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Local Cerebral Blood Flow during Lidocaine-induced Seizures in Rats

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Neurophysiologic and local cerebral metabolic mapping techniques indicate that seizures associated with lidocaine toxicity originate in subcortical brain structures. Normally local cerebral blood flow (l-CBF) is quantitatively coupled to local cerebral metabolic rate for glucose (l-CMR_g). In the present study the response of l-CBF to a lidocaine-induced preconvulsive state (localized seizure activity in the absence of a grand mal seizure) was evaluated in rats anesthetized with 60% nitrous oxide. Lidocaine administered as a bolus (20 mg/kg) followed by an infusion (4 mg/kg) over 5.5 min resulted in progressive alteration in the electroencephalogram (EEG). L-CBF was studied with the ^{14}C-iodoantypyrine autographic method when the preconvulsive EEG pattern consisted of a repetitive spike and wave complex at a frequency of $14 \pm 1 \cdot min^{-1}$ complexes, superimposed on practically isoelectric background activity. Under these conditions high doses of lidocaine significantly ($P < 0.05$) decreased (range −30% to −68%) l-CBF in 71% of the 34 brain regions studied. The greatest exception to this trend for l-CBF to decrease was observed in the limbic system wherein l-CBF remained within control ranges in eight of the 11 structures evaluated. Qualitative comparison of lidocaine l-CBF changes with l-CMR_g changes obtained under similar conditions indicated a general trend for local flow and metabolism to decrease in parallel. Exceptions to this were confined to certain limbic areas (amygdala and hippocampus) in which increases in l-CMR_g were more than 100% greater than slight ($P > 0.05$) increases in l-CBF. This comparison demonstrates uncoupling of local brain metabolism from blood flow during lidocaine-induced subcortical epileptoid discharges (preconvulsive state) in areas recognized to be prone to irreversible damage when seizure activity is much prolonged beyond the duration of this study. (Key words: Anesthetics, local: lidocaine. Brain: blood flow, regional; electroencephalography; seizures. Toxicity: lidocaine.)

SYSTEMIC ADMINISTRATION OF high doses of local anesthetics cause central nervous systemic toxicity that is manifested by seizure activity in animals.[1] Depth electrode studies demonstrate that the initial local anesthetic seizure activity begins in the limbic system, and quantitative autoradiographic measurements performed during these epileptoid discharges reveal increases in the local cerebral metabolic rate for glucose (l-CMR_g) within the limbic system.[2,3] These lidocaine-induced subcortical metabolic increases are associated with simultaneous reductions in l-CMR_g in the rest of the brain.[3]

Several of the subcortical brain regions exhibiting localized seizure discharges and enhanced l-CMR_g following high doses of lidocaine are areas recognized to be especially vulnerable to irreversible damage during seizures or other hypoxic-ischemic events.[4,5] Currently, it is not known whether enhanced neuronal activity *per se,* insufficient cerebral blood flow (CBF) compensatory response, or other factors are responsible for irreversible neuronal changes during seizures. In rats, prolonged seizures due to other epileptogenic drugs have shown correlations among structures demonstrating very high l-CMR_g and biochemical-histopathologic derangements.[6] If normal cerebral metabolism–blood flow coupling mechanisms are intact during toxic doses of lidocaine, then the compensatory distribution of CBF should be matched to areas of high metabolism.

Previous studies of overall CBF and cerebral metabolic rate (CMR) during lidocaine seizures do not permit evaluation of CBF/CMR relationships in localized areas involved in the seizure activity.[7] The present study was undertaken to evaluate the pattern of the l-CBF distribution during the preconvulsive seizure discharges induced by lidocaine in the rat. These results are also compared with l-CMR_g changes found under similar conditions in a prior study in our laboratory.[3]

Materials and Methods

SURGICAL PREPARATION

All experiments were performed on female Sprague-Dawley rats (250–350 g) given *ad lib* access to food and water. Anesthesia was induced in a plexiglass box with 4% halothane in O_2, and when unresponsive, the animals were tracheostomized and mechanically ventilated with a Harvard® rodent respirator to maintain normocapnia. During the remainder of the surgical procedure, anesthesia was maintained with 1% halothane in oxygen and nitrogen (30:70), using pancuronium bromide (0.2 mg iv

