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Influence of Bornyl Acetate on Blood Pressure and Aortic Strips Contractility of the Rat

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Abstract–The present study was conducted to investigate the effects of bornyl acetate on arterial blood pressure and vascular contractile responses in the normotensive rats and to establish the mechanism of action. Both phenylephrine (an adrenergicα_1-receptor agonist) and high potassium (a membrane-depolarizing agent) caused greatly contractile responses in the isolated aortic strips. These phenylephrine (10^{-5} M)-induced contractile responses were depressed in the presence of high concentrations of bornyl acetate (10~20 μg/ml), but not affected in low concentrations of bornyl acetate (2.5~5 μg/ml). High potassium (5.6×10^{-2} M)-induced contractile responses were also greatly inhibited in the presence of bornyl acetate (2.5~20 μg/ml) in a dose-dependent fashion. Bornyl acetate (1~10 mg/kg) given into a femoral vein of the normotensive rat produced a dose-dependent depressor response, which is transient (data not shown). Interestingly, the infusion of a moderate dose of bornyl acetate (3 mg/kg/30 min) made a significant reduction in pressor responses induced by intravenous norepinephrine. Collectively, these results obtained from the present study demonstrate that intravenous bornyl acetate causes a dose-dependent depressor action in the anesthetized rat at least partly through the blockade of adrenergic α_1-receptors. bornyl acetate also causes vascular relaxation in the isolated aortic strips of the rat via the blockade of adrenergic α_1-receptors, in addition to the unknown mechanism of direct vasorelaxation.

Keywords □ Bornyl acetate, Vasorelaxation, Blockade of Adrenergic α_1-Receptors

The bark of *Magnolia obovata* Thunberg (凹厚朴), a medicinal plant, has been well known as an important component of many Chinese traditional medicines for more than 2000 years. These have been used for the treatment not only of gastrointestinal disorders but also anxiety, which led us to consider that magnolia bark may influence the central and/or autonomic nervous systems. The Chinese traditional medical book mentions that magnolia bark itself has a tranquilizing action. Actually, the extract of magnolia bark has been shown to have depressant actions on the central nervous system (Watanabe *et al.*, 1973). On the other hand, various other ingredients have been isolated and identified from magnolia bark. They are β-eudesmol, α- and β-pinenes, and bornyl acetate, as essential oils; magnolol and honokiol, as diphenyl compounds; and magnocurarine and magnoflorine, as alkaloids. It also has been reported that some of these ingredients have pharmacological effects on nervous systems (Watanabe *et al.*, 1983; Chiou *et al.*, 1997). However, until now, there has been no evidence showing the influence of magnolia bark and its components on autonomic nervous systems and clarifying the relationship between the pharmacological effects of magnolia bark and those of its ingredients.

Recently, it has been reported that the crude extract of magnolia bark, an herbal drug, inhibited the secretion of catecholamines from bovine adrenal chromaffin cells stimulated by acetylcholine (ACh) in a concentration-dependent manner (Tachikawa *et al.*, 2000). These results indicate that magnolia bark contains some effective components inhibiting the secretion of catecholamines from bovine adrenal chromaffin cells stimulated by ACh due to the antagonism of Na^+ and Ca^{2+} influxes into the cells. However, inhibition by the extract of magnolia bark seems to be attributable to honokiol and bornyl acetate (Tachikawa *et al.*, 2000). Despite this, there has been remarkably little evidence on the cardiovascular system, especially on blood pressure. Therefore, the present study was designed to examine the effects of bornyl acetate on blood pressure in the anesthetized rat and contractile responses of isolated aortic strips of the rat and to establish the mechanism of action.

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MATERIALS AND METHODS

Experimental Procedure

Mature male Sprague-Dawley rats, weighing 150 to 350 g, were used in the experiment. The animals wereused individually in separate cages, and food (Cheil Animal Chow) and tap water were allowed *ad libitum* for at least a week to adapt to experimental circumstances. On the day of experiment, a rat was anesthetized with thiopental sodium (40 mg/kg) intraperitoneally, and tied in supine position on a fixing panel.

