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The Effects of Majarol on the Blood Pressure and Heart Rate in Rats and Isolated Frog Heart

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ABSTRACT

In our previous studies, we had clarified many pharmacological effects of majarine: the bacteriostatic effect in vitro; the potentiation of hypnotic action of alcohol; hypotensive effect in rats and hypothermic effect in mice. This study was undertaken to search for a new antihypertensive drug. Red crystalline was obtained from majarine (which was extracted from *Berberis koreana* Palibin) by chemical methods. And this crystalline was identified as $C_{19}H_{16}NO_4$ contained one hydroxy group instead of methoxy group of majarine in isoquinoline ring and named "Majarol" (5,6-Dihydro-9-hydroxy, 10-methoxybenzo-[g]-1,3-benzodioxolo [5,6-a] quinolizinium).

We examined the effects of majarol on blood pressure and heart rate in urethane anesthetized rats and the rate and amplitude of contraction of isolated frog heart. Several drugs: atropine sulfate, diphenhydramine chloride, hexamethonium bromide, phentolamine, epinephrine, propranolol and isoproterenol were used to clarify the mechanism of the hypotensive action of majarol.

The results of experiments were as follows;

1. In low dose (0.5-2 mg/kg, i.v.), majarol showed a typical transient hypotensive effect and slight decrease in heart rate. In high dose (5-10 mg/kg, i.v.), majarol showed a typical transient and a subsequent prolonged hypotensive effect and a significant prolonged decrease in heart rate was followed.
2. The hypotensive effects of majarol was not abolished by the pretreatments with atropine sulfate, hexamethonium bromide and diphenhydramine. The pretreatment with phentolamine inhibited significantly the hypotensive effects of majarol and the pretreatment wtih majarol blocked markedly the hypertensive effect of epinephrine. The positive chronotropic effect of isoproterenol was not blocked by the pretreatment with majarol.
3. In low dose, majarol increased the amplitude and decreased rate of contraction, but in high dose, majarol inhibited the amplitude and rate of contraction of isolated frog heart.

Key Words: Majarine, Majarol, Blood Pressure, Heart Rate

INTRODUCTION

Recently, the prevention and therapy of hypertension became more important because the death ratio of adult by hypertension increased. But chronic administration of antihypertensive drug resulted in many side effects. The selection of antihypertensive drug was more difficult. Therefore, the search of

a new antihypertensive drug was required seriously.

In our experimental laboratory, we have collected folk plants and medicinal plants and reported their pharmacological effects. We extracted yellow crystalline, majarine (alkaloid), from *Berberis koreana* Palibin distributed only in Korea and investigated its pharmacological effects: the bateriostatic effect in vitro (Cho *et al.*, 1963); the potentiation of hypnotic action of alcohol and reduction of rectal temperature in mice (Cho *et al.*, 1974); hypotensive effect in rats (Cho *et al.*, 1984); the depressor response on blood pressure after intracerebroventricular injection of several drugs and locomotor activity in ats (Park *et al.*, 1984) and hypothermic effect in mice (Park *et al.*, 1985).

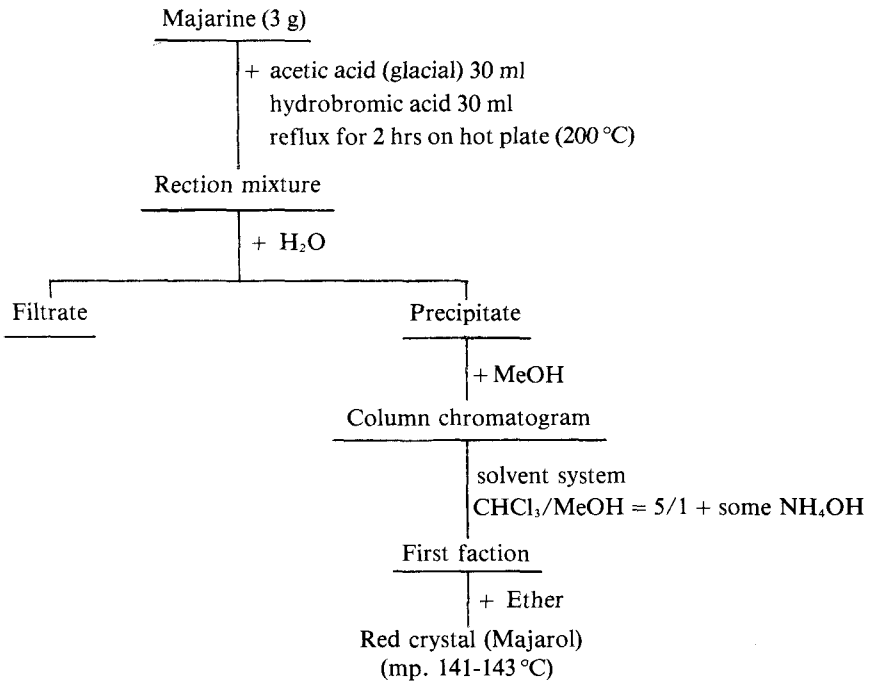
Recently, we have examined the pharmacological effects of the derivatives of majarine. In this paper, we reported that the effects of majarol (replaced methoxy group in isoquinoline ring of majarine by hydroxy group) on the blood pressure and heart rate in urethane anesthetized rats and the amplitude and rate of contraction of isolated frog heart.

