Age-dependent Alterations in the Response of Isolated Rat Aortas to Thiobarbiturates

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Responses to thiamylal and thiopental were compared in helical strips of rat thoracic aortas of different ages (5–6, 10–12 and 20–22 weeks old), precontracted partially with phenylephrine or prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Thiamylal and thiopental, in concentrations of 3×10^{-5} to 10^{-4}M, produced a dose-dependent relaxation in aortas at 5–6 weeks of age, no significant change of tension in those at 10–12 weeks of age, and a marked constriction in those at 20–22 weeks of age. These thiobarbiturates, in a high concentration of 10^{-3}M, produced a profound relaxation in aortas at any age studied. It is concluded that the responses to thiobarbiturates of thoracic aorta precontracted with phenylephrine or $PGF_{2\alpha}$ alter with age. (Key words: vascular smooth muscle, thiamylal, thiopental, age)

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Vascular tissue undergoes a number of alterations during the aging process including changes in structure and composition[1,2] and enzyme activities[3], and the vascular responses to chemical substances alter differently with age in a variety of vessels from the same animal and the same vessel from various animals[4–6]. Our previous study[7] demonstrated that aortic strips under resting tension isolated from Wistar Kyoto rats of any age were contracted with thiobarbiturates in a dose-dependent manner, and that there was no age-related differences in the responses. The present study was undertaken to compare the response to thiamylal and thiopental of isolated thoracic aorta precontracted with alpha-adrenergic agonist or prostanoid, since the responses of precontracted strips to thiobarbiturates would differ from those under the resting tension[8,9].

Male Wistar Kyoto rats of 5–6, 10–12 and 20–22 week-old were used. The rats were killed by bleeding from common carotid arteries under pentobarbital anesthesia (50 $mg \cdot kg^{-1}$, i.p.), and thoracic aortas were isolated. The aortas were cut helically into strips of approximately 17 mm long. The specimen was vertically fixed between hooks in an organ bath of 10-ml capacity, containing Krebs' bicarbonate solution (pH, 7.4 ± 0.05), which was aerated with a gas mixture of 95% O_2 and 5% CO_2 and maintained at 37.0 ± 0.5°C. The resting tension for thoracic aortic strips was adjusted to 1.0 g[10]. 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. Changes in isometric tensions were displayed on an ink-writing oscillograph (Rectigraph 8K, Nihondenki San-ei, Japan). The contractile response to 30 mM KCl was first obtained, and the preparations were

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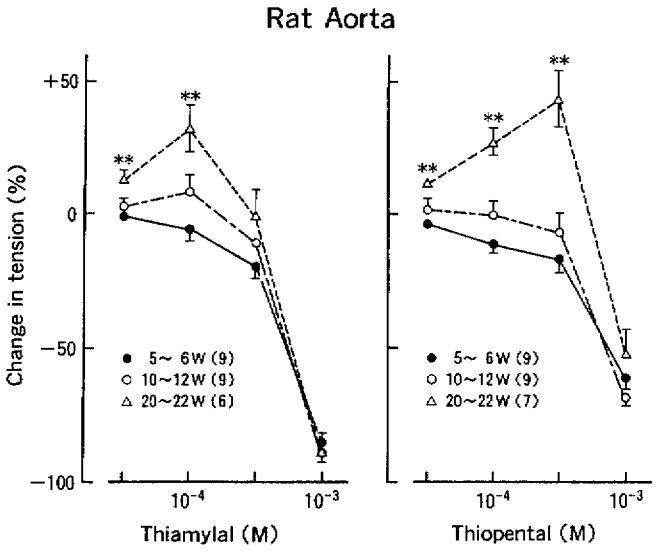

Fig. 1. Responses to thiamylal (left) and thiopental (right) of aortic strips from 5–6, 10–12 and 20–22 week-old rats. The strips were precontracted partially with phenylephrine. The absolute values of the maximum relaxation induced by papaverine (10^{-4}M) were taken as 100%; mean absolute values in 5–6, 10–12 and 20–22 weeks of age for thiamylal were 438 ± 24 mg, 487 ± 59 mg and 296 ± 56 mg, respectively, and those for thiopental were 470 ± 56 mg, 368 ± 45 mg and 236 ± 33 mg, respectively. + and − represent contractions and relaxations from the level prior to addition of thiopental, respectively. W, week-old. **, $P < 0.01$ significantly different from values in 5–6 weeks of age. Numbers in parentheses indicate the number of experiment studied.

