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# *Selective Metabolic Activation of the Hippocampus during Lidocaine-Induced Pre-seizure Activity*

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**Neurophysiologic studies indicate that local anesthetic-induced seizures are generated in subcortical brain structures. The authors utilized a quantitative autoradiographic technique to measure cerebral metabolism during lidocaine-induced seizure activity in rats anesthetized with nitrous oxide. Local cerebral metabolic rate for glucose (l-$CMR_g$) was determined when lidocaine infusion resulted in sustained electroencephalographic patterns consisting of approximately 100–125-$\mu$volt discharges with a frequency of about 9 Hz, lasting 1–2 sec, and superimposed upon almost isoelectric periods lasting 1–3 sec. Significant reductions in l-$CMR_g$ (30–70 per cent decreases) occurred in 19 of 26 regions surveyed. All areas of cerebral cortex had decreased glucose uptake following lidocaine administration. The hippocampus developed a striking increase in l-CMRg of 237 per cent, while the amygdala and other related nuclei sustained metabolic rates similar to those present before lidocaine was given. This study demonstrates a coupling of metabolic activity with functional activity in subcortical structures recognized to be involved in the generation of local anesthetic seizure activity. Additionally, it reveals a heterogeneous response of cerebral metabolism to lidocaine infusion in the presence of subcortically localized seizures. (Key words: Anesthetics, local: lidocaine. Brain: convulsions; hippocampus; metabolism. Toxicity: convulsions.)**

LIDOCAINE and other local anesthetics have anticonvulsant effects in low doses, and convulsant effects in higher doses.[1] Subconvulsant doses of local anesthetics in dogs can maximally depress the overall cerebral metabolic rate by 30 per cent while convulsant doses increase cerebral oxygen consumption.[2] Since it is recognized that local anesthetic seizure discharges emanate mainly from the amygdala, hippocampus, and other limbic system nuclei,[3] studies of overall cerebral metabolism may not accurately reflect metabolic rate within specific brain locations. Utilizing a quantitative autoradiographic technique that permits quantitative measurement of local cerebral glucose uptake (l-$CMR_g$) in brain areas as small as 0.5 mm in diameter, we found a regionally heterogeneous response of brain metabolism during subcortical seizures initiated by lidocaine.

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## Methods

Fourteen adult Sprague-Dawley rats of either sex, weighing 268 ± 4 g, were permitted access to food and water *ad lib*. Anesthesia was induced with halothane, 4 per cent, in oxygen. Lidocaine hydrochloride, 1 per cent, (0.2 ml total) was infiltrated in all incision sites for local anesthesia. Following a tracheostomy, the animals were ventilated with a Harvard rodent respirator at a rate of 2–3 cycles/sec and a tidal volume of 10–15 ml/kg. Inspired gases were changed to halothane, 1 per cent, in nitrous oxide, 60 per cent, and oxygen for the remaining part of the surgical procedure. Polyethylene catheters (PE-50) were placed in the left femoral vein for infusion of isotope and drugs. To reduce sampling dead space, an arteriovenous shunt catheter with a side port for arterial blood sampling was placed in the right femoral artery and vein.

Gallamine triethiodide (20 mg/kg, iv, *q*/20 min) was administered to produce muscle relaxation. Heparin (200 units, iv) was given to prevent clotting of blood in the catheters. Temperature was monitored rectally and maintained at 37° C with a servocontrolled heat lamp. The electroencephalogram (EEG) was recorded with two needle electrodes mounted across the midline over the parietal bone on one channel of the polygraph. Following completion of the surgical procedure, halothane administration was discontinued, and approximately 20–30 min elapsed prior to l-$CMR_g$ determinations. Normalization of cerebral metabolism occurred over this period following the withdrawal of halothane administered under similar conditions of rats.[4] Sixty per cent nitrous oxide–oxygen provided maintenance anesthesia postoperatively for the control and lidocaine-treated groups (n = 7). During this period, the respirator was adjusted to maintain an arterial blood carbon dioxide tension ($Pa_{CO_2}$) of 35–38 torr and an arterial blood oxygen tension ($Pa_{O_2}$) of 140–200 torr. Duplicate measurements of blood-gas values (150-$\mu$l samples) were made prior to flow determinations on a Radiometer microelectrode system analyzer.

