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The Effects of Propofol Anesthesia on Local Cerebral Glucose Utilization in the Rat

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The autoradiographic ^{14}C-2-deoxy-D-glucose method was used to determine local cerebral glucose utilization (LCGU) during propofol anesthesia and recovery in 52 regions of the rat brain. Control rats intravenously received 5 ml · kg^{-1} · h^{-1} of the egg-oil-glycerol emulsion that constitutes the vehicle for propofol. Anesthetized animals received an iv bolus of propofol (20 mg/kg) followed by continuous infusion of the anesthetic at 12.5, 25, or 50 mg · kg^{-1} · h^{-1} for 1 h prior to injection of ^{14}C-2-deoxy-D-glucose and for the following 45 min. In addition, a fifth group of animals were studied immediately after awakening from a 20 mg/kg bolus of propofol as indicated by the first reappearance of head lift. All rats were spontaneously breathing room air throughout the experimental procedure. The general pattern of the cerebral metabolic response to propofol anesthesia was a dose-related, widespread depression of LCGU. At the three infusion rates of propofol tested, overall mean LCGU was reduced by 33%, 49%, and 55%, respectively, and significant decreases were observed in 60%, 85%, and 90% of the regions assayed. These effects were rapidly reversible, since in the recovery group, LCGU returned to near control values in the majority of the brain areas. Although all of the anatomofunctional systems (sensorimotor, extrapyramidal, limbic, and reticular) were involved, forebrain structures showed a greater sensitivity to the depressant action of propofol than did hindbrain regions. The only structures in which glucose use was spared, even when the highest dose of propofol was infused, were the nuclei related to the auditory-vestibular system (cochlear and vestibular nuclei, lateral lemniscus, and superior olive). The pattern of metabolic changes produced by propofol resembles that observed after barbiturates, Althesin®, and etomidate. (Key words: Anesthetics, intravenous: propofol. Brain: glucose utilization; metabolism, regional.)

PROPOFOL (2,6-diisopropylphenol) is an intravenous anesthetic characterized by rapid onset, short duration of action, and a high therapeutic index and clearance rate.[1] The pharmacokinetic-dynamic profile of the drug makes it suitable for induction and, as an alternative to conventional inhalant techniques, for maintenance of general anesthesia for short duration surgical procedures.[2] In addition, although the role of propofol in longer and more invasive operations is debated,[3] its use in patients undergoing neurosurgical procedures might be encouraged because of the favorable influence on cerebral blood flow and cerebral oxygen consumption in humans.[4,5]

Studies on overall cerebral blood flow and metabolism, however, may overlook important insights with respect to regionally specific alterations produced by anesthetic agents.[6–13] We therefore used the ^{14}C-2-deoxy-D-glucose (^{14}C-DG) method[14] for measuring local cerebral glucose utilization (LCGU) in anatomically discrete regions of the rat brain in response to different doses of propofol.

Materials and Methods

PREPARATION OF ANIMALS

This study was approved by the institutional Animal Care and Use Committee. The experiments were performed on 25 male, 3-month-old (weight, 225–275 g), Fischer-344 rats (Charles River Italia, Como, Italy). They were allowed free access to water until the day of the experiment, and food was withheld the night before to provide steady plasma glucose concentration.

Under isoflurane anesthesia, polyethylene catheters (PE 50) were introduced into both femoral arteries (for continuous blood pressure measurement and collection of timed arterial blood samples) and veins (for infusion of the anesthetic and injection of the isotope). The incision sites were infiltrated with 0.25% bupivacaine hydrochloride.

After surgery, a loose-fitting plaster cast was applied around the lower abdomen, and the rats were allowed to recover for 3 hours in a temperature-controlled, sound-insulated wooden box.

EXPERIMENTAL GROUPS

Five experimental groups of five rats each were studied. Since propofol is currently formulated in an egg-oil-glycerol emulsion, the control group received that vehicle alone without propofol, infused at the maximum rate used in our experiments (5 ml · kg^{-1} · h^{-1}). The vehicle was infused for 1 h prior to the injection of ^{14}C-DG and for 45 min thereafter.

