Anesthesiology
68:777–782, 1988

Metabolic Activation of Intercortical and Corticothalamic Pathways during Enflurane Anesthesia in Rats

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The purpose of this study was to examine the effects of enflurane on local cerebral glucose utilization (LCGU), and to provide further insight into the mechanism of the epileptogenic properties of enflurane. Twenty-four male Wistar rats were divided into four groups; three groups with intact cortex received 0.5, 2, or 4% enflurane, and one group with unilateral cortex excised received 4% enflurane. LCGU was measured at each anesthetic concentration using the autoradiographic 2-[^{14}C]deoxyglucose method. LCGU in ten of 33 structures examined during 2% enflurane decreased by 19–33%, and LCGU in 22 structures during 4% enflurane decreased by 19–65%, when compared with that during 0.5% enflurane. While LCGU, in most structures, decreased in a dose-related manner, LCGU in the corpus callosum, thalamic ventrobasal complex, and hippocampal CA3 field during 4% enflurane increased by 31–70%, compared with that during 0.5% and/or 2% enflurane. With unilateral cortical excision during 4% enflurane, the increase in LCGU in the ventrobasal complex was obliterated in the excision side, and the increase in the corpus callosum was attenuated. High LCGU in the hippocampal CA3 field and contralateral ventrobasal complex was not affected with cortical excision. These results indicate that intercortical and corticothalamic pathways are metabolically activated during deep enflurane anesthesia, suggesting that the epileptogenic property of enflurane is related to activation of these pathways. (Key words: Anesthetics, volatile: enflurane. Brain: glucose metabolism.)

IT HAS BEEN SHOWN that anesthetics have different metabolic effects on cortical and subcortical structures. Myers and Shapiro[1] reported that local cerebral glucose utilization (LCGU) in the hippocampus and associated limbic structures, including the habenulo-interpeduncular system, was preserved, while LCGU in other many structures was significantly decreased during enflurane anesthesia. They related these findings to the epileptogenic properties of the drug. However, the observation of preserved LCGU in the habenulo-interpeduncular system is common to other anesthetics, including ether[2] and barbiturates.[2,3] Moreover, preservation of LCGU in the hippocampus has been also reported with halothane,[4,5] which has no epileptogenic properties. These apparently conflicting interpretations led us to again examine the local cerebral glucose metabolism during enflurane anesthesia. We found that intercortical and corticothalamic pathways were metabolically activated during deep enflurane anesthesia.

Materials and Methods

Preparation of Animals

The experiments were performed on 24 male Wistar rats, weighing 265–350 g. Anesthesia was induced with 4% enflurane and maintained with 2.5% enflurane during the 40-min operative procedure. Following tracheostomy, the rats were paralyzed with d-tubocurarine chloride (1.5 mg/kg iv) and mechanically ventilated (Harvard® pump). Both femoral arteries were cannulated, one for blood pressure recording, and the other for the determination of arterial blood gases, *p*H, plasma glucose, and 2-[^{14}C]deoxyglucose (2-[^{14}C]DG) concentrations. Both femoral veins were cannulated for the administration of the drugs and 2-[^{14}C]DG. Rectal temperature was maintained at 36.8–37.2° C by external means in all rats except those decorticated, in which case brain surface temperature was maintained within the same range. Bilateral bipolar EEGs were recorded from the frontoparietal areas throughout the experiment, except on the decorticated side in cerebral cortex-excised rats. Heparin was given intravenously in a dose of 100 units.

Experimental Groups

Following approval by the Animal Experimental Committee of Yamaguchi University, groups of six rats were assigned to each of the following four groups; three groups with intact cortex received 0.5, 2, and 4% (inspired) enflurane, and one group with unilateral cortex excised received 4% enflurane. In cortex-excised rats, the cerebral cortex from frontal to occipital area was carefully excised, minimizing injury to subcortical structures. A thermister was placed on the decorticated region for monitoring of brain surface temperature, and the skin was tightly sutured. After the surgical pro-

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Received from the Departments of Anesthesiology and Critical Care Medicine, Yamaguchi University, School of Medicine, 1144 Kogushi, Ube, Yamaguchi 755, Japan; and Kokura Memorial Hospital, Kokura, Kitakyushu, Fukuoka 802, Japan. Accepted for publication January 4, 1988. Supported in part by Grant-in-Aid for Scientific Research of Japan (project number: 60440073, 62480329).

