Comparison of the vasodilator effects of thiopentone and pentobarbitone

Tsutomu Yakushiji MD, Kumi Nakamura MD, Yoshio Hatano MD,* Kenjiro Mori MD FCAnaesth

The aim of this study was to elucidate the vasodilator mechanisms of barbiturates. In helical strips of dog mesenteric artery, the effects of pretreatment with thiopentone and pentobarbitone on the contractions induced by KCl (2.0×10^{-2} M) and norepinephrine (10^{-5} M) in normal bathing fluid, and those induced by norepinephrine and caffeine (2.5×10^{-2} M) in Ca^{++}-free fluid were tested, and their effects on caffeine-induced contractions in skinned strips were also examined. Thiopentone, at concentrations over 10^{-4} M, inhibited the KCl-induced contractions in normal bathing fluid and those induced by caffeine in Ca^{++}-free fluid and, at concentrations over 3×10^{-4} M, inhibited norepinephrine-induced contractions in normal and Ca^{++}-free bathing fluids significantly. Pentobarbitone, at concentrations over 3×10^{-4} M, inhibited KCl- and norepinephrine-induced contractions in normal bathing fluid significantly, whereas contractions in Ca^{++}-free fluid induced by norepinephrine and caffeine were inhibited only by a high concentration (10^{-3} M) of pentobarbitone. Caffeine-induced contractions of chemically skinned fibres were more susceptible to inhibition by thiopentone than by pentobarbitone. These results suggest that the vasodilator effect of thiopentone is mediated via its intracellular inhibitory effect and that, in contrast, the vasodilator effect of pentobarbitone can be attributed mainly to its Ca^{++}-channel blocking action.

Le but de cette étude était d'élucider les mécanismes vasodilatateurs des barbituriques. Sur des bandelettes spiralées de l'artère mésentérique du chien, nous avons vérifié les effets d'un traitement préparatoire au moyen de thiopental et de pentobarbital sur les contractions induites par du KCl ($2,0 \times 10^{-2}$ M) et de la norépinéphrine (10^{-5} M) dans un liquide de bain normal, ainsi que sur celles induites par de la norépinéphrine et de la caféine ($2,5 \times 10^{-2}$ M) dans un liquide ne contenant pas d'ions Ca^{++}. Sur des bandelettes dénudées, nous avons également examiné leurs effets sur les contractions induites par la caféine. Le thiopental, à des concentrations supérieures à 10^{-4} M, inhibait les contractions induites par le KCl dans un liquide de bain normal et celles induites par la caféine dans le liquide sans Ca^{++} et, à des concentrations supérieures à 3×10^{-4} M, inhibait significativement les contractions induites par la norépinéphrine dans les liquides de bain normal et sans Ca^{++}. Le pentobarbital, à des concentrations supérieures à 3×10^{-4} M, inhibait significativement les contractions induites par le KCl et la norépinéphrine dans le liquide de bain normal, alors que les contractions induites par la norépinéphrine et la caféine dans le liquide sans Ca^{++} étaient inhibées seulement par une forte concentration (10^{-3} M) de pentobarbital. Pour les fibres dénudées chimiquement, les contractions induites par la caféine étaient plus susceptibles à une inhibition par le thiopental que par le pentobarbital. Ces résultats suggèrent que l'effet d'inhibition intracellulaire du thiopental sert de médiateur à son effet vasodilatateur et que, par contraste, l'effet vasodilatateur du pentobarbital peut être attribué principalement à son action de bloqueur des canaux calciques.

Key words
ANAESTHETICS, INTRAVENOUS: thiopentone, pentobarbitone;
MUSCLE: smooth;
ARTERIES: mesenteric.

From the Department of Anesthesia, Kyoto University Hospital, Sakyo-ku, Kyoto 606-01, Japan.
*Present address: Department of Anesthesiology, Wakayama Medical College, 7-1, Wakayama-shi 640, Japan.
Address correspondence to: Dr. K. Nakamura.
Accepted for publication 16th February, 1992.