Isolation of Aortic Strips : The thorax was opened by a midline incision, and placing three-hook retractor exposed the heart and surrounding area. The heart and portion of the lung were not removed, but pushed over to the right side and covered by saline-soaked gauge pads in order to obtain enough working space for isolating aortic vessel. The aorta was isolated from the proximal part of the heart to the vicinity of liver and immediately immersed in cold Krebs solution. The blood within the aorta was rapidly removed. The aorta was cut into the ring of 4-5 mm length.

Preparation of Arterial Cannulation : The animal was tied in supine position on fixing panel to insert a T- formed cannula into the trachea for securing free air passage. The rectal temperature was maintained at 37-38°C by a thermostatically controlling blanket and heating lamp throughout the course of the experiment.

Recording of Mechanical Activity

The ring segment of aorta was mounted in a muscle bath by sliding the ring over two parallel stainless-steel hooks (0.15 mm in diameter). The lower hook was fixed on bottom of the bath and the upper was connected to isometric transducer (Grass FT. 03). The signal from the transducer was displayed on a polygraph (Grass Instruments Model 79). The volume of bath was 25 ml and the bath solution was saturated with 95% O_2 and 5% CO_2 at 37°C (Fig. 1). The composition (mM) of Krebs was: NaCl, 118.4; KCl, 4.7; $CaCl_2$, 2.5; $MaCl_2$, 1.18; $NaHCO_3$, 25; KH_2PO_4, 1.2; glucose, 11.7. The final pH of the solution was maintained at 7.4-7.5. During an equilibration period of 2 hours, the resting tension was adjusted to 0.5 g. After the equilibration period, the ring was challenged with 35 mM KCl two times, and if it responded with a contraction, the proper experiment was started. Vasoconstrictors were administered into the bath in order to obtain dose-response curves. In the subsequent experiments, under the presence of green tea extract, some vasoconstrictors were administered, respectively.

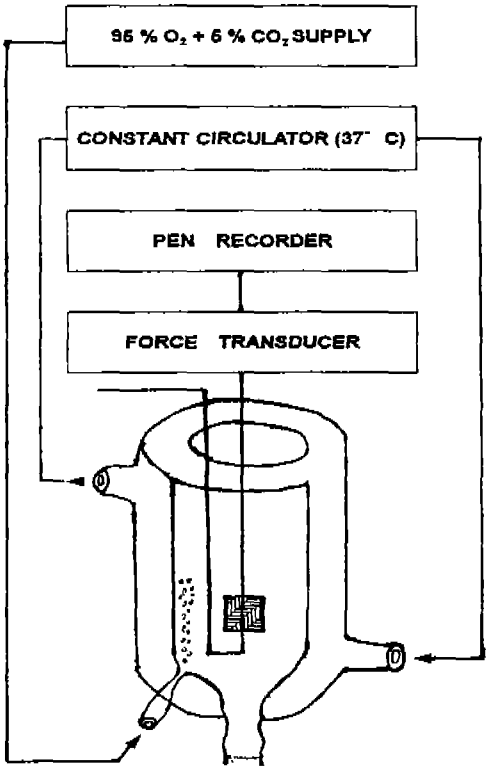

Fig. 1. A schematic representation of the isometric contraction recording system with a vertical chamber. The chamber (25 ml) was maintained at 37°C with temperature-regulated circulator and aerated with 95% O_2 and 5% CO_2.

The data were expressed as % of the control tension.