Three groups of rats received an intravenous bolus of propofol (20 mg/kg), followed by an infusion of the an-

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esthetic at 12.5, 25, or 50 $mg \cdot kg^{-1} \cdot h^{-1}$, respectively. These infusion rates were established (on the basis of previous experiments) to achieve different levels of anesthesia without severely interfering with the cardiocirculatory and respiratory parameters. To ensure a steady anesthetic state, the infusion was maintained for 1 h prior to the injection of ^{14}C-DG and, subsequently, for the 45-min period after isotope administration.

In a fifth group of animals, changes in LCGU were examined following recovery from anesthesia induced by a bolus of propofol (20 mg/kg). The bolus of ^{14}C-DG was injected as head-lift occurred.[15]

Physiologic Assessment

For the entire experimental period, arterial blood pressure and heart rate were monitored continuously. Hematocrit, pH_a, Pa_{O_2}, and Pa_{CO_2} were determined prior to the ^{14}C-DG administration and then 10, 25, and 40 min later. Body temperature was monitored with a rectal probe and maintained at 37 ± 0.2° C by regulated external heating. Bilateral frontoparietal electroencephalogram (EEG) was recorded with subcutaneous needle electrodes.

Determination of Local Cerebral Glucose Use

Local cerebral glucose utilization was quantitatively determined as described previously.[12] Briefly, a bolus of 125 μCi/kg body weight of ^{14}C-DG (Spec. Act. 55 μCi/mmol; Amersham International, London, UK) was injected. Timed arterial samples were drawn to measure plasma glucose (Glucose Analyzer II, Beckman Instruments, Fullerton, CA) and ^{14}C-DG (Liquid Scintillation Spectrometer model B2450, Packard, Downers Grove, IL) concentrations. At the end of the 45-min period, the rats were killed with an overdose of thiopental. The brains were removed, frozen in isopentane at −50° C, and cut with a cryostat (Cryocut E, Reichert-Jung, West Germany) at −22° C. The coronal sections (20 μm thick) were exposed to x-ray film (Kodak SB-5) for 7 days, together with a set of precalibrated ^{14}C-methylmethacrylate standards. Sections immediately adjacent to those used for autoradiography were stained with cresyl violet for histologic identification of brain structures according to the atlas of Paxinos and Watson.[16]

Local tissue ^{14}C concentrations were determined in 52 brain regions using a computer-based densitometer (BRS2 System, MCID, Ontario, Canada) comparing the optical densities of the autoradiographic sections with those of the calibrated ^{14}C standards. Twelve determinations were made for each region in the left and right sides of the brain. Local cerebral glucose utilization was calculated from brain and plasma radioactivities and plasma glucose concentrations according to equations and constants for transport and phosphorylation of ^{14}C-DG given by Sokoloff *et al.*[14]

Statistical Analysis

Significant differences between the control and experimental groups were determined by one-way analysis of variance (ANOVA). Significance of differences between individual means was assessed with the two-tailed Dunnett *t* test for multiple comparisons.[17] The correlations between cerebral glucose utilization and infusion rate of propofol were evaluated by the Pearson's r coefficient. Statistical significance was taken as $P < 0.05$.

Results

Behavior

The induction of anesthesia was accompanied, in most cases, by a transient, short-lasting shivering. After a few seconds, the animals lost consciousness with rapid loss of both the corneal reflexes and the withdrawal response to pain. In animals receiving 25 and 50 $mg \cdot kg^{-1} \cdot h^{-1}$, neither the corneal reflexes nor withdrawal to pain returned. At the 12.5 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion rate, withdrawal reflexes reappeared within 10 min after the bolus injection of the anesthetic and persisted until the ^{14}C-DG administration and for the subsequent 45 min.

When no infusion of the anesthetic followed the bolus injection, head-lift, preceded by the reappearance of withdrawal and corneal reflexes, occurred in 13 ± 2 min, whereupon the rats appeared completely awake.

