Effects of Lidocaine on Cerebral Energy State and Glycolytic Metabolism in the Rat

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ABSTRACT

The effects of intravenously administered lidocaine on the cerebral cortical energy state and glycolytic metabolism were studied in rats. 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 (0.75mg/min), there were no significant changes from the control group in the cerebral energy state except for a modest increase in phosphocreatine 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. It is concluded that neither a non-seizure nor seizure dose of lidocaine caused any reduction in the cerebral energy charge. There was no evidence of increased anaerobic metabolism in the cerebral cortex during lidocaine-induced seizures.

Key words: lidocaine; seizure; cerebral metabolism; electroencephalography

INTRODUCTION

The cerebral metabolic response to intravenous lidocaine is not directly dose-related. In dogs, Sakabe and co-workers observed that lidocaine decreased cerebral metabolic rate for oxygen ($CMRo_2$) to 70 per cent of control at a non-seizure dose, but then increased $CMRo_2$ to 112 per cent of control with the onset of seizures[1]. It is well known that the common convulsants strikingly increase $CMRo_2$ 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 the previous study the changes in $CMRo_2$ 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.

METHODS

Twenty-five unstarved male rats, weighing 290 to 370 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. Ventilation was kept constant after the start of lidocaine infusion. 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. Blood loss due to sampling was replaced by fresh heparinized blood. Body temperature was kept at 37 ± 0.0°C (mean±SEM) by a warming blanket and hematocrit was maintained at 45.4 ± 1.5 per cent.

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 synchronized pattern 1 min more, and with the seizure pattern 30 sec more. The desynchronized pattern had a duration of 3.4 ± 0.9, the synchronized pattern 7.7 ± 0.8 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, the synchronized and the seizure patterns had occurred, respectively. In the recovery group the brain was frozen 60 min after the end of seizure.

In all rats, the brain was frozen in situ by pouring liquid nitrogen into a funnel over the intact skull bone following Pontén's technique[3], and cerebral cortical tissue samples were kept and dissected in liquid nitrogen. After weighing, the cerebral tissue was extracted with HCl-methanol perchloric acid below 0°C. The techniques of Lowry and Passonneau[4] were used for determination of phosphocreatine (PCr), ATP, ADP, AMP, glucose, glucose-6-phosphate (G-6-P), lactate, and pyruvate concentrations in the cerebral cortical tissue. The energy charge (EC) was calculated as suggested by Atkinson[5]: $EC = (ATP + 1/2\ ADP)/(ATP + ADP + AMP)$.

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 were obtained from Boehringer Mannheim Gm6H, West Germany. Statistical differences were compared between control and the lidocaine groups using the one-way analysis of variance with critical-difference testing. $P < 0.05$ was considered to be significant.

RESULTS

Representative EEG patterns in the rats are shown in Figure 1. Control EEG was characterized by 1 to 2 Hz waves, superimposed by 4 Hz waves. With lidocaine infusion, there were two distinguishable EEG stages before the onset of seizures, namely, desynchronized and synchronized stages. In some rats, a transient desynchronized pattern was interposed during the synchronized stage. The synchronized stage was followed by the irregular appearance of large spike and slow waves and then a typical seizure pattern.

Table I summarizes the physiological parameters before freezing of the brain. $Paco_2$ and mean arterial pressure (MAP) decreased significantly from control except for recovery group in $Paco_2$ and for synchronized and recovery groups in MAP, though there was no statistical significance between control and the values before lidocaine infusion in lidocaine groups. Figures 2, 3 and 4 illustrate the high-energy phosphate com-