Barbiturates exert relaxant effects on vascular smooth muscle even in clinically relevant concentrations.[1-10] Some investigators have ascribed this effect to a Ca^{++}-channel blocking action.[2,6] However, we have demonstrated that thiamylal inhibits contractions which are mediated via the release of intracellularly stored Ca^{++}, as well as those mediated by influx of extracellular Ca^{++}, and that it exerts a relaxant effect even in Ca^{++}-contracted skinned fibres.[11] These results suggest that thiamylal reduces the sensitivity of the intracellular contractile machinery to Ca^{++} ions. However, since it has been demonstrated that thiobarbiturates, including thiamylal

and thiopentone, have a potent vasoconstrictor effect and oxybarbiturates such as pentobarbitone do not have the effect,[8,12] the mechanisms of relaxation induced by thiobarbiturates and oxybarbiturates may also differ. This study was designed to examine whether thiopentone and pentobarbitone, which are corresponding oxy- and thiobarbiturates, have such intracellular actions as thiamylal.

Methods

The experimental protocol was approved by the Kyoto University Animal Use Committee. Nineteen male mongrel dogs, weighing 10 to 15 kg, were anaesthetized with ketamine (10 mg · kg^{-1} *iv*) and killed by exsanguination. Distal portions of mesenteric arteries (0.6–0.9 mm outer diameter) were isolated and cut into helical strips (approximately 20 mm long) with intact endothelium. Each strip was placed in a 10-ml organ bath containing Krebs-bicarbonate solution, which was maintained at 37.0 ± 0.5° C and aerated with a mixture of 5% CO_2 and 95% O_2 to maintain the pH between 7.35 and 7.45. The hook anchoring the upper end of each strip was connected to the lever of a force-displacement transducer (Toyo Baldwin T7-240, Japan) and changes in isometric tension were displayed on an ink-writing oscillograph (Rectigraph 8K, Nihon-denki Sanei Co., Japan). The resting tension was adjusted to 1.5 g, which has been determined to be optimal for the induction of maximal contractions.[13] Before starting the experiments, each arterial strip was allowed to equilibrate for 90–120 min in the control bathing fluid, which was replaced every 15 min.

Some arterial strips were chemically skinned by exposing them to saponin (25 μg · ml^{-1}) for 20 min, as described previously.[11] These strips were bathed in a relaxant solution, which contained 2.0 × 10^{-3} M ethyleneglycol-bis-N,N′-tetraacetic acid (EGTA), during the saponin exposure and in a relaxant solution, which contained 10^{-4} M EGTA, thereafter. These solutions were aerated with 100% oxygen and maintained at 25° C throughout.

Potassium chloride- and norepinephrine-induced contraction

Repeated contractions with KCl (2.0 × 10^{-2} M) or norepinephrine (NE, 10^{-5} M) were induced in normal bathing fluid until the tensions induced by two successive applications were identical, which were designated 100% in each experiment. Between applications, the preparation was washed at least three times with fresh bathing fluid. In order to study the effects of thiopentone and pentobarbitone on the KCl- and NE-induced contractions in normal bathing fluid, each arterial strip was exposed to thiopentone or pentobarbitone (10^{-4} to 10^{-3} M), or equivalent volumes of distilled water (control study) for 20 min, and the tension changes induced by the required vasoconstricting agent were measured. In order to examine the effects of the barbiturates on the NE-induced contractions in Ca^{++}-free bathing fluid, each strip was treated with thiopentone or pentobarbitone (10^{-4} to 10^{-3} M) (or equivalent volume of distilled water for control study) for 15 min in normal bathing fluid and then bathed in Ca^{++}-free Krebs-bicarbonate solution, which contained 2.0 × 10^{-3} M EGTA and the same concentration of barbiturates, for five minutes prior to exposure to NE. Norepinephrine-induced contractions in Ca^{++}-free fluid was examined only once in each strip, and they were expressed in relative values taking the prior contractions induced by NE in Ca^{++}-containing solution in each strip as 100%.

