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The Contractile Responses of Isolated Dog Cerebral and Extracerebral Arteries to Oxybarbiturates and Thiobarbiturates

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In helical strips of dog cerebral, coronary, mesenteric, renal, and femoral arteries, the addition of thiamylal and thiopental, 10^{-5} to 10^{-3} M, caused a dose-related contraction; the contraction was significantly more intense in cerebral than in extracerebral arteries. Secobarbital caused a slight contaction only in the cerebral artery. In contrast, pentobarbital did not produce a contraction in any artery studied. The thiamylal-induced contraction was not affected by treatment with phentolamine, diphenhydramine, or cinanserin but was attenuated by treatment with Ca entry blockers, such as nifedipine or diltiazem. In the cerebral artery soaked in Ca^{++}-free media for 60 min, the addition of Ca^{++} produced triphasic responses; a transient contraction followed by a relaxation and a slowly developing, persistent contraction. The persistent contraction was potentiated by 10^{-4} M thiamylal but abolished at 10^{-3} M. In the mesenteric artery soaked in Ca^{++}-free media, the addition of Ca^{++} produced only a slight contraction, which was potentiated by thiamylal (10^{-4} and 10^{-3} M). It is concluded that thiobarbiturates are more potent vasoconstrictors than oxybarbiturates and that the barbiturates produce greater contraction in cerebral arteries than in extracerebral arteries. The thiamylal-induced contraction appears to be associated mainly with influx of Ca^{++} from extracellular fluids. (Key words: Anesthetics, intravenous: pentobarbital; secobarbital; thiamylal; thiopental. Artery: cerebral; coronary; mesenteric; renal. Brain, blood flow. Muscle, smooth: vascular.)

IT HAS BEEN DEMONSTRATED that in intact animals and humans barbiturates produce reduction of cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR_{O_2}).[1–4] The change of CBF by barbiturates is often ascribed secondarily to the reduction of metabolic activity, although a direct effect of barbiturates on cerebrovascular resistance has not been fully investigated.[1–3] However, barbiturates have been shown to alter systemic vascular resistance when given intravenously to humans[5–7] and dogs.[8] Thiopental and thiamylal contracted the isolated rabbit or rat aorta, and pentobarbital and secobarbital did not produce contractions.[9–12] Some barbiturates with convulsant properties have also been shown to have intense vasoconstrictor effects on rabbit aorta, and the relationship between structures and vasoconstrictor activities were suggested.[12,13] Cerebral arteries respond to vasoactive agents differently from extracerebral arteries.[14,15] Thus, the present study evaluated quantitatively the direct effects of thiobarbiturates and oxybarbiturates on isolated cerebral and extracerebral arteries and determined the role of Ca^{++} on the mechanism of their contractile action.

Methods

The protocol was approved by the Kyoto University Animal Use Committee. Forty mongrel dogs of either sex, weighing 8–15 kg, were anesthetized with pentobarbital, 30 mg/kg and killed by bleeding from the common carotid arteries. The brain, heart, and kidney were rapidly removed. Basilar and middle cerebral arteries (0.6–0.8 mm, OD), ventral interventricular branches of the left coronary artery (0.6–0.9 mm, OD), and intrarenal interlobular branches of renal artery (0.6–0.9 mm, OD) were isolated. Distal portions of the mesenteric (0.6–0.9 mm, OD) and femoral arteries (0.6–1.2 mm, OD) were also isolated. The arteries were helically cut into strips, the length and width being approximately 17 and 1.0 mm, respectively. The specimen was vertically fixed between hooks in a muscle bath of 10 ml capacity containing Krebs bicarbonate solution of the following composition (mM): NaCl, 118.2; KCl, 4.6; $CaCl_2$, 2.5; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $NaHCO_3$, 24.8; and dextrose 10 (*p*H 7.4), which was maintained at 37.0° ± 0.5° C and aerated with a mixture of 95% O_2 and 5% CO_2. Hooks anchoring the upper end of the strips were connected to the lever of a force-displacement transducer (Toyo Baldwin T7-240, Japan). The resting tension was adjusted to 1.5 g, which was determined to be optimal for obtaining maximum contraction.[16,17] Before the start of experiments, all preparations were allowed to equilibrate for 90–120 min in the control media, during which time the fluids were replaced every 10–15 min.