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TABLE 1. Physiological Variables

	0.5% (n = 6)	2% (n = 6)	4% (n = 6)	4% with Cortical Excision (n = 6)
Body weight (g)	301 ± 11	303 ± 12	301 ± 11	290 ± 8
Temperature (°C)	37.0 ± 0.1	37.1 ± 0.1	36.9 ± 0.03†	37.0 ± 0.03
MAP (mmHg)	125 ± 4	91 ± 4*	80 ± 1*†	76 ± 4*†
Pa_{O_2} (mmHg)	123 ± 5	138 ± 8	142 ± 8	142 ± 9
Pa_{CO_2} (mmHg)	37 ± 1	38 ± 1	38 ± 1	39 ± 0.5
*p*H	7.42 ± 0.003	7.46 ± 0.02*	7.39 ± 0.01*†	7.37 ± 0.01*†
Hematocrit (%)	43 ± 1	41 ± 1	41 ± 1	42 ± 1
Plasma glucose (mg/dl)	201 ± 9	231 ± 25	163 ± 13†	154 ± 11*†

Values are mean ± SE.
* Significantly different from the values at 0.5%.
† Significantly different from the values at 2%.

cedure, anesthesia was maintained with each preselected anesthetic concentration for 30 min before administration of 2-[^{14}C]DG for the determination of LCGU. With 4% enflurane, phenylephrine administration (2–8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv) and blood transfusion (total, 2–4 ml before 2-[^{14}C]DG iv) were necessary to maintain mean arterial pressure (MAP) above 70 mmHg.

Determination of Local Cerebral Glucose Utilization

LCGU was quantitatively measured by the 2-[^{14}C]DG method described by Sokoloff *et al.*[6] 2-[^{14}C]DG (New England Nuclear, specific activity, 49–52 mCi/mmol), 150 μCi/kg in 0.5 ml saline, was intravenously administered, and timed arterial blood samples were taken for measurement of concentration of plasma glucose (Glucose Analyzer II®, Beckman Instruments) and plasma 2-[^{14}C]DG (Tri-carb 4640, Packard). Rats were decapitated 45 min after 2-[^{14}C]DG administration, and the brains were removed quickly and frozen in isopentane (−50° C). Following serial sectioning (20 μm thickness), the tissue sections were exposed to x-ray film (Kodak SB-5) for 10 days, along with a set of calibrated [^{14}C]-methylmethacrylate standards (The Radiochemical Center, Amersham). In two of six rats in each group, brain sections immediately adjacent to those used for autoradiography were stained with hematoxylin-eosin for histologic identification of brain structures.

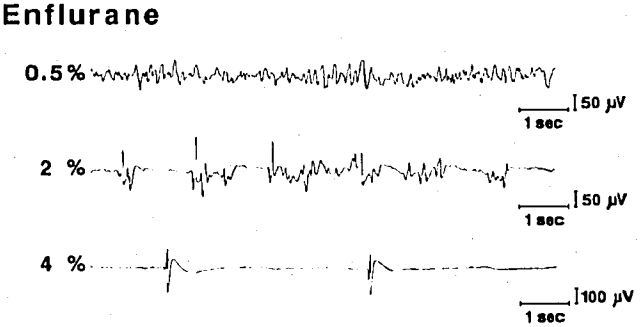

FIG. 1. Typical EEGs during 0.5, 2, and 4% enflurane.

Autoradiograms were analyzed with a microdensitometer (4200FP, Nac) with an aperture diameter of 100–500 μm. Three to six determinations of optical densities were made for each region in the left and right sides of the brain, and the means for the two sides were averaged except in the cortex-excised rats. LCGU was calculated from brain and plasma radioactivities and plasma glucose concentrations, using the equations and constants given by Sokoloff *et al.*[6]

Statistical Analysis

Statistical differences among groups were tested by one-way analysis of variance. If the F statistic of analysis of variance was significant, the least significant difference was applied for the multiple comparisons. $P < 0.05$ was considered statistically significant.