Caffeine-induced contractions

As caffeine-induced contraction is dependent on the amount of Ca^{++} stored in the cell,[14-16] in this experiment arterial strips with intact plasma membranes or which had been skinned were treated first with 2.5 × 10^{-2} M caffeine in a Ca^{++}-free solution, which contained 2.0 × 10^{-2} M EGTA (Ca^{++}-free Krebs-bicarbonate solution for intact fibres or relaxant solution for skinned fibres) to deplete their intracellular stores of Ca^{++}, after which they were bathed for 20 min in Ca^{++}-containing solutions (2.5 × 10^{-3} M Ca^{++} for intact fibres and 10^{-4} M for skinned fibres), followed by exposure to the appropriate Ca^{++}-free bathing fluid for ten minutes and subsequent exposure to caffeine (2.5 × 10^{-2} M). Before the third application of caffeine, strips were untreated (control) or treated with thiopentone or pentobarbitone (10^{-5} to 10^{-3} M).

Drugs and fluids

The drugs used were thiopentone sodium (Tanabe Pharmaceutical Co., Tokyo, Japan), pentobarbitone sodium, norepinephrine and caffeine (Nacalai Tesque, Kyoto, Japan). Caffeine was dissolved to a concentration of 10^{-2} M in Ca^{++}-free bathing solutions (Ca^{++}-free Krebs' solution or the appropriate relaxant solution) and the normal bathing fluid was replaced by these solutions for the experiments which involved exposure to caffeine. Norepinephrine was dissolved in a solution of 0.1% w/v sodium pyrosulfate in distilled water. All the other drugs were dissolved in distilled water and added directly to the bathing fluid; the volumes added were less than 100 μl. Equivalent volumes of the appropriate diluents were added for the control studies. The pH of 10^{-1} M thiopentone and pentobarbitone were 10.6 and 9.2 respectively, and the addition of 100 μl of them to the bath did not alter the pH of the bathing solution.[12]

The Krebs-bicarbonate solution contained (× 10^{-3} M):

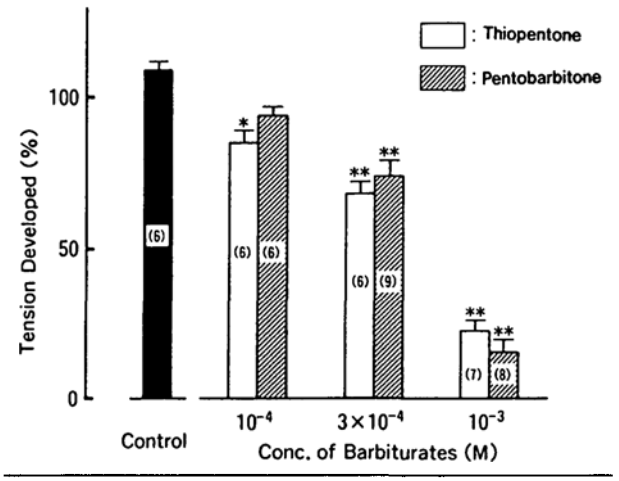


FIGURE 1 Modification by thiopentone and pentobarbitone of contractions induced by KCl (2.0×10^{-2} M). The KCl-induced contraction of each strip prior to treatments was designated 100%; the mean absolute value was 898 ± 484 mg (n = 19). Values in parentheses indicate the number of strips studied; $*P < 0.05$, $**P < 0.01$ versus control values.