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TABLE 1. Physiologic Conditions During l-CBF Measurements

	Control (n = 6)	Lidocaine (n = 6)
Pa_{O_2} (mmHg)	118 ± 6	166 ± 8*
Pa_{CO_2} (mmHg)	36.9 ± 0.4	37.7 ± 0.3
pH_a	7.41 ± 0.01	7.44 ± 0.01
MABP (mmHg)	137 ± 3	126 ± 12
Hct (%)	42.2 ± 1.1	44.5 ± 1.4

Values are mean ± SEM.
MABP = mean arterial blood pressure; Hct = hematocrit.
* Significantly different from control: $P < 0.001$.

q 20 min) for muscle relaxation. A femoral artery and vein were cannulated (PE-50, Becton-Dickinson, Rutherford, NJ) for continuous blood pressure (BP) measurement, injection of drugs and isotope, and anaerobic sampling of blood (100 μl) for Pa_{O_2}, Pa_{CO_2}, and pH_a determination (Radiometer BMS-3MK2® unit). In order to obtain rapid blood sampling for plasma ^{14}C activity, a low deadspace arteriovenous shunt catheter was introduced in the contralateral femoral vessels. All surgical incisions were infiltrated with 0.25% bupivacaine hydrochloride (0.2 ml total), and heparin (200 IU) was administered to prevent catheter clotting. Rectal temperature was maintained at 37°C with a servocontrolled heating lamp (Yellow Springs Instruments, Yellow Springs, OH). The electroencephalogram (EEG) and electrocardiogram (ECG) were obtained with subcutaneous platinum needle electrodes, and recorded on a Beckman Accutrace® EEG machine at a gain of 7.5 μV/mm. At the end of the surgical procedure, halothane was discontinued and animals were ventilated with 60% N_2O in O_2 for 1 h to permit halothane elimination (stabilization period) before lidocaine administration was started. Nitrous oxide was maintained during the l-CBF determination in control and lidocaine groups.

Six rats received 20 $mg \cdot kg^{-1}$ of lidocaine hydrochloride over a 1-min period followed by 4 $mg \cdot kg^{-1}$ bolus doses as needed to sustain EEG seizure activity consisting of high voltage spike and wave complexes superimposed on an isoelectric EEG. L-CBF was measured after 5 min of this epileptoid activity. Epileptoid discharge frequency was determined by counting spike and wave complexes for each minute following initiation of the first such complex. The mean dose of lidocaine required to obtain the EEG pattern was 41 $mg \cdot kg^{-1} \cdot 6\ min^{-1}$ (range 29 mg to 67 $mg \cdot kg^{-1} \cdot 6\ min^{-1}$). Six animals served as the control group (no drug treatment) and were given saline intravenously in volumes equal to that used with lidocaine infusions.

L-CBF

L-CBF was measured according to Sakurada.[8] In brief, 75 $\mu Ci \cdot kg^{-1}$ of ^{14}C-iodoantipyrine (NEC-712®, New England Nuclear, Boston, MA), dissolved in 1.0 ml of normal saline was infused at a constant rate for 30 s. During the infusion period, 16 to 18 arterial blood samples (20 μl) were discontinuously collected from the shunt catheter for determination of ^{14}C activity by liquid scintillation counting (Nuclear-Chicago, ISOCAP 300®). The animals were decapitated at the end of the isotope infusion and the brains were rapidly removed and frozen in 2-methyl-butane cooled to −41° C with Freon 22®. Brain coronal sections (20 μm) were cut in a cryostat (−20° C, American Optical, Buffalo, NY) and the coverslip-mounted sections were rapidly dried on a hot plate. The brain sections were subsequently exposed, along with six ^{14}C-methyl-methacrylate standards, to single emulsion x-ray film (Kodak® SB-5) for 11 days. The optical density of any selected region was determined with an autoscanning densitometer (Optronics, P-1000®, International, Inc., Chelmsford, MA) with an aperture of 200 μm, and all data collected on line with a Prime computer for calculation of l-CBF.[8] Brain structures (n = 34) were identified with a stereotaxic brain atlas.[9]

L-CBF/l-CMR_g *Relationships.* Calculation of local flow-metabolism ratios during lidocaine-induced preconvulsive EEG activity was performed using l-CMR_g data from an earlier lidocaine study.[3] Autoradiograms from that study were reprocessed with the current scanning densitometer (prior study used a spot densitometer) and anatomic definitions and l-CMR_g were recalculated and submitted to statistical analysis as indicated in the following.