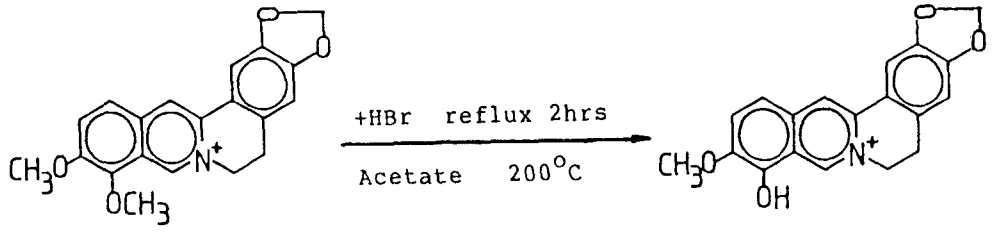
MATERIALS AND METHODS

Synthesis of Majarol

Majarine (3 g) was dissolved in acetic acid (glacial. 30 ml) and hydrobromic acid (30 ml). This mixture was refluxed on hot plate (200 °C) for 2h. Red-yellowish crystalline was obtained from this reaction mixture by addition of water. This crystalline was dissolved in methanol and refined by means of column chromatogram (solvent system; $CHCl_3$/MeOH (5/1) + some NH_4OH), the first elution fraction from column was collected and evaporated with vacuum evaporator. Red crystalline was obtained by addition of ether. (Scheme, Fig. 1)

Scheme: The synthesizing procedure of majarol from majarine





Majarine Majarol

Fig. 1. The structures of majarine and majarol and synthesizing process of majarol from majarine.

Physical and chemical analysis of majarol

IR spectrum ($Vmax^{KBr}$): 1035, 920 (O-CH_2-O), 1600 (C = C), 3000 (CH_2, CH_3), 3200-3500 (hydrogen bonded OH), 3600 (free OH)

NMR spectrum (80 MHz, in DMSO-d_6): 1.24 (H, s, OH), 3.10 (2H, t, CH_2) 3.91 (3H, s, OCH_3), 4.50 (2H, t, CH_2), 6.00 (2H, s. O-CH_2-O), 6.56, 6.76 (2H, s, A ring), 7.24, 7.50 (2H, d, D ring), 7.70, 8.24 (2H, s, C ring)

G-Mass spectrum (m/e): 321 (M^+), 306 (M^+-CH_3), 278 (M^+-OCH_3-OH), 44 (Co_2)

M.P. of this crystalline was 141-143 °C, this crystalline was identified as $[C_{19}H_{16}NO_4]^+$ by physical and chemical analysis. This crystalline was named "Majarol (5,6-Dihydro-9-hydroxy, 10-methoxybenzo-[g]-1,3-benzodioxolo [5,6-a] quinolizinium)," because this crystalline was obtained from majarine and contained hydroxy group (Fig. 1,2,3,4).

Measurement of blood pressure and heart rats in rats

Sprague-Dawley rats of either sex were anesthetized by intraperitoneal administration of urethane (1.25 g/kg). The trachea was cannulated with a short polyethylene tube. Intravenous injections were made through a fine polyethylene tube tied into the left femoral vein. A polyethylene tube, filled with 200 unit/ml of heparin in saline (0.95% w/v sodium chloride in distilled water) was tied into the right carotid artery and connected to a Consolidated Electrodynamics pressure transducer. The amplitude output was displayed on a Divices 8K21 recorder and the heart rate was recorded with a San-Ei recorder. Drugs were dissolved in saline.

Care was taken to ensure that the maximum volume of drug solution and saline follower injected intravenously at one time was 0.2 ml.

Measurement of the amplitude and rate of contraction of isolated frog heart

Frog (25-30g) was collected in group of 6. Heart of frog was perfused according to Yagi's method (Yakagi, k, Ozawa, H. 1969). Each of the compounds was administered directly into the perfusion cannula. Rate and amplitude of contraction were recorded on polygraph (San-Ei) 8K21 recorder. Ringer's solution was used as normal medium.

Drugs used

Atropine sulfate (Merck Chem. Co.), hexamethonium bromide (Sigma), diphenhydramine chloride (Sigma), phentolamine (Sigma), epinephrine (Sigma), majarine (synthesized in our Lab.), majarol (synthesized in our Lab.)