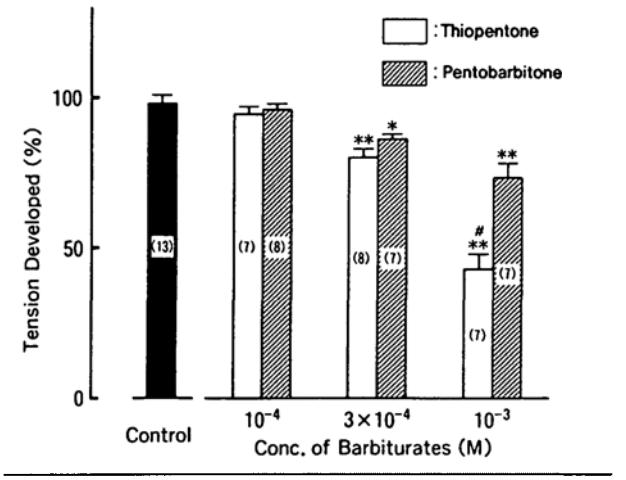


FIGURE 2 Modification by thiopentone and pentobarbitone of contractions induced by NE (10^{-5} M) in normal bathing solution. The NE-induced contraction of each strip prior to treatments was designated 100%; the mean absolute value was 2757 ± 1374 mg (n = 21). Values in parentheses indicate the number of strips studied; $*P < 0.05$, $**P < 0.01$ versus control values. $\#P < 0.05$ thiopentone versus pentobarbitone in the same concentrations.

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. The Ca^{++}-free Krebs'-bicarbonate solution contained no Ca^{++} but did contain 2.0×10^{-3} M EGTA and the other constituents were as described for the Krebs-bicarbonate solution. The relaxant solution contained ($\times 10^{-3}$ M): KCl 130; Tris-malate 20; $MgCl_2$ 2; adenosine triphosphate (ATP) 3 and NH_4, which was added to adjust the pH to 6.75–6.85.

Statistical analysis

Each response was expressed as a percentage of the response obtained prior to treatment in the same strip except for the response to NE in Ca^{++} free condition, which was expressed relative to that in Ca^{++}-containing solution. The control value represents the response of strips treated with distilled water alone, in a volume equal to the barbiturate-containing solution, relative to the previous response in the same strip. The data were expressed as means ± SEM and analyzed by analysis of variance and Newman Keuls' multiple range test. A P value <0.05 was considered to be significant.

Experimental design

The effects of pretreatment with thiopentone and pentobarbitone on the contractions induced by KCl and NE in normal bathing fluid and on those induced by NE and caffeine in Ca^{++}-free fluid in intact strips, and on caffeine-induced contractions in skinned strips were examined.

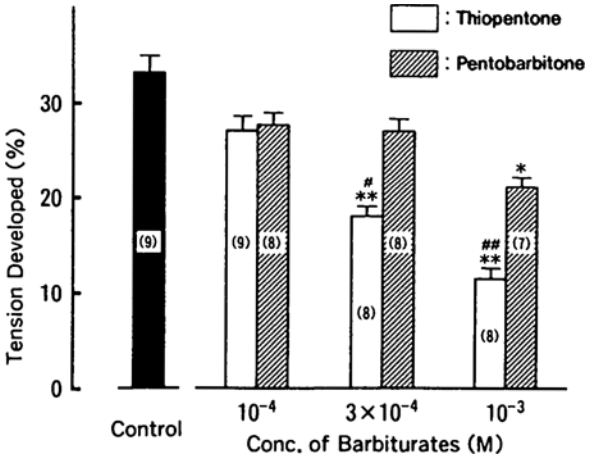


FIGURE 3 Modification by thiopentone and pentobarbitone of contractions induced by NE (10^{-5} M) in Ca^{++}-free solution. The NE-induced contraction of each strip in normal bathing fluid prior to treatment was designated 100%; the mean absolute value was 3677 ± 1246 mg (n = 30). Values in parentheses indicate the number of strips studied; $*P < 0.05$, $**P < 0.01$ versus control values. $\#P < 0.05$, $\#\#P < 0.01$ thiopentone versus pentobarbitone in the same concentrations.