Electroencephalographic Patterns

Typical changes induced by different rates of propofol infusion on the EEG activity are shown in figure 1. The high frequency-low amplitude EEG activity of the awake rats was replaced by a moderately slower background activity at an infusion rate of 12.5 $mg \cdot kg^{-1} \cdot h^{-1}$. When the infusion rate was 25 $mg \cdot kg^{-1} \cdot h^{-1}$, theta-delta and delta waves appeared with occasionally intermixed sharp waves and single spikes. At an infusion rate of 50 $mg \cdot kg^{-1} \cdot h^{-1}$, the EEG activity consisted of intermittent sharp waves on a predominant frequency of 2.5/s.

An EEG pattern similar to that of the awake rats was recorded in the recovery group at the time of ^{14}C-DG injection and persisted for the subsequent 45 min.

Physiologic Parameters

The physiologic data are summarized in table 1. Mean arterial blood pressure was significantly decreased and

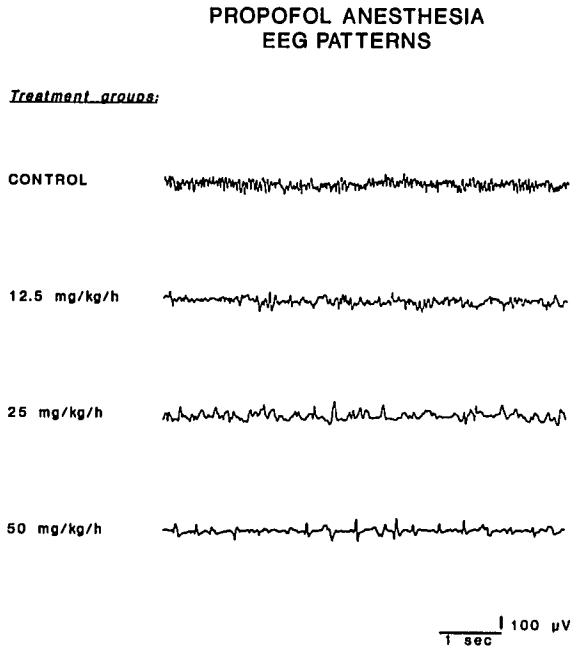

FIG. 1. Typical EEG patterns in awake rats (CONTROL) and in animals anesthetized with different infusion rates of propofol (12.5, 25, and 50 mg · kg^{-1} · h^{-1}).

Pa_{CO_2} significantly increased by the highest infusion rate. However, the observed changes were not large enough to account for LCGU variations.[18,19]

LOCAL CEREBRAL GLUCOSE USE

Control rats showed LCGU values similar to those previously reported for awake, untreated rats.[12,20,21] Propofol anesthesia caused a widespread and profound depression of cerebral metabolic activity. The magnitude of those effects calculated, as previously described,[11,21] by the number of significantly affected regions and overall arithmetic mean change in LCGU increased with the rate of infusion of propofol (fig. 2). Propofol significantly reduced LCGU in 60%, 85%, and 90% of the regions examined

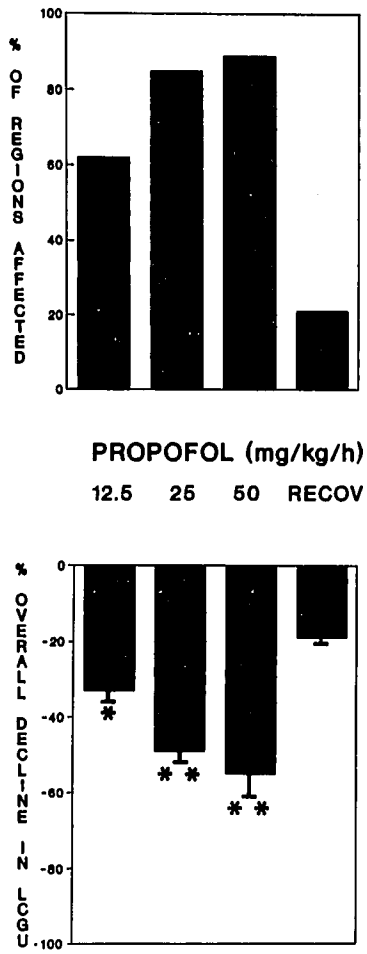

FIG. 2. Per cent of affected regions (*above*) and percent overall mean (±SEM) decrease of LCGU from control values (*below*) during propofol anesthesia at different infusion rates (12.5, 25, and 50 mg · kg^{-1} · h^{-1}, and during recovery [RECOV]). *, ** Significant differences from mean control value, $P < 0.05$ and $P < 0.01$, respectively.

