Anesthesiology
82:574–580, 1995

J. B. Lippincott Company, Philadelphia

Effect of Vasoconstrictive Agents Added to Lidocaine on Intravenous Lidocaine-induced Convulsions in Rats

Masataka Yokoyama, M.D., Masahisa Hirakawa, M.D.,† Hiroshi Goto, M.D.‡*

Background: **Epinephrine is reported to decrease the threshold of intravenous lidocaine-induced convulsions. However, the mechanism underlying this effect is not clear. Therefore, we carried out a study to examine the role of vasopressor-induced hypertension.**

Methods: **Fifty-six awake Wistar rats were assigned to seven groups of eight. All groups received a continuous intravenous infusion of lidocaine at a rate of 4 mg·kg^{-1}·min^{-1} until generalized convulsions occurred. The control group (group C) received plain lidocaine. The acute hypertensive groups received lidocaine with epinephrine (group E), norepinephrine (group N), or phenylephrine (group P) to increase mean arterial blood pressure (MAP) to 150 ± 5 mmHg. Sodium nitroprusside (SNP) was added to prevent an increase in mean arterial pressure in the remaining three groups (vasopressor-SNP groups).**

Results: **The acute hypertensive groups required significantly smaller cumulative doses of lidocaine to produce convulsions compared with control (C = 41.5 ± 2.9 > E = 24.1 ± 2.7, N = 27.1 ± 2.8, P = 26.7 ± 2.5 mg·kg^{-1}; values are mean ± SD, $P < 0.01$). In addition, plasma lidocaine concentrations (C = 11.0 ± 0.7 > E = 7.4 ± 0.5, N = 7.9 ± 0.6, P = 8.1 ± 0.8 μg·ml^{-1}, $P < 0.01$) and brain lidocaine concentrations (C = 50.9 ± 4.5 > E = 32.6 ± 4.2, N = 34.5 ± 4.8, P = 37.1 ± 4.5 μg·g^{-1}, $P < 0.01$) were less in the acute hypertensive groups at the onset of convulsions. In the vasopressor-SNP groups, the plasma and brain lidocaine concentrations at the onset of convulsions returned to the control values, although epinephrine and norepinephrine, but not phenylephrine, still decreased cumulative convulsant doses of lidocaine significantly ($P < 0.01$) compared with control (E + SNP = 30.8 ± 2.9 < N + SNP = 34.8 ± 2.8, $P < 0.01$) < P + SNP = 40.2 ± 3.0 mg·kg^{-1}, $P < 0.01$). The brain/plasma concentration ratios were similar for the seven groups.**

Conclusions: **An equal degree of acute hypertension induced by these three different vasopressors may play a role in reducing the threshold (plasma and brain lidocaine concentrations) as well as the cumulative convulsant doses associated with lidocaine-induced convulsions. (Key words: Anesthetics, local: lidocaine. Sympathetic nervous system: epinephrine; norepinephrine; phenylephrine. Toxicity: convulsions; local anesthetics. Vasodilator: sodium nitroprusside.)**

ADDING vasoconstrictors, such as epinephrine, norepinephrine, and phenylephrine, to local anesthetics to produce regional anesthesia may provide several beneficial effects such as decreasing the peak plasma concentrations of local anesthetics and increasing the duration of the block.[1,2] In contrast, Yagiela§ and Torbiner *et al.*[3] reported that an intravenous injection of lidocaine with epinephrine decreased the convulsant as well as the lethal doses of lidocaine in rats. However, the mechanism by which epinephrine decreases the convulsant doses of lidocaine is not clear.

We[4] reported that the greater the concentration of added epinephrine, the lower the cumulative convulsant dose of lidocaine; and the greater the increase in mean arterial blood pressure, the lower the threshold of lidocaine-induced convulsions in rats. Therefore, we speculated that acute hypertension might play a principal role. The purpose of this study was to determine whether equal degree of acute hypertension induced by epinephrine, norepinephrine, or phenylephrine leads to equal reduction of the threshold of lidocaine-induced convulsions and whether the addition of sodium nitroprusside to prevent hypertension modulates

* Junior Staff, Department of Anesthesiology and Resuscitology, Okayama University Medical School.