Measurement of Blood Pressure

In order to observe the change of arterial pressure, one of the common carotid arteries or of the femoral arteries was catheterized with polyethylene tubing [outside diameter (o.d): 0.5 mm]. The tubing was connected to a pressure transducer (Gould Co., U.S.A.) and pulse of mean arterial blood pressure was recorded on a biological polygraph (Grass Co., U.S.A.) continuously. The chart speed was adjusted to 2 cm per minute. The artery tubing was filled with heparin solution (400 I.U.) to prevent blood coagulation during the experiment. Another cannulation with polyethylene tubing (o.d.: 0.3 mm) was made into a femoral vein for the administration of drugs and supplemental anesthetic agents as needed to maintain light surgical anesthesia. Each rat was left undisturbed for at least 30 minutes after completion of the operative procedures to permit cardiovascular parameters to be stabilized and the drugs under investigation were administered at intervals of 60 minutes.

Statistical Analysis

The statistical significance between groups was determined by the Student's *t*- and *ANOVA*- tests. A P-value of less than 0.05 was considered to represent statistically significant changes unless specifically noted in the text. Values given in the text refer to means and the standard errors of the mean (S.E.M.). The statistical analysis of the experimental results was made using the computer program described by Tallarida and Murray (1987).

Drugs and Their Sources

The following drugs were used: bornyl acetate (Wako Pure Chemical Industry Ltd., Japan), phenylephrine hydrochloride, potassium chloride, and norepinephrine bitartrate (Sigma Chemical Co., U. S. A.), thiopental sodium and heparin sodium (Dachan Choongwae Pharm. Co., Korea). Drugs were dissolved in distilled water (stock) and added to the normal Krebs or saline solution as required. However, bornyl acetate was dissolved in dimethyl sulfoxide. The concentration of dimethyl sulfoxide in the aortic bath was less than 1%, which had no effect on the vascular contractility and blood pressure under the conditions employed in this study. Concentrations of all drugs used are expressed in terms of molar base and gram.

RESULTS

Effects of borny acetate on contractile responses induced by phenylephrine and high K^+ in the rat aortic strips

The resting (basal) tension from the isolated rat aortic strips reached a steady state after perfusion with oxygenated Krebs-bicarbonate solution for 90 min before the experimental protocol was initiated. The resting tension was adjusted to 0.5 g. The effect of bornyl acetate on phenylephrine- as well as high potassium chloride-mediated contractile responses in the rat aorta was examined. In the present study, bornyl acetate itself did not produce any effect on the resting tension in the aortic strips isolated from the rat (data not shown).

When 10^{-5} M concentration of phenylephrine was administered into the aortic bath, its active tension amounted to 2.3 ± 0.2 g from the resting tension level. In the presence of bornyl acetate at low concentrations of 2.5~5.0 mg/ml, 10^{-5} M-phenylephrine-induced tension amounted to 100~96.5% of the control contractile responses. There was no statistical difference between treated- and nontreated-groups with bornyl acetate (Fig. 2 and 3). However, in the presence of high concentration of bornyl acetate (10~20 mg/ml), 10^{-5} M-phenylephrine-induced contractile responses were dose-dependently inhibited to 75~57% of the control responses(Fig. 2 and 3).

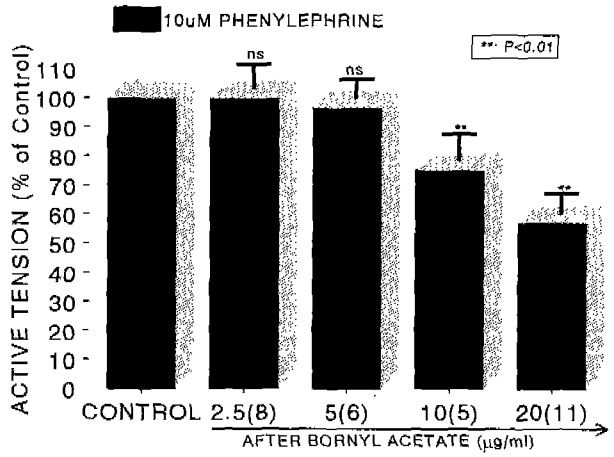

Fig. 2. Influence of bornyl acetate on phenylephrine (PE)-induced contractile response in the isolated rat aortic strips. The contractile response was induced by adding 10 μM of PE after adaptation with normal Krebs solution for two hours prior to initiation of the experimental protocol. "CONTROL" denotes active tension induced evoked by PE before adding Platycodin D (100%). Numerals in the parenthesis indicate number of experimental rat aortic strips. Vertical bar represents the standard error of the mean (S.E.M). Ordinate: the active tension (% of control). Abscissa: concentration of bornyl acetate (μg/ml). Statistical difference was obtained by comparing the control with the bornyl acetate-pretreated groups (2.5, 5, 10 and 20 μg/ml). **: $P < 0.01$, ns: Statistically not significant.

