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Epinephrine Increases the Extracellular Lidocaine Concentration in the Brain

A Possible Mechanism for Increased Central Nervous System Toxicity

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Background: **Local anesthetics exert central nervous system (CNS) toxicity by inhibiting intracerebral neuronal activity, while epinephrine augments the CNS toxicity of intravenously administered local anesthetics. Viewed together, increases of extracellular concentrations of local anesthetics in the brain may be directly associated with increased CNS toxicity. The authors examined the hypothesis that epinephrine enhances the CNS toxicity of lidocaine by increasing the extracellular concentration in the brain.**

Methods: **An awake, spontaneously breathing rat model was used. Twenty male Sprague-Dawley rats received an intravenous infusion of lidocaine (3 mg · kg^{-1} · min^{-1}; group C) or lidocaine with epinephrine (3 mg · kg^{-1} · min^{-1} and 2 μg · kg^{-1} · min^{-1}, respectively; group E) for 10 min (n = 10 in each group). Effects of epinephrine on the convulsive dose and concentrations of total (protein-bound and unbound) and unbound lidocaine in plasma were examined. Concentrations of extracellular lidocaine in the cerebral nucleus accumbens were quantitatively determined by a microdialysis method.**

Results: **The convulsive dose of lidocaine was significantly lower in group E than in group C (22.4 ± 5.5 *vs.* 27.9 ± 3.1 mg/kg, respectively; $P < 0.05$). Overall concentrations and area under the plasma concentration–*versus*–time curve of unbound lidocaine in group E were significantly higher than those in group C. Concentrations of extracellular lidocaine in the nucleus accumbens in group E were comparable to those of unbound fraction in plasma and were also significantly higher than those in group C.**

Conclusions: **Concomitant administration of epinephrine significantly enhanced the CNS toxicity of intravenously administered lidocaine. Increased extracellular concentration in the brain would be related to this mechanism.**

EPINEPHRINE enhances the central nervous system (CNS) toxicity of intravenously administered local anesthetics[1–3]; however, its mechanism is still unclear. Previous studies have shown that epinephrine decreases the convulsive doses of lidocaine and bupivacaine by increasing their plasma concentrations *via* peripheral vasoconstriction.[1,2] Other studies have demonstrated that epinephrine decreases the threshold for convulsions, *i.e.*, the concentrations of lidocaine in plasma and in the brain at the onset of convulsions.[3] In these studies, however, investigations were focused on the concentrations of total (protein-bound and unbound) fraction of local anesthetics in plasma or in the brain, and accordingly, the mechanism accounting for such an enhanced CNS toxicity by epinephrine was not elucidated. Because potentiating the excitatory neuronal activity by inhibiting intracerebral γ-aminobutyric acid–mediated neurons is closely involved in the development of the CNS toxicity of local anesthetics,[4] and only the unbound fraction is accessible to the neuronal cells, eventual increase of the extracellular concentration of the unbound, pharmacologically active fraction would play an important role in these situations. Nevertheless, there have been no studies directly addressing the effects of epinephrine on the extracellular concentration of lidocaine in the brain *in vivo*. We sustained the hypothesis that epinephrine would augment the CNS toxicity of lidocaine by increasing its intracerebral concentration, which was determined by microdialysis in awake, spontaneously breathing rats. For quantitative measurement of lidocaine in the brain, we used a retrodialysis technique with *in vivo* calibration.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

Animal Preparation

After approval from the Institutional Animal Care and Use Committee of the Graduate School of Medicine, Osaka City University, Osaka, Japan, 20 male Sprague-Dawley rats aged 8–10 weeks and weighing 350–400 g (CLEA Japan, Inc., Tokyo, Japan) were included in the study. During general anesthesia with intraperitoneal ketamine, the animals were placed on the stereotaxic instrument (Narishige, Tokyo, Japan), and the guide cannulas (12 mm length and 0.5 mm OD, GI-12; Eicom, Kyoto, Japan) were inserted so that the tips were placed into the nucleus accumbens (anterior 1.7 mm, lateral 1.4 mm, vertically 6.0 mm from the bregma suture). Two or 3 days later, during general anesthesia with sevoflurane, the carotid artery and the jugular vein were cannulated