† Professor and Chairman, Department of Anesthesiology and Resuscitology, Okayama University Medical School.

‡ Professor, Department of Anesthesiology, The University of Kansas Medical Center, Kansas City, Kansas.

Received from the Department of Anesthesiology and Resuscitology, Okayama University Medical School, Okayama City, Okayama, Japan, and the Department of Anesthesiology, The University of Kansas Medical Center, Kansas City, Kansas. Submitted for publication July 18, 1994. Accepted for publication October 27, 1994.

Address correspondence and reprint requests to Dr. Yokoyama: Department of Anesthesiology and Resuscitology, Okayama University Medical School, Okayama City, Okayama 700, Japan.

§ Yagiela JA: Intravascular lidocaine toxicity: Influence of epinephrine and route of administration. Anesthesia Progress 32:57–61, 1985.

the effects of these vasoactive agents on the threshold in rats.

Materials and Methods

This study was approved by the institutional animal care and use committee. The animals were fasted for 6 h (water was supplied *ad libitum*), and the experiments were performed between 1 and 5 PM.

Fifty-six male Wistar rats weighing 200–250 g (aged 7–8 weeks) were anesthetized with halothane in oxygen during surgical preparation. One of the femoral arteries was cannulated with a polyethylene catheter to monitor mean arterial blood pressure (MAP) and heart rate (HR) and for blood sampling. The femoral vein was cannulated for infusion of drugs. The proximal ends of these catheters were tunneled subcutaneously to the posterior cervical region so that the animals could move freely. Before emergence from anesthesia, the animals were placed in a plastic container to recover for 2 h before the experiment.

The animals were assigned to seven groups of eight depending on the agents given (table 1). Doses of added epinephrine (group E), norepinephrine (group N), and phenylephrine (group P) had been predetermined to increase MAP to 150 ± 5 mmHg, and doses of sodium nitroprusside (SNP) to prevent the increase in MAP by epinephrine, norepinephrine, and phenylephrine were predetermined in the preliminary study. All groups received a continuous intravenous infusion of lidocaine (15 $mg \cdot ml^{-1}$) at a rate of 4.0 $mg \cdot kg^{-1} \cdot min^{-1}$ (0.053–0.067 $ml \cdot min^{-1}$) by infusion pump (Model 2176, Harvard) until tonic/clonic activity occurred. Cumulative lidocaine doses from the beginning of infusion to the onset of convulsions were calculated for each animal as infusion rate × infusion time.

Arterial blood pressure and HR were monitored and recorded continuously, and the animals were observed for tonic/clonic activity.

Arterial blood, 0.5 ml, was drawn just before the beginning of the lidocaine infusion and 1.5 ml at the onset of convulsions to determine blood gas tensions, *p*H, serum sodium, serum potassium, blood glucose, and plasma lidocaine concentrations. Immediately after blood sampling, a catheter was inserted in the aorta. The brain was perfused with saline for 1 min to remove blood from cerebral vessels, and the brain was rapidly removed and weighed. Homogenates were made from the whole brain, and brain lidocaine was extracted and analyzed. For determination of serum electrolytes, blood glucose, and plasma lidocaine concentrations, blood samples were centrifuged, and the serum and plasma were frozen at −80°C until analyzed. Serum electrolyte concentrations were measured with a Ciba-Corning blood gas analyzer (model 288, Medfield, MA), and blood glucose was determined by the glucose oxidase method. Lidocaine concentrations were determined by high performance liquid chromatography (HPLC) with a UV spectrometer using a LC-6A pump and SPD-6A detector (Shimadzu, Kyoto, Japan). We employed the method of analysis introduced by Satoh. Procaine was used as an internal standard, and plasma and brain samples were extracted with benzene and chloroform. The analytic conditions were as follows: the column, Shim-Pack (ODS) 4.6 × 250 mm (Shimadzu); the mobile phase, 0.05 M KH_2PO_4, 0.05 M K_2HPO_4/acetonitrile *p*H 4.0 (88:12 vol/vol).