The animals in the lidocaine-treated group received an initial dose of lidocaine hydrochloride (20 mg/kg, iv) 3 to 5 minutes prior to l-$CMR_g$ determination. Supplemental doses of lidocaine (4 mg/kg, iv) were given as needed during l-$CMR_g$ measurement to sustain

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TABLE 1. Physiologic Conditions during Local Cerebral Metabolic Glucose Determinations (Mean ± SEM)

| | Control (n = 7) | Lidocaine (n = 7) |
|---|---|---|
| $Pa_{CO_2}$ (torr) | 36.4 ± 0.3 | 36.5 ± 0.4 |
| $Pa_{O_2}$ (torr) | 161 ± 11 | 171 ± 6 |
| $pH_a$ | 7.43 ± 0.01 | 7.43 ± 0.02 |
| Mean blood pressure (torr) | 142 ± 8 | 63 ± 1* |
| Plasma glucose (mg/dl) | 226 ± 29 | 198 ± 30 |

* Significant difference, $P < 0.01$, Student's $t$ test for unpaired data.

EEG seizure activity. In preliminary experiments, these doses of lidocaine were necessary to produce an EEG pattern consisting of a very clear continuous burst suppression pattern.

The l-$CMR_g$ method employs $^{14}$C-2-deoxyglucose in trace amounts as a marker for tissue glucose uptake according to the technique developed by Sokoloff *et al.*[5] $^{14}$C-2-Deoxyglucose (New England Nuclear) was injected as a bolus (50 μCi/kg), and flushed with five times the catheter dead space within 4 sec using heparinized saline solution. Twenty arterial blood samples (50 μl) were taken from the shunt catheter side port over a 30-min period for determination of the $^{14}$C level in plasma. These samples were centrifuged and a 20-μl volume of plasma from each was pipetted into scintillation vials containing 20 ml of Biofluor (New England Nuclear). The vials were counted in a beta scintillation counter (Nuclear Chicago, Isocap 300). The counting efficiency was calculated from the external standard ratios. Three arterial blood samples were also taken for analysis of plasma glucose levels on a Beckman Glucose Analyzer.

At the end of the 30-min period, the animals in both groups were immediately sacrificed with a 2-ml intravenous infusion of saturated potassium chloride. The brains were rapidly removed and frozen in freon-22 cooled in isopentane (−35°C). The brains were then sectioned in a cryostat (American Optical, −20°C) into slices 20 μm thick from approximately 35 different levels of the brain. These sections were exposed to a single-emulsion x-ray film (Kodak SB-54) along with a set of calibrated $^{14}$C-acrylic standards for 12 days.

The developed films were analyzed on a microdensitometer (Gamma Scientific with an aperture of 0.1 mm. In some of the larger heterogeneous structures clear divisions into regional nuclei was not possible, and as many as 30 densitometric measurements spaced over the entire structure were averaged to compute l-$CMR_g$. All data were collected on-line with a PDP-11 computer. The final values for regional glucose uptake were calculated according to the formula developed by Sokoloff *et al.*[5] Statistical analysis was performed with Student's $t$ test for unpaired data (NS = not significant, $P > 0.05$).