Statistical Analysis

In Table 1, differences between groups were evaluated using Student's *t* test for unpaired data. L-CBF and l-CMR_g data in table 2 were considered to be nonparametric and differences between control and lidocaine groups were tested using Mann-Whitney test for unpaired data.[10] Program PSS of the BMDP statistical package was used for calculations.[10] A *P* value less than 0.05 was considered significant.

Results

Physiologic Conditions

Table 1 lists physiologic conditions prevailing during measurement of l-CBF in control rats and in those given high doses of lidocaine. Except for a significantly higher Pa_{O_2} in the lidocaine group, Pa_{CO_2}, pH_a, and the mean arterial pressure were the same. The reason for the higher lidocaine oxygen tension is not readily apparent.

EEG Patterns

Lidocaine administration caused progressive alterations in the EEG as indicated in Figure 1. Initially, diffuse slow-

TABLE 2. Local Cerebral Blood Flow (l-CBF ml · 100 g^{-1} · min^{-1}) and Local Cerebral Metabolic Rate for Glucose (l-CMR_g μmol · 100 g^{-1} · min^{-1})*

	Abbreviation	l-CBF		l-CMR_g	
		Control (60% N_2O)	Lidocaine	Control (60% N_2O)	Lidocaine
Auditory System					
Cortex (temporal)	AC	325 ± 110	135 ± 29†	58 ± 21	39 ± 11
Medial geniculate	MG	227 ± 61	101 ± 24†	82 ± 19	34 ± 11‡
Inferior colliculus	IC	205 ± 62	75 ± 26†	77 ± 31	22 ± 4†
Olivary body	OB	226 ± 89	76 ± 11†	52 ± 18	24 ± 6†
Cochlear nucleus	CN	262 ± 88	133 ± 20†	68 ± 21	74 ± 26
Lateral leminiscus	LL	117 ± 21	72 ± 18†	45 ± 29	19 ± 6‡
Visual System					
Cortex	VC	202 ± 80	118 ± 33‡	53 ± 20	32 ± 8‡
Lateral geniculate	LG	157 ± 12	74 ± 16†	34 ± 16	27 ± 5
Superior colliculus	SC	196 ± 41	85 ± 23†	48 ± 14	26 ± 9†
Sensorimotor System					
Sensorimotor cortex (parietal)	SM	259 ± 103	103 ± 19†	42 ± 18	40 ± 6
Thalamus, ventrolateral	VT	182 ± 18	109 ± 29†	54 ± 14	37 ± 7†
Thalamus, dorsomedial	DT	194 ± 13	96 ± 21†	46 ± 15	36 ± 6
Periventricular gray	PG	110 ± 25	58 ± 13†	28 ± 7	19 ± 5‡
Cerebellar cortex	CG	138 ± 49	64 ± 13†	21 ± 8	24 ± 5
Extrapyramidal System					
Caudate-putamen	CP	243 ± 130	60 ± 15†	57 ± 13	59 ± 14
Globus pallidus	GP	109 ± 34	53 ± 11†	24 ± 12	32 ± 11
Substantia nigra	SU	115 ± 19	74 ± 18†	26 ± 13	34 ± 15
Limbic System					
Claustrum	CL	187 ± 69	117 ± 24	37 ± 12	39 ± 18
Septal nucleus	SN	135 ± 57	129 ± 27	28 ± 12	36 ± 10
Piriform cortex	PC	209 ± 91	97 ± 12†	59 ± 33	41 ± 12
Amygdala	AM	117 ± 25	137 ± 32	21 ± 11	46 ± 19†
Hypothalamus	HT	105 ± 13	73 ± 14†	21 ± 10	28 ± 8
Hippocampus, Ammon's Horn	AH	109 ± 21	93 ± 15	23 ± 10	92 ± 12†
Hippocampus, CA1	HH	131 ± 27	171 ± 43	33 ± 9	67 ± 9†
Hippocampus, CA3 (dentate)	DH	126 ± 28	139 ± 31	28 ± 9	79 ± 19†
Hippocampus, CA1 + CA3 (ventral)	VH	146 ± 33	199 ± 53	38 ± 14	55 ± 10‡
Entorhinal cortex	EC	147 ± 40	205 ± 130	29 ± 11	39 ± 16
Interpeduncular nucleus	IN	236 ± 77	102 ± 22†	64 ± 19	42 ± 12
Myelinated Fiber Tract					
Corpus callosum	CC	69 ± 9	27 ± 7†	7 ± 5	9 ± 7
Internal capsule	IW	55 ± 14	33 ± 9†	6 ± 2	5 ± 4
Cerebellar white	CW	59 ± 20	32 ± 6†	6 ± 2	5 ± 4
Cerebral Association, Area					
Frontal cortex	FC	290 ± 124	94 ± 16†	33 ± 8	47 ± 12†
Reticular Formation	RF	105 ± 24	51 ± 12†	13 ± 3	27 ± 15†
Pineal Body	PB	147 ± 52	74 ± 13‡	30 ± 4	47 ± 13‡

