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Cerebral Energy State and Glycolytic Metabolism during Lidocaine Infusion in the Rat

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The effects of intravenously administered lidocaine on the cerebral cortical energy state and glycolytic metabolism were studied in rats. In one series, rats were divided into five groups according to EEG patterns, *i.e.*, control, desynchronized, synchronized, seizure (1-min duration) and recovery groups. With lidocaine infusion (0.75 mg/min), there were no significant changes from the control group in the cerebral energy state except for a modest increase in phosphocreatine (PCr) in the seizure group and a small decrease in ADP in the non-seizure groups. The cerebral energy charge remained unchanged. Lactate and pyruvate significantly decreased in the non-seizure groups. In a second series, rats were divided into five groups, *i.e.*, control, lidocaine seizure groups (5-min duration, 1.5 mg/min) at hypocapnia, normocapnia and hypercapnia, and a bicuculline (1.2 mg/kg) seizure group. The metabolic changes during lidocaine seizure were essentially the same as those observed in the seizure group in the first series. However, the increase in PCr during lidocaine seizure was significant only in the hypocapnic and the normocapnic groups. Bicuculline-induced seizures were accompanied by a significant decrease in high energy phosphates. In summary, neither a non-seizure nor seizure dose of lidocaine caused any reduction in the cerebral energy charge nor was there any evidence of increased anaerobic metabolism in the cerebral cortex during lidocaine-induced seizures. (Key words: Anesthetics, local: lidocaine. Brain: carbon dioxide tension; convulsions; electroencephalography; metabolism; oxygenation; seizure threshold. Pharmacology: bicuculline. Toxicity: convulsions.)

THE CEREBRAL METABOLIC RESPONSE to intravenous lidocaine is not directly dose-related. Thus in dogs, we observed that lidocaine decreased cerebral metabolic rate for oxygen (CMR_{O_2}) to 70 per cent of control at a non-seizure dose, but then increased CMR_{O_2} to 112 per cent of control with onset of seizures.[1] It is well known that the common convulsants strikingly increase CMR_{O_2} and alter the normal intracellular state of metabolism.[2] Thus it is reasonable to expect a possible cerebral metabolic derangement during lidocaine-induced seizures. However, in our previous study, the changes in CMR_{O_2} were accompanied by parallel changes in cerebral blood flow (CBF) and there was no suggestive evidence of anaerobic metabolism as judged by the oxygen glucose index or the cerebral venous oxygen tension.[1] To gain further insight into this question the levels of high energy phosphates, glycolytic intermediates and endproducts during lidocaine administration at both non-seizure and seizure doses need to be determined. Accordingly, the present study was designed to evaluate the effects of lidocaine on the cerebral energy state and glycolytic metabolism during lidocaine infusion at different EEG stages. It was found that neither non-seizure nor seizure doses of lidocaine have any significant effect on the cerebral energy charge.

Materials and Methods

Forty-nine unstarved male rats, weighing 290–390 g, were anesthetized with 1.5 per cent halothane, and 70 per cent nitrous oxide in oxygen. The rats were ventilated via a tracheotomy with an animal ventilator (Rodent respiration pump 681®, Harvard Apparatus Co., U. S. A.) and were paralyzed with d-tubocurarine, 0.5 mg/kg initially followed by 0.25 mg/kg every 30 min. The right femoral artery and vein were catheterized for monitoring direct arterial blood pressure, blood sampling, and the injection of fluid and drugs. The skull was exposed and the EEG was recorded from bipolar frontoparietal leads, using screw electrodes. After completion of the operation, halothane was discontinued and the rats were ventilated with 70 per cent nitrous oxide in oxygen. Thereafter at least 30 min were allowed to elapse in order to obtain stable blood pressure, blood gas values, and body temperature. Blood samples for gas analysis (BMS2 Mk 2® blood micro system and PHM 72 Mk 2® digital acid-base analyzer, Radiometer Ltd., Denmark) were taken at frequent intervals, including a sample immediately before freezing of the brain. The concentration of lidocaine in blood taken immediately before freezing of the brain, was analyzed by gas chromatography.[3] Blood loss due to sampling was replaced by fresh heparinized blood. Body temperature was

