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Synthesis of Higenamine and its Cardiovascular Effects in Rabbit: Evidence for β-Adrenoceptor agonist

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ABSTRACT

Higenamine, dl-1-(4-hydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline has been synthesized and evaluated for hemodynamic actions using rabbits under pentobarbital anesthesia. Concentration-related fall of mean blood pressure was observed, where diastolic blood presure was significantly lowered at 10 ug/kg/min or above ($p<.05$), while the systolic blood pressure was slightly increased or unaffected, thereby, causing increment of pulse pressure.

No significant change was occured in heart rate, however, carotid artery blood flow was significantly ($p<.05$) increased. These actions were inhibited with pretreatment of 0.3 mg/kg of propranolol, beta-adrenoceptor antagonist, 5 minutes before infusion of higenamine indicating that higenamine compete with propranolol for the so-called beta adrenergic receptor. As comparison, the same procedure was applied to isoproterenol as well, where typical antagonism of propranolol against isoproterenol was shown. From these findings the vasodilating and diastolic blood pressure lowing effects could be explained in terms of cardiac beta stimulating action, however, dopamine receptor activation could not be excluded because no significant changes observed in chronotropism.

Key Words: Higenamine, beta-adrenergic receptor, positive inotropic action

Abbreviation: nBFA; n-butanol fraction of aconite tuber

INTRODUCTION

Along with the recent development of analytical instruments and technology, much interests are being imposed on folk medicines. Among them Aconite tuber, the root of Aconiti radix, which belongs to one of Ranunculaceae family has long been used as a heart stimulant, diuretic agent and analgesics in Chinese herbal medicine. However, its active component was not known until 1978, when a group of Japanese pharmacologists isolated a colorless plate compound from the Aconite root by limited combination of gel filtration through Sephadex LH-20 and count current distribution and named it higenamine (Kosuge *et al.*, 1978). So far, the known effects of higenamine are marked positive inotropic effect in isolated rabbit heart (Chang *et al.*, 1981) and accelerating calcium induced calcium release on sarcoplasmic reticulum of porcine heart (Kim *et al.*, 1982), promoting calcium influx through sarcolemma during action potential (Kwon *et al.*, 1981) as well as showing synergistic effect with extracellular calcium in the positive inotropic action (Chang *et al.*, 1981). Recently, Park *et al.* (1984) suggested effects of higenamine account for its cardiac beta adrenoceptor stimulation. The higenamine content in plant, however, are quite low to provide enough higenamine for biological testings *in vivo*. In addition, the separation and purification of higenamine from plant sources are complex and time consuming. Therefore, we attempted here the total synthesis

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of higenamine from the commercially available, inexpensive starting materials and investigated the action mechanism by *in vivo* trials, such as blood pressure, heart rate and peripheral resistance.

MATERIALS AND METHODS

Synthesis of Higenamine

N-(3′,4′-dimethoxyphenylethyl)-4-methoxyphenylacetamide. (IV) 4-Methoxyphenylacetyl chloride was prepared from 4-methoxyphenylacetic acid (8.3g, 0.05 mole) (I) by the procedure of Sims *et al.* (1971). After removal of the solvent and excess thionyl chloride, the crude 4-methoxyphenylacetyl chloride (II) was directly utilized to the next reaction without further purification. The above crude acid chloride was dissolved in 30ml of benzene and was added dropwise to the solution of β-(3,4-dimethoxyphenyl) ethylamine (III) (18.2g, 0.1 mole) in 40ml benzene. The reaction mixture was refluxed for 5 hrs. After cooling, the precipitate was filtered. It was dissolved in chloroform and washed with d-HCl. Removal of the solvent from the organic layer and recrystallization from ethanol provided amide (12.2g, yield 75%); mp 122-123° C; IR (KBr) 1640cm^{-1} (CONH); NMR δ ($CDCl_3$) 7.04 (2H, d, J=8 Hz), 6.78 (2H, d, J=8 Hz), 6.65 (1H, s), 6.55 (2H, s), 5.3 (1H, b, NH), 3.83 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.45 (2H, s, $COCH_2$), 3.36 (2H, t, J=7 Hz, CH_2), 2.65 (2H, t, J=7 Hz, CH_2); Analysis calc. for $C_{19}H_{23}NO_4.1/4\ H_2O$: C, H, N.