All data are mean ± SD. l-CBF (ml · 100 g^{-1} · min^{-1}); l-CMR_g (μmol · 100 g^{-1} · min^{-1}). CBF groups: n = 6. Tests for statistical significance from control were performed using Mann-Whitney tests for unpaired data.

Lidocaine l-CBF was evaluated 20 ± 2 min after starting lidocaine administration.

Lidocaine l-CMR_g was measured 5 min after starting lidocaine administration.

* Reprocessed from previously published lidocaine l-CMR_g data.[5]

† $P < 0.01$.

‡ $P < 0.05$.

ing of the EEG frequency accompanied by modest voltage reduction occurred (fig. 1*B*). Within the first min this pattern was replaced with epileptoid discharges characterized by high-voltage (>100 μV) spike and wave complexes occurring with a frequency of 36 ± 4 complexes/min (fig. 1*C*). Figure 2 graphs the frequency of the spike and wave complexes until the time of the l-CBF determination. At the time of the flow study, the spike and wave complex discharges had stabilized at an average of 14 ± 1/min. These epileptoid seizure discharges were superimposed on a nearly isoelectric EEG, and generalized seizures were not observed.

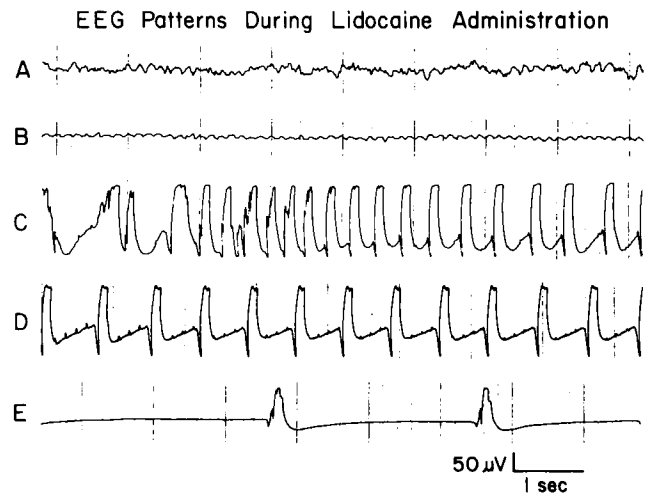

FIG. 1. Representative electroencephalographic (EEG) patterns during lidocaine administration. These tracings represent a composite drawn from two rats. *A:* 60% N_2O, before starting lidocaine injection. *B:* 18 s after starting lidocaine. *C:* first appearance of EEG epileptoid activity. *D:* 70 s after starting lidocaine. *E:* 3 min and 30 s after starting lidocaine. See text for further elaboration.

l-CBF

Table 2 lists the l-CBF values obtained during control conditions (60% nitrous oxide) and with lidocaine administration superimposed on the same conditions. Lidocaine caused a significant decrease in l-CBF (range −30% to −68%) in a majority (71%) of the brain structures evaluated when contrasted with control l-CBF. In the remainder of the brain structures l-CBF remained unchanged from control values; no significant increases in local flow occurred. The absence of an l-CBF increase was most exaggerated within certain limbic system structures, with only two extralimbic areas not attaining a significant flow reduction. Within the limbic system eight of the 11 divisions or subdivisions studied did not show a l-CBF reduction; several had an insignificant flow increase.