Table 1. Experimental Groups

Group		Agents Given
Control	C	1.5% lidocaine
Hypertensive	E	1.5% lidocaine with 10 $\mu g \cdot ml^{-1}$ epinephrine
	N	1.5% lidocaine with 7.5 $\mu g \cdot ml^{-1}$ norepinephrine
	P	1.5% lidocaine with 50 $\mu g \cdot ml^{-1}$ phenylephrine
Vasopressor SNP	E + SNP	Group E + 7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ sodium nitroprusside
	N + SNP	Group N + 12.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ sodium nitroprusside
	P + SNP	Group P + 15.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ sodium nitroprusside

See Table 2 for abbreviations.

Obtained data were expressed as mean ± SD. Cumulative convulsant doses of lidocaine, plasma lidocaine concentrations, and brain lidocaine concentrations were compared between groups by one-way analysis of variance followed by Duncan's method. Two-way analysis of variance followed by Duncan's method was used to compare MAP, HR, values of blood gases, electrolytes, and blood glucose between and within groups. Values were considered statistically significant when $P < 0.05$.

Results

Baseline MAP and HR were similar for the seven groups (fig. 1). The MAP did not change in group C

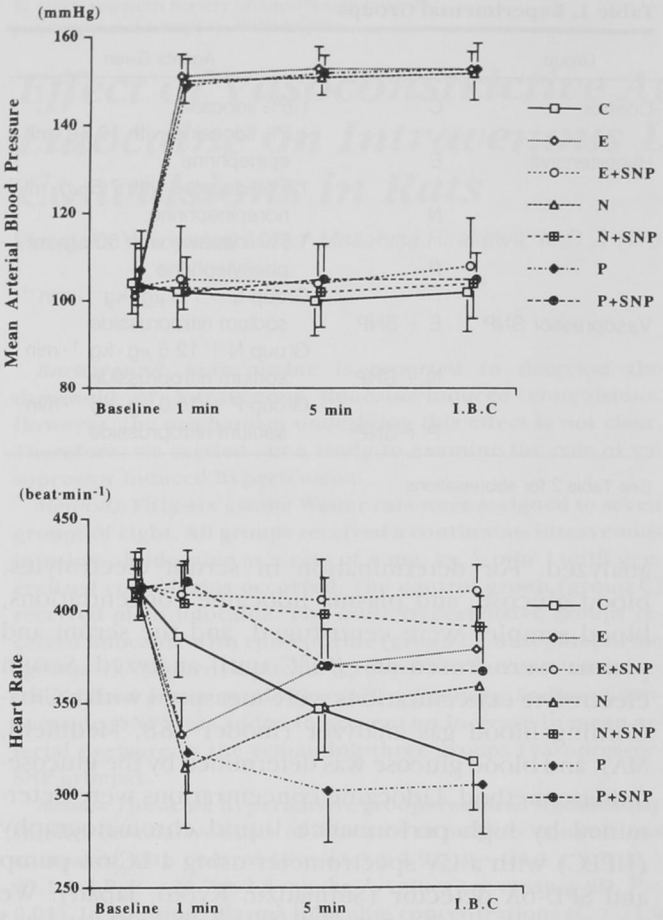

Fig. 1. (*Top*) Changes in mean arterial blood pressure (MAP) during intravenous infusion of lidocaine. The MAP did not change in group C and vasopressor-SNP groups (groups E + SNP, N + SNP, P + SNP). The MAP significantly increased after 1 min of infusion in the hypertensive groups (groups E, N, P; $P < 0.01$), and there were no significant differences in the MAP among the three groups. (*Bottom*) Changes in heart rate (HR) during intravenous infusion of lidocaine. The HR in group C continuously decreased. The HRs significantly decreased after 1 min of infusion in the hypertensive groups (groups E, N, P; $P < 0.01$). The HRs in group E + SNP and N + SNP did not change. The HR in group P + SNP significantly decreased after 5 min of infusion ($P < 0.01$). Values are means ± SD; n = 8. C = control (plain lidocaine); E = lidocaine with epinephrine; E + SNP = lidocaine with epinephrine + sodium nitroprusside; I.B.C. = immediately before convulsions; N = lidocaine with norepinephrine; N + SNP = lidocaine with norepinephrine + sodium nitroprusside; P = lidocaine with phenylephrine; P + SNP = lidocaine with phenylephrine + sodium nitroprusside.

and vasopressor-SNP groups until the onset of convulsions. The addition of epinephrine, norepinephrine, and phenylephrine produced acute hypertension to MAP of 150 mmHg. Changes of HR varied significantly among groups until convulsions. In the control and P + SNP groups, HRs were significantly decreased immediately before convulsions.