1-(4′-Methoxybenzyl)-6,7-dimethoxy-3,4-dihydroxyisoquinoline (V) hydrochloride. The mixture of 5g (0.015 mole) of N-(3′,4′-dimethoxyphenylethyl)-4-methoxyphenyl acetamide and 2g (0.013 mole) of phosphorus oxychloride in 50ml of dry toluene was refluxed for 2 hrs. Toluene and phosphoryl chloride are removed under the reduced pressure and the mixture was treated with d-HCl and ether. Crude product was collected and recrystalized from isopropanol providing comp. V as hydrochloride salt (4.3g, yield 82%); mp 139-140° C; IR (KBr) 1634 cm^{-1} (C=NH); NMR δ (D_2O) 7.4 (1H, s), 7.31 (2H, d, J=8Hz), 7.01 (1H, s), 6.95 (2H, d, J=8 Hz), 4.41 (2H, s,ϕ-CH_2), 3.92 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.8 (2H, m, CH_2), 3.08 (2H, t, J=8 Hz, CH_2); Analysis calc. for $C_{19}H_{22}NO_3.3/2\ H_2O$: C, H, N. The above hydrochloride was dissolved in water, basified with d-NH_4OH and extracted with $CHCl_3$. After drying with anhydrous Na_2SO_4 and evaporation of the solvents from the $CHCl_3$ layer, comp. V was obtained as free base.

1-(4′-Methoxybenzyl)-6, 7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI) hydrochloride. To the solution of 3.1g (0.01 mole) of 1-(4-methoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline in 30 ml of ethanol, was added sodium borohydride (0.8g) in 30 ml of ethanol slowly with cooling. The reaction mixture was treated as usual and the base was extracted with chloroform. Removal of the solvent from the dried extract gave crude 1-(4′-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. (VI) This comp. VI was purified in the form of hydrochloride by recrystallization from isopropanol (3.3g, yield 93%): mp 104-106°C; IR (KBr) 1608 cm^{-1}; NMR δ (free base)($CDCl_3$) 7.14 (2H, d, J=8 Hz), 6.81 (2H, d, J=8 Hz), 6.6 (lH, s), 6.55 (lH, s), 3.81 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 2.6-3.3 (7H, m); Analysis calc. for $C_{19}H_{24}NO_3Cl.3/4\ H\ O$; C, H, N.

1-(4′-Hydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (VII) hydrochloride.

1-(4′-Methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI) hydrochloride (3.5g, 0.01 mole) was refluxed with 15 ml of 47% hydriodic acid for 2 hrs. On cooling, crude product was precipitated out. It was recrystallized from the mixture of ethanol and either to give rise higenamine hydriodide (3.2g, yield 83%); mp 234-235°C; IR (KBr) 1605 cm^{-1}; UV (EtOH) nm 225, 286.5; NMR δ(DMSO) 8.3-9.3 (3H, m), 7.16 (2H, d, J=8 Hz), 6.77 (2H, d, J=8Hz), 6.60 (1H, s), 6.55 (1H, s), 4.55 (1H, m), 2.7-3.6 (6H, m); MS (m/e) 271, 178, 164, 149, 128 (HI), 107; Analysis calc. for $C_{16}H_{18}NO_3I$; C, H, N.

Instrument

IR spectra; Perkin-Elmer 283, UV; Gilford 2600, NMR; Varian FT-80A, Mass Spectra; Hewlett-Packard 9585B and Elemental analysis; Perkin-Elmer 240.