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with polyethylene catheters to monitor mean arterial blood pressure (MAP) and heart rate (HR) and also for blood sampling and infusion of drugs. These catheters were tunneled subcutaneously to the posterior cervical region so that the animals could move freely. Before emergence from anesthesia, the microdialysis probe (A-UI-12-02, 2 mm membrane length, 0.35 mm OD, molecular weight cutoff 50 kd; Eicom) was inserted through the guide cannula and was perfused with artificial cerebrospinal fluid consisting of electrolytes (147 mM Na^+, 4 mM K^+, 2.3 mM Ca^{2+}, 155.6 mM Cl^-) and containing 3′-hydroxylated bupivacaine (200 ng/ml). The animals were placed in a semidark, closed cardboard box to recover fully for a few hours before the experiment, and the arterial catheter was connected to a pressure transducer. MAP and HR were recorded continuously on a polygraph (RM-6000; Nihon Kohden, Tokyo, Japan).

Experimental Protocol

After preparation, the animals were randomly assigned to the control (group C) or epinephrine (group E) group ($n = 10$ in each group). After baseline measurement, lidocaine alone (3 mg · kg^{-1} · min^{-1}; group C) or lidocaine with epinephrine (3 mg · kg^{-1} · min^{-1} and 2 μg · kg^{-1} · min^{-1}, respectively; group E) was intravenously administered for 10 min. Neither of these agents contains antioxidants, and pH was 6.5 for both. MAP and HR were continuously monitored, and the animals were observed for detection of the onset of convulsions, defined as tonic–clonic movements, by one of the authors (Y.O.), who was unaware of the group allocation. Arterial blood samples (0.3–0.5 ml) were drawn before infusion of lidocaine (baseline); at the onset of partial muscle twitch preceding convulsions; and 10, 13, 16, 20, 25, 30, 40, 55, 70, 100, 130, and 160 min after the start of intravenous lidocaine infusion for measurement of blood gases and/or plasma concentrations of lidocaine. Blood was replaced with an equal volume of heparinized saline. At the onset of convulsions, supply of oxygen to the box was started to prevent convulsion-induced hypoxia and lasted for 30 min.

In Vitro *and* in Vivo *Microdialysis Probe Calibration Study*

For quantitative measurement of the extracellular concentration of lidocaine in the brain, we used a retrodialysis technique based on the principle that relative loss (RL) of an internal standard is related to the relative recovery (RR) of the solutions of interest.[5] The dialysis probe was calibrated *in vitro* and *in vivo* at room temperature using 3′-hydroxylated bupivacaine (200 ng/ml), a metabolite of bupivacaine with no reported CNS toxicity, as an internal standard following a method reported previously.[5] The *in vivo* and *in vitro K* factors, defined as the ratios of RL_{BUP} to RL_{LID}, were 0.60 ± 0.19 and 1.04 ± 0.12, respectively.

Calibration curves for lidocaine were constructed for each run over the range of 1–100 ng (0.1–10 μg/ml), and r^2 was greater than 0.999. The limit of detection was 0.5 ng. Within-day coefficients of variation of lidocaine were 2.9% and 4.8%, whereas day-to-day coefficients of variation were 3.0% and 5.2% at 1 and 10 μg/ml, respectively. RR_{LID} and RL_{BUP} were almost equal and were not affected by the extracellular concentration of lidocaine (data not shown).

Analysis of Plasma and Intracerebral Lidocaine Concentrations

Plasma concentrations of lidocaine were determined by high-performance liquid chromatography with an ultraviolet detector as reported previously.[6] Concentrations of unbound lidocaine in plasma were measured after ultrafiltration with a membrane (Centricon YM-30; Amicon, Inc., Beverly, MA). Concentrations of unbound lidocaine in the extracellular fluid in the brain were measured by the following microdialysis method. Indwelling microdialysis probes were perfused with the previously described cerebrospinal fluid containing 3′-hydroxylated bupivacaine at a rate of 1 μl/min by a microsyringe pump (ESP-32; Eicom). The perfusate was collected and directly injected into an electrochemical detector (HTEC-500; Eicom) every 10 min by auto-injector (EAS-20; Eicom). A mobile phase consisting of 10 mM NaH_2PO_4 (pH 4.5) with 27% methanol (vol/vol) was delivered at a flow rate of 0.6 ml/min through a C_{18} reversed-phase column (Eicompak SC-50DS, 2.1 × 150 mm, 5 μm particle size; Eicom), which was maintained at room temperature. Concentrations of lidocaine and 3′-hydroxylated bupivacaine in the dialysate were measured with an electrochemical detector fitted with a flow cell with a pure graphite working electrode (WE-PG; Eicom) and a salt bridge Ag–AgCl reference electrode. The working potential was set at 950 mV. The signal from the current–potential converter (the integrator output) was filtered with a low-pass in-line noise filter and integrated by a computerized data acquisition system using chromatography data software (PowerChrom; AD-Instruments Pty Ltd., Castle Hill, New South Wales, Australia). The extracellular concentration of lidocaine (LID_{ex}) was calculated as $LID_{ex} = LID_{dialysate} \times K/RL_{BUP}$, where $LID_{dialysate}$ is the concentration of lidocaine in the dialysate, and K is RL_{BUP}/RL_{LID} measured *in vivo*.[7] After completion of the microdialysis experiment, the animals were killed with intravenous thiopental (100 mg/kg), and brain specimens were prepared for histology to confirm the location of the microdialysis probe.