in the 12.5, 25, and 50 mg · kg^{-1} · h^{-1} groups, respectively. The overall mean glucose use was depressed by propofol by 33%, 49%, and 55% in the three treatment groups,

TABLE 1. Physiologic Parameters in Control and Propofol-Anesthetized Rats

	Control	Propofol Infusion (mg · kg^{-1} · h^{-1})			Recovery
		12.5	25	50	
Hematocrit (%)	45 ± 1	44 ± 2	44 ± 1	43 ± 1	45 ± 2
Heart rate (beats/min)	436 ± 11	401 ± 21	382 ± 11	380 ± 23	410 ± 5
Mean arterial pressure (mmHg)	125 ± 8	104 ± 7	102 ± 9	94 ± 4*	108 ± 3
pH_a	7.36 ± 0.02	7.36 ± 0.01	7.34 ± 0.02	7.33 ± 0.03	7.33 ± 0.02
Pa_{CO_2} (mmHg)	41 ± 1	42 ± 2	44 ± 2	47 ± 1*	41 ± 1
Pa_{O_2} (mmHg)	97 ± 1	100 ± 1	102 ± 3	91 ± 3	98 ± 1
Glucose (mg/dl)	133 ± 5	127 ± 4	150 ± 11	147 ± 8	128 ± 5

Physiologic conditions recorded 10 min after the injection of ^{14}C-DG.

Data represent mean ± SEM for five animals in each group.
* Significantly different from control mean, $P < 0.05$.

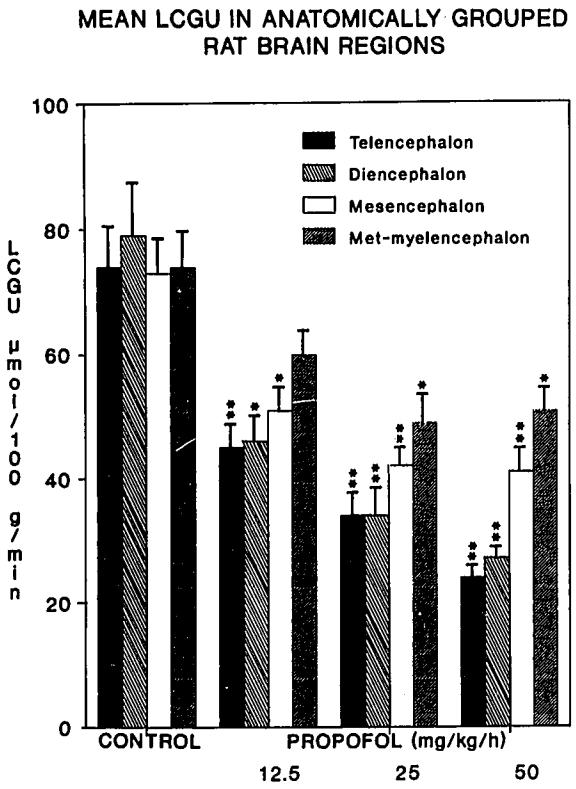

FIG. 3. Bars represent mean (±SEM) LCGU values in anatomically grouped brain regions in control rats and in animals infused with propofol at different rates. *, ** Significant differences from mean control value, at $P < 0.05$ and $P < 0.01$ levels, respectively.

respectively. This effect showed a positive correlation with the propofol infusion rate ($r = -0.88$; $P < 0.05$).