Baseline blood gas, electrolyte, and blood glucose data in all groups were similar. The changes in these data are shown in tables 2 and 3.

The hypertensive groups (groups E, N, and P) required significantly smaller cumulative doses of lidocaine (C = 41.5 ± 2.9 > E = 24.1 ± 2.7, N = 27.1 ± 2.8, P = 26.7 ± 2.5 $mg \cdot kg^{-1}$, $P < 0.01$) (fig. 2) and significantly lower plasma lidocaine concentrations (C = 11.0 ± 0.7 > E = 7.4 ± 0.5, N = 7.9 ± 0.6, P = 8.1 ± 0.8 $\mu g \cdot ml^{-1}$, $P < 0.01$) and brain lidocaine concentrations (C = 50.9 ± 4.5 > E = 32.6 ± 4.2, N = 34.5 ± 4.8, P = 37.1 ± 4.5 $\mu g \cdot g^{-1}$, $P < 0.01$) at the onset

Table 2. Analysis of Blood Gases

	Group	Baseline	Convulsions
*p*H	C	7.42 ± 0.02	7.41 ± 0.03
	E	7.42 ± 0.02	7.41 ± 0.02
	E + SNP	7.42 ± 0.03	7.41 ± 0.03
	N	7.42 ± 0.03	7.39 ± 0.03*
	N + SNP	7.41 ± 0.03	7.40 ± 0.02
	P	7.41 ± 0.02	7.40 ± 0.03
	P + SNP	7.42 ± 0.02	7.40 ± 0.02
Pa_{O_2} (mmHg)	C	87 ± 3	89 ± 5
	E	85 ± 3	79 ± 8*†
	E + SNP	83 ± 4	85 ± 4
	N	88 ± 5	78 ± 5*†
	N + SNP	85 ± 4	80 ± 5†
	P	86 ± 7	74 ± 6
	P + SNP	87 ± 3	84 ± 5‡
Pa_{CO_2} (mmHg)	C	38 ± 3	38 ± 2
	E	39 ± 2	38 ± 5
	E + SNP	38 ± 3	35 ± 3
	N	38 ± 3	40 ± 2
	N + SNP	38 ± 3	36 ± 2‡
	P	39 ± 5	41 ± 5
	P + SNP	37 ± 2	38 ± 2
HCO_{3^-} (mM/L)	C	24 ± 2	24 ± 1
	E	25 ± 1	24 ± 2
	E + SNP	24 ± 2	22 ± 1*
	N	25 ± 2	24 ± 1
	N + SNP	24 ± 2	23 ± 2
	P	24 ± 2	25 ± 2
	P + SNP	23 ± 2	23 ± 2

Values are mean ± SD; n = 8.

C = control (plain lidocaine); E = lidocaine with epinephrine; N = lidocaine with norepinephrine; P = lidocaine with phenylephrine; E + SNP = lidocaine with epinephrine + sodium nitroprusside; N + SNP = lidocaine with norepinephrine + sodium notroprusside; P + SNP = lidocaine with phenylephrine + sodium nitroprusside.

* $P < 0.05$ *versus* baseline.

† $P < 0.05$ *versus* C.

‡ $P < 0.05$ *versus* without SNP.