Statistics

Statistical analysis of the data was performed in each case according to Studient's t-test. Significance was taken as $p<0.05$.

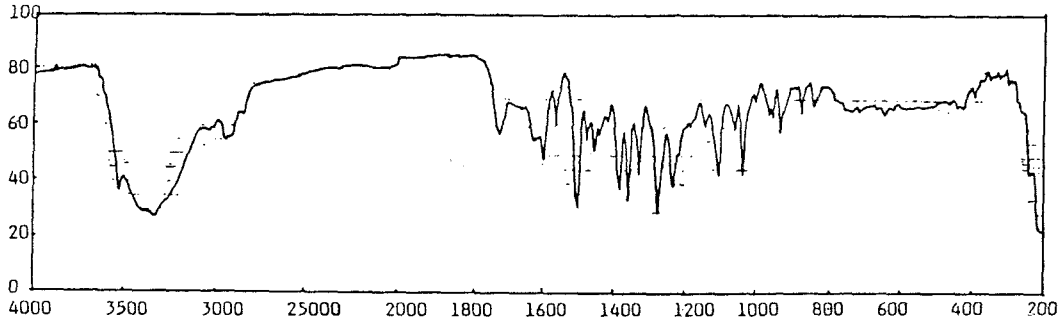


Fig. 2. IR spectrum of majarol in KBr.

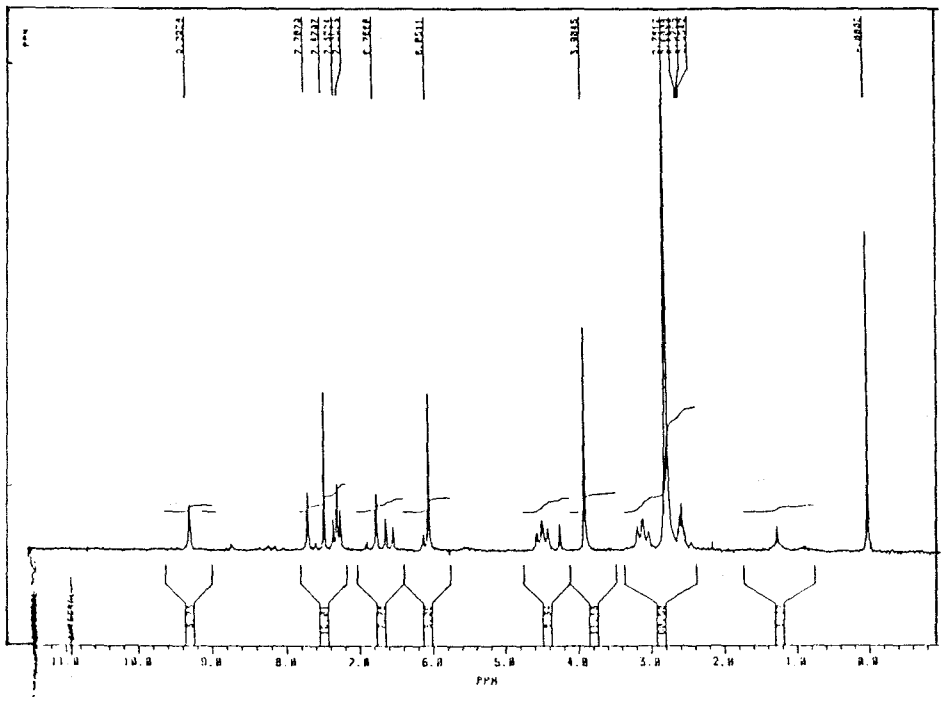


Fig. 3. NMR spectrum of majarol in DMSO-d6

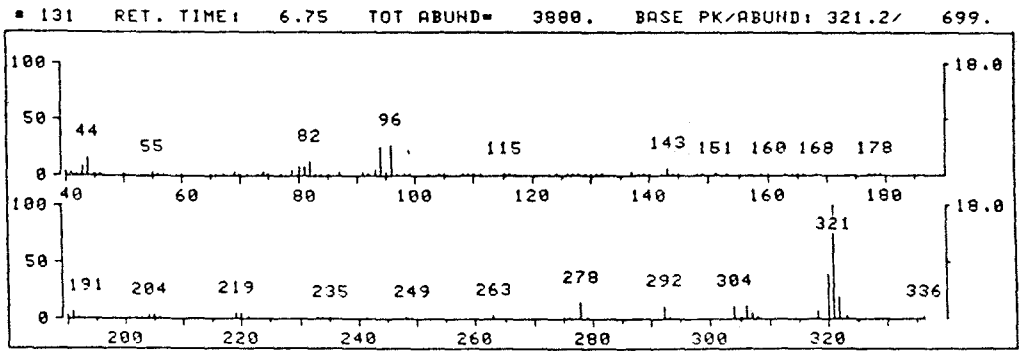


Fig. 4. GC-Mass spectrum of majarol.