Isometric contractions and relaxations were displayed on an ink-writing oscillograph (Rectigraph 8K, Nihonkoden Sanei Co., Tokyo, Japan). The contractile response to 30 mM KCl was first obtained, and preparations were washed three times with fresh media. Barbiturates were administered directly to the bathing media in cummulative concentrations. For the comparison of the contractile responses of different arteries to barbiturates, percent of

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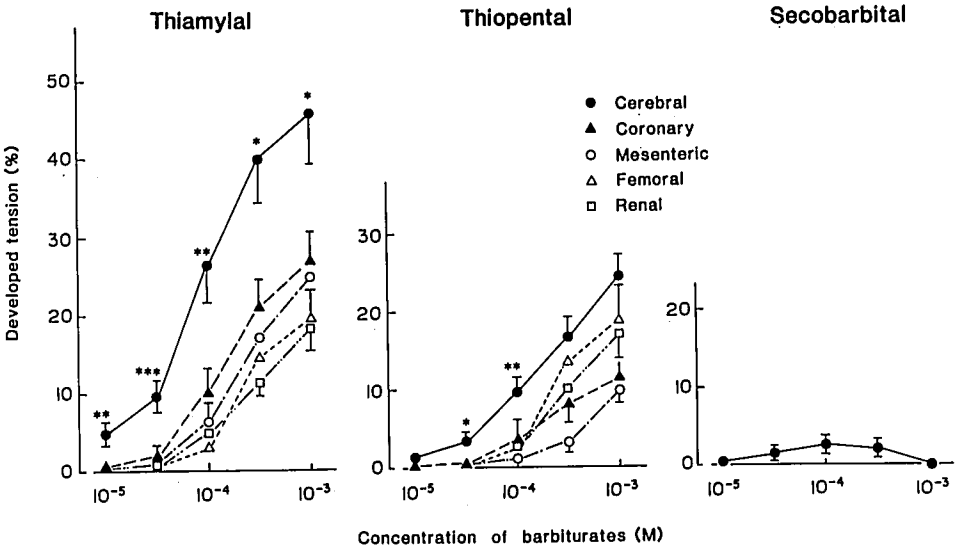

FIG. 1. Dose–response curves for thiamylal, thiopental, and secobarbital in cerebral and extracerebral arteries. Contractions induced by 30 mM KCl were taken as 100%. Mean absolute values in cerebral, coronary, mesenteric, renal and femoral arteries for thiamylal were 820 ± 130 mg (n = 10), 1;630 ± 340 mg (n = 8), 2,210 ± 200 mg (n = 14), 1,320 ± 380 mg (n = 8), and 3,460 ± 400 mg (n = 8), respectively; and those for thiopental were 1,020 ± 220 mg (n = 11), 1,710 ± 260 mg (n = 13), 1,850 ± 170 mg (n = 16), 1,730 ± 200 mg (n = 10), and 3,050 ± 270 mg (n = 12), respectively; and that in cerebral artery for secobarbital was 890 ± 110 mg (n = 14). $*P < 0.05$, $**P < 0.01$ *versus* all other vessel groups.

contraction relative to that induced by 30 mM KCl was presented. The dose–response relationship of thiamylal was obtained before and after 20 min exposures to blocking agents, such as phentolamine, diphenhydramine, cinanserin, diltiazem, or nifedipine. For the studies of arteries in a Ca^{++}-free condition, three strips of cerebral or mesenteric artery were obtained from each dog. In the normal media, contractile responses to thiamylal (10^{-4} and 10^{-3} M) were obtained. Arterial strips were then exposed to Ca^{++}-free media containing 0.1 mM EGTA for 60 min, during which time the fluids were replaced every 20 min. After 60 min of exposure, preparations were treated with thiamylal in concentrations of 10^{-4} or 10^{-3} M, or equivolume of distilled water (for control study) and 10 min later, Ca^{++}, 2.5 mM, was added. The effect of thiamylal, 10^{-4} and 10^{-3} M on the tension of cerebral or mesenteric arterial strips soaked in Ca^{++}-free media for 60 min was also observed.