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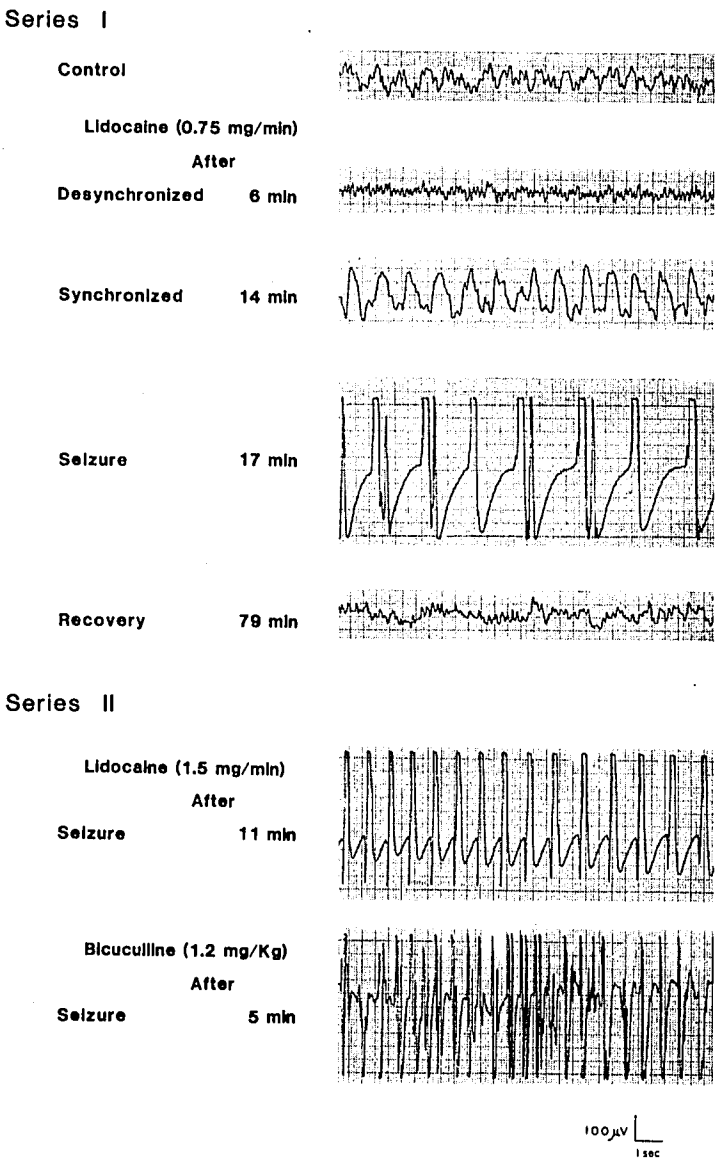

FIG 1. Representative EEG changes with increasing dose of lidocaine in series I and EEG seizures with lidocaine at normocapnia and bicuculline in series II. EEG patterns were divided into three stages in series I. EEGs taken at the indicated time after the start of drug administration were recorded immediately before freezing of the brain. During lidocaine seizures, the brain was frozen 1 and 5 min after the onset of seizures pattern in series I and II, respectively.

kept at 37 ± 0.1° C (mean ± SEM) by a warming blanket and hematocrit was maintained at 43.3 ± 1.5 per cent.