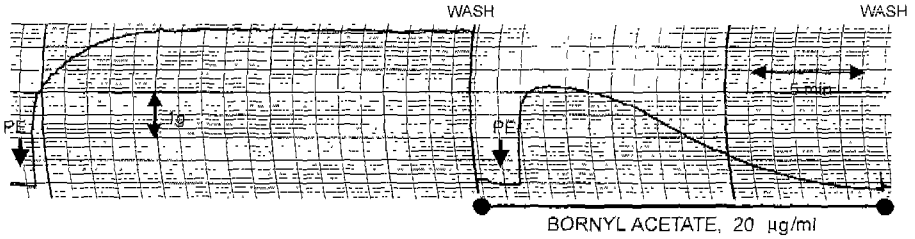

Fig. 3. The typical tracing showing the effect of bornyl acetate on phenylephrine (PE)-induced contractile responses in the rat aortic strips. Left: PE-induced contractile response (Control). Right: PE-induced contractile response in the presence of 20 μg/ml of bornyl acetate. At arrow mark, the indicated dose (10^{-5} M) of phenylephrine was added to the bath. The chart speed was 5 mm/min.

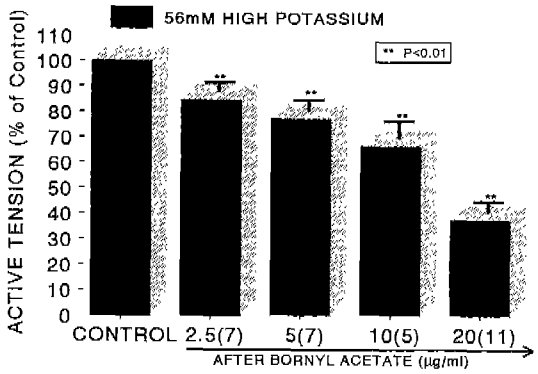

Fig. 4. Influence of bornyl acetate on high potassium-induced contractile responses in the isolated rat aorta. High potassium (56 mM) was added into the bath before and after pretreatment with 2.5, 5, 10 and 20 μg/ml of bornyl acetate. Other legends are the same as in Fig. 2. **: $P < 0.01$.

High potassium exerts two distinct effects on cells: (1) depolarization of cell membrane, and (2) depolarization-induced influx of calcium via voltage-dependent calcium channels (Wada *et al.*, 1985). When added through the bath, high potassium at the concentration of 5.6×10^{-2} M, which is a membrane-depolarizing agent, caused an increased aortic contraction (2.4 ± 0.2 g). As shown in Fig. 4, high potassium (5.6×10^{-2} M)-induced contractile responses after pre-loading with 2.5~20 mg/ml of bornyl acetate were inhibited by 84~37% of their corresponding control responses in a dose-dependent fashion (Fig. 4 and 5).

Effect of bornyl acetate on norepinephrine-induced hypertensive responses in the anesthetized rats

Since bornyl acetate greatly inhibited phenylephrine-induced contractile responses of the isolated aortic smooth muscle as shown in Fig. 2 and 3. It suggests that bornyl acetate could cause hypotension through the blockade of peripheral adrenergic α-receptors. It is of interest to examine the effect of intravenous bornyl acetate on norepinephrine-evoked pressor responses. In 14 rats, norepinephrine at doses of 1, 3 and 10 mg/kg caused