Pharmacokinetic Analysis

Moment analyses were performed on both plasma and extracellular concentrations of lidocaine in the brain to calculate the model-independent parameters by WinNonlin Professional 4.1 (Pharsight Corporation, Moun-

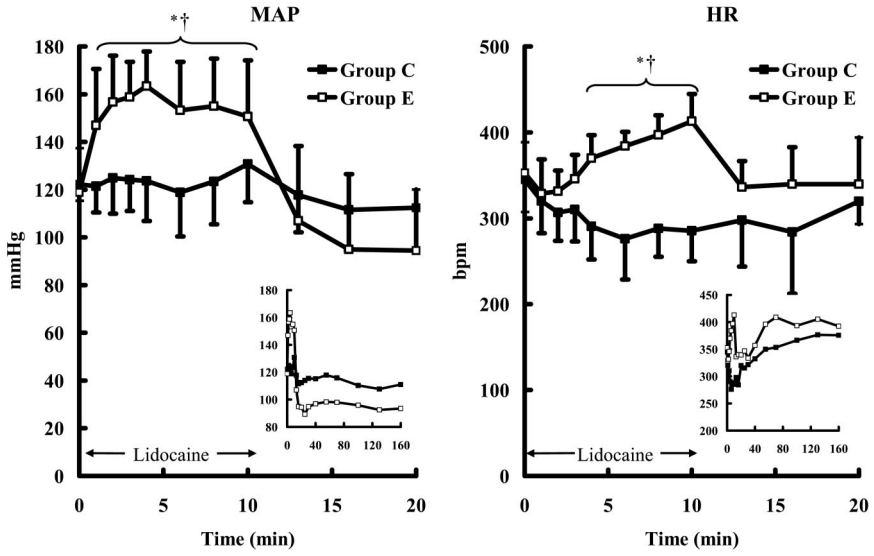

Fig. 1. Mean arterial blood pressure (MAP) and heart rate (HR) during infusion (0–10 min) and after termination of the infusion of lidocaine in groups C and E. *Insets* show MAP and HR during the whole experimental period. Data are expressed as mean ± SD of 10 experiments. * $P < 0.05$ compared with baseline within the study group. † $P < 0.01$ compared with group C at the same time point. bpm = beats/min.

tain View, CA). The midpoints of the collection time were taken as the corresponding time points to pharmacokinetic analysis and graphical presentation of the extracellular concentration of lidocaine in the brain. The terminal elimination rate constant (β) in the blood and in the brain was determined by log-linear regression, and the elimination half-life ($T_{1/2}$) was determined by the following equation: $T_{1/2} = 0.693/\beta$. The area under the plasma concentration–*versus*–time curve (AUC) and area under the first moment of the concentration-*versus*-time curve (AUMC) were calculated using the trapezoidal method with linear interpolation during increasing concentrations and log-linear interpolation during decreasing concentrations. Clearance was calculated as the dose of lidocaine (30 mg/kg) divided by AUC, whereas mean residential time was obtained as the ratio of AUMC to AUC. The volume of distribution at steady state (Vd_{SS}) was calculated according to the following equation[8]:

$$Vd_{SS} = \text{Dose} \times \text{AUMC}/(\text{AUC})^2$$

The same equations were used for calculating the apparent clearance and apparent volume of distribution of extracellular lidocaine in the brain, where F is the bioavailability from the blood to extracellular fluid in the brain.

Statistical Analysis

All values are expressed as mean ± SD. The number of animals in each group was determined based on our previous study,[6] in which the convulsive dose of lidocaine was 31.6 ± 6.0 mg/kg. Based on the formula for normal theory and assuming a type I error protection of 0.05 and a power of 0.80 allowing us to detect a 25% change in the convulsive dose, 10 animals were required for each group.