Drugs used were thiamylal sodium (Kyorin Seiyaku, Tokyo, Japan), thiopental sodium carbonate mixture (60 mg Na_2CO_3/g thiopental) (Tanabe Seiyaku, Osaka, Japan), secobarbital sodium (Yoshitomi Seiyaku, Osaka, Japan), pentobarbital sodium (Nakarai Chem., Kyoto, Japan), diltiazem hydrochloride (Tanabe Seiyaku, Osaka, Japan), nifedipine (Bayer), chlorpheniramine maleate (Nakarai Chem., Kyoto, Japan), cinanserin (Squibb & Sons, Inc., Princeton, New Jersey), and phentolamine mesylate (Ciba-Geigy). Barbiturates were dissolved in distilled water to the concentration of 10^{-1} M and added directly to the bathing media. The *p*H of 10^{-1} M thiamylal, thiopental, secobarbital, and pentobarbital were 10.8, 10.6, 10.1, and 9.2, respectively. In a preliminary study, the addition of 100 μl of these barbiturates (10^{-3} M) did not alter the *p*H of the nutrient solution significantly and 0.05 M bicarbonate (*p*H 10.7) failed to change the arterial tension. Nifedipine was dissolved in the solution containing 15% ethanol and 15% polyethylen glycol #400. The solution of nifedipine and the muscle bath used in experiments with nifedipine were covered with black paper to avoid light-induced breakdown of the drug.

Data are expressed as mean values ± SEM. Student's *t* test for unpaired data was used to analyze the effect of phentolamine, diphenhydramine, or cinanserine on thiamylal-induced contraction. Other data were analyzed statistically by analysis of variance and Newman-Keuls multiple range test. *P* values of less than 0.05 were considered significant.

Results

Responses of Different Arteries to Barbiturates

In helically cut strips of dog cerebral, coronary, mesenteric, renal, and femoral arteries, the addition of thiamylal and thiopental in concentrations ranging from 10^{-5} to 10^{-3} caused dose-related contraction (fig. 1, *left* and *middle*). The contraction induced by thiamylal was significantly more intense in cerebral than in other arteries. Secobarbital in concentrations from 10^{-5} to 10^{-4} caused slight contraction only in ten of 14 cerebral arteries, and an increase in the concentrations to 3×10^{-4} and 10^{-3} M decreased the arterial tension. Secobarbital failed to contract extracerebral arteries (six arterial strips for each vessel group). Pentobarbital did not produce any contractions of arterial strips used, but only a slight relaxation was observed in higher concentrations. The contractions or relaxations were reversed by washing. Maximum con-