RESULTS

Hypotensive effects of majarol

The administration of majarol(0.5-2 mg/kg, i.v.) into urethane anesthetized rats resulted in a typical transient fall in arterial blood pressure and a mild decrease in heart rate. As shown in table 1, intravenous injections of majarol, 1 and 2 mg/kg caused the arterial blood pressure to fall by a mean value of 17 mm Hg and 28 mmHg and the heart rate by a mean of 9 beats/min and 23 beats/min, respectively. This fall in blood pressure was transient (recover within 4 min) (Fig. 5). Higher concentra-

Table 1. Effects of majarol on blood pressure and heart rate in urethane anesthetized rats

Treatment	Dose (mg/kg)	N	Mean blood pressure (mm Hg) & Heart rate (beats/min)			
			before		after treatment	
Majarol	1	5	115 ± 11	370 ± 18	98 ± 9	361 ± 20
	2	5	117 ± 9	373 ± 17	89 ± 11[a]	350 ± 15
	5	5	113 ± 9	367 ± 22	69 ± 12[b]	322 ± 20[a]
	10	5	115 ± 10	375 ± 17	55 ± 13[b]	298 ± 23[b]

The results are mean ± S.E., N: Number of experiments in each group

a: Significance of difference ($p < 0.01$) compared with the corresponding control values

b: Significance of difference ($p < 0.001$) compared with the corresponding control values

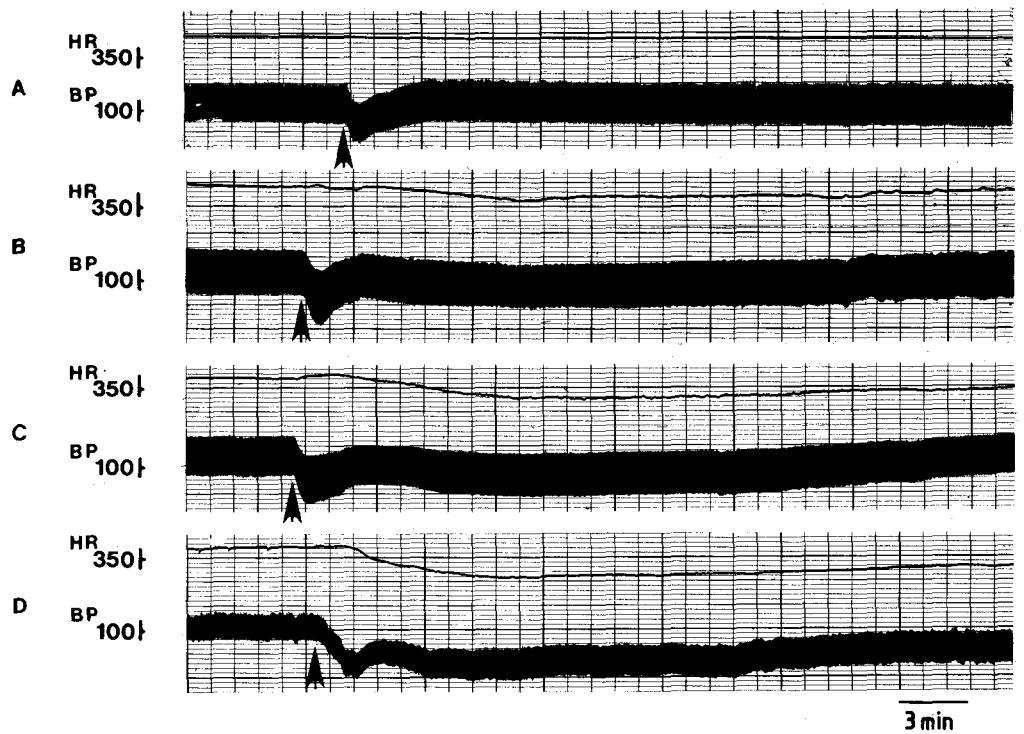


Fig. 5. Effects of majarol on blood pressure and heart rate in urethane anesthetized rats. In each panel, the upper recording is heart rate (HR) in beats/min and the lower panel is blood pressure (BP) in mmHg. Drug was given by intravenous injection. A; 1 mg/kg, B; 2 mg/kg, C; 5 mg/kg and D; 10 mg/kg of majarol.