In Vitro Studies

1) Isolated heart: Left atria and right atrial pacemaker preparations from the hearts of albino rabbits (1.5-2 kg) were used. After the animal killed by a sharp blow on the skull, their hearts were rapidly removed and immersed in the isotonic solution at room temperature for dissection of the atrial preparations. The preparations were mounted in a 10 ml of organ bath on Krebs' solution. The spontaneously beating right atrium was attached to a force displacement transducer (F-60). The amplified output from the force displacement transducer was

used to drive a physiograph. This arrangement allowed continuous monitoring of rate and contractility. The left atrium was mounted in a similar way and attached to a force displacement transducer (F-60). A driving stimulus was applied through a pair of platinum electrodes in contact with the left atrium. The atrial smooth muscle was driven at one second intervals by square-wave pulses of 5 msec. duration. Stimulus intensity was just above threshold in order to prevent release of endogenous noradrenaline from adrenergic nerve endings. The contraction was recored on a Narco Bio-System MK-IV physiograph.

2) Medium: The Krebs' medium used was the following composition (mM): NaCl, 118; KCl, 4.69; $MgSO_4$, 1.17;KH_2PO_4, 1.2; $CaCl_2$, 2.5;$NaHCO_3$, 25; glucose, 11. It was continuously gassed with 95% O_2-5% CO_2 and was kept at 37°C (pH 7.4). Higenamine ($10^{-8}-10^{-5}$M) was introduced cumulatively for quantitating the sensitivity of tissue to the drug.

In Vivo Studies

General: Albino rabbits of both sexes ranging 1.5-2 kg were anesthetized with sodium pentobarbital (35 mg/kg, iv). Catheters were placed in the right carotid artery and left jugluar vein.

1) Blood pressure, heart and respiration rate: Blood pressure was monitored by the cather in the right carotid artery using RP-1500 transducer. After a control period during which parameters were measured, higenamine (1 μg-100 μg/kg/min.) was introduced into the jugular vein through the cannular by way of infusion pump. The heart rate was recorded by biotachometer utilizing the R wave of ECG of lead II or the arterial blood pressure signals as trigger. The respiration rate was recorded using impedence pneumograph connected to the pin electrodes on either side of the chest preferably between the fifth and sixth rib interface.

2) Blood flow: the carotid artery blood flow was measured continuously by way of the electromagnetic blood flowmeter. In all experiment, blood coagulation was prevented by heparin.

RESULTS

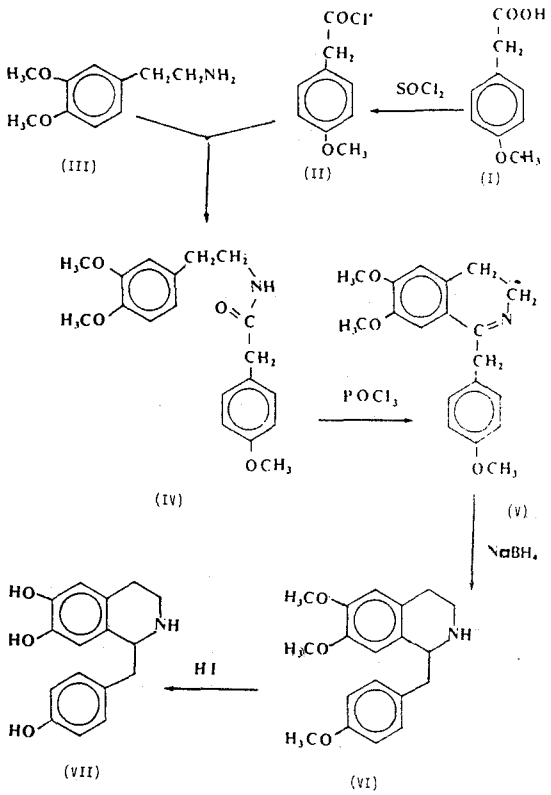
Cardiac Inotropic Action

Figure 1,2 illustrate the effect of higenamine of isolated heart and cumulative dose-response curves respectively. In left atria, higenamine exhibited marked positive inopropic action with the ED50 of 6.3×10^{-7} M, and dp/dt was also increased as the drug accumulated in the organ bath.

While spontaneously beating right atria, higenamine showed both positive intropic and chronotropic action. More than 10^{-5} M, however, arrythmia sometimes occurred.