The rats were divided into two series. In series I, lidocaine was administered at a constant rate of 0.75 mg/min. With this technique, there were two distinguishable EEG stages before the onset of seizure: desynchronized and synchronized stages. Twenty-five rats were randomly assigned into five groups before the lidocaine infusion, *i.e.,* control (6 rats), desynchronized (4 rats), synchronized (5 rats), seizure (5 rats) and recovery (5 rats) groups. Desynchronized, synchronized and seizure patterns appeared at 5.2 ± 0.5, 8.6 ± 0.8 and 16.2 ± 0.9 min after the start of lidocaine infusion, respectively. After the desynchronized pattern appeared, the infusion was continued for 30 sec more, with the synchronzied pattern 1 min more, and with the seizure pattern 30 s more. The desynchronized pattern had a duration of 3.4 ± 0.9 min, the synchronized pattern 7.7 ± 0.8 min, and the seizure pattern 3.2 ± 1.0 min, which were measured in the recovery group. The brain was frozen 1, 5 and 1 min after the onset of the desynchronized, synchronized and seizure patterns, respectively. In the recovery group the brain was frozen 60 min after the end of seizure. In series II, twenty-four rats were randomized into five groups, *i.e.,* control (5 rats), lidocaine-induced seizures at hypocapnia (5 rats), at

TABLE 1. The Physiological Parameters of Control, Lidocaine and Bicuculline Groups and Lidocaine Concentration in Arterial Blood in Series I and II

	n	Pa_{O_2} (torr)	Pa_{CO_2} (torr)	*p*H	MAP* (torr)	Lidocaine (μg/ml)
Series I						
Control	6	107 ± 4	37.5 ± 0.7	7.44 ± 0.01	139 ± 3	—
Lidocaine						
Desynchronized	4	107 ± 3	32.5 ± 1.3†	7.46 ± 0.01	120 ± 2†	4.4 ± 0.7‡
Synchronized	5	119 ± 3	32.2 ± 0.8†	7.46 ± 0.02	130 ± 5	7.3 ± 0.4‡@
Seizure	5	113 ± 4	29.4 ± 2.0†	7.48 ± 0.02	91 ± 9†	9.3 ± 0.8‡@
Recovery	5	110 ± 2	34.3 ± 1.4	7.48 ± 0.02	137 ± 4	2.2 ± 0.4†
Series II						
Control	5	113 ± 6	37.3 ± 0.6	7.45 ± 0.01	146 ± 4	—
Lidocaine						
Hypocapnia	5	128 ± 8	19.8 ± 1.7†	7.49 ± 0.02	60 ± 8†	35.7 ± 2.4‡
Normocapnia	5	129 ± 5	35.2 ± 1.1	7.41 ± 0.02	67 ± 5†	23.0 ± 3.2‡
Hypercapnia	4	121 ± 8	68.9 ± 2.4†	7.21 ± 0.02†	86 ± 9†	14.8 ± 2.6‡
Bicuculline	5	86 ± 6†	31.3 ± 1.2†	7.33 ± 0.02†	187 ± 3†	—

* MAP: mean arterial pressure.

† Significantly different from control ($P < 0.05$). The values are means ± SEM.

‡ Significantly different between groups ($P < 0.05$) except for the difference between synchronized and seizure groups (@).

normocapnia (5 rats) and at hypercapnia (4 rats) and bicuculline-induced seizure (5 rats) groups. The ventilation was kept constant and desired levels of Pa_{CO_2} were obtained by changing the concentration of inspired carbon dioxide, and at least 15 min were allowed to elapse before the administration of the drugs. The onset of seizure was 7.4 ± 1.0, 6.1 ± 0.5 and 3.5 ± 0.4 min after the start of lidocaine infusion (1.5 mg/min) at hypocapnia, normocapnia and hypercapnia, respectively, and was 5–6 sec after the intravenous injection of bicuculline (1.2 mg/kg). After the lidocaine seizure patterns appeared, the infusion was continued 3 min more. The brain was frozen 5 min after the onset of seizure in series II.