Table 2. Effects of atropine sulfate, diphenhydramine chloride and hexamethonium bromide on majarol-induced fall in blood pressure and decrease in heart rate in urethane anesthetized rats

Pretreatment		Majarol	N	Mean blood	Heart rate
antagonist	dose (mg/kg)	(mg/kg)		pressure (mmHg)	(beats/min)
Saline	—	—	5	117 ± 11	376 ± 27
—	—	2	5	89 ± 11	354 ± 15
Atropine	1	2	5	87 ± 13	365 ± 19
Diphenhydramine	10	2	5	95 ± 9	341 ± 21
Hexamethonium	10	2	5	85 ± 9	346 ± 18

The results are mean ± S.E., N: Number of experiments in each group.
Injection of atropine alone did not change blood pressure in rats.

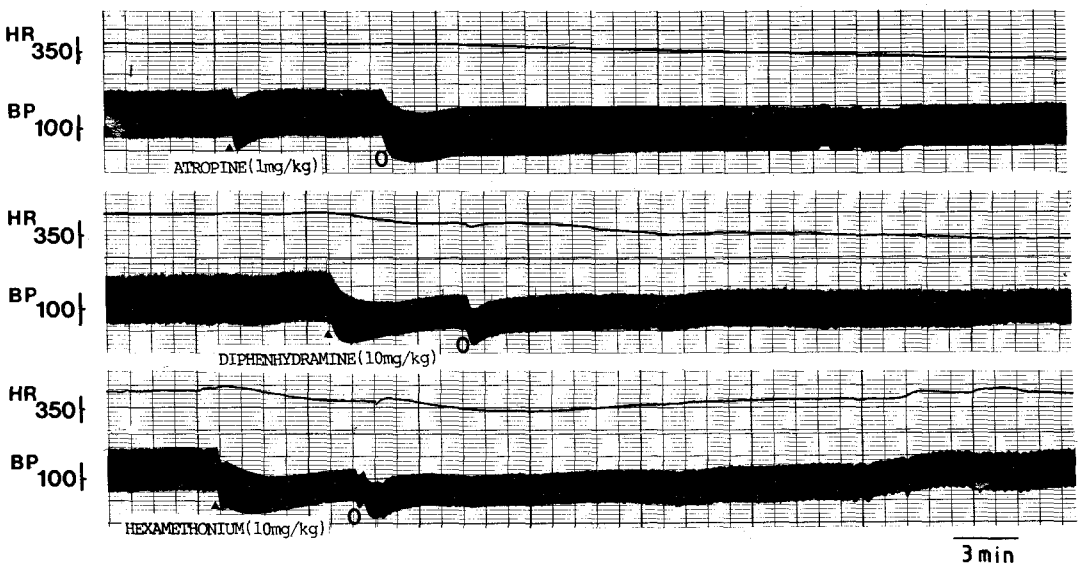


Fig. 6. Effects of atropine sulfate, diphenhydramine chloride and hexamethonium bromide on majarol-induced fall in blood pressure and decrease in heart rate in urethane anesthetized rats. In each panel, the upper recording is heart rate (HR) in beats/min; and the lower panel is blood pressure (BP) in mmHg. Drugs were given intravenously.
O; 2 mg/kg of majarol

tion of majarol (5-10 mg/kg) showed a typical transient fall and a subsequent prolonged decrease in arterial blood pressure and a significant decrease in heart rate. As shown in table 1 and figure 5, majarol (5 and 10 mg/kg) caused the arterial blood pressure to fall by a mean value of 44 mm Hg and 60 mm Hg and the heart rate by a mean of 45 beats/min and 73 beats/min, respectively. Majarol induced a subsequent prolonged fall in blood pressure was measured by a mean of 26 mm Hg and 39 mm Hg, respectively. The fall in blood pressure and decrease in heart rate by majarol (5-10 mg/kg) was of long duration, a period of 30-60 min being required, for the arterial blood pressure and heart rate to return to normal.

Table 3. Drug interactions of majarol, epinephrine and phentolamine on blood pressure in urethane anesthetized rats

Treatment	Dose (x/kg)	N	Mean blood pressure (mmHg)	Pretreament phentolamine (0.5mg/kg)	Pretreament majarol (5mg/kg)
Control	—	5	113 ± 9	—	—
Majarol	5 mg	5	69 ± 12[b]	102 ± 11[a]	—
Epinephrine	5 μg	5	163 ± 11[b]	—	131 ± 13[a]

The results are mean ± S.E.. N: Number of experiments in each group
Significance of difference ([a]$p<0.01$, [b]$p<0.001$) compared with the corresponding control values