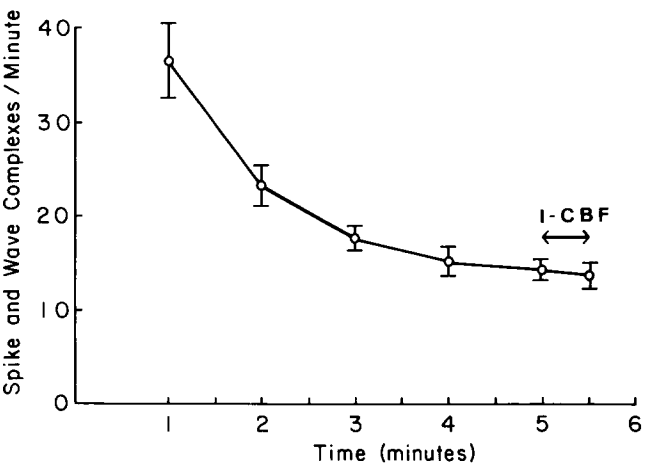

FIG. 2. Seizure activity (expressed as number of spike and wave complexes/min) during lidocaine administration. The epileptoid electroencephalographic activity began 63 ± 10 s after starting lidocaine administration. Local cerebral blood flow (l-CBF) was measured after 5 min of seizure activity, over a 30-s period. Data are mean ± SEM in six animals.

l-CBF–Metabolic Relationships

Table 2 also contains reprocessed l-CMR_g data obtained under similar conditions in a previous study.[3] These l-CMR_g data represent an expansion of the number of structures previously reported and contain identical matching of anatomic areas subjected to densitometry. Significant biphasic l-CMR_g changes took place with local metabolism increasing and decreasing in 12% of the structures and remaining unchanged in the majority (76%) of brain areas.

Figure 3 shows the percentage change from control values in local blood flow and metabolism following administration of high doses of lidocaine and permits qualitative analysis of the degree of relative coupling or matching of l-CBF to l-CMR_g. A general trend for local flow and metabolism to decrease in most structures is apparent in figure 3. Excluding the limbic structures and the myelinated tracts (where large percentage changes occurred due to very low initial values), the percentage decrease in l-CBF was greater than the decrease in l-CMR_g in most brain areas. In only four instances were significant l-CBF and l-CMR_g changes matched, and these structures were distributed among various brain functional categories (inferior colliculus, olivary body, ventrolateral thalamus, and reticular formation).

In contrast with the rest of the brain, limbic system local flow and metabolism changes were quite heterogenous. Flow decreased significantly in three limbic structures (piriform cortex, hypothalamus, and interpeduncular nucleus), and l-CMR_g was significantly increased in four different limbic areas (amygdala, and three hippocampal subdivisions). In several limbic areas the percentage increase in local metabolism far exceeded (>100%) any change in local flow; these included amygdala and the Ammon's horn and CA3 areas of the hippocampus.

Discussion

Our study reveals heterogenous l-CBF changes during administration of lidocaine in doses sufficient to produce a preconvulsive state characterized by high-voltage spike and wave complexes superimposed on an essentially isoelectric background EEG activity. Under similar conditions a prior study in our laboratory found striking increases in l-CMR_g in hippocampal areas in which, in the present study, local blood flow increases did not occur.[3] Because the hippocampal region is known to be especially vulnerable to irreversible neuronal changes during prolonged seizures due to other convulsants, our findings indicate that a similar potential exists with toxic doses of

lidocaine. Before further elaboration of this possibility a number of factors inherent to our protocol require discussion.

Lidocaine Preseizure State

Lidocaine administration can elicit several different EEG phases prior to the onset of generalized convulsions. The expression of these phases is dependent on species and the lidocaine dose and administration rate. Seo *et al.* correlated behavior in cats with surface and depth EEG recordings during progressive elevations in lidocaine infusions.[11] In Seo's experiment the immediate preseizure style changes were preceded by signs of brain depression and excitation.[11] Other investigators have described similar neurophysiologic changes just prior to lidocaine-induced generalized seizures.[12] Wagman indicated that the initial EEG change associated with lidocaine intoxication was subcortical amygdala epileptiform discharges in cats, which were not apparent in the cortical EEG.[13] Munson described diffuse EEG slowing in monkeys as the earliest manifestation of the immediate preseizure state, followed by high-voltage slow waves just prior to succeeding generalized seizure activity.[14]