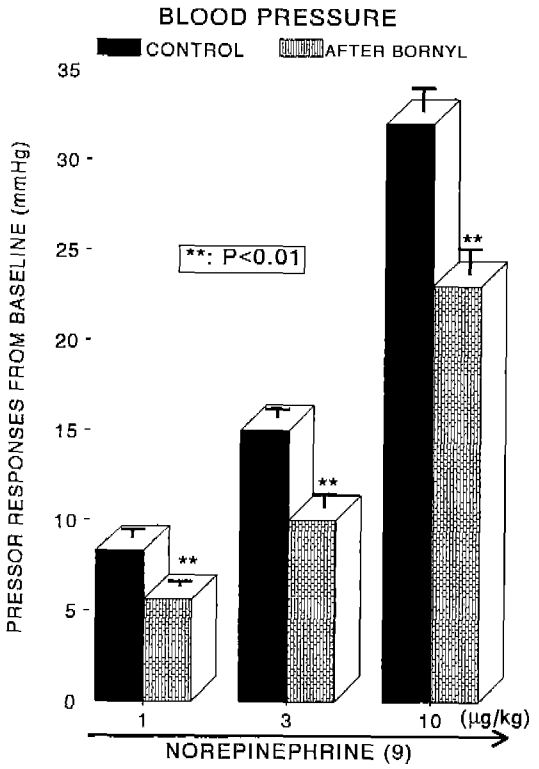

Fig. 6. Influence of intravenous bornyl acetate (BORNYL) on norepinephrine-evoked pressor responses. Ordinate: Changes of blood pressure from baseline level in mmHg. Abscissa: Intravenous doses of norepinephrine in μg/kg. Vertical bar on the top of each column indicates standard error of mean. There was statistically significant difference in changes of norepinephrine-evoked pressor responses between before and after pretreatment with BORNYL. BORNYL was infused into a femoral vein with a rate of 3 mg/kg/30 min after obtaining the corresponding control responses of intravenous norepinephrine. Numeral in the paren-thesis denotes number of animals used in the experiment. The original base-line of arterial blood pressure was 122 ± 13 mmHg.

dose-dependent pressor responses of 9 ± 5 mmHg, $15 \pm .5$ mmHg and 32 ± 1.3 mmHg from the original baseline (122 ± 13 mmHg), respectively. However, after infusion of bornyl acetate with a rate of 3 mg/kg/30 min, they were significantly

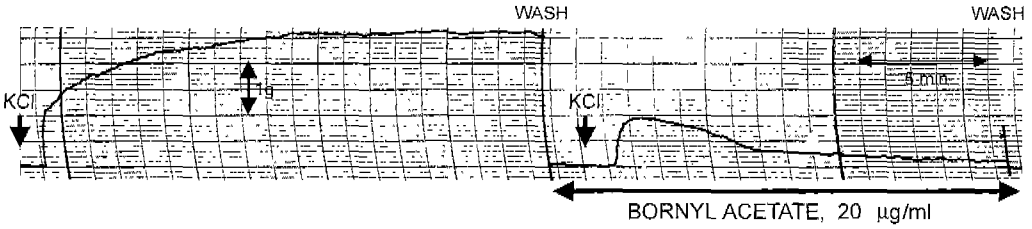

Fig. 5. The typical tracing showing the effect of bornyl acetate on high potassium (KCl)-induced contractile responses in the rat aortic strips. Left: KCl-induced contractile response (Control). Right: KCl-induced contractile response in the presence of 20 μg/ml of bornyl acetate. At arrow mark, the indicated dose of KCl (56 mM) was added to the bath. The chart speed was 5 mm/min.