When the regions were grouped into major anatomic divisions (fig. 3), however, the metabolic depression induced by propofol did not appear homogeneously distributed. In fact, a significant correlation between mean LCGU decrease and propofol infusion rate was observed in the telencephalic ($r = -0.91$; $P < 0.05$) and diencephalic regions ($r = -0.88$; $P < 0.05$) but not in the mesencephalon and brain stem. In these regions, near maximum depression of metabolic activity was reached at the lowest infusion rate of propofol without further consistent decline. Hence, deep propofol anesthesia was accompanied by a rostral-to-caudal gradient of LCGU depression.

No LCGU increases were observed during propofol anesthesia in any of the 52 regions examined (table 2). Declines in LCGU were equally distributed in all of the anatomofunctional systems (sensorimotor, extrapyramidal, limbic, and reticular). The only exceptions were some regions connected with the vestibular-auditory system (cochlear and vestibular nuclei, lateral lemniscus, and superior olive) and the fasciculus retroflexus, in which metabolic activity was spared. Moreover, oculomotor mesencephalic structures affected by the 12.5 and 25 $mg \cdot kg^{-1} \cdot h^{-1}$ doses returned to near control values at the 50 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion rate.

In the recovery group, LCGU values were not statistically different from control values in most of the regions examined. In this group, overall mean LCGU was reduced by 19%, and significant decreases were observed in 11 brain areas (fig. 2). As shown in table 2, the great majority of the telencephalic and diencephalic regions showed LCGU rates similar to those of the control group. Only some mesencephalic and brain stem structures (median raphe, dorsolateral tegmental nucleus, and locus coeruleus) continued to show evidence of metabolic depression during recovery.

Discussion

Propofol anesthesia is associated with a profound depression of metabolic activity in the rat brain. The magnitude and extent of LCGU reductions correlated with the doses of drug infused and paralleled the deepening of anesthesia and the suppression of the EEG activity. The effects of propofol on cerebral metabolism were rapidly reversible, and LCGU returned to near-control levels in most areas about 10 min after the bolus injection of the anesthetic, reflecting the short duration of propofol following single or repeated doses.[15] Recovery from propofol anesthesia was not associated with enhanced glucose metabolism in any of the regions examined.

The metabolic changes induced by propofol closely resemble the homogeneous depression caused by barbiturates,[10,11,14] Althesin®,[22] and etomidate,[23] and differ from those produced by ketamine,[7,24] phencyclidine,[25] and inhalation anesthetics,[9,12,13,26] which promote both increases and decreases in LCGU. In this regard, our study indicates that propofol belongs to the class of anesthetics that produce widespread inhibitory effects on brain metabolism without promoting increases in LCGU in any region.

The regional profile of the LCGU changes produced by different anesthetics has been interpreted in terms of functional brain alterations linked to anesthesia. Nevertheless, there is no consistent relationship between the anesthetic state and regional differences in metabolic change. For instance, the relative sparing of metabolic activity in hindbrain, with respect to forebrain, structures during Althesin®[22] or etomidate,[23] but not barbiturate[10,11,14] anesthesia, has been related to the minor effect of the former agents on blood pressure and respiratory regulation. In our study, however, propofol decreased LCGU more in the forebrain than in the hindbrain, even though it depresses physiologic parameters to a similar

TABLE 2. Local Cerebral Glucose Use During Propofol Anesthesia and Recovery in Rats