## Results

As shown in table 1, the physiologic conditions existing during determinations of local glucose uptake in rats given lidocaine and in the control group were generally similar. Only the blood pressure was significantly lower ($P < 0.01$) in the experimental group. Lidocaine profoundly altered the electroencephalographic pattern (fig. 1). Following administration of an intravenous bolus of lidocaine, the EEG developed periods (lasting 1–12 sec) of repetitive high-voltage

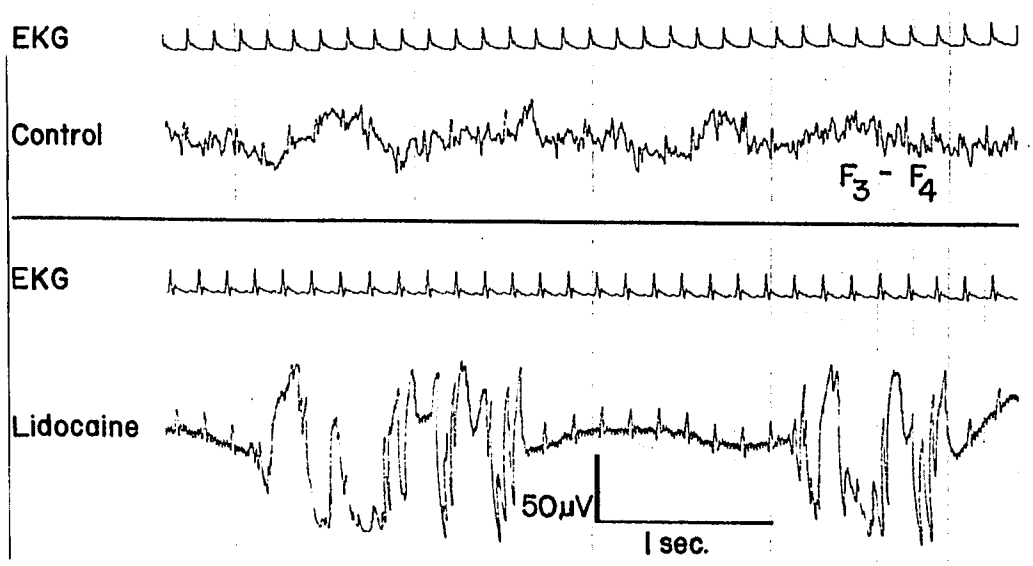


FIG. 1. Representative electroencephalograms (EEG) from a rat maintained on nitrous oxide (60 per cent) and oxygen before and after administration of lidocaine, 20 mg/kg, resulting in subcortical EEG seizure discharges.