Results

The physiological variables are given in table 1. MAP decreased in a dose-related manner with increased concentrations of enflurane, but remained above 70 mmHg in all rats. The mean arterial *p*H, although significantly different at the different anesthetic concentration, was, however, within the physiologic range. Mean plasma glucose concentration at 4% enflurane with or without cortical excision was significantly lower than that at 0.5% and/or 2%. Plasma glucose concentrations in individual rats varied from 100 to 350 mg/dl, but remained relatively unchanged during the measurement.

Representative EEGs in each group are shown in figure 1. During 0.5% enflurane, the EEG consisted of 8–15 Hz activity, occasionally intermingled with 3–5 Hz waves. During 2% enflurane, the EEG showed polyspikes and waves interrupted by suppression of 0.5–2 s

TABLE 2. Local Cerebral Glucose Utilization during Enflurane Anesthesia

Structures	0.5% (n = 6)	2% (n = 6)	4% (n = 6)	4% with Cortical Excision (n = 6)	
				Ipsilateral to Excision Side	Contralateral to Excision Side
Cerebral association area					
Frontal cortex	72 ± 4	51 ± 1*	51 ± 7*		50 ± 5*
Parietal cortex	79 ± 4	53 ± 2*	53 ± 4*		47 ± 5*
Auditory system					
Cortex	88 ± 5	68 ± 3*	51 ± 4*†		48 ± 3*†
Medial geniculate	74 ± 6	53 ± 5*	52 ± 5*	38 ± 3*†‡	40 ± 3*
Inferior colliculus	106 ± 9	86 ± 6*	37 ± 4*†	35 ± 2*†	37 ± 2*†
Visual system					
Cortex	73 ± 2	54 ± 3*	42 ± 3*†		43 ± 4*†
Lateral geniculate	65 ± 5	52 ± 2*	49 ± 4*	37 ± 3*†‡	42 ± 3*
Superior colliculus	57 ± 4	57 ± 4	45 ± 3*†	40 ± 2*†	42 ± 2*†
Sensorimotor system					
Cortex	64 ± 5	53 ± 5	59 ± 4		58 ± 5
Thalamus mediodorsal	66 ± 4	52 ± 3*	39 ± 3*†	36 ± 3*†	37 ± 4*†
ventrobasal	59 ± 4	49 ± 3	64 ± 3†	36 ± 2*†‡	70 ± 6*†§
Cuneate nucleus	62 ± 5	59 ± 5	38 ± 4*†	43 ± 5*†	43 ± 5*†
Gracile nucleus	64 ± 4	64 ± 5	44 ± 5*†	50 ± 6	49 ± 5*
Cerebellar gray	37 ± 5	41 ± 3	37 ± 3	39 ± 5	40 ± 4
Extrapyramidal system					
Caudate-putamen	73 ± 3	61 ± 3	51 ± 5*	49 ± 6*	54 ± 5*
Substantia nigra	55 ± 5	66 ± 4	58 ± 4	67 ± 4	66 ± 4
Limbic system					
Septal nucleus	46 ± 3	47 ± 3	33 ± 3*†	35 ± 4*†	36 ± 4†
Amygdala	60 ± 4	51 ± 3	43 ± 3*	42 ± 3*	44 ± 3*
Hypothalamus	43 ± 3	46 ± 3	35 ± 3*†	36 ± 2†	37 ± 3†
Hippocampus CA1	61 ± 5	45 ± 2*	46 ± 5*	46 ± 6*	41 ± 4*
'A3	61 ± 5	71 ± 4	85 ± 4*	90 ± 9*	88 ± 10*
Entorhinal cc ·x	56 ± 5	55 ± 4	41 ± 3*†	40 ± 3*†	41 ± 2*†
Mammillary c.nplex	82 ± 6	75 ± 5	51 ± 3*†	46 ± 4*†	46 ± 3*†
Habenula medial	67 ± 3	83 ± 5	154 ± 15*†	143 ± 13*†	139 ± 12*†
lateral	89 ± 4	79 ± 4	65 ± 4*	58 ± 6*†	62 ± 8*†
Interpeduncular nucleus	95 ± 5	101 ± 6	148 ± 18*†	123 ± 13	121 ± 10
Reticular formation	42 ± 5	45 ± 3	33 ± 2*†	31 ± 1*†	32 ± 1*†
Accumbens nucleus	82 ± 4	57 ± 2*	43 ± 4*†	40 ± 3*†	41 ± 3*†
Pontine nuclei	49 ± 3	45 ± 6	34 ± 2*†	35 ± 2*†	35 ± 2*
Pineal body	120 ± 6	136 ± 15	135 ± 15	143 ± 9	
Central gray	47 ± 4	50 ± 3	42 ± 2†	39 ± 2†	40 ± 3†
Dorsal raphe	60 ± 4	65 ± 4	58 ± 3	52 ± 3	53 ± 3
Myelinated fiber tract					
Corpus callosum	29 ± 2	27 ± 2	46 ± 1*†		38 ± 3*†‡