Hemodynamic Effects on Anesthetized Rabbits

The hemodynamic effects including blood pressure, heart rate, respiratory rate and blood flow were investigated as increases the agonist concentration ranging from 1 μg/kg/min to 100 μg/kg/min. Figure 3, shows a typical example of higenamine effect on blood pressure. Both systolic and diastolic blood pressure were decreased dose-dependently and above the concentration of 10 μg/kg/min, the duration of action was more prolonged. As shown in Figure 4, though systolic and diastolic blood pressure were reduced as increases the concentration of drug, the former was not significantly affected, whereas, the latter was significantly ($p<.05$) reduced allowing increase in pulse pressure. No significant changes were observed in heart rate. On the other hand,



The Scheme for the syntnesis of higenamine.

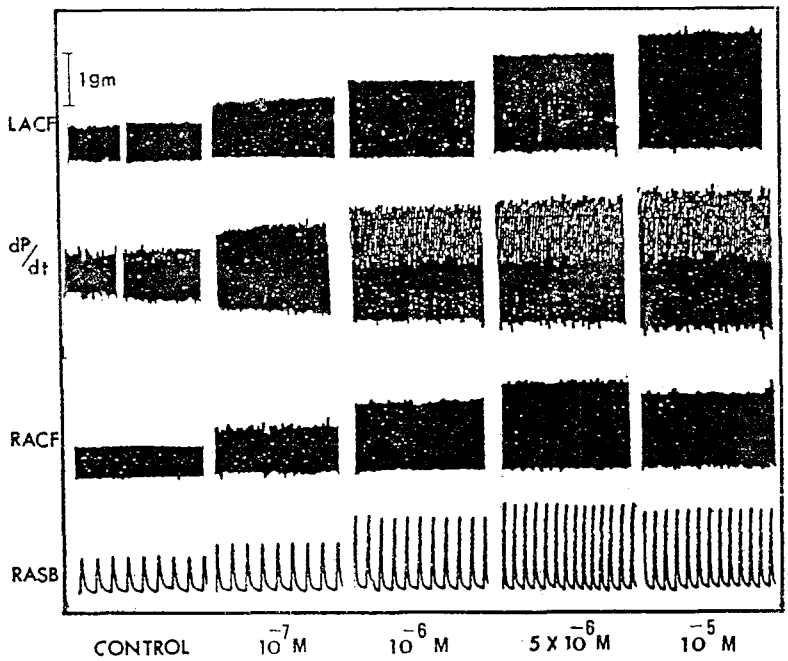


Fig. 1. The positive inotropic and chronotropic effects of higenamine on isolated rabbit heart. Left atria and right pacemaker preparations were used to determine the sensitivity of agonist on contractility and heart rate, respectively. LACF indicates left atrial contractile force, dP/dt; maximal rate of contractile force, RACF; right atrial contractile force, and RASB means right atrial spontaneous beat.

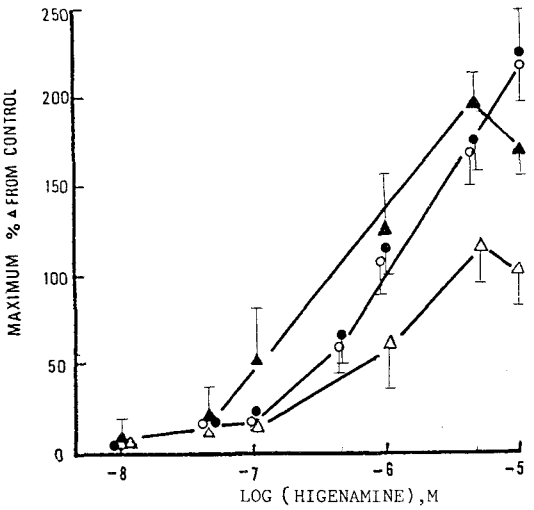


Fig. 2. Concentration- response curves of higenamine on peak contractile force (●), maximal rate of contractile force (○) in electrically driven left atria as well as peak contractile force (▲) and rate of spontaneous contractions (△) in isolated right atria. Ordinate: % increase of control value. Abscissa: logarithms of the molar concentrations of higenamine. Vertical lines indicate the s.e mean of 3 experiments.

respiration was stimulated and deepened transiently and carotid blood flow was significantly ($p<.05$) increased dose dependent manner. Table 1 summarized the result of experiment.