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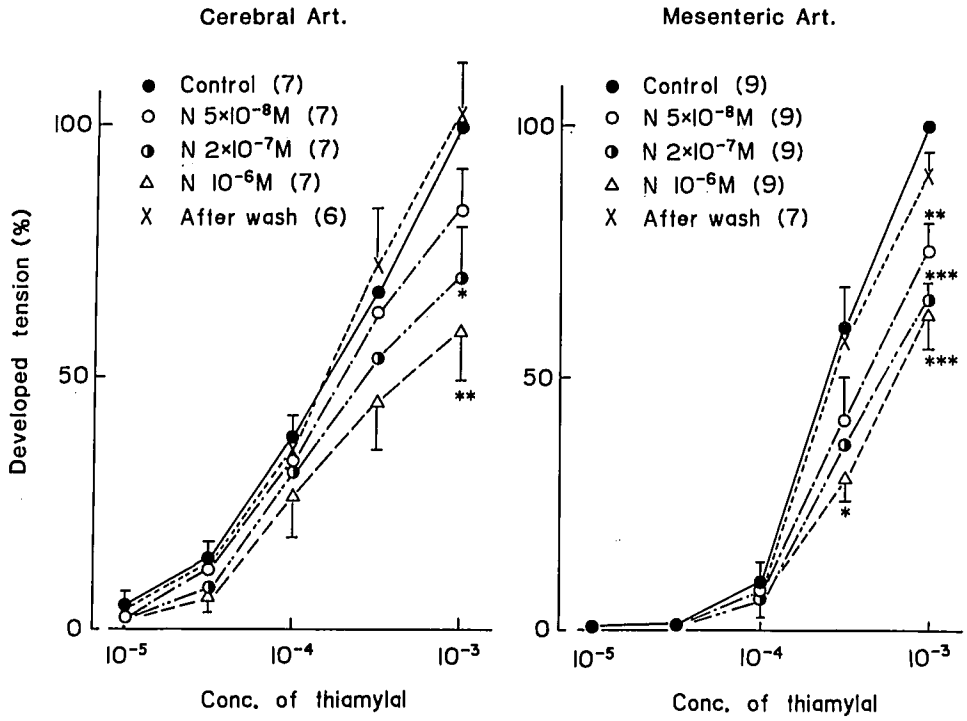

FIG. 2. Modification by nifedipine of the contractile response to thiamylal of cerebral (left) and mesenteric (right) arteries. Contraction induced by 10^{-3} M thiamylal in control media was taken as 100%. Mean absolute values in cerebral and mesenteric arteries were 621 ± 78 mg (n = 7) and 772 ± 71 mg (n = 9), respectively. N = nifedipine. Values in parentheses indicate the number of preparations studied. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ *versus* control values.

traction of cerebral arteries induced by 10^{-3} M thiamylal, 10^{-3} M thiopental and 10^{-4} secobarbital, relative to those induced by 30 mM KCl, averaged 45.8% ± 6.5% (n = 10), 24.4% ± 3.2% (n = 11), and 2.8% ± 1.1% (n = 14), respectively. The contractions of cerebral and mesenteric arteries produced by 10^{-4} M thiamylal or thiopental slowly developed and leveled off within 10 min, whereas those produced by 10^{-3} M were transient and were followed by a relaxation. The following experiments were performed using thiamylal in cerebral and mesenteric arteries because thiamylal was revealed to be the most potent constrictor among barbiturates tested and the effect was most prominent in the cerebral artery among arteries examined. Mesenteric arteries were also used because there may be a difference in the mechanism of contraction in cerebral and extracerebral arteries.

The contractile response of cerebral arteries to thiamylal was not affected by pretreatment for 20 min with 10^{-6} M phentolamine, 10^{-6} M diphenhydramine, or 10^{-5} M cinanserin. Nifedipine and diltiazem shifted the dose–response curve of cerebral and mesenteric arteries for thiamylal to the right and downward (figs. 2 and 3); average inhibitions by 2×10^{-7} nifedipine of the contractile response to 10^{-3} M thiamylal in cerebral and mesenteric arteries were 30.0% ± 10.7% (n = 7) and 35.3% ± 3.1% (n = 9), respectively, and those by 10^{-6} M diltiazem were 10.6% ± 8.4% (n = 9) and 29.6% ± 7.6% (n = 10), respectively. The inhibition was reversed by repeated washing. Inhibitions by nifedipine, 2×10^{-7} M, of contractile responses of cerebral and mesenteric arteries to 20 mM KCl were 87.7% ± 3.7% (n = 6) and 83.4% ± 4.9% (n = 5), respectively, and that by diltiazem, 5×10^{-6} M, were 91.2% ± 3.7% (n = 6) and 94.2% ± 3.1% (n = 4) respectively; Ca entry blockers produced greater inhibitory effect on contraction induced by potassium than on contraction by thiamylal.

CONTRACTILE RESPONSE TO Ca^{++} IN CEREBRAL AND MESENTERIC ARTERIES SOAKED IN Ca^{++}-FREE MEDIA

In cerebral and mesenteric arterial strips exposed to Ca^{++}-free media for 60 min, the addition of thiamylal (10^{-4} and 10^{-3} M) failed to produce a significant contraction.