In all rats, the brain was frozen in situ by pouring liquid nitrogen into a funnel over the intact skull bone following Ponten's technique,[4] and cerebral cortical tissue samples were stored and dissected in liquid nitrogen. After weighing, the cerebral tissue was extracted with methanol-perchloric acid below 0°C. The techniques of Lowry and Passonneau[5] were used for determination of phosphocreatine (PCr), ATP, ADP, AMP, glucose, glucose-6-phosphate (G-6-P), lactate (L), and pyruvate (P) concentrations in the cerebral cortical tissue. The energy charge (EC) was calculated as suggested by Atkinson.[6] All enzymatic analyses were done by a Hitachi spectrophotometer 124® (Hitachi, Ltd., Japan) with an attached linear-log recorder and were done in duplicate except for glucose and lactate. Enzymes and coenzymes for the assay are commercially available (Boehringer Mannheim Gm6H, West Germany). Statistical differences were compared between control and the drug groups using the one-way analysis of variance with critical-difference testing. Differences in lidocaine concentration between groups were analyzed using Student's *t* test for unpaired data. $P < 0.05$ was considered to be significant.

Results

Representative EEG patterns in the rats of series I and the EEG seizures induced with lidocaine at

TABLE 2. Effects of Lidocaine on the Cerebral Cortical Energy State in Series I

	PCr* (μmol/g)	ATP* (μmol/g)	ADP* (μmol/g)	AMP* (μmol/g)	EC*
Control	5.42 ± 0.13	3.04 ± 0.04	0.382 ± 0.005	0.042 ± 0.007	0.934 ± 0.002
Desynchronized	5.48 ± 0.24	3.04 ± 0.04	0.359 ± 0.006†	0.033 ± 0.008	0.938 ± 0.003
Synchronized	5.28 ± 0.14	2.97 ± 0.02	0.345 ± 0.007†	0.027 ± 0.003	0.941 ± 0.001
Seizure	6.00 ± 0.08†	3.09 ± 0.03	0.365 ± 0.006	0.034 ± 0.001	0.938 ± 0.001
Recovery	5.50 ± 0.06	3.01 ± 0.01	0.360 ± 0.006†	0.032 ± 0.004	0.938 ± 0.001

* PCr: phosphocreatine; ATP: adenosine triphosphate; ADP: adenosine diphosphate; AMP: adenosine monophosphate; EC: energy charge.

† Significantly different from control ($P < 0.05$). The values are means ± SEM.

TABLE 3. Effects of Lidocaine on the Cerebral Cortical Glycolytic Metabolism in Series I

	Glucose (μmol/g)	G-6-P* (μmol/g)	Lactate (μmol/g)	Pyruvate (μmol/g)	L/P*
Control	2.73 ± 0.26	0.145 ± 0.019	1.44 ± 0.07	0.137 ± 0.008	10.7 ± 0.6
Desynchronized	3.51 ± 0.19	0.117 ± 0.019	1.04 ± 0.08†	0.097 ± 0.008†	10.8 ± 0.2
Synchronized	3.06 ± 0.26	0.131 ± 0.013	0.90 ± 0.06†	0.093 ± 0.005†	9.6 ± 0.6
Seizure	3.66 ± 0.43	0.154 ± 0.013	1.51 ± 0.05	0.124 ± 0.002	12.2 ± 0.4
Recovery	2.55 ± 0.26	0.125 ± 0.019	1.27 ± 0.06	0.134 ± 0.013	9.8 ± 0.9

* G-6-P: glucose-6-phosphate; L/P: lactate/pyruvate ratio.

† Significantly different from control ($P < 0.05$). The values are means ± SEM.

normocapnia and with bicuculline in the rats of series II are shown in figure 1. Control EEG was characterized by 1–2 Hz waves superimposed by 4 Hz waves. With lidocaine infusion, there were two distinguishable EEG stages before the onset of seizure, namely, desynchronized and synchronized stages. In some rats, a transient desynchronized pattern was interposed during the early synchronized stage. The synchronized stage was followed by the irregular appearance of large spike and slow waves and then a typical seizure pattern. The seizure pattern induced by lidocaine contained fewer spikes compared with that induced by bicuculline.