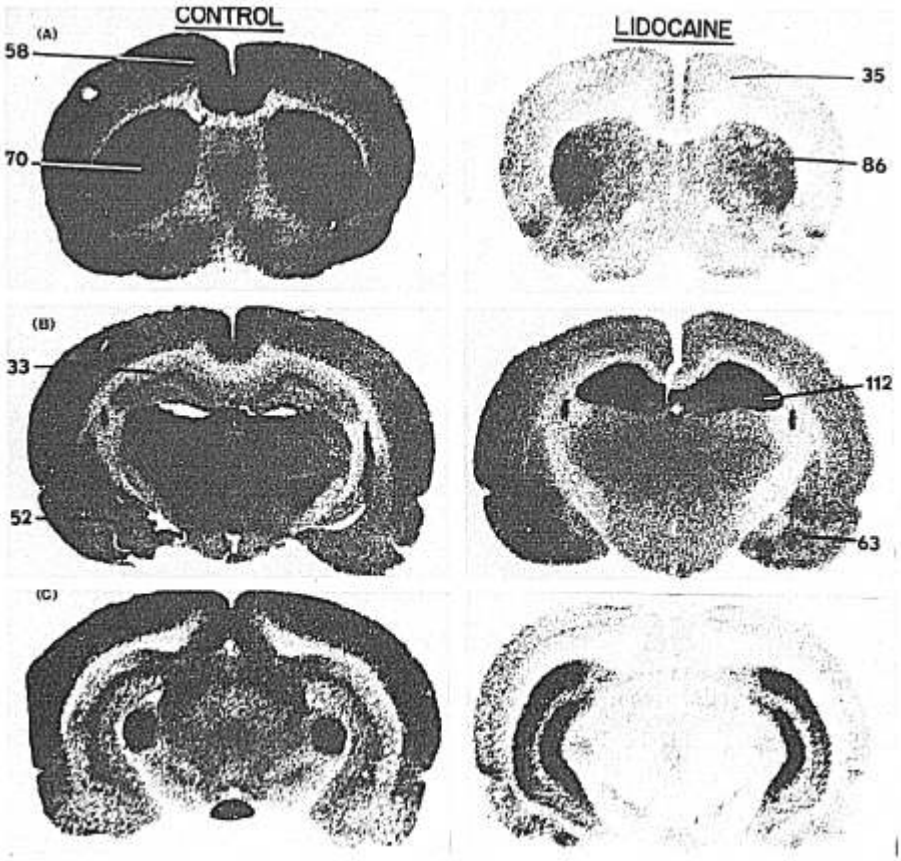


FIG. 2. Representative autoradiograms of corresponding brain sections (*A*, B, C) from a control rat and a lidocaine-treated rat. The metabolic rate ($\mu$mol·100 g$^{-1}$·min$^{-1}$ and a line are drawn to several selected structures. In section *A*, the local cerebral metabolic rate for glucose (l-$CMR_g$) rates for the frontal cortex (58::35) and the caudate/putamen (70::86) are identified and compared. In section *B*, the l-$CMR_g$ rates for the hippocampus (33::112) and amygdala (52::63) are compared. All data are mean ± SEM, and all enlargements are to the same scale.

(≅100 $\mu$volt) discharges at a frequency of about 9 Hz superimposed over periods of an almost isoelectric background voltage lasting 1–2 sec.

Figure 2 shows a composite of representative autoradiographic brain sections from a control rat and a lidocaine-treated rat. Table 2 lists the l-$CMR_g$ rates ($\mu$mol·100 g$^{-1}$·min$^{-1}$) in 25 structures for the control group and for the lidocaine-treated group. With lidocaine, significant decreases ($P < 0.05$) in l-$CMR_g$ occurred in 19 of the 25 structures examined. Rates of l-$CMR_g$ for lidocaine-treated animals remained unchanged from control values in the putamen, hypothalamus, septal nuclei, amygdala, and some brainstem nuclei. The hippocampus and choroid plexus developed marked increases ($P < 0.001$) in glucose uptake of 237 per cent and 65 per cent, respectively. Although the average l-$CMR_g$ values are reported for the amygdala and basal ganglia, the ranges of values within these structural areas were quite wide. For instance, in the lidocaine-treated group, the l-$CMR_g$ range among different nuclei in the amygdala was 30 ± 2 to 58 ± 7 $\mu$mol·100 g$^{-1}$·min$^{-1}$. The variability within the amygdala can be seen to some extent in figure 2 (sections *B* and *C*).

## Discussion

Lidocaine produces dose-related changes in cerebral electrical activity and behavior that require definition prior to discussion of its effect on l-$CMR_g$. As frankly toxic blood levels of lidocaine are approached, signs of CNS depression such as slurred speech and drowsiness occur.[3] This is accompanied by subcortical discharges consisting of the development of self-sustaining spike or spike-and-wave spindle bursts which may be difficult to record with standard EEG techniques.[3] The present study was performed in rats maintained in this subcortical seizure state in the absence of generalized convulsive activity. Higher doses of lidocaine lead to generalized seizures.

During lidocaine-induced irregular EEG spiking and spike-and-wave discharges, analysis of local cerebral glucose uptake reveals a regionally heterogeneous metabolic response. This is manifest as a generalized reduction in l-$CMR_g$ in most brain structures, including the cerebral cortex, accompanied by a 237 per cent increase in l-$CMR_g$ in the hippocampus (table 2). Using a modification of the Kety-Schmidt technique, which measures average cerebral blood