The addition of Ca^{++} to cerebral arteries exposed for 60 min to Ca^{++}-free media elicited a rapidly developing, transient contraction (A in fig. 4) followed by a relaxation (B in fig. 4); then the tension gradually increased and leveled off 10–20 min later (C in fig. 4). Treatment with 10^{-4} M thiamylal for 10 min before the addition of Ca^{++} significantly potentiated Ca^{++}-induced sustained contraction (fig. 5), whereas treatment with 10^{-3} M thiamylal abolished it. In contrast to cerebral arteries, the addition of Ca^{++} to mesenteric arteries exposed to Ca^{++}-free media elicited only a slight, transient contraction. In the arteries treated with thiamylal, the addition of Ca^{++} produced

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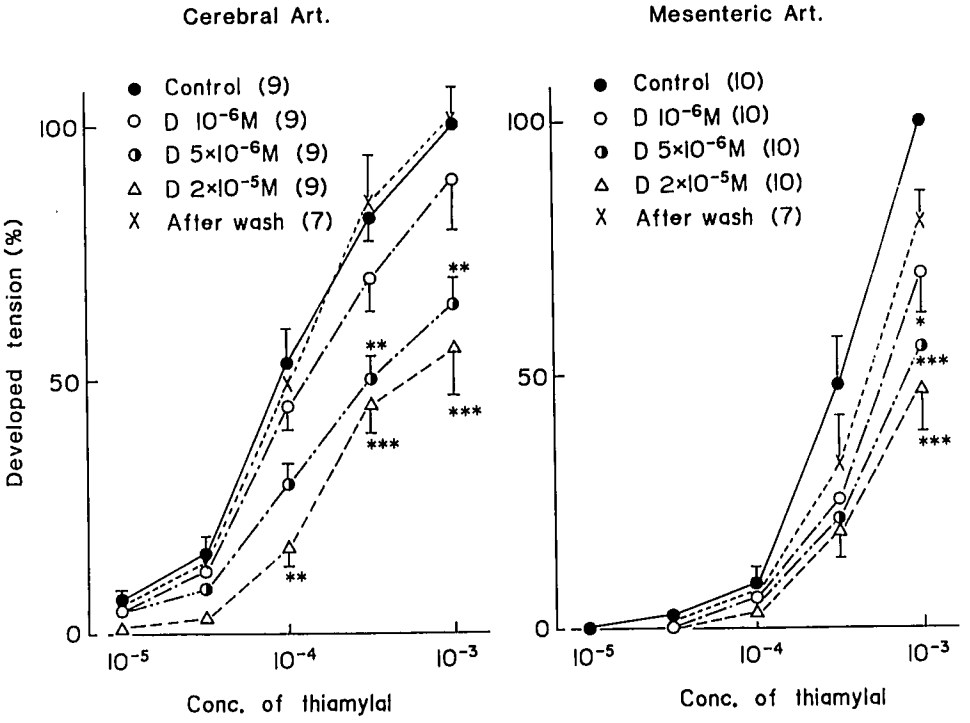

FIG. 3. Modification by diltiazem of the contractile response to thiamylal of cerebral (left) and mesenteric (right) arteries. Contraction induced by 10^{-3} M thiamylal in control media was taken as 100%. Mean absolute values in cerebral and mesenteric arteries were 503 ± 52 mg (n = 9) and 700 ± 160 mg (n = 10), respectively. D = diltiazem. Values in parentheses indicate the number of preparations studied. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ *versus* control values.

triphasic responses; the persistent contraction was dependent on concentrations of the barbiturate (fig. 6).

Discussion

The present study examined the vasoconstrictor effect of thiobarbiturates and oxybarbiturates on the isolated dog arteries under resting conditions and revealed that the potency of vasoconstriction, which is greater in cerebral than in extracerebral arteries, is in the order of thiamylal > thiopental ⩾ secobarbital > pentobarbital. These findings suggest that the vasoconstrictor activity is a function of the structure of barbiturates (fig. 7).