The surface EEG recordings obtained in our rats is likely representative of several elements contained in the preceding studies in that they represent central nervous system depression and excitation. While the volume relationships of cortical and subcortical anatomy may preclude EEG recording of subcortical activity in larger and more complex brains, recording of activity in these subcortical structures in the rat, with its relatively thin cortical mantle and relatively large volume of the hippocampus and amygdala, should be possible, especially when the surface EEG is quiescent. Our previous l-CMR_g study of lidocaine toxicity corroborates this possibility as EEG background activity was practically isoelectric and cortical metabolism was reduced by about 43%.[3] Other studies have reported onset of EEG isoelectricity when cerebral metabolic rate is depressed by 50%.[15] Given the coupled relationship between localized brain electrophysiologic activity and local metabolism, it is difficult to postulate a different source for the EEG discharges than the subcortical limbic system in our earlier lidocaine l-CMR_g and present l-CBF studies.

L-CBF

Our "control" l-CBF state reflects high values when compared with other controls collected in awake animals in our laboratory and others.[16,17] These high flows most likely represent a combination of light anesthesia and the CBF effects of 60% nitrous oxide anesthesia in laboratory animals. However, these effects were unavoidable in our study as we sought to provide nearly similar physiologic conditions to evaluate the effects of high doses of lidocaine

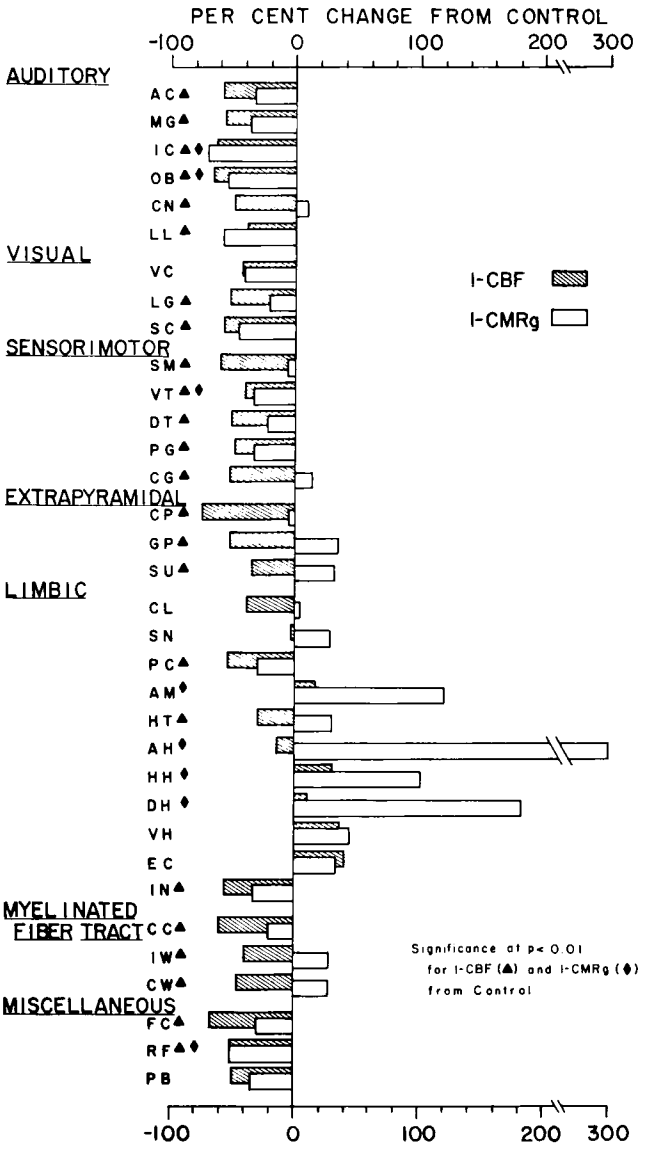

FIG. 3. Percentage change from control values in local blood flow and metabolism following administration of high doses of lidocaine. See text for further description and abbreviations. *Triangle* and *diamond* symbol, respectively, represent significant l-CBF and l-CMR_g changes from the control state as derived from Table 2.

on l-CBF. This necessitated ventilatory support, use of muscle relaxants, and a relatively light anesthetic. Under these conditions it is not possible to isolate the specific l-CBF effects of N_2O from the more general influences of light anesthesia and other environmental stimuli.