TABLE 2. Local Cerebral Glucose Utilization ($\mu$mol·100 g$^{-1}$·min$^{-1}$) (Mean ± SEM)

| | Control (n = 7) | Lidocaine (n = 7) | Per Cent Change | Significance* |
|---|---|---|---|---|
| Grey matter | | | | |
| Cortex | | | | |
| Frontal | 58 ± 6 | 35 ± 1 | −39 | .001 |
| Temporal | 63 ± 10 | 41 ± 2 | −35 | .001 |
| Parietal | 63 ± 5 | 34 ± 3 | −45 | .001 |
| Visual | 62 ± 7 | 38 ± 3 | −39 | .01 |
| Olfactory | 84 ± 13 | 38 ± 4 | −55 | .01 |
| Subcortex | | | | |
| Thalamus, radial nucleus | 70 ± 8 | 35 ± 2 | −50 | .01 |
| Thalamus, ventral nucleus | 75 ± 10 | 34 ± 3 | −54 | .01 |
| Lateral geniculate ganglion | 43 ± 6 | 21 ± 3 | −51 | .001 |
| Medial geniculate ganglion | 83 ± 9 | 38 ± 2 | −54 | .001 |
| Putamen/caudate nucleus | 70 ± 6 | 86 ± 8 | +21 | NS |
| Hippocampus: Ammon's horn | 33 ± 4 | 112 ± 8 | +237 | .001 |
| Hippocampus: dentate ganglion | 54 ± 4 | 49 ± 5 | −9 | NS |
| Amygdala | 52 ± 6 | 63 ± 12 | +21 | NS |
| Septal nucleus | 39 ± 3 | 46 ± 3 | +17 | NS |
| Pineal body | 64 ± 2 | 41 ± 3 | −36 | .001 |
| Hypothalamus | 34 ± 4 | 26 ± 3 | −26 | NS |
| Paraventricular nucleus | 35 ± 3 | 27 ± 1 | −24 | .05 |
| Interpeduncular nucleus | 81 ± 4 | 51 ± 2 | −37 | .001 |
| Brainstem | | | | |
| Inferior colliculus | 123 ± 8 | 36 ± 2 | −71 | .001 |
| Superior colliculus | 66 ± 5 | 33 ± 3 | −50 | .001 |
| Reticular formation | 39 ± 4 | 24 ± 2 | −39 | .01 |
| Cerebellar grey matter | | 30 ± 1 | −19 | NS |
| White matter | | | | |
| Corpus Callosum | 20 ± 3 | 13 ± 2 | −35 | .05 |
| Internal capsule | 15 ± 8 | 7 ± 2 | −57 | .05 |
| Medial lemniscus | 49 ± 4 | 24 ± 3 | −51 | .001 |
| Cerebellar white matter | 19 ± 7 | 8 ± 2 | −57 | .01 |

* By Student's $t$ test for unpaired data; NS = not significant, $P > 0.05$.

flow and metabolism in the cerebral cortex and adjacent white matter, Sakabe and colleagues found a 30 per cent decrease in the cerebral metabolic rate for oxygen ($CMR_{O_2}$) when lidocaine was infused in amounts just less than that necessary to produce generalized seizures.[2] Once the generalized seizures occurred, $CMR_{O_2}$ increased from 12 to 100 per cent above control values.[2] We found a similar 35 to 50 per cent reduction in local cortical glucose uptake during maintenance of a pregeneralized convulsive discharge pattern.

The low cortical metabolic rate existing simultaneously with normal or very high metabolic rates in subcortical structures may indicate that the epileptic discharges in our rats were recorded through an electrically silent cortex. This would be consistent with the hypothesis that lidocaine-induced seizures occur when subcortical structures are released from inhibition usually maintained by the cerebral cortex. The existence of this inhibition is supported in microelectrode studies by Wagman and De Jong.[6,7] Other factors possibly contributing to subcortical foci for lidocaine-induced seizures might include a selective lidocaine sensitivity and/or increased drug uptake in those brain structures showing increases in l-$CMR_g$ rates. Diazepam has been shown to selectively reduce local glucose uptake by 20–40 per cent in subcortical structures that include the thalamus, hippocampus, and amygdala.[8] This specific depression of lidocaine-related seizure generator sites may explain the effectiveness of diazepam in blocking or treating local anesthetic-induced seizures.[3]

Our finding of an increase in l-$CMR_g$ of more than 200 per cent in the hippocampus is consistent with reports indicating 60–300 per cent increases in cerebral metabolism during continuous generalized seizure activity.[9] However, because the $^{14}$C-deoxyglucose technique employed in our study cannot differentiate between aerobic or anaerobic glucose uptake, the percentage increase in local metabolic rate may not be stoichiometrically precise.