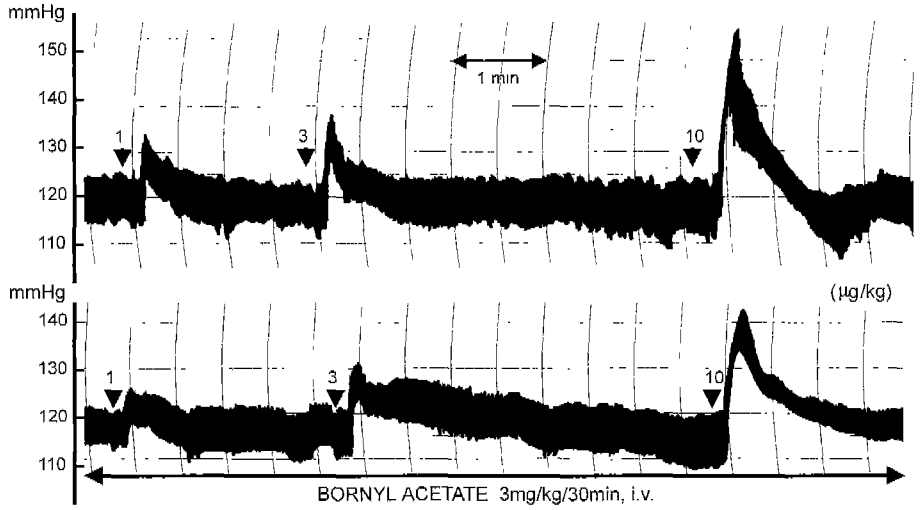

Fig. 7. The representative tracing of bornyl acetates effect on intravenous norepinephrine (NE)-induced pressor response in the anesthetized rat. At arrow marks, the indicated doses (1, 3 and 10 μg/kg) of NE were administered into a femoral vein. Upper: NE-induced hypertensive responses in a non-treated rat. Lower: NE-induced pressor responses in a bornyl acetate-pretreated rat. Bornyl acetate was infused into a femoral vein with a rate of 3 mg/kg/30 min. ABP: arterial blood pressure in mmHg. The chart speed was 20 mm/min.

depressed to 6 ± 0.3 mmHg ($P < 0.01$), 10 ± 0.8 mmHg ($P < 0.01$) and 23 ± 1.4 mmHg ($P < 0.01$) at the above same doses, respectively (Fig. 6 and 7). Fig. 7 shows that norepinephrine-evoked pressor responses are greatly attenuated after pretreatment with intravenous bornyl acetate.

DISCUSSION

The present experimental results demonstrate that intravenous bornyl acetate causes a dose-dependent depressor action in the anesthetized rat. It seems that bornyl acetate also causes vascular relaxation in the isolated aortic strips of the rat via the blockade of adrenergic α_1-receptors, in addition to the unknown mechanism of the direct vasorelaxation.

In support of this idea, one of active ingredients contained in *Magnolia obovata* Thunberg, terpenoid, bornyl acetate, greatly inhibited ACh-evoked secretion, but it only slightly suppressed high K^+-induced secretion in the cultured bovine adrenal chromaffin cells (Tachikawa *et al.*, 2000). This is the first report showing the effect of bornyl acetate on nervous systems. Accordingly, honokiol and bornyl acetate are probably at least active ingredients responsible for the inhibition of ACh-evoked catecholamine secretion by the extract of magnolia bark. However, amounts of β-eudesmol (above 13 mM) and magnolol (above 84 mM) sufficient to inhibit secretion are contained in the magnolia bark extract used in this study (above 400 mg/ml). In terms of these findings, the results obtained from the present study seem likely that bornyl acetate can cause the depressor effect. Moreover, The bark of *M. obovata* Thunberg is prescribed in many Chinese traditional medicines against anxiety. Actually, the extract of magnolia bark with ester has been reported to act as a depressant on the central nervous system, i.e. sedation, loss of righting reflex, and depression of drug-induced convulsions (Watanabe *et al.*, 1973). It has been demonstrated that the crude extract obtained by hot water treatment of magnolia bark, which contains both hydrophilic and hydrophobic substances, inhibited the secretion of catecholamines from bovine adrenal chromaffin cells stimulated by ACh (Tachikawa *et al.*, 2000). This suggests that magnolia bark contains some effective ingredients inhibiting the activity of the sympathetic nervous system in addition to suppressing that of the central nervous system. This inhibition seems likely to be relevant to vasorelaxant effect of bornyl acetate.