Mechanism of Action

In order to explore the mechanism of action, propranolol, non-selective beta adrenoceptor antagonist, was pretreated (0.3 mg/kg) 5 minutes before infusion of higenamine with two separate doses 30μg, 100 μg/kg/min. in sodium pentobarbital anesthetized rabbits, which were compared with non-treated ones. Figure 5 shows a typical experiment in which both blood pressure decreasing effect and respiratory stimulating action of higenamine were inhibited by propranolol, indicating that higenamine compete with propranolol for cardiac beta adrenergic receptor. As comparison, the same procedure was applied to isoproterenol (3 μg, 10 μg/kg/min.) as well. Typical antagonistic effect of propranolol against isoproterenol was dipicted in Figure 6.

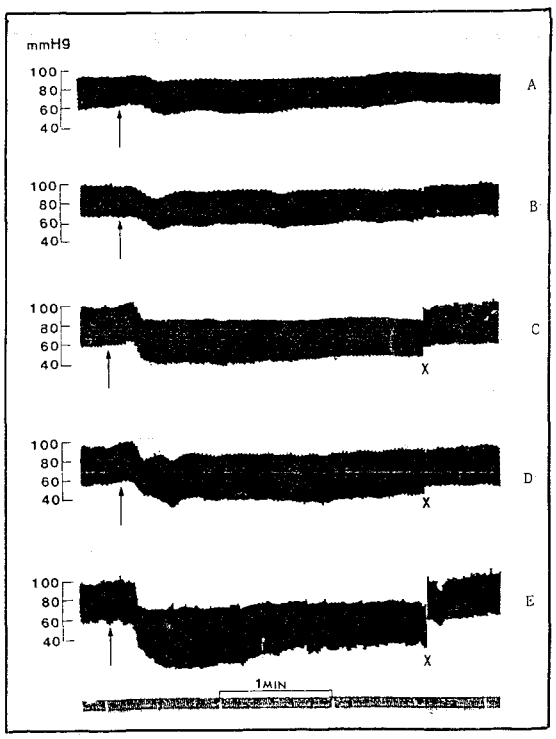


Fig. 3. The hypotensive effect of higenamine in sodium pentobarbital (35mg/kg) anesthetized rabbit. Five different concentrations of higenamine per weight kilogram (A: 1μg, B: 3μg, C: 10μg, D: 30μg and E: 100μg) were preferentially selected and introduced into jugular vein for one minute through cannular by way of infusion pump. Arrow indicates start of infusion and X means 3 minutes after stopping infusion.

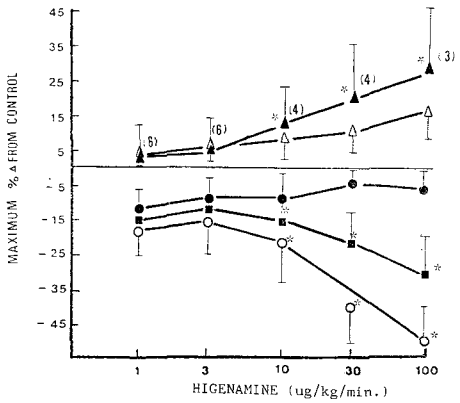


Fig. 4. The hemodynamic effect of higenamine in sodium pentobarbital (35mg/kg) anesthetized rabbit. Both systolic (●) and diastolic (○) pressure were reduced as increases the concentration of drug. The former was not, but the latter was significantly ($p<.05$) affected, thereby, allowing decrease in mean blood pressure (■). Carotid artery blood flow (▲) also significantly increased, whereas no significant change was observed in heart rate (△).* indicates significantly different from control value ($p<.05$).