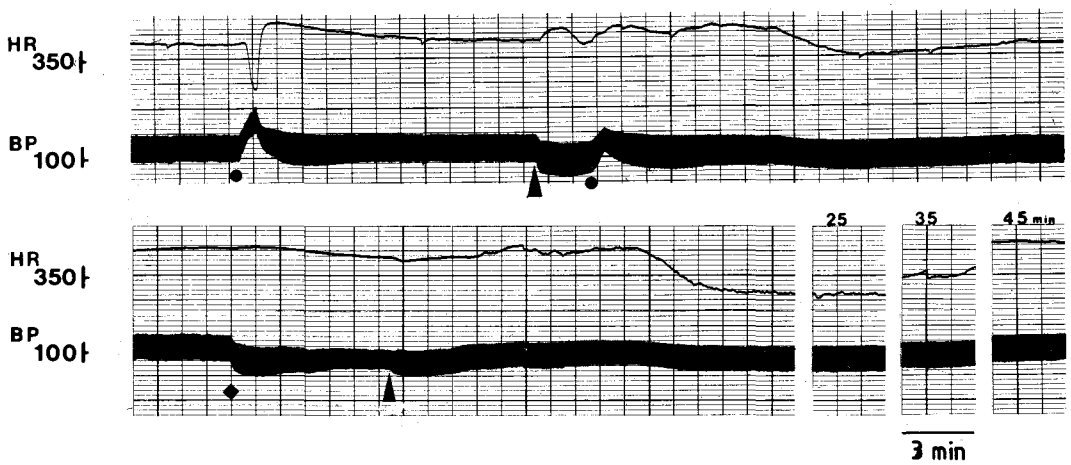


Fig. 7. Effects of majarol on epinephrine-induced rise in blood pressure and increase in heart rate and effects of phentolamine on majarol-induced fall in blood pressure and decrease in heart rate. In each panel, the upper recording is heart rate (HR) in beats/min; and the lower panel is blood pressure (BP) in mmHg. Drugs were given by intravenous injection. ●; epinephrine 5 μg/kg, ◆;phentolamine 0.5 mg/kg and ▲;majarol 5 mg/kg.

In subsequent experiments, atropine sulfate (1 mg/kg), hexamethonium bromide (10 mg/kg) and diphenhydramine (10 mg/kg) were administered intravenously, usually 5-7 min before giving the initial dose of majarol (2 mg/kg). The typical transient hypotensive effect of majarol was not abolished by these pretreated drugs (Table 2 and Fig. 6). The pretreatment with phentolamine (0.5 mg/kg, i.v.) inhibited the majarol induced depressor response by 65-75 % and intravenous pretreatment with majarol (5 mg/kg) blocked the epinephrine induced pressor response by 60-70 % (Tabled 3 and Fig. 7).

Higher doses of majarol resulted in a subsequent prolonged fall in arterial blood pressure usually accompanied by a decrease in heart rate. The pretreatment with propranolol (1 mg/kg, i.v.), a potent sympathetic ß-adrenoceptor blocking agent, did not abolish the hypotensive and bradycardiac effects produced by majarol. The positive chronotropic effect of isoproterenol was not blocked by the pretreatment with majarol (5 mg/kg) (Fig. 8).

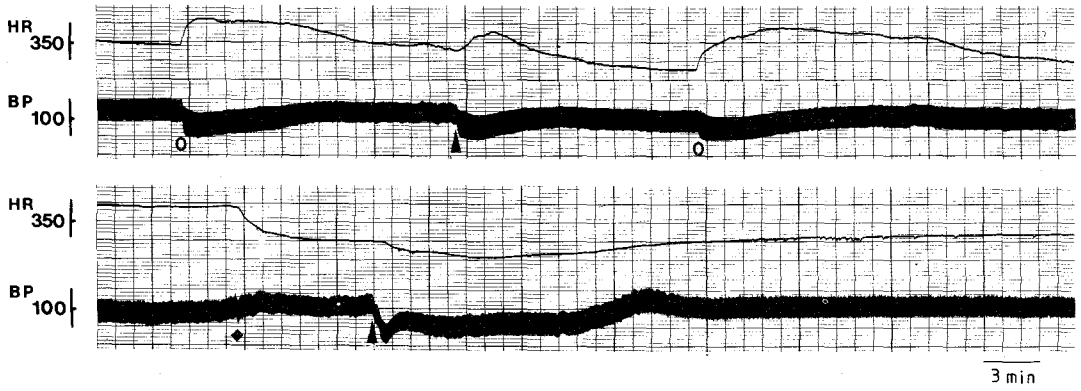


Fig. 8. Effects of majarol on isoproterenol-induced positive chronotropic effect on heart and effects of propranolol on majarol-induced fall in blood pressure and decrease in heart rate in urethane anesthetized rats. In each panel, the upper recording is heart rate (HR) in beats/min; and the lower panel is blood pressure (BP) in mmHg. Drugs were given by intravenous injection. O; isoproterenol 10 μg/kg, ◆; propranolol 1 mg/kg and ▲; majarol 5 mg/kg.