Results

The contractions induced by KCl were inhibited by thiopentone and pentobarbitone, at concentrations greater than 10^{-4} M and 3×10^{-4} M respectively ($P < 0.05$), but the inhibition produced by thiopentone was not dif-

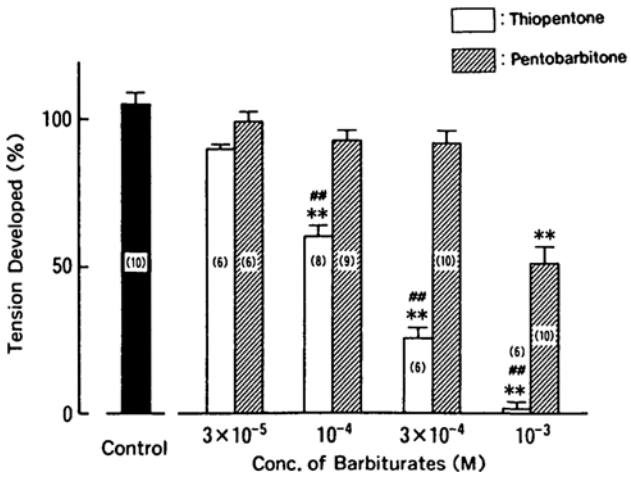


FIGURE 4 Modification by thiopentone and pentobarbitone of contractions induced by caffeine (2.5×10^{-2} M) in intact fibres. The caffeine-induced contraction of each strip prior to treatment was designated 100%; the mean absolute value was 411 ± 207 mg (n = 18). Prior to each application of caffeine, the arterial strips were loaded with Ca^{++} (2.5×10^{-3} M) for 20 min and then bathed in Ca^{++}-free relaxant solution, with or without thiopental and pentobarbital. Values in parentheses indicate the number of strips studied; $*P < 0.01$ versus control values. $\#\#P < 0.01$ thiopentone versus pentobarbitone in the same concentrations.

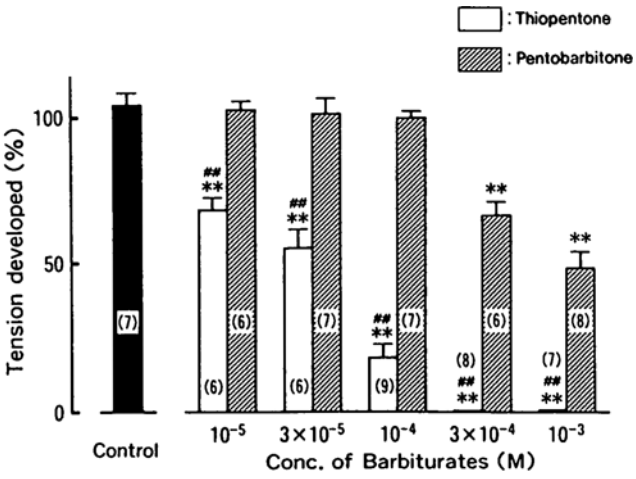


FIGURE 5 Modification by thiopentone and pentobarbitone of contractions induced by caffeine (2.5×10^{-2} M) in chemically skinned fibres. The caffeine-induced contraction of each strip prior to treatments was designated 100%; the mean absolute value was 329 ± 148 mg (n = 35). Prior to each application of caffeine, the arterial strips were loaded with Ca^{++} (10^{-4} M) for 20 min and then bathed in Ca^{++}-free relaxant solution, with or without barbiturates. Values in parentheses indicate the number of strips studied; $**P < 0.01$ versus control values. $\#\#P < 0.01$ thiopentone versus pentobarbitone in the same concentrations.

ferent from that by pentobarbitone at corresponding concentrations (Figure 1).

Norepinephrine-induced contractions in normal bathing fluid (Ca^{++} 2.5×10^{-3} M) were attenuated by thiopentone and pentobarbitone, at concentrations greater than 3×10^{-4} M ($P < 0.05$), and the attenuation induced by 10^{-3} M thiopentone was greater than that induced by 10^{-3} M pentobarbitone ($P < 0.05$) (Figure 2).

Norepinephrine-induced contractions in Ca^{++}-free bathing fluid, the mean of which was 32.2 ± 7.5% of that in normal bathing fluid (control group), were inhibited by thiopentone and pentobarbitone at concentrations greater than 3×10^{-4} M and 10^{-3} M respectively ($P < 0.05$) (Figure 3). The attenuations induced by thiopentone ($\geqq 3 \times 10^{-4}$ M) were greater than those of pentobarbitone at corresponding concentrations ($P < 0.05$).