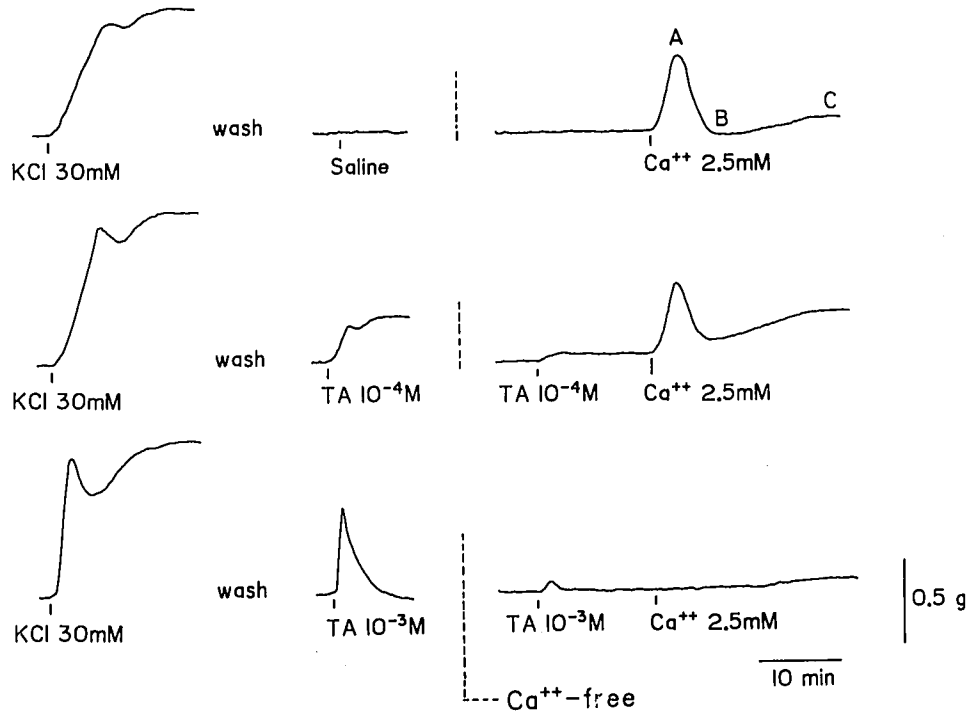

FIG. 4. Response to Ca^{++} (2.5 mM) of cerebral arterial strips soaked in Ca^{++}-free media in the absence (upper right) and presence (middle and lower right) of thiamylal (10^{-4} or 10^{-3} M). TA = thiamylal. The addition of the Ca^{++} elicited triphasic responses: a rapid transient contraction (A) followed by a relaxation (B) and a persistent contraction (C).

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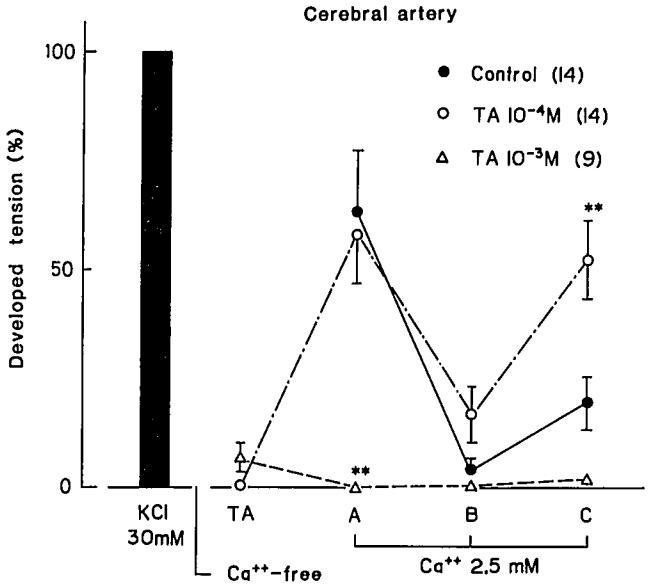

FIG. 5. Modification by thiamylal of the contractile response to Ca^{++} of cerebral arterial strips soaked in Ca^{++}-free media. Contraction of cerebral artery induced by 30 mM KCl in control media was taken as 100%. Mean absolute value was 1,154 ± 100 mg (n = 37). A, B, and C on the abscissa are the same as illustrated in figure 4. TA = thiamylal. Values in parentheses indicate the number of preparations studied. $**P < 0.01$ *versus* control values.