Table 3. Analysis of Electrolytes and Blood Glucose

	Group	Baseline	Convulsions
Na^+ (mEq/L)	C	142 ± 1	143 ± 2
	E	140 ± 3	139 ± 4
	E + SNP	141 ± 3	141 ± 3
	N	139 ± 1	140 ± 2
	N + SNP	141 ± 3	140 ± 2
	P	141 ± 3	141 ± 3
	P + SNP	142 ± 2	141 ± 3
K^+ (mEq/L)	C	4.2 ± 0.3	3.5 ± 0.3*
	E	4.2 ± 0.3	3.7 ± 0.5*
	E + SNP	4.1 ± 0.1	3.7 ± 0.4*
	N	4.1 ± 0.2	3.5 ± 0.4*
	N + SNP	4.0 ± 0.2	3.6 ± 0.4*
	P	4.0 ± 0.2	3.7 ± 0.3*
	P + SNP	4.0 ± 0.2	3.6 ± 0.3*
Blood glucose (mg/dl)	C	119 ± 11	149 ± 20*
	E	127 ± 8	190 ± 17*†
	E + SNP	124 ± 14	154 ± 22*‡
	N	126 ± 18	187 ± 19*†
	N + SNP	116 ± 11	150 ± 11*‡
	P	123 ± 14	173 ± 19*†
	P + SNP	117 ± 9	148 ± 14*‡

Values are mean ± SD; n = 6.

C = control (plain lidocaine); E = lodocaine with epienphrine; N = lidoaine with norepinephrine; P = lidocaine with phenylephrine; E + SNP = lidoccaine with epinephrine + sodium notroprusside; N + SNP = lidocaine with norepinephrine + sodium nitroprusside; P + SNP = lidocaine with phenylephrine + sodium nitroprusside.

* $P < 0.05$ *versus* baseline.

† $P < 0.05$ *versus* C.

‡ $P < 0.05$ *versus* without SNP.

of convulsions compared with the control group (fig. 3). These values were similar for the three hypertensive groups. Administration of SNP along with epinephrine, norepinephrine, or phenylephrine increased cumulative convulsant doses as well as plasma and brain concentrations toward the control levels (figs. 2 and 3). Although the cumulative convulsant doses in group P + SNP returned to control values, E + SNP and N + SNP groups still required significantly smaller cumulative convulsant doses as compared with the control levels ($P < 0.01$), and there were significant differences among the three vasopressor-SNP groups; *i.e.*, E + SNP = 30.8 ± 2.9 < N + SNP = 34.8 ± 2.8 ($P < 0.01$) < P + SNP = 40.2 ± 3.6 $mg \cdot kg^{-1}$ ($P < 0.01$). The plasma lidocaine concentrations (E + SNP = 10.6 ± 0.8, N + SNP = 10.2 ± 0.8, P + SNP = 10.6 ± 1.1 $\mu g \cdot ml^{-1}$) and the brain lidocaine concentrations (E + SNP = 48.5 ± 7.9, N + SNP = 46.5 ± 4.0, P + SNP = 50.9 ± 5.4 $\mu g \cdot g^{-1}$) were similar to the control levels. The brain/plasma concentration ratios were similar for all seven groups.

Discussion

Our data indicate that equal degree of hypertension produced by epinephrine, norepinephrine, or phenylephrine causes equal reduction of the threshold of lidocaine-induced convulsions. The decreased threshold of lidocaine-induced convulsions returned to the control levels when sodium nitroprusside, in an amount sufficient to counteract the hypertensive effects of these agents, was added. Therefore, it appears that acute arterial hypertension may be a major factor for reduction of the lidocaine-induced seizure threshold. However, our study does not clearly elucidate how hypertension decreased the seizure threshold, nor does it reveal other factors responsible for the reduction of the seizure threshold.