Caffeine-induced contractions in intact fibres were inhibited by thiopentone at over 10^{-4} M and pentobarbitone at only 10^{-3} M ($P < 0.01$) (Figure 4). The inhibitory effects of thiopentone ($\geqq 10^{-4}$ M) were greater than those of pentobarbital at corresponding concentrations ($P < 0.01$). Caffeine-induced contractions of skinned fibres were inhibited by thiopentone at concentrations greater than 10^{-5} M and pentobarbitone 3×10^{-4} M ($P < 0.01$) (Figure 5). The inhibitory effects of thiopentone ($\geqq 10^{-5}$ M) were greater than those of pentobarbitone at corresponding concentrations ($P < 0.01$).

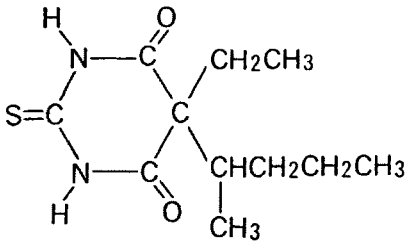
Discussion

We have previously demonstrated that endothelium-independent vasodilation is induced by pentobarbitone at concentrations over 10^{-4} M, and by thiopentone and thiamylal at over 3×10^{-4} M, in dog mesenteric arteries precontracted with KCl or prostaglandin $F_{2\alpha}$.[8] The plasma level of thiopentone necessary for anaesthesia has been reported to be 1.5×10^{-4} M in humans,[17] and the peak level of barbiturates following rapid induction, or that of oxybarbiturates when large doses were administered for cerebral protection may be higher than this. Therefore, concentrations of barbiturates which induced vasodilatation in the dog mesenteric artery may be close to clinically relevant concentrations in humans.

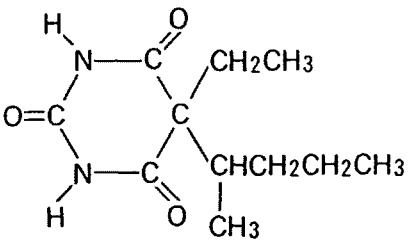
In this study, we compared the influence of thiopentone and pentobarbitone on contractions elicited by KCl, NE and caffeine, which induce contractions via different mechanisms. Potassium chloride elicits contractions by increasing Ca^{++}-influx through voltage-dependent Ca^{++} channels and caffeine induces contraction by facilitating Ca^{++} induced Ca^{++} release from the sarcoplasmic reticulum (SR).[15,16] Norepinephrine increases Ca^{++}-influx through receptor-operated Ca^{++}-channels and increases the release of intracellularly stored Ca^{++}, which is mediated by inositol 1,4,5-triphosphate (IP3).[18,19] Therefore, NE-induced contractions in normal bathing fluid can be considered to be due to the summation of those mediated

TABLE The minimum concentrations of barbiturates required to inhibit contractions significantly

	Thiopentone	*Pentobarbitone*
KCl-induced contraction	10^{-4} M	3×10^{-4} M
NE-induced contraction in normal Ca^{++} solution	3×10^{-4} M	3×10^{-4} M
NE-induced contraction in Ca^{++}-free solution	3×10^{-4} M	10^{-3} M
Caffeine-induced contraction of intact strips	10^{-4} M	10^{-3} M



Thiopentone



Pentobarbitone

FIGURE 6 The chemical structures of thiopentone and pentobarbitone.

by Ca^{++}-influx and Ca^{++}-release and contraction in Ca^{++}-free fluid, containing 2.0×10^{-3} M EGTA, can be considered to approximate that mediated by Ca^{++}-release alone.[5,19]