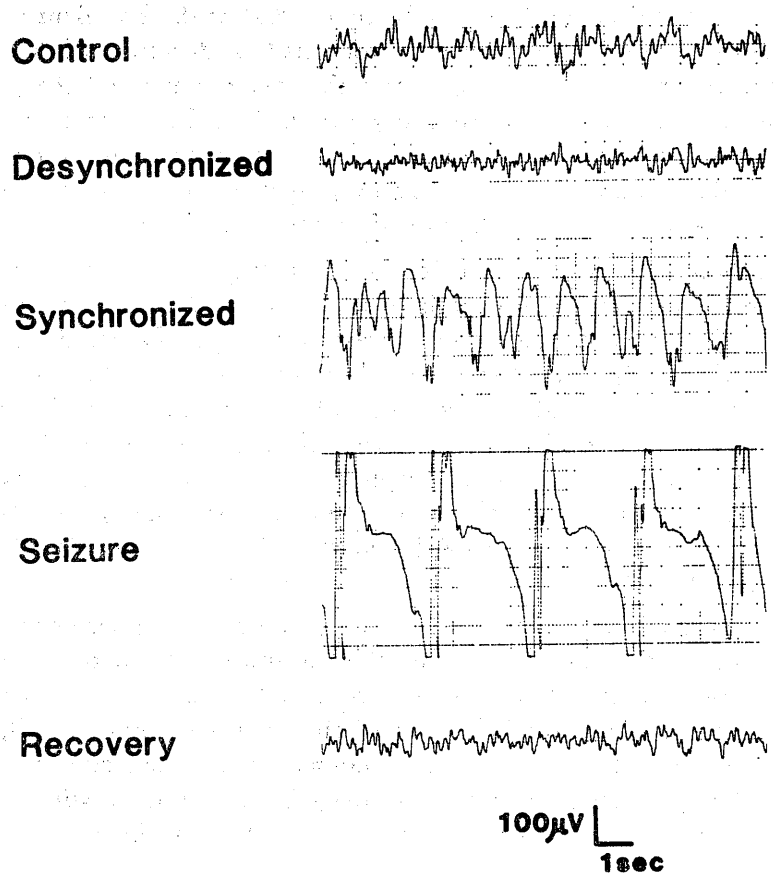

Fig. 1. Representative EEG changes with increasing doses of lidocaine, which were divided into three stages. EEGs were recorded immediately before freezing of the brain.

pounds, glycolytic metabolites, EC and lactate/pyruvate (L/P) ratios in the cerebral cortical tissue in the rats. PCr increased significantly in the seizure group. EC remained unchanged in the all groups, though ADP decreased significantly with non-seizure doses of lidocaine. Lactate and pyruvate decreased significantly with non-seizure doses, however, L/P ratio did not change significantly with non-seizure and seizure doses.

DISCUSSION

In the present study, there are at least two distinguishable EEG patterns before the onset of lidocaine-induced seizures. This sequence

Table I The physiological parameters of control and lidocaine groups.

	n	Pa_{O_2} torr	Pa_{CO_2} torr	pH	MAP torr
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*
Synchronized	5	119±3	32.2±0.8*	7.46±0.02	130±5
Seizure	5	113±4	29.4±2.0*	7.48±0.02	91±9*
Recovery	5	110±2	34.3±1.4	7.48±0.02	137±4

n: number of animals
MAP: mean arterial pressure
All values show mean±SEM.
* Significantly different from control ($P<0.05$).

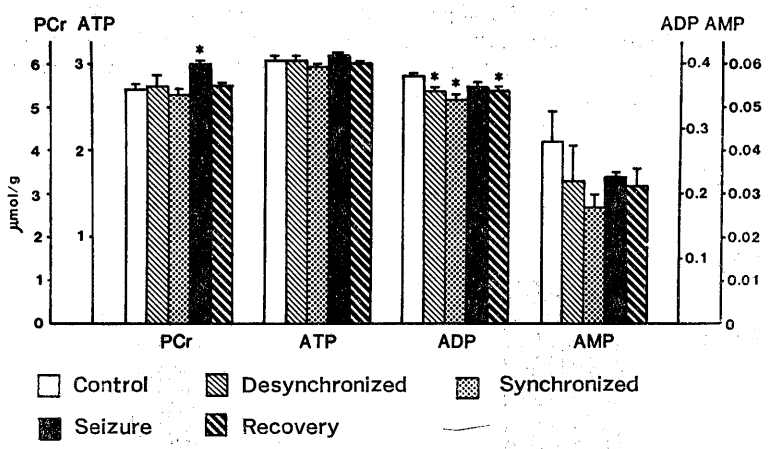

Fig. 2. Effects of lidocaine on the cerebral energy state in the rats. PCr: phosphocreatine. All values show mean ± SEM. Control values: PCr; 5.42±0.13, ATP; 3.04±0.04, ADP; 0.382±0.005, AMP; 0.042 ±0.007. * Significantly different from control ($P<0.05$).