Table 1 summarizes the physiological variables and blood lidocaine concentrations in the rats of series I and II. The mean arterial pressure (MAP) during lidocaine infusion was higher in series I than in series II. In series II, MAP decreased significantly in the lidocaine groups, whereas it increased in the bicuculline group. Lidocaine concentrations in blood were significantly different among the groups except for the difference between the synchronized and the seizure groups in series I. Tables 2, 3, 4 and 5 summarize the cerebral cortical energy phosphates, glycolytic metabolites, EC, and the lactate/pyruvate (L/P) ratios in the rats of series I and II. In series I, EC remained unchanged, though ADP decreased significantly with non-seizure doses and PCr increased with seizure doses. Lactate and pyruvate decreased significantly with non-seizure doses. In series II, with lidocaine, EC remained unchanged and PCr increased in the hypocapnia and the normocapnia groups. Lactate did not change during normocapnic seizure. With bicuculline, PCr, ATP, EC and glucose decreased significantly and unproportional increases in lactate and pyruvate resulted in an increase in L/P ratio.

Discussion

In the present study, there are at least two distinguishable EEG patterns before the onset of lidocaine seizure. This sequence of EEG changes suggests a complex alteration of cerebral function with increasing doses of lidocaine. However, such alterations were not accompanied by large shifts in the cerebral energy state or in glycolytic metabolism (tables 2 and 3). Even at seizure doses lidocaine did not cause any reduction in the cerebral energy charge. Seizures induced by common convulsants, *i.e.*, bicuculline, pentylentetrazol, homocystaine, or electrical stimulation are associated with increases in both CBF and CMR_{O_2}. The increase in CBF usually exceeds that in CMR_{O_2}[2]. However, such seizures are accompanied by a decrease in PCr and ATP, an increase in ADP and AMP, no change or a decrease in glucose, and an increase in lactate and L/P ratio.[2] Presumably in these circumstances, a generalized increase in neuronal activity occurs, and only up to some critical level of neuronal activity can energy production be increased sufficiently to maintain the cerebral energy state. The

TABLE 4. Effects of Lidocaine- and Bicuculline-induced Seizures on the Cerebral Cortical Energy State in Series II

	PCr* (μmol/g)	ATP* (μmol/g)	ADP* (μmol/g)	AMP* (μmol/g)	EC*
Control	5.32 ± 0.04	3.07 ± 0.03	0.383 ± 0.012	0.019 ± 0.003	0.939 ± 0.001
Hypocapnia	5.71 ± 0.16†	2.98 ± 0.06	0.369 ± 0.013	0.022 ± 0.004	0.939 ± 0.002
Normocapnia	5.92 ± 0.05†	2.99 ± 0.05	0.362 ± 0.004	0.020 ± 0.005	0.941 ± 0.002
Hypercapnia	5.59 ± 0.10	3.07 ± 0.06	0.363 ± 0.015	0.017 ± 0.003	0.943 ± 0.002
Bicuculline	3.85 ± 0.12†	2.86 ± 0.04†	0.400 ± 0.019	0.023 ± 0.006	0.932 ± 0.003†

* PCr: phosphocreatine; ATP: adenosine triphosphate; ADP: adenosine diphosphate; AMP: adenosine monophosphate; EC: energy charge.

† Significantly different from control ($P < 0.05$). The values are means ± SEM.