This study demonstrated that the sensitivities of the contractions induced by KCl, NE and caffeine to the inhibitory effects of pentobarbitone or thiopentone differ (Table). Pentobarbitone inhibited KCl-induced contractions to a greater extent than those mediated via Ca^{++}-release, including those induced by caffeine and by NE in Ca^{++}-free fluid. Furthermore, contractions induced by NE in normal Ca^{++}-containing fluid were more susceptible to pentobarbitone than those in Ca^{++}-free fluid. These results agree with those of other authors[1,3-8] and support the hypothesis that pentobarbitone inhibits Ca^{++}-influx through both voltage-dependent and receptor-operated channels of plasma membranes.[2,6] However, in contrast to pentobarbitone, thiopentone inhibited contractions induced by caffeine to the same extent as those induced by KCl, which suggests that the mechanism underlying the relaxant effects of thiopentone and pentobarbitone differ.[21]

Treatment with saponin renders plasma membranes porous and such muscle fibres are described as chemically skinned. Therefore, using skinned fibres, the effects of any agent in the absence of the influence of Ca^{++}-movement across the plasma membrane can be studied. Our previous study[11] demonstrated that thiamylal inhibited Ca^{++}-induced contractions in dog mesenteric arterial skinned fibres strongly, which indicates that thiamylal reduced the sensitivity of the intracellular contractile machinery to Ca^{++}. In this study, we tested the effects of barbiturates on caffeine-induced contraction of skinned and intact fibres, and found that thiopentone exerted inhibitory effects on caffeine-induced contractions of skinned fibres at very low concentrations, which indicates that the action of thiopentone is not limited to the plasma membranes. Furthermore, these findings with thiopentone can be explained by the hypothesis that thiopentone, but not pentobarbitone, reduced the sensitivity of the vascular smooth muscle intracellular contractile machinery to Ca^{++} in the same, or a similar manner, as thiamylal.[11] Moreover, as thiopentone and pentobarbitone are corresponding thio- and oxybarbiturates (Figure 6), these results suggest that different mechanisms may underlie the relaxations induced by thio- and oxybarbiturates.

In addition, although it has been generally accepted that plasma membranes are quite permeable to barbiturates, the finding that caffeine-induced contractions of muscle fibres with intact plasma membranes were less susceptible to thiobarbiturates than those which had been skinned, indicates that a barbiturate concentration gradient across the intact plasma membrane may exist.

In this study, contractions induced by NE were less susceptible to thiopentone than those induced by KCl and caffeine, which agrees with the results obtained with thiamylal in our previous study.[11] It has been demonstrated that thiobarbiturates, such as thiopentone and thiamylal, in concentrations of 10^{-5} to 10^{-4} M, potentiate NE-induced contractions of the rabbit isolated pulmonary artery or rat isolated aorta.[7,20,21] This effect may counteract the relaxant effect of thiopentone and could, therefore, account for the lower susceptibility of NE-induced contractions to thiopentone compared with those of KCl- or caffeine-induced contractions.

In summary, thiopentone inhibited contractions elicited by Ca^{++}-influx and Ca^{++}-release to the same extent, whereas pentobarbitone inhibited contractions elicited by

Ca^{++} influx selectively. We hypothesize that the vasodilator effect of pentobarbitone is due mainly to a non-specific Ca^{++}-channel blocking action, whereas thiopentone, as does thiamylal, reduces the sensitivity of the vascular smooth muscle intracellular contractile machinery to Ca^{++}.

References

1 *Altura BT, Altura BM.* Barbiturates and aortic and venous smooth-muscle function. Anesthesiology 1975; 43: 432–44.

2 *Altura BM, Turlapaty PDMV, Altura BT.* Pentobarbital sodium inhibits calcium uptake in vascular smooth muscle. Biochim Biophys Acta 1980; 595: 309–12.

3 *Edvinson L, McCulloch J.* Effects of pentobarbital on contractile responses of feline cerebral arteries. J Cereb Blood Flow Metab 1981; 1: 437–40.

4 *Marin J, Lobato RD, Rico ML, Salaices M, Benitez J.* Effects of pentobarbital on the reactivity of isolated human cerebral arteries. J Neurosurg 1981; 54: 521–4.