L-CBF values obtained in awake unrestrained rats in our laboratory are in close agreement with those reported by Dahlgren *et al.*[17] However, when they administered 70%–80% nitrous oxide to rats restrained in a small chamber, they found l-CBF decreases in several brain areas, including the hippocampus.[17] In the present study administration of 60% nitrous oxide caused increases in l-CBF in a majority of brain regions when compared with

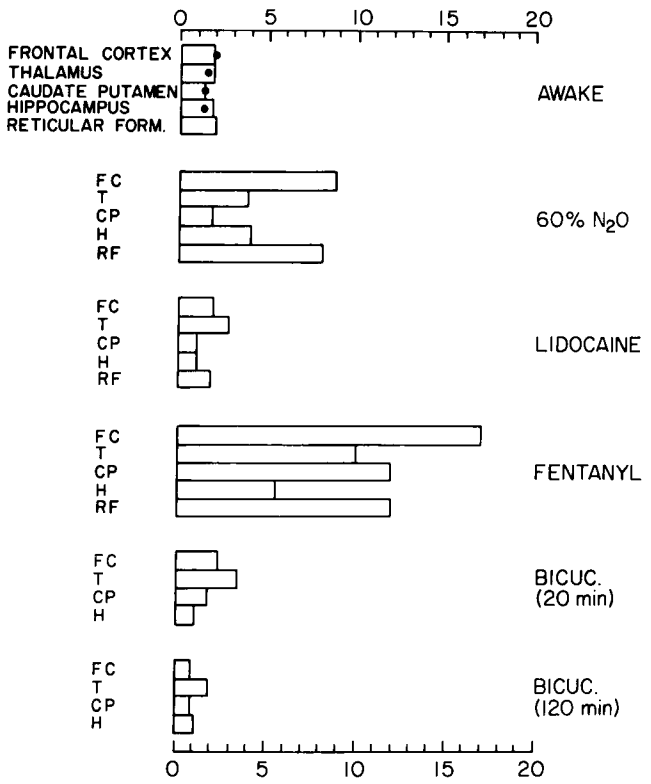

FIG. 4. Compilation of local flow–metabolic ratios obtained during preconvulsive and generalized convulsive EEG activity in the rat. Data sources are drawn from references 3, 6, 16, and 18. Bicuc = bicuculline.

our previously reported control values in awake rats.[16] Other investigators employing different methods for measuring cortical blood flow and metabolism in rats during 70% N_2O anesthesia found increases in CBF and cerebral metabolic rate for oxygen.[17]

The cerebral autoradiographic techniques for the measurement of local metabolism and flow lend themselves to the mapping of localized changes in these variables during experimental seizures. L-CBF studies of fentanyl effects during EEG discharge patterns similar to that seen with lidocaine in the present study revealed one- to three-fold increases in l-CBF involving almost all of the structures evaluated.[16] These results, obtained with a potent narcotic, should be contrasted with our present lidocaine effects on l-CBF, wherein flow decreased or remained unchanged in a majority of structures. Thus, doses of lidocaine and fentanyl sufficient to cause preconvulsive epileptoid EEG activation cause similar qualitative patterns of l-CMR_g cortical depression and absolute or relative subcortical metabolic enhancement, but their effect on local flow responses is considerably different.

Differences in l-CBF and l-CMR_g matching during seizure activity may provide insight into mechanisms regulating CBF during the administration of these drugs. Because brain metabolism is closely linked to CBF control, further discussion of l-CBF responses within the context of information detailing the l-CMR_g alterations during preconvulsive or seizure states should be useful.

L-CBF and L-CMR_g Relationships with Drug-Induced Seizures

As noted previously, local cerebral metabolism and blood flow have been measured in several different models of pharmacologically induced seizure activity.[3,6,16,18] Direct comparison of local metabolic-flow alterations in each animal are currently not possible due to methodologic limitations. Investigators are presently constrained to study local metabolism in one group of animals and compare those findings with local flow studies obtained in a different group of animals under similar conditions. The l-CBF and l-CMR_g techniques require that physiologic conditions remain stable during the duration of the study. However, l-CBF studies can be performed in less than 1 min, while l-CMR_g measurements require 45 min. Maintenance of identical and stable physiologic conditions for the l-CMR_g study may not be strictly possible, especially when drugs with cardiovascular depressant actions and/or evanescent neurophysiologic effects are administered. Cognizant of these drawbacks, the following consideration of local flow and metabolic relationships during drug-induced epileptoid activity is offered within the qualifying context of semiquantitative or qualitative interpretations of data obtained by another laboratory or at different times within our laboratory.