DISCUSSION

At the present moment, 170 species of Aconitum Genus are reportedly known in which only 40 species are being used medicinal purposes; such as anodyne, antirheumatic, asthmolytic and cardiotonic (Xaio peigen, 1983). The positive inotropic activity of Aconite root, chloroform insoluble fraction, was first demonstrated in vitro using the isolated frog heart by Isaku in 1958. Several years later, Kim *et al.*, (1973) had reported that the inotropic action in chloroform insoluble fraction of Aconite tuber was potentiated by n-butanol fractionation, and there have been many reports to characterize the potent positive inotropic effect of n-butanol fraction of Aconite tuber (nBFA) extract (Yoon, 1976; Yang, 1976; Shin, 1976; Lim, 1977; Hong, Kim, 1981). Analyzing all the results concerning nBFA, Park *et al.*, (1981) concluded that the positive inotropic effect of nBFA might different from that of digitalis cardiac glycosides and would have broader range in

Table 1. Elemental Analysis of Compounds

Compound	Formula		C	H	N
IV	$C_{19}H_{23}NO_4 \cdot 1/4H_2H$	Calculated	68.43	7.11	4.19
		found	68.43	7.05	4.21
V	$C_{19}H_{22}NO_3Cl \cdot 3/2H_2H$	Calculated	60.85	6.73	3.73
		found	60.51	6.47	3.79
VI	$C_{19}H_{24}NO_3Cl \cdot 3/4H_2O$	Calculated	62.78	7.08	3.85
		found	62.60	7.10	3.96
VII	$C_{16}H_{18}NO_3I$	Calculated	48.13	4.55	3.51
		found	48.28	4.66	3.62

Table 2. The effect of higenamine on the hemodynamics of the anesthetized rabbit

	1 μg/kg		3 μg/kg		10 μg/kg		30 μg/kg		100 μg/kg	
	Before	After	Before	After	Before	After	Before	After	Before	After
S.P (mmHg)	99.2±2.4	89.1±3.3	100.8±2.1	92.5±3.7	99.6±6.3	92.6±5.2	103.3±3.1	99.8±1.3	102.0±3.6	96.2±3.7
D.P (mmHg)	71.6±3.6	60.6±4.9	68.8±4.2	59.2±7.1	70.5±2.8	57.4±9.5*	73.3±3.2	52.3±9.6*	72.5±4.1	49.2±6.0*
H.R (rate/min)	234.2±2.3	243.7±3.1	234.8±2.9	247.3±3.2	235.1±3.8	253.5±4.2	233.9±4.5	256.4±5.7	234.7±6.2	264.9±6.1
P.B.F (ml/min)	103.2±4.2	106.2±3.8	96.9±4.4	102.7±4.5	98.7±6.2	110.3±5.1*	101.8±5.3	124.6±7.5*	103.2±3.7	131.8±6.4*

S.P indicates systolic blood pressure; D.P. diastolic blood pressure; H.R, heart rate and P.B.F means peripheral blood flow rate, all values are means±SE. *: $p<.05$