In general, among drugs that interfere with peripheral sympathetic function, adrenergic α-receptor blocking agents alone cause reversal of the epinephrine pressor response (Constantine *et al.*, 1973). When epinephrine is administered to untreated animals, its α-agonist properties predominate, resulting in a rise in mean arterial pressure. However, in the presence of adrenergic α-receptor blockade, the peripheral β_2-agonist properties of epinephrine predominate and a fall in arterial pressure or reversal of the pressor response is observed. In contrast, the pressor responses to norepinephrine are impaired by adrenergic α-receptor blockade, but are not reversed (Freis *et al.*, 1951) as this agent processes little β_2-agonist activity (Ablad *et al.*, 1975). In terms of the fact that phenylephrine-evoked contrac-

tile response is greatly depressed by bornyl acetate, it is thought that bornyl acetate has vascular dilatatory activity through the adrenergic α-receptor blockade. In view of these reports, in the present work, the finding that bornyl acetate attenuated the norepinephrine-induced pressor responses demonstrated that bornyl acetate possesses the antagonistic activity of adrenergic α_1-receptors.

Generally, it is well known that potassium chloride (KCl) opens voltage-dependent calcium channels by depolarizing the cell membrane of vascular smooth muscle, resulting in increased influx of extracellualr Ca^{2+} (Bolton, 1979; Schwartz & Taira, 1983; Dube *et al.*, 1985; 1988). Kim and his colleagues (1989) have shown that the contractile responses of vascular smooth muscle induced by $CaCl_2$ and KCl may result most likely from increased influx of extracellular Ca^{2+} through the voltage-dependent calcium channels. In terms of these results, the present findings that bornyl acetate inhibited the contraction of rat aortic smooth muscle evoked by not only phenylephrine (an α_1-adrenergic receptor agonist) but also by KCl (a membrane depolarizer) indicate that the vascular relaxation of bornyl acetate is mediated by the blockade of α_1-adrenergic receptors, in addition to the unknown mechanism of direct action.

In previous studies, three cellular mechanisms have been proposed to explain relaxant response of vascular smooth muscle: (i) blockade of extracellular Ca^{2+} entry into cells (Fleckenstein, 1977; Schwartz & Triggle, 1984), (ii) increase in binding or sequestration of intracellular Ca^{2+} (Watkins & Davidson, 1980; Imai & Kitagawa, 1981), and (iii) inhibiting the release of intracellular stored Ca^{2+} (Imai & Kitagawa, 1981; Ito *et al.*, 1980a;1980b). In contrast, the contractions of vascular smooth muscles induced by neurohumoral agents have been composed of two components: Phasic contraction induced by the Ca^{2+} released from inside the cell and tonic tension related to the Ca^{2+} influx (Bevan, 1982; Dube *et al.*, 1988), both leading to increased intracellular calcium. In light of these findings, it could not be ruled out that bornyl acetate can dilatate the contractile responses of vascular smooth muscle evoked by phenylephrin through the blockade of extracellular Ca^{2+} entry into the muscle cells. Furthermore, Tachikawa and his co-workers (2000) have found that â-eudesmol and honokiol (1-100 and 20-100 μM), which are active components derived from *Magnolia obovata* Thunberg, inhibited the ACh-induced Na^+ influx in the cultured bovine adrenal chromaffin cells. Also, â-eudesmol (5-100 μM) diminished both ACh (at 50 μM)-induced and high K^+-induced $^{45}Ca^{2+}$ influxes.

Taken together, these experimental results demonstrate that intravenous bornyl acetate causes a dose-dependent depressor action in the anesthetized rat at least partly through the blockade of adrenergic α_1-receptors. bornyl acetate also causes vascular relaxation in the isolated aortic strips of the rat via the blockade of adrenergic α_1-receptors, in addition to the unknown direct vasorelaxation.

ACKNOWLEDGEMENTS

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