Figure 4 is a compilation of local flow-metabolic ratios obtained during the awake state, 60% N_2O, and with preconvulsive and generalized convulsive activity in the rat. The ability of 60% nitrous oxide to increase greatly this ratio over awake values, resulting in relative hyperperfusion in several areas, is illustrated in figure 4. With 60% N_2O the increased flow-metabolism ratio is due to a combination of relatively small decreases in l-CMR_g (−30% to −70%) and a wider range of l-CBF increases (2% to 120%) when contrasted with the awake values.

Increases in the l-CBF/l-CMR_g ratios observed with 60% nitrous oxide and high doses of fentanyl represent uncoupling of the normal demand and supply relationship between flow and metabolism in the structures evaluated.[3,16,18] During 60% N_2O anesthesia in paralyzed, ventilated rats, the flow increase has been in part ascribed to stress during light anesthesia.[19,20] If this response was entirely stress-related, then one would expect l-CMR_g also to be increased instead of being decreased. In this situation, nitrous oxide may also possess direct cerebral vasodilator actions and/or modify neurogenic mechanisms involved in CBF control. Prior to eliciting generalized convulsions, fentanyl causes modest decreases in CBF and cerebral metabolism.[21] However, when subcortical epileptoid discharges occur, l-CBF greatly increases in the cerebral cortex, while l-CMR_g remains decreased.[16,18,21,22]

Under those conditions, fentanyl may achieve uncoupling of flow and metabolism mainly by neurogenic circulatory modulation.

As indicated in figure 4, during lidocaine-induced preconvulsive EEG activity, flow-metabolism ratios remained close to those observed in awake rats. These ratios were maintained by approximately parallel reductions in l-CBF (−13% to −39%) and l-CMR_g (−25% to −52%), except in the hippocampus (l-CBF = 13%, l-CMR_g = +75%) and caudate-putaman (l-CBF = −75%; l-CMR_g = −5%) wherein the l-CBF/l-CMR_g ratios decreased below awake values. Qualitatively, lidocaine, when compared with either 60% N_2O or high doses of fentanyl, appears to maintain coupling of flow to metabolism in most brain regions in a manner similar to that observed globally with barbiturates.[16] The mechanism for this coupling remains unknown. The decrease in the l-CBF/l-CMR_g ratio to below awake values is of interest as those subcortical regions are recognized to be vulnerable to neuronal death during prolonged seizures.[4–6]

Administration of bicuculline, a gamma-aminobutyric acid (GABA) receptor blocker, causes sustained, generalized seizure activity. Under these conditions l-CBF initially (after 20 min) increased two- to four-fold in almost every structure studied.[6] When bicuculline-induced generalized seizures continued for 2 h, l-CBF in some cortical and limbic areas declined from levels established during preceding seizure activity. Under the same conditions heterogeneous increases in l-CMR_g were observed that were initially matched by flow increases. However, measurements of l-CBF and l-CMR_g performed after 2 h of bicuculline seizures indicated relative hypoperfusion in cortical and limbic areas (*infra vide*).[6]

Taken together, these l-CBF/l-CMR_g ratio alterations illustrate two points. One centers on the emergence of the hippocampus as a structure that develops low local flow-metabolism ratios during repetitive limbic system discharges due to high doses of several drugs used in anesthesia practice. This may relate to the recognized selective vulnerability of this region to hypoxic-ischemic or seizure related insults.[4–6] The other point is illustrated by the decline in l-CBF/l-CMR_g ratios in limbic and other brain regions with prolonged seizures due to bicuculline, which are secondary to a decline in l-CBF in some structures despite maintenance of a high l-CMR_g. Whether or not a secondary and/or relative local circulatory failure could supervene during prolonged lidocaine or fentanyl preconvulsive states remains unanswered.

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