Brain regions	Control	Propofol Infusion ($mg \cdot kg^{-1} \cdot h^{-1}$)			Recovery
		12.5	25	50	
Telencephalon					
Cerebral cortex					
Cingulate anterior	79 ± 8	54 ± 6	36 ± 3†	26 ± 2†	76 ± 8
Frontal	103 ± 10	52 ± 5†	35 ± 3†	24 ± 3†	74 ± 2
Somatosensory	98 ± 9	52 ± 4†	34 ± 3†	24 ± 3†	71 ± 4
Auditory	134 ± 8	70 ± 5†	47 ± 4†	40 ± 4†	98 ± 5
Visual	92 ± 8	52 ± 4†	42 ± 4†	31 ± 4†	68 ± 4
Cingulate posterior	88 ± 6	40 ± 5†	26 ± 1†	22 ± 1†	58 ± 4†
Entorhinal	51 ± 4	37 ± 3*	27 ± 2†	21 ± 1†	43 ± 3
Rinencephalon					
Dorsal hippocampus					
CA_3 field	51 ± 5	35 ± 4	26 ± 3†	23 ± 2†	44 ± 2
Dentate gyrus	43 ± 4	34 ± 4	25 ± 3†	19 ± 2†	39 ± 2
Presubiculum	85 ± 7	45 ± 5†	28 ± 1†	24 ± 1†	60 ± 4*
Lateral amygdala	61 ± 6	45 ± 4	34 ± 4†	23 ± 3†	62 ± 4
Medial septum	44 ± 8	32 ± 3	24 ± 3	18 ± 2*	38 ± 2
Diagonal band n.	57 ± 4	30 ± 2†	24 ± 2†	19 ± 2†	40 ± 4*
Basal ganglia					
Caudate-putamen	92 ± 10	60 ± 7	39 ± 5†	28 ± 2†	77 ± 2
Globus pallidus	38 ± 5	27 ± 2	23 ± 3	19 ± 2*	34 ± 2
Nucleus accumbens	73 ± 9	49 ± 6	36 ± 6†	24 ± 2†	71 ± 6
Diencephalon					
Lateral geniculate					
Medial geniculate	61 ± 7	37 ± 2*	31 ± 2†	26 ± 2†	42 ± 1
Lateral habenula	113 ± 13	61 ± 8*	39 ± 3†	30 ± 4†	77 ± 4
Medial habenula	109 ± 12	66 ± 7*	53 ± 4†	42 ± 2†	80 ± 5
Thalamus	75 ± 7	48 ± 4†	42 ± 4†	35 ± 2†	50 ± 4
Lateral posterior n.	83 ± 11	42 ± 5*	30 ± 4†	24 ± 2†	59 ± 5
Mediodorsal n.	57 ± 6	40 ± 4	30 ± 3†	24 ± 2†	46 ± 4
Ventromedial n.	75 ± 9	40 ± 4†	32 ± 3†	27 ± 2†	54 ± 4
Anteroventral n.	86 ± 9	50 ± 6*	33 ± 3†	25 ± 2†	66 ± 4
Reuniens n.	62 ± 7	42 ± 4	30 ± 4†	22 ± 1†	58 ± 5
Subthalamic n.	76 ± 8	39 ± 4†	32 ± 2†	25 ± 2†	49 ± 2*
Mammillary bodies	102 ± 7	46 ± 5†	30 ± 4†	22 ± 2†	67 ± 4†
Suprachiasmatic n.	46 ± 4	36 ± 3†	31 ± 4†	26 ± 3†	52 ± 7
Mesencephalon					
Deep mesencephalic n.	51 ± 6	35 ± 4	26 ± 1†	24 ± 1†	38 ± 2
Central gray	49 ± 4	32 ± 2†	26 ± 1†	25 ± 1†	40 ± 2
Substantia nigra					
Compacta	59 ± 6	37 ± 3*	28 ± 2†	25 ± 1†	44 ± 3
Reticulata	43 ± 5	29 ± 1*	25 ± 1†	21 ± 2†	30 ± 1
Red n.	62 ± 7	41 ± 4*	30 ± 1†	29 ± 2†	46 ± 1
Interpeduncular n.	100 ± 11	68 ± 4*	54 ± 4†	49 ± 4†	80 ± 1
Colliculus					
Superior	64 ± 6	47 ± 4	42 ± 2†	43 ± 4*	44 ± 2*
Inferior	160 ± 8	130 ± 3*	105 ± 9†	95 ± 6*	161 ± 7
Oculomotor complex	67 ± 5	41 ± 4†	44 ± 4†	61 ± 6	46 ± 1†
Brainstem and cerebellum					
Reticular formation					
Pontine	44 ± 4	32 ± 3	27 ± 1†	27 ± 1†	36 ± 2
Medullary	47 ± 4	34 ± 3*	26 ± 2†	28 ± 1†	39 ± 1
Superior olive	99 ± 6	116 ± 4	103 ± 9	107 ± 7	122 ± 9
Medial vestibular n.	92 ± 7	71 ± 4*	65 ± 5	77 ± 7	83 ± 5
Dorsal cochlear n.	104 ± 4	106 ± 4	83 ± 8	79 ± 7	114 ± 5
Median raphe	84 ± 5	45 ± 4†	34 ± 1†	30 ± 1†	58 ± 2†
Dorsolat. tegmental n.	83 ± 5	40 ± 4†	32 ± 2†	32 ± 2†	53 ± 2†
Locus coeruleus	58 ± 4	41 ± 4*	35 ± 2†	41 ± 4*	45 ± 1*
V spinal tract n.	49 ± 4	38 ± 4	30 ± 2†	32 ± 2†	44 ± 2
Lateral lemniscus n.	88 ± 13	94 ± 7	73 ± 7	70 ± 5	94 ± 3
Cerebellar vermis	67 ± 6	41 ± 3†	32 ± 1†	35 ± 3†	53 ± 2
Myelinated fiber tracts					
Corpus callosum	24 ± 4	17 ± 2	13 ± 2	11 ± 2*	14 ± 2
Fasciculus retroflexus	52 ± 6	51 ± 5	40 ± 4	34 ± 3	58 ± 3
Internal capsule	23 ± 4	16 ± 2	13 ± 1*	11 ± 2	14 ± 2
Medial forebrain bundle	41 ± 4	24 ± 1†	20 ± 3†	16 ± 2†	28 ± 1*