Most *in vitro* studies have demonstrated the depressor effects of barbiturates on vascular smooth muscle.[9,10,18–21] Our finding that pentobarbital elicits relaxation of cerebral arteries is in agreement with those reported by other authors.[18–21] However, the vascular effects of thiobarbiturates appear to be more complex. The application of thiobarbiturates to cerebral arteries under resting conditions elicited a sustained contraction at low concentrations and a transient contraction followed by a marked relaxation attaining the basal tension at high concentrations. It has been suggested that the vasodilating effects will be more prominent when the agents are applied to isolated arteries previously contracted with vasoconstrictors than to those under resting conditions.[22] For example, Sanchez-Ferrer *et al.*[21] demonstrated only the vasodilating action of thiopental on the isolated human cerebral arteries previously contracted with norepinephrine, serotonin, or KCl. Their failure to observe the vasoconstrictor effect of thiopental may derive in part from the fact that the arteries were maximally contracted with high concentrations of vasoconstrictors before the application of thiopental.

The involvement of alpha-adrenergic, serotonergic, and histaminergic H1 mechanisms would be excluded in thiamylal-induced contraction because pretreatment with phentolamine, cinanserin, and chlorpheniramine did not affect it. The contraction is likely to depend on the Ca^{++} influx from extracellular fluids because exposure of cerebral or mesenteric arterial strips to Ca^{++}-free media abolished the contraction. However, the possibility of a contribution of intracellular Ca^{++} to the contraction is not excluded from this experiment, as during the exposure to Ca^{++}-free media, parts of cellular Ca^{++} could also be depleted.[23]

The contraction induced by thiamylal was less sensitive to the inhibition by nifedipine and diltiazem than the contraction induced by KCl. Ca entry blockers are believed to block the voltage-dependent Ca^{++} influx more intensely than the influx caused by the stimulation of drug receptors.[24] These findings may indicate that the transmembrane influx of Ca^{++} induced by thiamylal is not mediated by the voltage-dependent Ca^{++} channel.

The addition of Ca^{++} to the bath in which cerebral arteries were exposed to Ca^{++}-free media elicits a transient contraction followed by a relaxation and a slowly developing persistent contraction. The former contraction is thought to be due to an increased Ca^{++} permeability induced by a long exposure to Ca^{++}-free media and the latter contraction may result from a slow increase in the

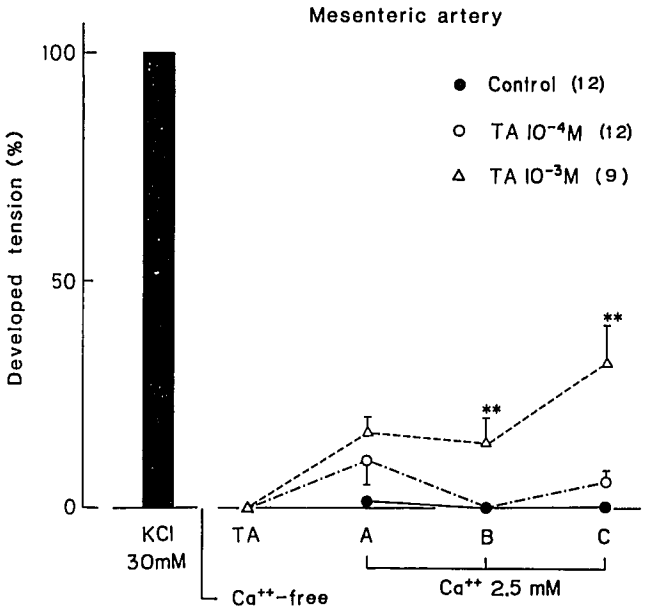

FIG. 6. Modification by thiamylal of the contractile response to Ca^{++} of mesenteric arterial strips soaked in Ca^{++}-free media. Contraction of mesenteric artery induced by 30 mM KCl in control media was taken as 100%. Mean absolute value was 2,173 ± 152 mg (n = 33). A, B, and C on the abscissa are the same as illustrated in figure 4. TA = thiamylal. Values in parentheses indicate the number of preparations studied. $**P < 0.01$ *versus* control values.