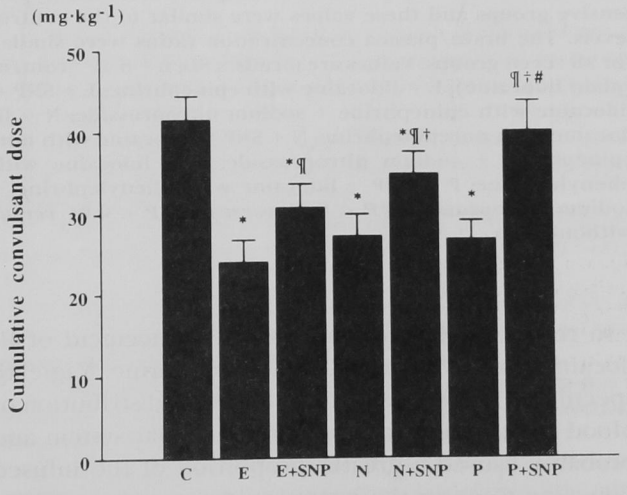

Fig. 2. Cumulative convulsant dose among seven groups. The hypertensive groups (groups E, N, P) required significantly smaller cumulative convulsant doses of lidocaine compared with the control group (group C), and these values were similar for the three hypertensive groups. Administration of SNP along with E, N, or P (groups E + SNP, N + SNP, P + SNP) increased cumulative convulsant doses compared with the hypertensive groups. However, groups E + SNP and N + SNP still required significantly smaller cumulative convulsant doses as compared with the control levels. Values are means ± SD; n = 8. C = control (plain lidocaine); E = lidocaine with epinephrine; E + SNP = lidocaine with epinephrine + sodium nitroprusside; N = lidocaine with norepinephrine; N + SNP = lidocaine with norepinephrine + sodium nitroprusside; P = lidocaine with phenylephrine; P + SNP = lidocaine with phenylephrine + sodium nitroprusside. *$P < 0.01$ *versus* C. ¶$P < 0.01$ *versus* without SNP. †$P < 0.01$ *versus* E + SNP. #$P < 0.01$ *versus* N + SNP.

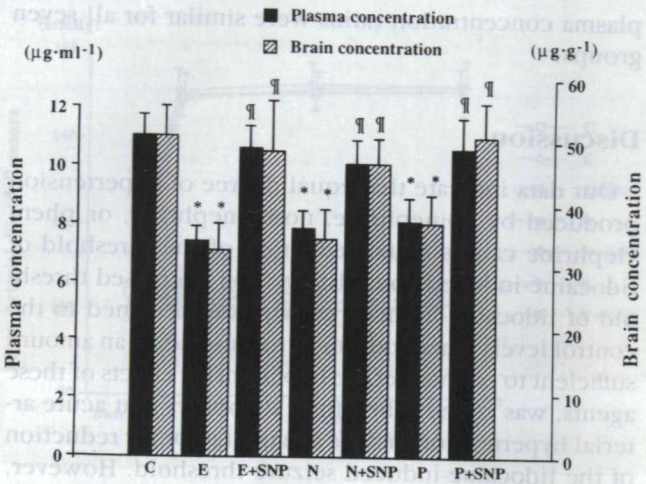

Fig. 3. Plasma and brain concentrations of lidocaine at the onset of convulsions. The hypertensive groups (groups E, N, P) had significantly lower plasma and brain concentrations of lidocaine at the onset of convulsions compared with the control group (group C), and these values were similar for the three hypertensive groups. Administration of SNP along with E, N, or P (groups E + SNP, N + SNP, P + SNP) increased plasma and brain concentrations compared with the hypertensive groups and these values were similar to the control levels. The brain/plasma concentration ratios were similar for all seven groups. Values are means ± SD; n = 8. C = control (plain lidocaine); E = lidocaine with epinephrine; E + SNP = lidocaine with epinephrine + sodium nitroprusside; N = lidocaine with norepinephrine; N + SNP = lidocaine with norepinephrine + sodium nitroprusside; P = lidocaine with phenylephrine; P + SNP = lidocaine with phenylephrine + sodium nitroprusside. *$P < 0.01$ *versus* C. ¶$P < 0.01$ *versus* without SNP.

In regard to the mechanism of enhancement of lidocaine toxicity by 1:100,000 epinephrine, Yagiela§ speculated that epinephrine altered the distribution of blood by its effects on the cardiovascular system and probably caused a greater proportion of the infused lidocaine to enter the central nervous system (CNS). Sokrab *et al.*[6] investigated regional cerebral blood flow in acute hypertension (MAP 158–168 mmHg) induced by epinephrine, norepinephrine, or phenylephrine in the conscious rat, and they found that only epinephrine significantly increased local cerebral blood flow. Several investigators[7–9] have reported that acute hypertension increases the permeability of the blood-brain barrier in animals. Häggendal and Johnsson[10] reported that the change in permeability of the blood-brain barrier depends on the rate at which the blood pressure is increased. It also has been reported that epinephrine induces more disturbance of the blood-brain barrier than other vasoactive substances in conscious rats.[11]