washed three times with fresh media. For evaluation of both contracting and relaxing effects of thiobarbiturates[8,9], the sustained contractions in a range of 30% to 70% of the contraction induced by 30 mM KCl were induced by phenylephrine (10^{-8} to 2×10^{-7}M) or prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 10^{-7} to 2×10^{-6}M). After the contraction induced by phenylephrine or $PGF_{2\alpha}$ had been levelled off, thiamylal or thiopental was administered to the bathing medium in cumulative concentrations. At the end of the response to barbiturates, papaverine, 10^{-4}M, was administered to obtain the maximum relaxation, and the changes of tension induced by barbiturates were expressed as a percentage of the maximum relaxation induced by papaverine. Barbiturates were dissolved in distilled water to the concentration of 10^{-1}M. The pH of 10^{-1}M thiamylal and thiopental were 10.8 and 10.6, respectively. In a preliminary study, the addition of 100 μl of these barbiturates (10^{-3}M) did not alter the pH of the nutrient solution significantly and 0.05 M bicarbonate (pH 10.7) failed to change the arterial tension. The values are expressed as means + SEM. Analysis of variance and Newman-Keuls multiple range test were used for statistical analysis. P values less than 0.05 were considered statistically significant.

The responses to thiamylal and thiopental of helical strips of thoracic aortas from rats of different ages, precontracted with phenylephrine are shown in figure 1. In the strips from 5–6 week-old rats, the administration of thiamylal and thiopental (10^{-5} to 10^{-3}M) caused a dose-related relaxation. At the age of 10–12 weeks, thiobarbiturates in low concentrations did not significantly change the arterial tension but in high concentrations (10^{-3}M) they elicited a profound relaxation. At 20–22 weeks of age, these thiobarbiturates in low concentrations caused a significant contraction and in high concentrations a profound relaxation. Similar results were also obtained in aortas of any ages, when precontracted with $PGF_{2\alpha}$. Typical recordings of the response to thiopental of thoracic aortas from 5 and 21 week-old rats precontracted with phenylephrine are presented in figure 2.

It has been suggested that smooth muscle contractility may develop with time from 30 days to 3 month after birth, as cellularity in the rat aorta is decreased with age[11], and an age-related increase in contractile response to vasoactive agents such as catecholamine, serotonin and KCl has been demonstrated in vitro[10]. However, with further aging after 3 months, the vascular

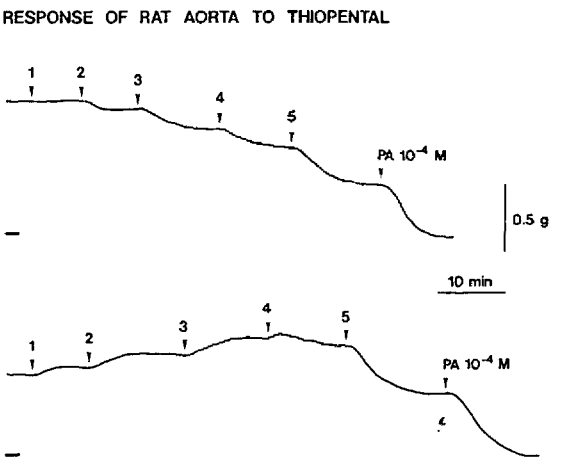

Fig. 2. Actual recordings of response to thiopental or rat aortic strips from 5 weeks and 21 weeks old. Aortic strip was precontracted partially with 10^{-8}M phenylephrine. Horizontal lines just left of each tracing represent level before addition of phenylephrine. Concentrations of thiopental from 1 to 5 = 10^{-5}, 3×10^{-5}, 10^{-4}, 3×10^{-4} and 10^{-3}M, respectively.

responses of isolated rat aorta to chemical agents do not always increase or even decrease as reported in the response to norepinephrine[3,13]. In fact, there appeared to be a tendency for phenylephrine-induced contraction to fall with age[7]. Further, the contractile response of aortic strips under the resting tension to thiobarbiturates was not age-related[7]. Accordingly, it is apparent that the changes in the responses of precontracted aortic strips to thiobarbiturates with age cannot be ascribed to the age-dependent increase in constrictor activity of vascular smooth muscle.

It has been demonstrated that thiobarbiturates have a potentiating effect on contractions induced by alpha-adrenergic agonists in rabbit pulmonary artery[14]. Our previous study demonstrated that thiobarbiturates potentiate contractions elicited by Ca^{++} influx from extracellular fluids through $PGF_{2\alpha}$– operated Ca channels in dog mesenteric artery[9]. Thus, it is likely that thiobarbiturates, in rat aorta as well, enhance Ca^{++} influx in the presence of agonists including phenylephrine and $PGF_{2\alpha}$. The present study, therefore, suggests that the enhancement by thiobarbiturates of Ca^{++} influx through receptor-operated Ca channels is age-related in rat aorta, although the constrictor effect of thiobarbiturates in the absence of agonists is not age-dependent. Further studies are necessary to clarify this hypothesis.

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