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 glycolytic metabolism (Figure 2, 3 and 4). Lidocaine at seizure doses neither reduced EC nor increased lactate and L/P ratio, rather it caused an elevation of PCr. Seizures induced by common convulsants, i.e., bicuculline, pentylentetrazol, homocysteine, or electrical stimulation are associated with increases in both CBF and $CMRo_2$. The increase in CBF usually exceeds that in $CMRo_2$[2]. However, such seizures are accompanied by a decrease in PCr and ATP, an increase in ADP and AMP, no change or a decre-

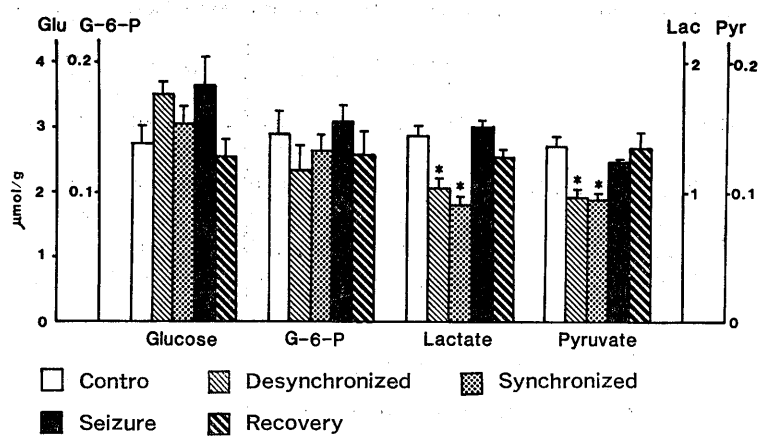

Fig. 3. Effects of lidocaine on the cerebral glycolytic metabolism in the rat. G-6-P: Glucose-6-phosphate. All values show mean ± SEM. Control values: glucose; 2.73 ± 0.26, G-6-P; 0.145 ± 0.019, lactate; 1.44 ± 0.07, pyruvate; 0.137 ± 0.008. *Significantly different from control ($P<0.05$).

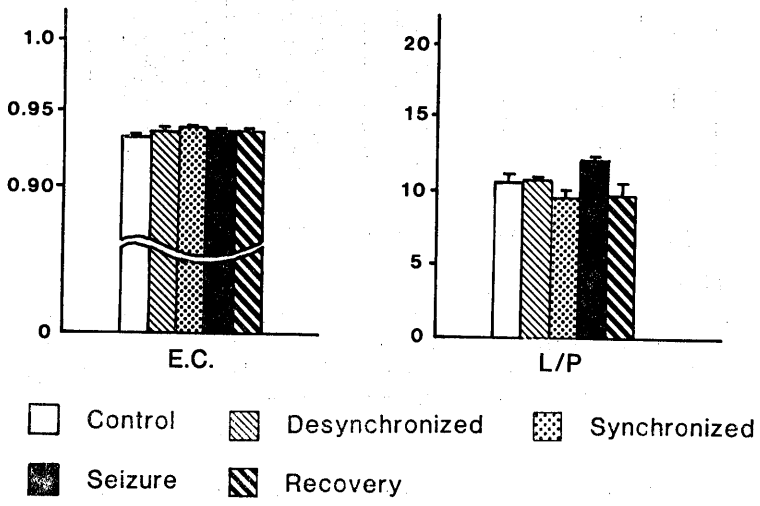

Fig. 4. Effects of lidocaine on the cerebral energy charge and lactate/pyruvate (L/P) ratio in the rat. EC: energy charge. All values show mean ± SEM. Control values: EC; 0.934±0.002, L/P; 10.7±0.6.

ase 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 energy production can be increased sufficiently to maintain the cerebral energy state. Therefore, the effects of lidocaine-induced seizures can not be compared

to those induced by common convulsants. 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 to 15 sec, and returns to a normal rate only gradually[2]. To clarify this question in lidocaine-induced seizures, determination of glycolytic metabolites and high energy phosphates at 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[6]. The increase in PCr during lidocaine-induced seizure had not been anticipated since it is unlikely that seizures would produce high energy state, and moreover common convulsants were known to decrease PCr and ATP[2]. MacMillan and Siesjö[7] found an increase in PCr during barbiturate anesthesia and suggested that barbiturate might induce an alkaline shift in intracellular pH, and hence the increase in PCr level might be at least in part, due to a pH-dependent shift in the creatine phosphokinase equilibrium, since the increase in PCr was reversed when intracellular pH was brought back to normal by addition of carbon dioxide. Further study is mandatory in applying a similar explanation to the present results. Of more importance is the unchanged level of lactate during lidocaine-induced seizures, which indicates no evidence of increased anaerobic metabolism. In the absence of seizures, the small decreases in ADP, lactate and pyruvate (Figure 2 and 3) were similar to those observed with barbiturate.[8,9] Goldberg et al.[10] found a decrease in ADP during the 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. Decrease in MAP during lidocaine infusion was caused by its depressant effects on cardiovascular system. However, CBF was apparently adequate since there was no evidence of increased anaerobic glycolysis in the seizure group. It is known that biochemical derangement during seizures could be minimized by maintenance of ventilation and circulation[11], 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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