Statistical analysis was performed using StatView 5.0 (SAS Institute Inc., Cary, NC) or SigmaStat 3.0 (Systat Software Inc., Richmond, CA). The frequency of the convulsion between the two groups was evaluated using a chi-square test. Differences in plasma and intracerebral concentrations of lidocaine between the two groups were examined using analysis of variance for repeated measures and were tested using an unpaired *t* test for each time point. The convulsive dose of lidocaine was examined by unpaired *t* test, assuming that it was 30 mg/kg when convulsions were not induced during 10 min of lidocaine infusion. Pharmacokinetic parameters between the two groups were examined by unpaired *t* test. Within-group differences in MAP and HR and blood gases were tested by one-way analysis of variance. Differences in MAP and HR between groups at the same time point were examined by unpaired *t* test. Values were considered significant when *P* was less than 0.05.

Results

Two rats in group E died of cardiac arrest after the onset of convulsions during infusion of lidocaine and epinephrine, and they were replaced by two additional animals. There were no differences in MAP or HR between the two groups at baseline. In group E, both MAP and HR significantly increased after the start of infusion of lidocaine with epinephrine and were significantly higher than in group C during infusion. After termination of the infusion, both MAP and HR decreased in group E, and there were no differences in these values between groups C and E (fig. 1). There were no differences in arterial blood gas data at baseline, before convulsions, and at the end of experiments within the same study group or between the two groups (table 1).

The number of rats with convulsions in group E was significantly larger than in group C (10 and 6, respectively; $P < 0.05$). The convulsive dose of lidocaine in group E was significantly smaller than in group C (22.4 ±

Table 1. Blood Gas Data

	Baseline	Before Convulsions	End of Experiments
Group C			
pH	7.5 ± 0.03	7.5 ± 0.02	7.52 ± 0.04
Pa_{O_2}, mmHg	92.9 ± 3.1	91.3 ± 18.5	91.0 ± 9.4
Pa_{CO_2}, mmHg	26.3 ± 2.0	27.0 ± 3.3	24.6 ± 5.0
HCO_3^-, mM	20.4 ± 1.9	20.7 ± 2.2	19.5 ± 9.4
Base excess, mM	−1.2 ± 2.3	−0.8 ± 1.9	−1.3 ± 2.4
Group E			
pH	7.5 ± 0.03	7.46 ± 0.05	7.54 ± 0.05
Pa_{O_2}, mmHg	90.8 ± 7.0	82.8 ± 10.5	98.4 ± 5.6
Pa_{CO_2}, mmHg	25.8 ± 2.7	30.5 ± 7.4	23.7 ± 3.9
HCO_3^-, mM	20.0 ± 0.9	20.2 ± 1.8	19.9 ± 2.1
Base excess, mM	−1.1 ± 0.8	−2.2 ± 2.0	−0.67 ± 1.7

Values are mean ± SD of 10 experiments. There were no significant differences between groups C and E at the same time point or among baseline, before convulsions, at the end of experiments within the same group.

HCO_3^- = bicarbonate; Pa_{CO_2} = arterial carbon dioxide tension; Pa_{O_2} = arterial oxygen tension.

5.5 and 27.9 ± 3.1 mg/kg, respectively; $P < 0.05$). Plasma concentrations of total (protein-bound and unbound) lidocaine were similar during the experiment in the two groups, and there were no differences in the pharmacokinetic parameters between these groups (fig. 2 and table 2). Overall concentrations of unbound lidocaine in group E were significantly higher than in group C ($P < 0.01$; fig. 2). The AUC of unbound lidocaine in group E was significantly larger than in group C, which would result from a smaller volume of distribution (table 2). *In vivo* microdialysis study revealed that extracellular concentrations of lidocaine in the brain reached the highest level at 25 min after the start of lidocaine infusions in both groups (fig. 2). Overall concentrations of lidocaine in group E were significantly higher than in group C and were also significantly higher in group E than in group C at 25 and 35 min after the start of lidocaine infusion (11.3 ± 3.6 *vs.* 7.7 ± 3.5 and 8.5 ± 3.5 *vs.* 5.3 ± 2.0 μg/ml, respectively; $P < 0.05$). Except peak concentrations, there were no pharmacokinetic differences in the concentration of extracellular lidocaine between groups C and E (table 3).

