/kg (3)	7.43 ± 0.02	86 ± 4	42.8 ± 2.1*
20 mg/kg (4)	7.45 ± 0.01	86 ± 3	40.8 ± 1.2*

Values are given as means ± SEM with the number of rats in parentheses. Blood was drawn 9.5 min after the injection of Althesin®. These rats were also used for measurement of regional CMRglc (Table 3). The number of observations differ from those of table 3 because, due to experimental difficulties, measurements were not made on one rat in each of the drug-treated groups.

* Statistically significant values ($P < 0.05$) compared with 0 mg/kg dose. See "Methods" for statistical methods.

Regional CMRglc was measured over a 10-min period that began 2-min after the injection of Althesin®. During this period, the circulating concentrations of anesthetic steroids were changing and the low-dose group was close to awakening when the experiments were terminated. Nevertheless, it must be emphasized that all the rats studied were unconscious throughout the entire period that regional CMRglc was measured. Therefore, the results represent the anesthetized state and not induction or recovery.

A depression of regional CMRglc was observed in many cerebral structures (Table 3). Interestingly, the forebrain seemed to be most affected. The reduction of regional CMRglc in the 20 mg/kg group ranged from 48% to 60% in the telencephalon, whereas many hindbrain structures were not affected significantly. There appeared to be a rostral-to-caudal gradient of metabolic depression, which can be seen most clearly by inspecting computer-compiled images of coronal brain sections taken from different areas of the brain (figs. 1 and 2). For this analysis, CMRglc was color coded and displayed as previously described.[28] A comparison was made between the mean CMRglc images obtained from four control rats and analogous images from five rats in the 20 mg/kg group. The left panel of figure 2 shows the regional CMRglc in the control rats. It should be noted that the sections shown are not selected representatives; they are composite images using the data from four individual control rats, assembled with computer assistance. (The fifth control rat was not included because the autoradiographs were not entirely satisfactory.) The right panel is a point-by-point analysis of the percentage decrease in the mean metabolic rate obtained in the group given the maximal dose of Althesin® (20 mg/kg). The images show a trend in metabolic depression from front to back; regional CMRglc appeared to be decreased the most in the frontal pole, less in the central brain structures, and the least effect was seen in the hindbrain and cerebellum.

Dose dependency, as indicated by differences between the 4 and 20 mg/kg groups, could be detected only in