TABLE 5. Effects of Lidocaine- and Bicuculline-induced Seizures on the Cerebral Cortical Glycolytic Metabolism in Series II

	Glucose (μmol/g)	G-6-P* (μmol/g)	Lactate (μmol/g)	Pyruvate (μmol/g)	L/P*
Control	4.03 ± 0.41	0.126 ± 0.018	1.88 ± 0.09	0.120 ± 0.003	15.5 ± 0.8
Hypocapnia	4.48 ± 0.65	0.151 ± 0.029	3.53 ± 0.50†	0.134 ± 0.014	27.3 ± 4.0†
Normocapnia	4.15 ± 0.21	0.144 ± 0.020	1.40 ± 0.09	0.074 ± 0.006†	19.3 ± 1.9
Hypercapnia	5.05 ± 0.50	0.188 ± 0.013	0.63 ± 0.05†	0.047 ± 0.004†	13.6 ± 2.0
Bicuculline	1.19 ± 0.26†	0.128 ± 0.029	8.76 ± 0.19†	0.152 ± 0.005†	57.6 ± 1.1†

* G-6-P: glucose-6-phosphate; L/P: lactate/pyruvate ratio.

† Significantly different from control ($P < 0.05$). The values are means ± SEM.

present study shows that bicuculline decreased high energy phosphates and increased lactate (tables 4 and 5) and is in agreement with previous studies.[2,7] Therefore, the effects of lidocaine-induced seizures can not be compared to those induced by bicuculline or pentylentetrazol. There is, however, a possibility of perturbation of high energy phosphates during the early stage of lidocaine seizure which may have been missed in this study. It is known that in bicuculline or electroshock-induced seizures, the energy deficit is largest during the first 3–15 sec, and returns to a normal rate only gradually.[2] To clarify this question in lidocaine seizures, determination of glycolytic metabolites and high energy phosphates at a much earlier period of seizure is necessary. Moreover, there is a possibility that metabolic perturbation occurs in another part of the brain, particularly in the limbic system, which is known as a focus of lidocaine-induced seizures.[8] The increase in PCr during lidocaine seizure had not been anticipated since it is unlikely that seizures would produce a high energy state, and moreover, common convulsants decrease both PCr and ATP.[2] McMillan and Siesjö[9] found an increase in PCr during barbiturate anesthesia and suggested that barbiturates might induce an alkaline shift in intracellular *p*H, and hence the increase in PCr level was, at least in part, due to a *p*H-dependent shift in the creatine phosphokinase equilibrium. The increase in PCr was reversed when intracellular *p*H was brought back to normal by the addition of carbon dioxide. A similar explanation may be made for lidocaine. Cerebral lactate and pyruvate during lidocaine-induced seizures varied inversely with Pa_{CO_2} as expected (tables 1 and 5).[10] The increase in lactate and L/P ratio in the hypocapnia group may be due to the effect of intracellular alkalosis and/or stimulation of glycolysis by cerebral hypoxia due to a reduction of CBF.[11] However, it is known that biochemical derangement due to hypocapnia by itself occurs only at 10 torr of Pa_{CO_2}.[11] Of more importance is the unchanged level of lactate during lidocaine seizure at normocapnia, which indicates no evidence of increased anaerobic metabolism. In the absence of seizures, the small decreases in ADP, lactate and pyruvate (tables 2 and 3) were similar to those observed with barbiturates.[12,13] Goldberg *et al.*[14] found a decrease in ADP during pentobarbital anesthesia, and suggested that the hydrolysis of ATP might be minimized while tissue was being fixed and sampled from animals treated with barbiturate. This may also be the case for lidocaine.

Blood concentrations of lidocaine in the rats of series II reflected the effect of Pa_{CO_2} on the threshold of lidocaine seizures (table 1).[15] The systemic effects of lidocaine-induced seizures were also different from those of bicuculline seizures. An increase in MAP with bicuculline might maintain CBF during seizures. In contrast, MAP during lidocaine-induced seizures decreased significantly, particularly in the rats of series II, presumably because of higher blood concentration of lidocaine which caused cardiovascular depression. However, CBF was apparently adequate since there was no evidence of increased anaerobic glycolysis in the rats of series I. It is known that biochemical derangement during seizures can be minimized by maintenance of ventilation and circulation,[16] and that elementary cardiopulmonary support is essential to treat the toxic reactions induced by lidocaine. This is supported by the results of the present study.

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