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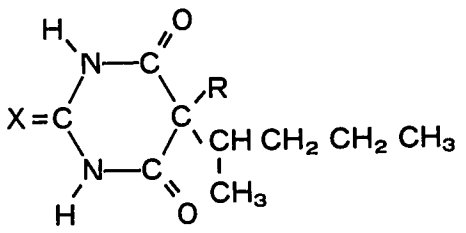

Barbiturate	R	X	Vasoconstricting Activity	
			cerebral	extra-cerebral
Thiamylal	allyl	S	+++	++
Thiopental	ethyl	S	++	+
Secobarbital	allyl	O	±	−
Pentobarbital	ethyl	O	−	−

FIG. 7. Relationship between structure of barbiturates and vasoconstricting activities.

Ca^{++} influx.[15] The treatment with 10^{-4} M thiamylal significantly potentiated the persistent contraction both in cerebral and mesenteric arteries. In contrast, treatment with 10^{-3} M thiamylal abolished the Ca^{++}-induced contraction of cerebral arteries but potentiated that of mesenteric arteries. Thiamylal at a concentration of 10^{-3} M appears to possess both contracting and relaxing activities; the latter is dominant in cerebral arteries. Previous authors have shown that barbiturates including thiopental in concentrations of 10^{-4} to 10^{-3} M inhibit the Ca^{++}-induced contraction of K^{+}-depolarized isolated rabbit aortas[10] and human cerebral arteries[21] exposed to Ca^{++}-free media. These findings suggest that the relaxing activity of 10^{-3} M thiamylal may be caused by the blockade of the influx of transmembrane Ca^{++}, although other mechanisms such as inhibition of Ca^{++} availability in contractile proteins cannot be excluded.

Plasma concentrations of thiamylal or thiopental in humans when given intravenously for anesthesia are roughly estimated at $1–3 \times 10^{-4}$ M.[25] Although there may exist a difference in responsiveness depending on the arteries of different regions and species,[26] these concentrations are expected to be large enough to produce significant contractions of large pial arteries but not sufficient to contract extracerebral arteries. It is known that cerebral blood flow (CBF) is decreased by the reduction of the cerebral metabolic activity induced by anesthetics *in vivo*.[1–3] Thus, we speculate that following rapid induction of anesthesia by thiobarbiturates their direct vasoconstrictor effects contribute to the reduction of CBF in addition to that produced by their effect on cerebral metabolism. However, when the plasma concentrations exceed 3×10^{-4} M, sustained direct vasodilatation may counteract the metabolic effect to reduce CBF.

Stullken *et al.*[4] demonstrated that in the dog with an infusion of thiopental 23 $mg \cdot kg^{-1} \cdot h^{-1}$, CBF declined rapidly during the first 25 min, and it remained depressed thereafter. The rapid CBF reduction can be ascribed to the secondary effect of the simultaneous depression of cerebral metabolism.[4] On the basis of our *in vitro* data, however, the rapid decline of CBF up to the dose of 11 mg/kg may be related to the direct vasoconstrictor effect of low concentrations of thiopental, and later the direct vasodilating effect of high concentrations may attenuate the decline of CBF.

In summary, the present study compared the contractile responses of cerebral and extracerebral arteries to barbiturates; thiamylal was the most potent constrictor among the barbiturates used, and the contractions were more intense in cerebral than in extracerebral arteries. Further investigations are required to elucidate the clinical importance of the direct effects of barbiturates on cerebrovascular smooth muscles.

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