TABLE 3. Regional Cerebral Glucose Utilization during Althesin® Anesthesia

	Control (5)	4 mg/kg (5)	Significant Decrease Compared with Control	8 mg/kg (4)	Significant Decrease Compared with Control	20 mg/kg (5)	Significant Decrease Compared with Control
Telencephalon							
Frontal cortex	73 ± 4.7	46 ± 3.6	37	41 ± 4.9	44	36 ± 2.8	51
Cingulate gyrus	79 ± 6.6	48 ± 3.9	39	42 ± 2.5	47	38 ± 1.9	52
Parietal cortex	73 ± 4.8	52 ± 4.1	29	44 ± 4.0	40	37 ± 1.8	49
Pyriform cortex	52 ± 3.9	31 ± 2.3	40	28 ± 2.0	46	21 ± 2.9	60
Insular cortex	62 ± 2.5	39 ± 3.0	37	34 ± 4.1	45	27 ± 2.8	56
Occipital cortex	75 ± 4.1	46 ± 3.5	39	36 ± 1.5	52	35 ± 2.8	53
Caudate nucleus	55 ± 3.8	37 ± 3.0	33	32 ± 3.1	42	27 ± 2.2	51
Globus pallidus	38 ± 2.3	24 ± 3.2	37	21 ± 1.7	45	19 ± 1.2	50
Amygdala	56 ± 4.3	37 ± 3.2	34	32 ± 2.8	43	28 ± 3.0	50
Hippocampus	46 ± 3.1	34 ± 4.0	26	30 ± 1.4	35	24 ± 2.5	48
Lateral septal nucleus	43 ± 3.0	26 ± 2.8	40	24 ± 2.0	44	20 ± 2.0	53
Corpus callosum	42 ± 4.7	30 ± 3.7	29	27 ± 1.4	36	21 ± 1.7	50
Diencephalon							
Habenula	75 ± 8.5	55 ± 5.1	27	54 ± 6.2	28	50 ± 3.1	33
Hypothalamus	54 ± 3.2	39 ± 3.8	28	35 ± 3.0	35	29 ± 2.8	46
Thalamus–anterior nucleus	83 ± 7.6	54 ± 4.0	35	49 ± 3.5	41	42 ± 2.7	49
Ventral nucleus	63 ± 5.0	39 ± 3.5	38	32 ± 2.9	49	30 ± 1.2	52
Medial geniculate	82 ± 8.4	51 ± 3.5	38	48 ± 4.3	41	47 ± 3.4	43
Lateral geniculate	72 ± 6.7	45 ± 2.9	38	41 ± 3.5	43	43 ± 2.4	40
Internal capsule	35 ± 3.8	30 ± 2.9		23 ± 0.6	34	24 ± 2.7	31
Mesencephalon							
Substantia nigra	49 ± 3.6	35 ± 2.4	29	32 ± 2.4	35	32 ± 1.9	35
Red nucleus	62 ± 5.6	44 ± 3.2	29	41 ± 2.3	34	40 ± 1.7	35
Occulomotor complex	76 ± 9.1	52 ± 4.3	32	56 ± 4.4	26	54 ± 4.1	29
Interpeduncular nucleus	89 ± 10.0	60 ± 3.5	33	59 ± 6.8	34	56 ± 3.8	37
Reticular formation	51 ± 3.8	33 ± 2.1	35	31 ± 2.8	34	29 ± 2.7	43
Superior colliculus	75 ± 5.7	53 ± 4.4	29	56 ± 6.8		56 ± 2.8	
Inferior colliculus	110 ± 17.3	73 ± 7.6		77 ± 4.8		92 ± 5.7	
Metencephalon							
Pons	67 ± 6.6	43 ± 3.4	36	39 ± 4.4	42	36 ± 2.0	46
Cerebellar gray—Molecular	50 ± 4.3	35 ± 2.1	30	34 ± 4.0	32	34 ± 1.6	32
—Granular	80 ± 10.0	53 ± 5.6		55 ± 6.5		60 ± 4.2	
—Vermis	70 ± 11.7	54 ± 6.8		50 ± 2.7		53 ± 7.3	
Dentate nucleus	66 ± 6.9	51 ± 3.9		45 ± 2.0		51 ± 4.8	
Cerebellar white	21 ± 2.8	24 ± 3.4		18 ± 1.3		20 ± 2.1	
Myelencephalon							
Vestibular nucleus	95 ± 13.7	68 ± 7.4		79 ± 6.1		81 ± 6.2	
Cochlear nucleus	90 ± 14.2	61 ± 3.9		68 ± 5.8		68 ± 6.2	
Superior olive	82 ± 6.3	64 ± 5.1		69 ± 7.4		80 ± 2.6	
Inferior olive	81 ± 7.7	57 ± 4.9	30	53 ± 1.5	35	63 ± 6.6	22

Rates are reported as mean ± SEM ($\mu mol \cdot min^{-1} \cdot 100\ g^{-1}$) with the number of rats in parentheses. Only those decreases that were significant at the 5% level are shown. Significant differences ($P < 0.05$) in the 8 and 20 mg/kg groups compared with the 4 mg/kg group are indicated by underlining. No other significant differences were found. See "Methods" for statistical methods.

the forebrain (cortex, hippocampus, and caudate). In these structures, depression of CMRglc at 20 mg/kg was significantly greater than at 4 mg/kg. No such trend was seen in other anatomic areas.

Discussion

In most circumstances, glucose is the prime fuel of brain energy metabolism, and there is a close correlation between glucose metabolism, blood flow, and function.[35] Knowledge of regional CMRglc is, therefore, a useful index of cerebral energy metabolism and a reflection of functional activity in brain. Many anesthetics, but not all, depress $CMRO_2$, CMRglc, CBF, and cerebral electrical activity, from which it may be concluded that a commensurate decrease in the activity of nerve cell populations has occurred. Barbiturates, in large doses, cause a 50–60% decrease in $CMRO_2$, CMRglc, and CBF,[12–16] in almost all brain structures.[17] Althesin® likewise can cause a very substantial decrease in these variables, but its main effect is on the forebrain; the hindbrain is affected much less or not at all. This finding affords an explanation for the observation that Althesin® does not seriously alter respiration, temperature, and blood pressure in rats.[1] Barbiturates, on the other hand, which affect the entire CNS, depress respiration, cause temperature to fall, and lower blood pressure. The selective effect of Althesin® on the various