Each number represents mean ± SEM for five animals in each group.
LCGU is expressed in $\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$.

* Significantly different from control mean, $P < 0.05$.
† Significantly different from control mean, $P < 0.01$.

extent as barbiturates.[15] Therefore, the previous hypothesis[22,23] that hemodynamic and respiratory stability with certain anesthetics reflects the cranial-to-caudal gradient of metabolic depression and relative sparing of brain stem regulatory centers is questionable. Because propofol, Althesin®,[22] and etomidate,[23] but not barbiturates,[11] share the property of sparing the metabolic activity in regions related to the vestibular-auditory system, the relatively high metabolic rate in those areas might account for the lesser depression observed in the hindbrain.

The relative or absolute activation of the habenulo-interpeduncular (MHb-IPN) system is a common finding with many anesthetic agents[6,9,11–13,25] and has been linked to the depth and duration of anesthesia[11,12] or the genesis of anesthetic-induced seizures.[27] However, this relationship is blurred by the fact that propofol, Althesin®, and etomidate decrease the metabolic activity in the MHb-IPN system.[22,23] Furthermore, the property of increasing glucose utilization in the MHb-IPN system is not specific for anesthetics, since it is shared by other centrally acting drugs, such as nicotine.[28] Finally, the activation of the MHb-IPN system may have different functional consequences since the dorsal diencephalic conduction system also has been implicated in sleep, analgesia, olfaction, ingestion, mating, and endocrine control.[29–31]

The metabolic activation of the locus coeruleus has been thought to mediate the reduction of cortical metabolism during halothane[9] and Althesin®[32] anesthesia. On the other hand, propofol and barbiturates[11] decrease both coeruleal and cortical LCGU. Furthermore, the recovery from propofol anesthesia was characterized by restoration of LCGU in cortical regions, whereas LCGU remained significantly depressed in locus coeruleus. Again, an increased activity in a definite region, locus coeruleus in this case, is not necessarily associated with the anesthetic state, and the exact role played by this area during anesthesia cannot be determined by metabolic studies alone.

In conclusion, considering our observations, it appears that many hypotheses concerning mechanisms of anesthetic action that are based on regional metabolic changes can be questioned. Specific patterns of LCGU may be more helpful in characterizing different anesthetics than they are in explaining the mechanisms by which the drugs produce anesthesia.

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