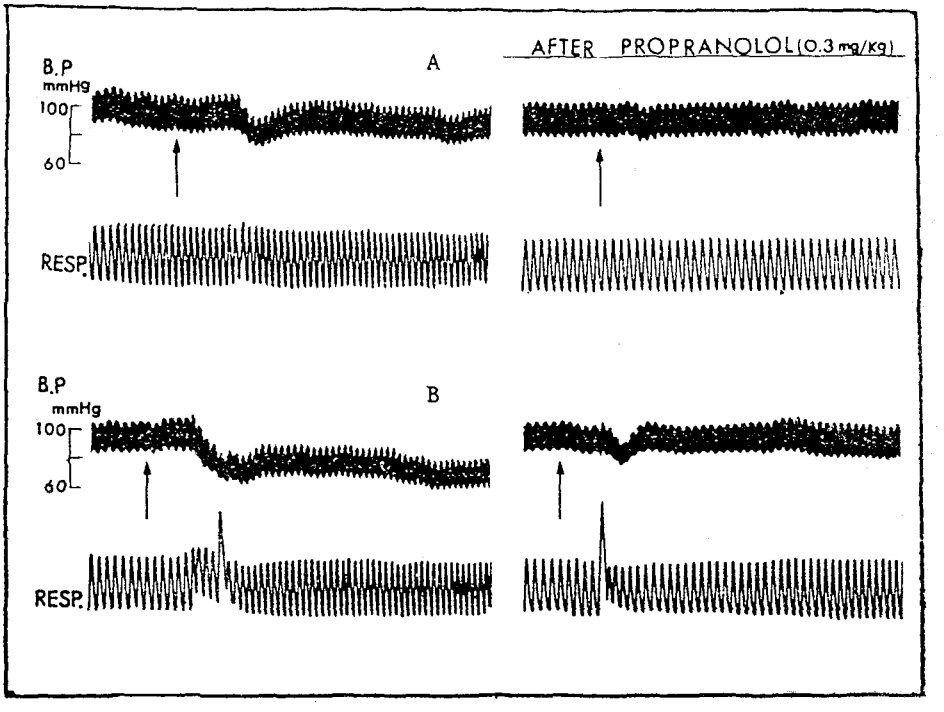


Fig. 5. Antagonism of beta adrenoceptor mediated response in blood pressure by propranolol with 2 different doses of higenamine. Arrow indicates start of infusion of agonist before (A: 30μg/kg, B: 100μg/kg) and after treatment with propranolol (0.3mg/kg). B.P. and RESP. indicated blood pressure and respiratory rate, respectively.

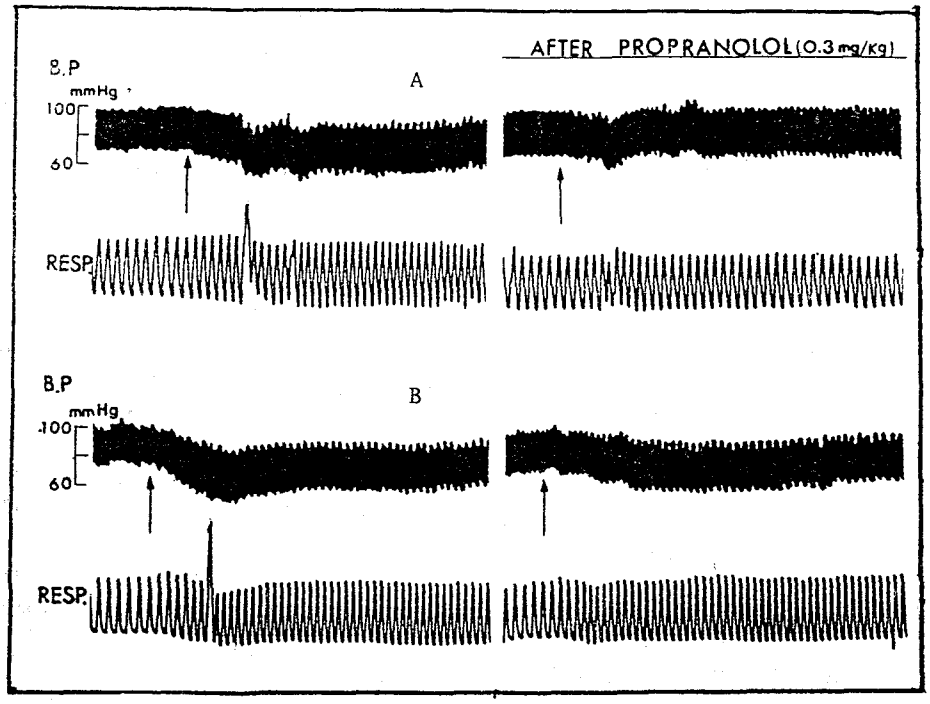


Fig. 6. Antagonism of beta adrenoceptor mediated response in blood pressure by propranolol with 2 different doses of isoproterenol. Arrow indicates start of infusion of agonist before (A: 3μg/kg, B: 10μg/kg) and after treatment with propranolol (0.3mg/kg). B.P and RESP. indicate blood pressure and respiratory rate, respectively.