Our results, however, showed that equal degree of hypertension induced by epinephrine, norepinephrine, or phenylephrine led to equal reduction of the cumulative convulsant doses of lidocaine, and these vasoconstrictive agents decreased the plasma and brain lidocaine concentrations to the equal degree at the onset of convulsions. Furthermore, the brain/plasma concentration ratios were similar among the hypertensive groups and the control group. This means that the added vasoconstrictive agents did not cause a greater proportion of the infused lidocaine to enter the CNS. However, we measured the whole brain lidocaine concentrations, and it may be possible that the lidocaine concentrations of a specific and minute area in the brain that affects lidocaine-induced convulsions increased equally by these vasoactive agents.

Epinephrine, norepinephrine, or phenylephrine directly might have affected excitatory neurotransmitters in the brain at a time when lidocaine toxicity was approaching. Under normal conditions, catecholamines are not able to enter the CNS,[12] and our preliminary study showed that continuous infusion of epinephrine, norepinephrine, or phenylephrine in normal saline solution at the same rate used in this study did not cause convulsions. However, catecholamines might have entered the brain in areas where blood-brain barrier permeability was increased due to acute hypertension[13,14] and decreased the threshold of lidocaine-induced convulsions by changing the cerebral metabolism[15] even functioning as excitatory neurotransmitters.[16] It has been reported that changes in the concentration of brain amines have an effect on lidocaine-induced convulsions.[17]

The threshold of lidocaine-induced convulsions may decrease if local cerebral ischemia is produced by intense α-action of these agents. Although acute hypertension induced by epinephrine, norepinephrine, or phenylephrine did not decrease local cerebral blood flow in rats according to the study by Sokrab *et al.*,[6] we did not measure cerebral blood flow, so that the possibility of local cerebral ischemia cannot be excluded in our study.

Arterial hypertension triggers peripheral receptors, such as baroreceptors, and can change various afferent nerve impulses to the CNS. It is possible, therefore, that these processes may decrease the threshold of lidocaine-induced seizure.

It is well known that the acid-base balance affects the threshold of lidocaine toxicity.[18,19] The changes in the values of *p*H, Pa_{CO_2}, and HCO_3^- in this study

were small, so that these changes probably did not contribute to lowering the threshold of convulsions. The concentrations of serum potassium in all groups were decreased at the onset of convulsions, and these concentrations were similar for all groups. Avery *et al.*[20] reported that a change in serum potassium (2.7–5.4 $mEq \cdot l^{-1}$) did not alter the cumulative convulsant doses of lidocaine in dogs. Therefore, it is unlikely that the reduction of serum potassium in the hypertensive groups affected the threshold of lidocaine-induced convulsions, but the reason for this reduction is not clear.

Increased blood glucose at the time of convulsions in animals has been reported.[21] Increased blood glucose was persistent in all groups at the onset of convulsions, and the values in the hypertensive groups were greater than in the normotensive groups. It has been reported that epinephrine increases blood glucose level more than phenylephrine,[6] but it is unknown whether the higher blood glucose levels in the hypertensive groups were related to reducing the threshold of lidocaine-induced convulsions.

We attempted to offset the hypertensive effects of vasoconstrictive agents with SNP, and the decreased seizure threshold (the plasma and brain lidocaine concentrations) returned toward the control level. This is most likely due to controlled mean arterial pressure but also might be due to a direct effect of SNP on the CNS. It is of interest that the cumulative convulsant doses of lidocaine were different among the three vasopressor-SNP groups. These differences might be due to differences in distribution volume of lidocaine and/or metabolism and clearance of lidocaine among the three vasopressor-SNP groups. The different doses of SNP to control blood pressure might have contributed to different cumulative convulsant doses. The cumulative convulsant doses of lidocaine were lowest in the E + SNP group and highest (equal to control level) in the P + SNP group. Because epinephrine has a stronger β-adrenergic effect than norepinephrine, phenylephrine has only an α-adrenergic effect, and vasoconstrictive effects were counteracted by SNP, the β-adrenergic effect might have played a role in the different cumulative convulsant doses of lidocaine in the vasopressor-SNP groups.