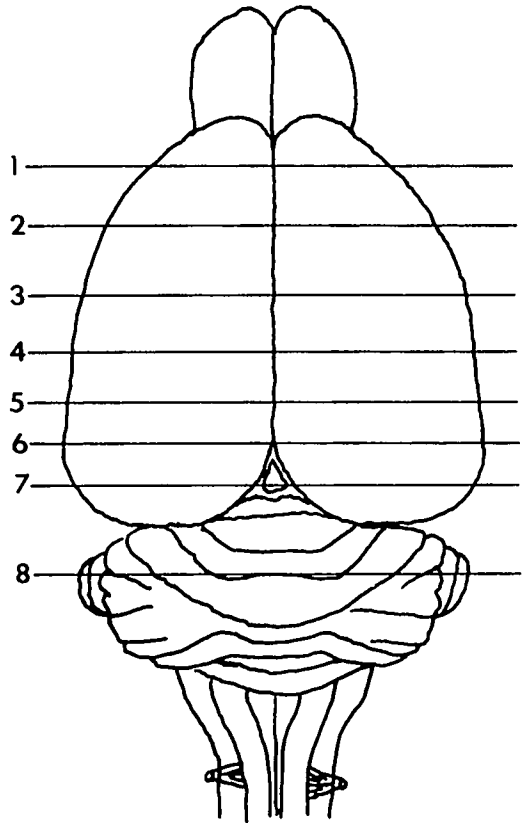

FIG. 1. Dorsal view of rat brain. The horizontal numbered lines show the positions of the coronal sections displayed in figure 2.

structures of the central nervous system is curious and raises the question of its mechanism of action.

Early ideas about anesthetic mechanisms were based on the postulate that anesthetics were inert lipid-soluble substances whose actions were nonspecific,[36] but as more information became available discrepancies arose that were not explained easily by a common mechanism.[37-39]

Complex effects on cerebral function and metabolism were found; some anesthetics depress cerebral energy metabolism considerably,[12-17] others have little or no effect on cerebral energy metabolism,[40,41] whereas some anesthetics may increase cerebral energy requirements.[42] Although most anesthetics are lipid soluble, not all lipid-soluble molecules cause anesthesia, and subtle differences in the molecular structure, which have little or no effect on the physical properties, can significantly influence anesthetic potency.[43] Barbiturate enantiomers, for instance, can have different biologic effects, emphasizing the importance of steric factors.[44] Thus, hydrophobic properties alone, although important, cannot account completely for the actions of anesthetics *in vivo*, and the existence of multiple sites of anesthetic action in the central nervous system has been proposed.[37,38]

The effects of Althesin® on CMRglc are unique and in accord with a complex mechanism of action. It has been suggested that Althesin® reacts with naturally occurring biologic receptors.[45,46] Richards and Hesketh[46] compared alphaxalone (the most active ingredient of Althesin®) and a closely related steroid, Δ16-alphaxalone, which has no anesthetic activity. (Δ16-Alphaxalone differs from alphaxalone only by a double bond in the D-ring of the steroid nucleus.) Δ16-Alphaxalone could block the activity of alphaxalone. This observation is not predicted by theories based on lipid solubility and raises the possibility of action on a naturally occurring biologic receptor. In support of this concept, Fink *et al.*[47] found that four times as much Althesin® was needed to anesthetize male rats as female rats. Castrated rats treated with estradiol required a significantly reduced dose of Althesin® compared with untreated control rats. Some steroids with anesthetic action have been isolated from pregnant women indicating that molecules similar to Althesin® occur naturally.[45] Taken together, these isolated observations are compatible with the hypothesis that steroid receptors exist in the brain, which may interact with Althesin® to cause anesthesia. If such receptors exist, it is interesting to wonder whether they have a greater density in the forebrain, thereby causing a greater depression of nerve cell activity.

There has been for some years a strong interest in protecting the brain of head-injured patients from further damage by inducing barbiturate coma. The desirable quality of barbiturates in this regard is their ability to markedly depress nerve function and hence CMRglc, $CMRO_2$, CBF and intracranial pressure. Because of the diffuse action of barbiturates on the central nervous system other consequences include depressed respiration, decreased body temperature, and lowered blood pressure. These effects make it difficult to manage patients in barbiturate coma. In addition, the reversal of barbiturate anesthesia is difficult because large quantities of barbiturates are absorbed by adipose tissue. After 2 days of constant administration by venous infusion, it takes 3–4 days to awaken patients.[8] Althesin® has many qualities that make it attractive as a potential agent for treating patients with head injuries. It caused a profound decrease in CMRglc, $CMRO_2$, CBF, and intracranial pressure. It can be administered for long periods of time, and its effects rapidly are reversed after discontinuing administration.[2] If the effects of Althesin® occur primarily in the forebrain of humans, as it does in rats, most of the cerebral mass will be affected. On the other hand, by sparing the brain stem, temperature regulation, blood pressure, and respiration are not affected seriously. Some studies of Althesin® suggest that caution is advisable. In addition to the well-known allergic responses, there are indications that damaged portions of the brain