Values are mean ± SE (μmol · 100 g^{-1} · min^{-1}).
* Significantly different from the values at 0.5%.
† Significantly different from the values at 2%.
‡ Significantly different from the values at 4% (without cortical excision).
§ Significantly different from the values on the excision side at 4%.

duration, and, during 4% enflurane, the EEG showed occasional spike-wave-like complexes with a frequency of 8–15/min, and was otherwise nearly isoelectric. In cortex-excised rats, there were no marked changes in EEG contralateral to the excision side when it was compared to that before excision.

LCGU values and representative brain autoradiograms of each group are shown in table 2 and figures 2 and 3, respectively. The mean LCGU during 0.5% varied from 29–120 μmol · 100g^{-1} · min^{-1}, depending on the brain structures examined. Among the gray matter, the LCGU was highest in the auditory system (above 70 μmol · 100g^{-1} · min^{-1}), but was low in the septal nucleus, hypothalamus, pontine nuclei, central gray, reticular formation, and cerebellar gray, (below 50 μmol · 100g^{-1} · min^{-1}). LCGU was also low in the white matter, the corpus callosum, being about half of the level observed in the gray matter.

LCGU during 2% enflurane, compared with that during 0.5% enflurane, decreased by 19–33% in ten of 33 structures examined. The decrease was principally limited to the auditory and visual system and frontal

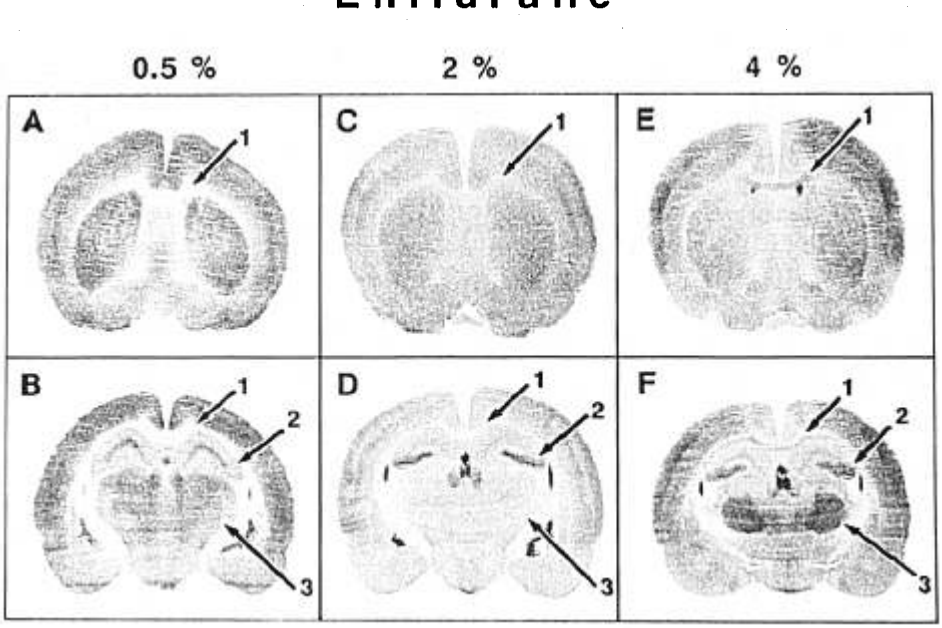

FIG. 2. Representative autoradiograms at two levels of coronal brain sections of rats anesthetized with enflurane, 0.5% (*A, B*), 2% (*C, D*), or 4% (*E, F*). The darker areas represent higher metabolic rates for glucose. Increased glucose utilization was shown in CA3 within the hippocampus at 2 and 4% enflurane (*D, F*) and in the thalamic ventrobasal complex and corpus callosum at 4% (*E, F*). The numbered structures are: 1 = corpus callosum; 2 = hippocampal CA3 field; 3 = thalamic ventrobasal complex.