In conclusion, our data indicate that acute hypertension caused by three different vasoconstrictive agents may play a role in reducing the threshold of lidocaine-induced convulsions in rats. Further study is necessary to elucidate the relationship of hypertension, α- and β-adrenergic pharmacodynamics, and other changes associated with induced hypertension to lidocaine-induced convulsions.

References

1. Tucker GT, Mather LE: Clinical pharmacokinetics of local anesthetics. Clin Pharmacokinet 4:241–278, 1979

2. Leicht CH, Carlson SA: Prolongation of lidocaine spinal anesthesia with epinephrine and phenylephrine. Anesth Analg 65:365–369, 1986

3. Torbiner ML, Yagiela JA, Mito RS: Effect of midazolam pretreatment on the intravenous toxicity of lidocaine with and without epinephrine in rats. Anesth Analg 68:744–749, 1989

4. Yokoyama M, Goto H, Ueda W, Hirakawa M, Arakawa K: Modification of intravenous lidocaine-induced convulsions by epinephrine in rats. Can J Anaesth 40:251–256, 1993

5. Satoh Y: Pharmacokinetics of lidocaine and monoethylglycinexylidide after the intratracheal administration of lidocaine. Masui 37:1192–1198, 1988

6. Sokrab TEO, Johansson BB: Regional cerebral blood flow in acute hypertension induced by adrenaline, noradrenaline and phenylephrine in the conscious rat. Acta Physiol Scand 137:101–105, 1989

7. Suzuki R, Nitsch C, Fujiwara K, Klatzo I: Regional change in cerebral blood flow and blood-brain barrier permeability during epileptiform seizures and in acute hypertension in rabbits. J Cereb Blood Flow Metabol 4:96–102, 1984

8. Mayhan WG, Faraci FM, Siems JL, Heistad DD: Role of molecular charge in disruption of the blood-brain barrier during acute hypertension. Circ Res 64:658–664, 1989

9. Auer L: Origin and localization of Evans blue extravasations in acutely-induced hypertension in cats. Eur Neurol 17:211–215, 1978

10. Häggendal E, Johansson B: On the pathophysiology of the increased cerebrovascular permeability in acute arterial hypertension in cats. Acta Neurol Scand 48:265–270, 1972

11. Johansson BB, Martinsson L: Blood-brain barrier to albumin in awake rats in acute hypertension induced by adrenaline, noradrenaline or angiotensin. Acta Neurol Scand 60:193–197, 1979

12. Oldendorf WH: Brain uptake of radiolabeled amino acids, amines, and hexoses after arterial injection. Am J Physiol 221:1629–1639, 1971

13. Steinman AM, Smerin SE, Barchas JD: Epinephrine metabolism in mammalian brain after intravenous and intraventricular administration. Science 165:616–617, 1969

14. Hardebo JE, Edvinsson L, MacKenzie ET, Owman C: Histofluorescence study on monoamine entry into the brain before and after opening of the blood-brain barrier by various mechanisms. Acta Neuropathol 47:145–150, 1979

15. Dahlgren N, Rosen I, Sakabe E, Siesjo BK: Cerebral function, metabolic and circulatory effects of intravenous infusion of adrenaline in the rat. Brain Res 184:143–152, 1980

16. Barchas JD, Ciaranello RD, Steinman AM: Epinephrine formation and metabolism in mammalian brain. Biol Psychiat 1:31–48, 1969

17. Mason ST, Carcoran ME: Catecholamine and convulsion. Brain Res 170:497–507, 1979

18. DeJong RH, Wagmen IH, Prince DA: Effect of carbon dioxide on the cortical seizure threshold to lidocaine. Experi Neurol 17: 221–232, 1967

19. Englesson S: The influence of acid-base changes on central nervous system toxicity of local anaesthetic agents: I. Acta Anaesthesiol Scand 18:79–87, 1974

20. Avery P, Redon D, Schaenzer G, Rusy B: The influence of serum potassium on the cerebral and cardiac toxicity of bupivacaine and lidocaine. ANESTHESIOLOGY 61:134–138, 1984

21. Belton NR, Etheridge JE, Millichap JG: Effect of convulsions and anticonvulsants on blood sugar in rabbits. Epilepsia 6:243–249, 1965