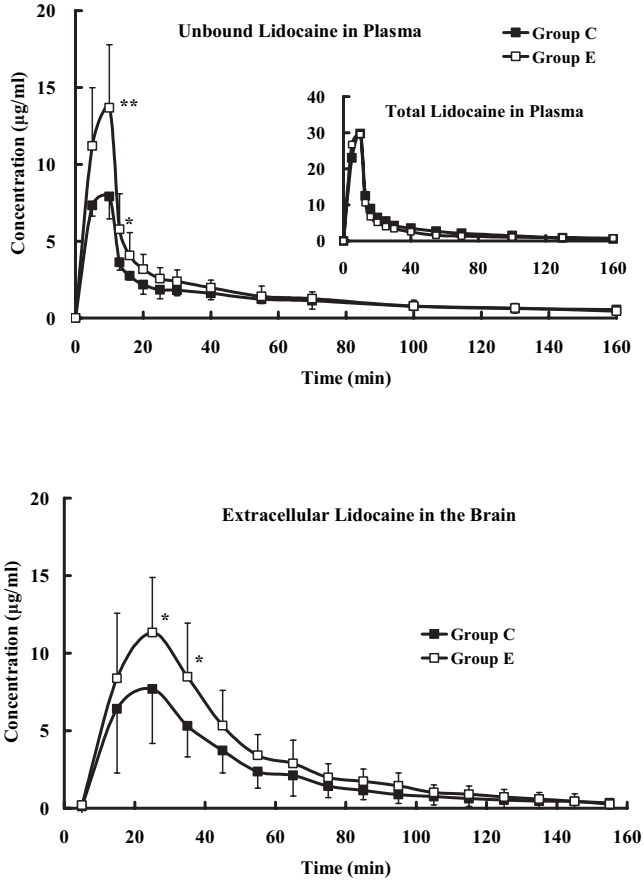

Fig. 2. Plasma concentrations of unbound (*top*), total (protein-bound and unbound; *top*, *inset*), and cerebral extracellular concentrations (*bottom*) of lidocaine. Data are expressed as mean ± SD of 10 experiments. Overall concentrations of plasma unbound and cerebral extracellular lidocaine in group E were significantly higher than in group C ($P < 0.01$ and 0.05, respectively). * $P < 0.05$ and ** $P < 0.01$ compared with group C at the same time point.

Discussion

In the current study, we have shown that epinephrine significantly increased the concentration of extracellular lidocaine in the brain. Because it was comparable to the unbound fraction in the peripheral blood vessels as reported previously,[9,10] our results suggest that only the unbound, pharmacologically active fraction is transported to the intracerebral neuronal cells, and an increased unbound fraction in the brain would account for the epinephrine-increased convulsive potency of lidocaine. To our knowledge, this is the first study showing the relations between the concentration of lidocaine in the brain and its CNS toxicity.

Our current findings, including a decreased convulsive dose of lidocaine and an unchanged threshold plasma concentration for convulsions induced by epinephrine, are consistent with those reported previously.[1,2] However, pharmacokinetic parameters such as clearance, elimination half-time, and peak plasma concentration of total lidocaine were not affected by epinephrine. Our results indicated that addition of epinephrine was associated with more rapid increase of the plasma concentration of lidocaine and more rapid decrease after the end of infusion. These changes produced by epinephrine would be attributed to the decreased volume of distribution during infusion and increased cardiac output, hepatic blood flow, and resultant increased biotransformation in the liver after the end of infusion.[11] Increased influx of lidocaine to the brain by increased cerebral blood flow, facilitated by transport of unbound lidocaine from blood vessels to extracellular fluid in the brain, would also contribute to this epinephrine-induced increase in concentration of lidocaine in the brain.[2] Increased MAP, HR, intracranial pressure, or acidosis

Table 2. Pharmacokinetic Parameters of Plasma Lidocaine

	Total Lidocaine		Protein-unbound Lidocaine	
	Group C	Group E	Group C	Group E
Peak concentration, μg/ml	29.7 ± 7.3	29.5 ± 5.7	7.9 ± 1.5	13.5 ± 3.9†
$T_{1/2}$, min	47 ± 15	47 ± 15	41 ± 12	47 ± 16
$AUC_{0-\infty}$, min · μg · ml^{-1}	454 ± 93	388 ± 99	122 ± 22	169 ± 65*
Clearance, ml · kg^{-1} · min^{-1}	70 ± 20	82 ± 22	254 ± 52	204 ± 86
$AUMC_{0-\infty}$, × 1,000 min^2 · μg · ml^{-1}	25.7 ± 8.5	21.6 ± 10.4	6.4 ± 2.0	10.1 ± 9.0
MRT, min	51 ± 15	49 ± 19	47 ± 10	47 ± 29
Vd_{SS}, × 1,000 ml/kg	3.5 ± 1.1	3.7 ± 1.3	11.6 ± 2.1	8.1 ± 3.5*

Values are mean ± SD of 10 experiments.