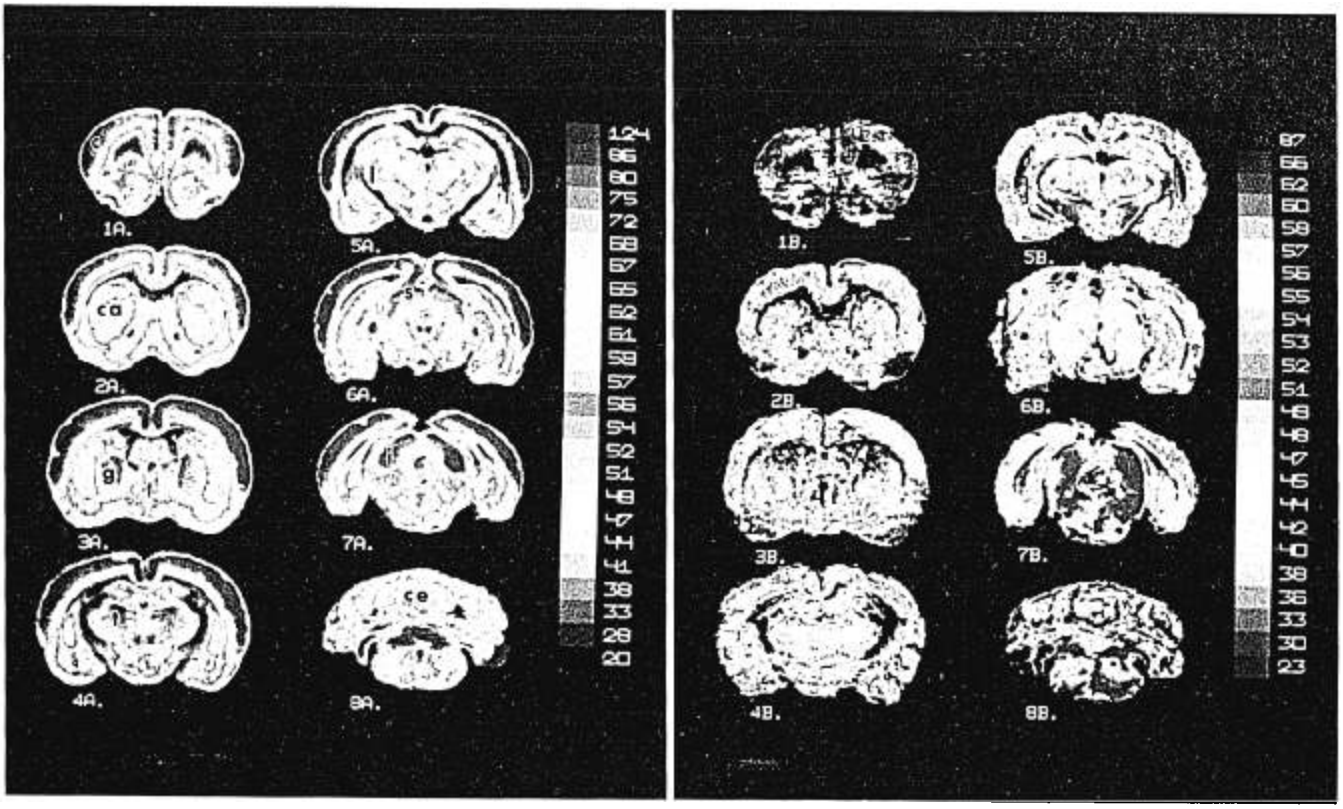

FIG. 2. Computer-assisted analysis of regional CMRglc. Autoradiographs of coronal sections from four control rats and five anesthetized rats (20 mg Althesin®/kg) were read by a computer-driven scanning densitometer (10,000 measurements/cm^2). The readings were converted to regional CMRglc,[25] and the individual sections were combined and averaged within each group as described in reference 28. The left panel (A) shows the mean images from the control rats. The key is expressed in $\mu mol \cdot min^{-1} \cdot 100\ g^{-1}$. Major structures are indicated by the following letters: c = cortex; ca = caudate; g = globus pallidus; t = thalamus; l = lateral geniculate; s = superior colliculus; i = inferior colliculus; ce = cerebellum. The right panel (B) shows the depression of regional CMRglc by Althesin® at a dose of 20 mg/kg. The data for this panel were calculated as [(control − Althesin®)/(control)] × 100 on a point-to-point basis. The key therefore is expressed as per cent reduction in regional CMRglc.

actually may show no decrease or a paradoxic increase in CBF.[21] Whether or not this is beneficial is open to question. Nevertheless, in view of the good qualities of Althesin®, it appears that further study of this drug or drugs with similar action is warranted.

In summary, Althesin® causes a marked reduction in CMRglc. The major effect is on the forebrain, while hindbrain structures are considerably less affected. This feature of Althesin® allows blood pressure, temperature, and respiration to remain in the normal range. There is good reason to believe that the effects of Althesin® differ from other lipid-soluble anesthetics and perhaps may be mediated by a receptor mechanism.

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