margin of safety. In 1978, the active component of nBFA was isolated by Kosuge *et al.*, which was named as higenamine. However, isolation of hignamine from crude sustance is not only boring, time-consuming but also poor yielding: from dry weight of Aconite root of 150 kg, for instance, only 100 mg of higenamine could be acquired (Kosuge *et al.*, 1978). From these stand point, it is necessary and essential to establish the method for harvesting larger quantities of active compound. For this reason total synthesis of higenamine was attempted here in this study. However, higenamine was also reported to be partially synthetized by demethylation of coclaurine with hydrobromic acid (Koshiyama *et al.*, 1970; Yamaguchi 1958). The method and procedure involved in this synthesis were shorter than those of Koshiyama and identification of synthesized compound was carried out by the IR, UV, NMR spectra and elemental analysis, which was compared with authentic higenamine data. The activities of synthetic compound were investigated both in vivo and in vitro. In isolated hearts, higenamine caused positive inotropic as well as chronotropic actions with the ED50 of 6.3×10^{-7}M. In vivo study, dose-related fall of mean blood pressure was observed, where the diastolic blood pressure was significantly lowered, while the systolic blood pressure was slightly increased, thereby, causing increment of pulse pressure. No significant change in heart rate and significant increase in carotid artery blood flow were observed. These findings are quite similar to those actions of beta adrenergic agonist, isoproterenol. Recently Park *et al.*, (1984) reported that higenamine showed the positive inotropic effect by accompanying of shortening of the time required to peak tension as well as total duration of contraction time that was the mechanical characteristic features of catecholamines and the pA_2 value against propranolol was quite similar to that of epinephrine when used in left rabbit atria. Higenamine exhibited concentration-dependent stimulating effects on adenylate cyclase activity in turkey erythrocyte membrane which was potentiated by GTP and blocked by propranolol. Low concentrations enhanced, while high concentrations reduced, the effect of isoproterenol on adenylate cyclase (Zhou Y. P.

1983). These results support further our present data that higenamine would act as beta-sympatomimentics. Finally, with respect to structure of higenamine, it is highly speculated, based on the hypothesis of Mukherjee *et al.*, (1976), that higenamine would exert its effect by stimulating cardiac beta adreneric receptor with both affinity, which is related with bulky substituent on nitrogen atom, and intrinsic activity, with catechol nucleus. From the present result, it is strongly suggested that the stimulation of cardiac beta adrenoceptor may be an action mechanism of higenamine.

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=국문초록=

Higenamine의 합성 및 가토의 심혈관계에 미치는 영향 : 베타-아드레날린성 효능 약물

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최근에 미나라아제비과 (Ranunculaceae)에 속하는 부자(Aconiti tuber)로부터 강심작용을 나타내는 성분을 분리하여 Higenamine이라 명명하였고 그 작용기전을 밝히려는 시도가 활발히 진행되고 있다. 그러나 생약제로 부터 얻을 수 있는 Higenamine은 극히 미량이고 그 과정 또한 복잡하다. 따라서 본 연구에서는 유효성분을 대량 얻기 위한 방법으로서 전합성(total synthesis)을 시도하였으며 IR, UV, NMR 및 elemental 분석등을 통하여 합성된 물질을 확인하였으며 가토에 대하여 in vivo에서 혈압, 심박동수, 호흡 및 말초저항에 미치는 영향과 아울러 in vitro에서 심근수축 증강작용(positive inotropic action) 및 심박속도 증강작용(positive chronotropic action)을 관찰 분석하여 다음과 같은 결론을 얻었다.

1) Higenamine은 1-10μg/kg/min 정맥주사시 수축기 및 이완기혈압 모두를 용량 의존적으로 하강시켰고 후자가 전자보다 더욱 현저하였으며 호흡은 촉진되었고 말초 혈류량은 증가되었으나 심박동수는 영향이 없었다.
2) 혈압에 대한 Higenamine의 작용은 propranolol 전처치에 의하여 억제되었다.
3) Higenamine의 catechol 핵과 커다란 아미노기는 베타 수용체기 대하여 전자는 활성을 후자는 친화력과 관계있을 것으로 추정하였다.

이상의 결과 Higenamine은 adrenergic β-수용체에 작용하여 그 작용을 발휘하는 것으로 사료되었다.