and parietal cortices. In the other 23 structures, the LCGU remained unchanged.

LCGU during 4% enflurane, compared with that during 0.5%, decreased by 19–65% in 22 structures, including cortical and subcortical regions. In contrast to the decrease in most structures, LCGU increased by 39–130% in the hippocampal CA3 field, corpus callosum, medial habenula, and interpeduncular nucleus. When compared with that during 2% enflurane, LCGU decreased by 16–57% in 15 structures, and increased by 31–86% in the thalamic ventrobasal complex (VB), corpus callosum, medial habenula, and interpeduncular nucleus. Within the range of concentrations studied, LCGU remained unchanged in the sensorimotor cortex, substantia nigra, dorsal raphe, pineal body, and cerebellar gray.

With unilateral cortical excision during 4% enflurane, the increased LCGU in the VB was completely suppressed on the excision side (fig. 3), and the LCGU in the corpus callosum was significantly decreased by 17%, compared with that observed in intact rats. Cortical excision did not affect LCGU in other brain regions, except in the medial and lateral geniculate bodies ipsilateral to the excision side. There was no difference in LCGU between ipsilateral and contralateral sides in any brain structures, except in the VB.

No histological change was observed in the VB in the cortex-excised rats.

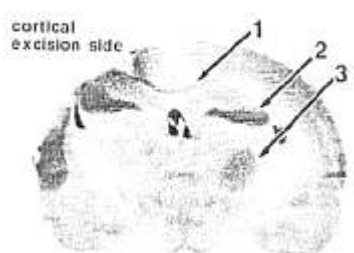

FIG. 3. A representative autoradiogram prepared from a coronal brain section at the level of the thalamus in the rat with unilateral cerebral cortex excised at 4% enflurane. The increased glucose utilization in the thalamic ventrobasal complex was obliterated on the excision side (left). The numbered structures are: 1 = corpus callosum; 2 = hippocampal CA3 field; 3 = thalamic ventrobasal complex.

Discussion

Increased LCGU in the Thalamic Ventrobasal Complex (VB) and Corpus Callosum

The present study revealed that the increased enflurane concentration (4%) was accompanied by an increased LCGU in the VB and corpus callosum. To our knowledge, these changes in LCGU have never been reported with other anesthetics, except ketamine, which increased the LCGU in the corpus callosum in a dose-related manner.[7] The increased LCGU in the VB at 4% enflurane indicates activation of neurons which terminate in the VB, since LCGU mainly reflects the activity of nerve terminals, rather than that of the cell body.[8] Pathways terminating in the VB mainly consist

of spinothalamic, trigeminothalamic, dorsal column-medial lemniscothalamic, and corticothalamic tracts.[9,10] To clarify whether the cortex is involved in the increased LCGU in the VB, we examined the effects of cortical excision on the LCGU in the VB during 4% enflurane. Obliteration of the increased LCGU in the VB with cortical excision indicates that the increased LCGU in the VB can be attributed to activation of the corticothalamic tracts. Although there may be other structures relaying between the cortex and the VB, it seems unlikely that such structures were involved in the increased LCGU in the VB, because cortical excision hardly influenced the LCGU in structures other than the VB. One may suspect that injury to nerve terminals of thalamocortical tracts might cause functional impairment of neurons in the VB, and that cortical excision might decrease LCGU in the VB by this functional impairment (not through the reduced inputs from the cortex to the VB). However, this is unlikely, because it has been reported that cortical excision increases the amplitude of evoked potential and the probability of discharge of neurons in the VB in response to stimulation.[11,12] The increased LCGU in the corpus callosum during 4% enflurane indicates metabolic activation of the interhemispheric corticocortical connection, since the corpus callosum is the pathway connecting the cerebral cortices. This is in agreement with our observation that the LCGU in the corpus callosum was decreased with unilateral cortical excision.