Table 4. Effects of majarol on the contraction force and contraction rate of isolated frog heart

Treatment	Dose ($\times 10^{-5}$M)	N	Contraction force(g)	Contraction rate (beats/min)
Control	—	7	1.5 ± 0.3	65 ± 4
Majarol	0.83	5	1.8 ± 0.3	63 ± 3
	1.70	5	2.2 ± 0.3[a]	60 ± 5
	3.40	5	2.6 ± 0.4[b]	57 ± 5
	13.60	5	arrhythmia	

The results are mean ± S.E., N: Number of experiments in each group
Significance of difference ([a]$p<0.01$, [b]$p<0.0001$) compared with the corresponding control values

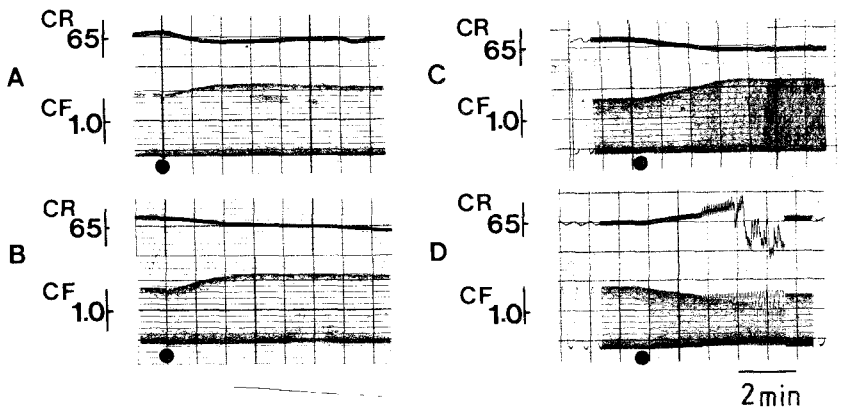


Fig. 9. Effects of majarol on the contraction force and contraction rate of isolated frog heart. In each panel, the upper recording is contraction rate (CR) in beats/min and the lower panel is contraction force (CF) in g. A; 0.83×10^{-5} M, B; 1.70×10^{-5} M, C; 3.40×10^{-5} M and D; 1.36×10^{-4} M of majarol.

Effects on isolated frog heart

In control experiments, infusion of isotonic glucose solution did not change rate and amplitude of contraction of isolated frog heart. The effects of test compound are shown in Fig. 9. Perfusion of majarol (final concentration of majarol $0.83\text{-}3.40 \times 10^{-5}$ M) resulted in an increase in amplitude and decrease in rate of contraction. A concentration of majarol 1.36×10^{-4}M caused an arrhythmia which returned to normal state after the solution was exchanged for drug free Ringer's solution.

DISCUSSION

Generally, the mechanisms of antihypertensive drugs are as follows; centrally block the adrenergic α_2-receptor (clonidine, Lowenstein, 1980.); peripherally block adrenergic α -receptor (phentolamine, Graham et al., 1977); block adrenergic ß-receptor (propranolol, Prichard, 1978); block ganglion (hexamethonium, Prichard, 1978.); directly dilate the vascular smooth muscle (hydralazine, Ablad, 1963); indirectly decrease blood pressure (diuretics) and inhibit the reflex of central sympathetic activity (veratrum alkaloid). The administration of majarol (0.5-2.0 mg/kg i.v.) into rats resulted in a typical transient fall in arterial blood pressure. And high dose of majarol (5-10 mg/kg) showed a typical transient fall and a subsequent prolonged decrease in arterial pressure accompanied by a decrease in heart rate. This typical transient hypotensive effect of majarol was not blocked by the pretreatments with atropine sulfate, diphenhydramine and hexamethonium bromide, respectively. From this result, it may be reasonable to cnsider that the typical transient fall in arterial pressure produced by a low dose of majarol was not mediated by peripheral cholinergic receptor, transient histamine releasing action or ganglion blocking action. The pretreatment with phentolamine inhibited significantly the transient hypotensive effect of majarol and majarol antagonized markedly the rise in arterial pressure produced by epinephrine. Therefore, it may be reasonable to consider that the blocking of peripheral α-adrenoceptor was one of the probable causes of the typical transient hypotensive responses to majarol.