5 *Sanchez-Ferrer CF, Marin J, Salaices M, et al.* Interference of pentobarbital and thiopental with the vascular contraction and noradrenaline release in human cerebral arteries. Gen Pharmacol 1985; 16: 469–73.

6 *Wendling WW, Haracal C.* Comparative actions of pentobarbital and verapamil on canine cerebral and peripheral arteries *in vitro*. Res Commun Chem Pathol Pharmacol 1985; 49: 189–202.

7 *Nakamura K, Hatano Y, Nishiwada M, Yakushiji T, Park JW, Mori K.* Effects of thiobarbiturates on smooth muscle reactivity in isolated aortas from spontaneously hypertensive rats. Anesth Analg 1990; 70: 267–74.

8 *Moriyama S, Nakamura K, Hatano Y, Harioka T, Mori K.* Responses to barbiturates of isolated dog cerebral and mesenteric arteries contracted with KCl and prostaglandin $F_{2\alpha}$. Acta Anaesth Scand 1990; 34: 523–9.

9 *Taga K, Fukuda S, Nishimura N, Tsukui A, Morioka M, Shimoji K.* Effects of thiopental, pentobarbital, and ketamine on endothelin-induced constriction of porcine cerebral arteries. Anesthesiology 1990; 72: 939–41.

10 *McShane AJ, Crowley K, Shayevitz JR, Michael JR, Adkinson NF, Traystman RJ.* Barbiturate anesthetics inhibit thromboxane-, potassium-, but not angiotensin-induced pulmonary vasoconstriction. Anesthesiology 1989; 70: 775–9.

11 *Nakamura K, Hatano Y, Nishiwada M, Mori K.* The vasodilator effect of thiamylal in dog mesenteric artery. Can J Phys Pharmac 1991; 69: 1163–7.

12 *Hatano Y, Nakamura K, Moriyama S, Mori K, Toda N.* The contractile responses of isolated dog cerebral and extracerebral arteries to oxybarbiturates and thiobarbiturates. Anesthesiology 1989; 71: 80–6.

13 *Toda N, Hatano Y, Hayashi S.* Modifications by stretches of the mechanical response of isolated cerebral and extracerebral arteries to vasoactive agents. Pflugers Arch Eur J Physiol 1978; 374: 73–7.

14 *Itoh T, Kuriyama H, Suzuki H.* Excitation-contraction coupling in smooth muscle cells of the guinea-pig mesenteric artery. J Physiol 1981; 321: 513–35.

15 *Su JY, Zhang CC.* Intracellular mechanism of halothane's effect on isolated aortic strips of the rabbit. Anesthesiology 1989; 71: 409–17.

16 *Kanmura Y, Yoshitake J, Casteels R.* Ketamine-induced relaxation in intact and skinned smooth muscles of the rabbit ear artery. Br J Pharmaco 1989; 97: 591–7.

17 *Becker KE.* Plasma levels of thiopental necessary to anesthesia. Anesthesiology 1978; 49: 192–6.

18 *Godfraind T, Miller RC.* Actions of prostaglandin $F_{2\alpha}$ and noradrenaline on calcium exchange and contraction in rat mesenteric arteries and their sensitivity to calcium entry blockers. Br J Pharmacol 1982; 75: 229–36.

19 *Hashimoto T, Hirata M, Itoh T, Kanmura Y, Kuriyama H.* Inositol 1,4,5 triphosphate activates pharmacomechanical coupling in smooth muscle of the rabbit mesenteric artery. J Physiol 1986; 370: 605–18.

20 *Fukuda S, Inomata I, Tsuji T, Takeshita H.* Thiopental potentiation of isolated rabbit pulmonary artery contractions with alpha receptor agonist. Anesthesiology 1984; 60: 187–92.

21 *Nishiwada M, Nakamura K, Hatano Y, Mori K.* The relaxing effects of barbiturates in vascular smooth muscle of rat aorta. Journal of Anesthesia 1991; 5: 380–7.