One might expect that activation of intercortical and corticothalamic pathways is accompanied by an increase in cortical metabolism during 4% enflurane. However, we did not observe any increase in LCGU in the cortex. We believe that this is because a large number of neurons terminating in the cortex, other than intercortical and corticothalamic neurons, may not be activated.

Myers and Shapiro[1] have examined the effects of enflurane on LCGU. Although their LCGU values are comparable to ours in many brain regions during similar (but not identical) anesthetic concentrations, there are marked differences in LCGU values in the thalamus and corpus callosum between two studies. They reported a 37% decrease in LCGU in the ventral region of the thalamus, which probably included the VB and a 27% decrease in the corpus callosum during 3.75% enflurane, when compared with that in awake rats. Differences between their results and ours cannot be readily explained. The concentrations of enflurane tested are not identical, and the control states selected for comparison are different; our control LCGU was during 0.5% enflurane, while theirs was in awake rats. However, these differences are not sufficient to account for an increase in LCGU in the VB and corpus callosum in our study and a decrease in theirs. One additional possible explanation for the difference is that we supported blood pressure with phenylephrine, while the report by Myers and Shapiro does not indicate that arterial blood pressure was supported. Therefore, it is possible that their rats were sufficiently hypotensive during 3.75% enflurane, such that metabolic depression occurred.

Activation of intercortical and corticothalamic pathways indicated by the increased LCGU in the corpus callosum and VB at 4% enflurane in the present study has also been reported during seizures induced by cortical injection of penicillin.[13] Collins[13] found that repeated penicillin injection into unilateral motor cortex increased LCGU in the VB and contralateral cerebral cortex, as well as in the seizure focus (injection site), and suggested activation of intercortical and corticothalamic pathways. From these similarities between the penicillin-induced seizures and deep enflurane anesthesia, we believe that activation of these pathways at 4% enflurane is related to epileptogenic properties of enflurane.

Increased LCGU in the Hippocampal CA3

Another characteristic metabolic effect of enflurane was found in the hippocampus. While, during 0.5% enflurane, there was no difference in LCGU between CA1 and CA3, at 2 and 4% enflurane, the LCGU in CA3 was uniformly higher than that in CA1 (fig. 2*D*, *F*). Myers and Shapiro[1] reported a numerical (but not significant) increase in LCGU in the hippocampus with enflurane. However, they measured LCGU in the hippocampus without discrimination between CA1 and CA3 fields. The increased LCGU in CA3 with enflurane observed in the present study should be related to activation of either interconnections within CA3[14] or pathways terminating in CA3; the latter consists of the perforant path from the entorhinal cortex, the mossy fibers from the dentate area,[15] and interhippocampal connection from contralateral CA3.[16] However, the present method does not allow us to define specific neurons or pathways responsible for the increased LCGU in CA3. With regard to epileptogenicity of enflurane, Myers and Shapiro[1] concluded that the hippocampus and associated limbic structures were the epileptogenic foci for seizures induced by enflurane. Their conclusions were based upon observed metabolic sparing or an increase in metabolism in the habenulo-interpeduncular system, hippocampus, and pineal body at 3.75 and 5% enflurane. However, metabolic sparing or an increase in metabolism in the habenulo-interpeduncular system is not a specific but common finding with many anesthetics; chloral hydrate,[2] barbiturates,[2,3] ether,[2] halothane,[5,17] and isoflurane.[18] A preserved or increased LCGU in the hippocampus was also reported with halothane.[4,5,17] Furthermore, an increase in LCGU in CA3

has been reported with isoflurane.[18] Therefore, if the characteristic epileptogenic properties of enflurane are related to the specific changes in LCGU, they are increased LCGU in the VB and corpus callosum, which appears to be characteristic for enflurane. Although not proven, involvement of the hippocampus in the development of enflurane-induced seizures seems unlikely.

In summary, our results suggest that the epileptogenic properties of enflurane are related to activation of intercortical and corticothalamic pathways.

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