During seizures cerebral blood flow increases in an effort to meet the high metabolic demands. In this situation assurance of normal blood pressure and arterial blood oxygen tension helps to moderate the development of cerebral metabolic abnormalities.[9] Even when this is accomplished, evidence for a decrease in the cerebral high-energy phosphate pool and an increase in cerebral acidosis can be found.[9] This becomes progressively worse when the seizures are prolonged. In our rats high $Pa_{O_2}$ was maintained; however, arterial blood pressure declined to 63 torr

in lidocaine-treated animals. This pressure is well above the hypotensive arterial blood pressure threshold (40 torr) for cerebral metabolic stress in rats reported by Siesjö; however, it may not be sufficient to supply the biochemical demands of the activated hippocampus.[10] When similar hippocampal seizure discharges were driven by enflurane in rats maintained at the same blood pressure as in the present experiment, the ratio of hippocampal local cerebral blood flow to metabolic rate did not change, while it increased in other brain areas.[11] This may indicate that local cerebral ischemia could develop during drug-induced focal seizure activity. Further studies utilizing a local blood flow measurement technique are needed to determine whether cerebral blood flow during lidocaine-induced seizures is redistributed to areas of high metabolic demand, *e.g.*, the hippocampus.

Depth electrode studies of electrical activity of the brain during local anesthetic infusions indicate a particular sensitivity of the basolateral nuclear group of the amygdala to seizure initiation.[3] These seizure discharges propagate to nearby subcortical structures without spreading to the cortex.[3] The present autoradiographic study has confirmed these neurophysiologically obtained insights in biochemical terms. The metabolic maps obtained in our study of lidocaine-induced seizures are similar to those found by Myers and Shapiro in a study of enflurane anesthesia.[12] In their study, performed with 1.0, 1.5, and 2.0 MAC enflurane, they found cortical metabolism decreased by 16, 38, and 46 per cent, respectively. In this study also, subcortical structures showed increased l-$CMR_g$. The l-$CMR_g$ for the hippocampus increased by 35 per cent at 1 MAC, by 14 per cent at 1.5 MAC, and by 4 per cent at 2 MAC.[12] When seizures are caused by a chemical irritative focus in the cortex, a different metabolic map occurs. By use of such a discrete focus, Collins showed increases in metabolic activity in the ipsilateral cortex, basal ganglia, thalamus, and contralateral cerebellum.[13] With a larger seizure focus a more generalized increase in l-$CMR_g$ occurred throughout the brain and included the limbic system.[13] This pattern is very different from that obtained by us with local and general anesthetics.[12]

Our study has confirmed the expected coupling of a high metabolic rate with increased neurophysiologic seizure activity caused by lidocaine. Whether or not this high local cerebral metabolic rate results in ischemia depends upon the adequacy of the local cerebral blood flow increase in response to the requirement for enhanced flow. In monkeys with seizures due to a cortical penicillin focus, local cerebral blood flow increases occurred in the focus and in certain ipsilateral subcortical structures.[14] A single monkey with the same seizure focus had qualitatively similar increases in l-$CMR_g$ in the same structures.[15] Quantitative data linking l-$CMR_g$ to local blood flow during seizures are not available. However, it is clear that sustained generalized seizure activity can lead to neuronal loss, and that the hippocampus is especially vulnerable to ischemic–hypoxic insults.[15,16] The influence upon the above mentioned pathologic process of a high concentration of lidocaine in the brain remains unknown.

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