In high dose, majarol showed a typical transient fall and a subsequent prolonged decrease in arterial pressure accompanied by a decrease in heart rate. Quinidine reduces the maximum rate of depolarization, increases the threshold of excitability, depresses conduction velocity, prolongs the effective refractory period, and reduces the spontaneous diastolic depolarization in pacemaker cell. This effects we are mediated by a direct action on cardiac muscle and partially anticholinergic effect (Bigger & Leahey, 1982). Propranolol depresses automaticity, prolongs AV conduction, reduces heart rate, and also decreases contractility. Propranolol exerts its cardio-inhibitory effect by acting on ß-adrenergic receptors (Goth, 1984; Wasserman & Proctor, 1978). The pretreatment with propranolol, a potent sympathetic ß-adrenoceptor blocking agent, did not abolish the subsequent prolonged hypotensive effect and bradycardiac effect of majarol. And majarol failed to antagonize the positive chronotropic effect of isoproterenol on heart. The failure of propranolol to modified this fall in blood pressure and decrease in heart rate and majarol to antagonized the positive chronotropic effect of isoproterenol apparently exclude the possibility of beta vascular receptor participation in the subsequent hypotensive and bradycardic response to majarol. In isolated frog heart, which was used to give some complementary result to the evidence for the experment in rats, majarol ($0.83\text{-}3.40 \times 10^{-5}$ M) caused an increase in a amplitude of contraction. In higher concentration (1.36×10^{-4} M), majarol decreased the amplitude of contraction and resulted in arrhythmia. Park, et al. reported that majarine (50 μg/kg, i.c.v.) showed a prolonged hypotensive effects in anesthetized rats. Probability remains that the effect of majarol on blood pressure and heart rate are partially due to the central action. Although the detailed action of majarol remains obscure, the typical transient hypotensive effects and the subsequent prolonged decrease in arterial pressure accompanied by a decrease in heart rate are concluded as a peripheral α-adrenoceptor blocking action and a direct cardiac smooth muscle inhibitory action.

Park *et al*, (1985) reported that the administration of majarine (50 ug/kg, i.c.v.) resulted in a decrease in arterial blood pressure in urethane anesthetized rats and approved the mechanism of hypotensive effect of majarine might be mediated by the central cholinoceptor. But in order to clarify exactly the mechanism of hypotensive effect of majarol, wider examinations are required; direct injection of majarol into posterior hypothalamus, and brain stem (Buccafusco *et al*, 1980), biochemical measurement the activity of central acetylcholinesterase (Marek *et al*, 1982 and Majocho *et al*, 1984), the effect of majarol on vasopressin concentration in blood (serum) related to hypothalamas pituitary gland neuron (Yvonne and Wei, 1983) or examination the blood renin concentration which participate partially in hypertension (Maxim *et al.*, 1980; David *et al.*, 1979).

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=국문초록=

Majarine 유도체인 majarol의 흰쥐에 있어서 혈압 및 심박동수에 대한 작용과 적출 개구리 심장에 대한 작용

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이종화, 박영현, 조병헌, 김유재, 김종배, 김천숙, 차영덕, 김영석

본 실험실에서는 한국 특산인 매자나무(***Berberis koreana*** Palibin)의 뿌리에서 majarine(isoquinoline alkaloid)을 분리하여 여러가지의 약리작용을 검토한 바 있다. 현재는 majarine의 화학적 구조를 변화시켜 그 유도체의 약리작용을 검색하고 있으며, 그 중 majarine의 isoquinoline ring에 치환되어 있는 두 methoxy group 중 하나를 hydroxy기로 치환된 majarol을 합성하였다. Majarol을 흰쥐 정맥내로 투여하여 혈압 및 심박동수의 변화와 epinephrine, phentolamine, isoproterenol, propranolol, atropine, diphenhydramine과 hexamethonium 등에 대한 약물 상호작용을 관찰하였으며 또 적출 개구리 심장에 대한 작용을 관찰하여 다음과 같은 성적을 얻었다.

Majarine을 저용량(0.5-2 mg/kg)에서 용량의존적으로 현저하고 일시적인 혈압 강하와 약간의 심박동수 감소를 나타냈으며, 고용량(>5 mg/kg)에서는 이차적으로 지속적인 혈압강하와 심박동수 감소를 나타냈다. 일시적인 혈압강하작용은 atropine sulfate, diphenhydramine 과 hexamethonium에 의해 억제되지 않았고, epinephrine의 혈압 상승작용은 majarol의 전처치로 현저하게 차단되었으며, majarol의 혈압 강하작용은 phentolamine의 전처치로 억제되었다. 고용량의 majarol 투여시 나타나는 지속적인 혈압강하는 심박동수 감소에 수반되어 나타났고 이는 propranolol에 의해 억제되지 않았으며, isoproterenol의 positive chronotropic effect는 majarol 전처치로 차단되지 않았다. majarol은 저용량에서 적출개구리 심장의 수축기 장력을 증가시켰으며 고용량에서는 개구리 적출심장에 대해 억제적으로 작용하였다.

이러한 결과로 보아 majarol의 일시적이고 현저한 혈압강하작용은 α-adrenoceptor 차단작용에 의한 것으로 사료되고, 이차적으로 나타나는 지속적인 혈압강하작용은 심박동수의 감소와 동시에 나타나는 것으로 보아 심장에 대한 작용인 것으로 추정되며, majarol의 심장에 대한 작용을 β-adrenoceptor에 대한 작용보다는 심근에 대한 직접적인 작용인 것으로 추정된다.