* $P < 0.05$ and † $P < 0.01$ compared with group C.

$AUC_{0-\infty}$ = area under the plasma concentration–*vs.*–time curve from zero to infinity; $AUMC_{0-\infty}$ = area under the first moment of the plasma concentration–*vs.*–time curve from zero to infinity; MRT = mean residential time; $T_{1/2}$ = elimination half-time; Vd_{SS} = volume of distribution at steady state.

induced by convulsions may also be responsible for this effect.[12]

We have measured the concentrations of extracellular lidocaine in the nucleus accumbens, which predominantly consists of γ-aminobutyric acid–mediated neurons and plays an important role in controlling convulsions.[13,14] The relations between concentrations of lidocaine in the nucleus accumbens and other cerebral regions were not examined in the current study. Moreover, the concentration of local anesthetics in various regions in the brain may depend on regional blood flow, which is influenced by the development of convulsions.[15] However, a previous microdialysis study revealed no differences in the concentrations of lidocaine in the extracellular fluid in different parts of the brain or in the bilateral hemisphere after intraarterial administration.[16] Our preliminary study also showed that there were no differences in the concentrations of lidocaine in various parts (cortex, hippocampus, limbic system, olfactory bulb, cerebellum, and medulla) of the brain, and convulsions were not induced by topical injection of lidocaine into the nucleus accumbens (data not shown). These findings indicate that an increase in the concentration of lidocaine in other parts as well as in the nucleus accumbens would contribute to triggering convulsions.

Table 3. Pharmacokinetic Parameters of Extracellular Lidocaine in the Brain

	Group C	Group E
Peak concentration, μg/ml	13.0 ± 5.4	18.8 ± 5.9*
$T_{1/2}$, min	29.6 ± 14.9	31.6 ± 17.5
$AUC_{0-\infty}$, min · μg · ml^{-1}	456 ± 181	643 ± 237
Cl/F, ml · kg^{-1} · min^{-1}	82 ± 55	52 ± 18
$AUMC_{0-\infty}$, × 1,000 min^2 · μg · min^{-1}	21.1 ± 13.6	25.5 ± 13.9
MRT, min	38.7 ± 18.2	34.3 ± 13.3
Vd/F, × 1,000 ml/kg	2.7 ± 1.2	1.8 ± 1.1

Values are mean ± SD of 10 experiments.

* $P < 0.05$ compared with group C.

$AUC_{0-\infty}$ = area under the plasma concentration–*vs.*–time curve from zero to infinity; $AUMC_{0-\infty}$ = area under the first moment of the plasma concentration–*vs.*–time curve from zero to infinity; Cl/F = apparent extracellular fluid clearance; MRT = mean residential time; $T_{1/2}$ = elimination half-time; Vd/F = apparent volume of distribution, where F is bioavailability.

There are several limitations in our study. First, some rats showed convulsions and others did not in group C, although there were no differences in the concentrations of lidocaine in the brain among rats with and without convulsions (data not shown). This might be attributable to an insufficient number of rats (n = 10). Also, the detailed mechanism for the increase of CNS toxicity of lidocaine by the increased unbound fraction is still unclear. Further study, including altering protein binding, would be required. Second, the concentration of lidocaine in the cerebral dialysate was determined at collection intervals every 10 min. The concentrations of lidocaine in the brain would also be rapidly changed during and just after the end of intravenous infusion, which prevented us from detecting the real peak concentrations. Once given simultaneously with epinephrine, concentrations of lidocaine in the brain increased more rapidly, as was the case with plasma. Despite these limitations, pharmacokinetic analyses suggested that the increased extracellular concentration of lidocaine would significantly contribute to the augmented toxicity by epinephrine.

In conclusion, concomitant administration of epinephrine increased the unbound fraction of intravenously administered lidocaine, leading to a significant increase in its concentration in the brain. This would be related to the increased CNS toxicity after intravenous administration of lidocaine together with epinephrine.

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