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Effect of Ethanol on the Cardiovascular System in Hypertensive Rats*

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＝抄　錄＝

에타놀이 高血壓 흰쥐의 血壓에 미치는 影響

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Ethanol 注入後에 心臟 및 循環系의 反應을 高血壓 및 正常血壓 쥐에서 實驗하였다. 腎臟의 70%를 除去한 5日後부터 1% 소금물을 마시게 하면 1週日이내로 收縮期血壓은 181±7mmHg, 弛緩期血壓은 125±5 mmHg 으로 高血壓이 誘發되었다. 動脈血壓을 測定하고 靜脈으로는 ethanol을 注入시키기 위해 大腿動脈과 靜脈에 catheter를 各各 挿入하였다. Ethanol은 30% 溶液을 1分當 2ml의 速度로 5分 또는 10分동안 大腿靜脈을 通하여 注入한 후 3時間동안 血壓을 繼續 記錄하였다. Ethanol을 5分 또는 10分동안 注入시킨 1時間 後의 血中 ethanol 濃度는 各各 132.6±13.0, 302.4±19.7mg%였다. 正常血壓 쥐에서는 ethanol 注入 30分後부터 血壓이 떨어지기 始作하여 3時間동안 낮게 維持되었다. Ethanol 5分 또는 10分 注入後의 收縮期 및 弛緩期血壓은 모두 15mmHg 程度 下降하였다. 高血壓쥐는 ethanol 注入 15分 後부터 血壓이 急激히 減少하여 3時間동안 正常血壓을 維持하였다. 高血壓 쥐에서 ethanol 5分 또는 10分 注入後의 收縮期血壓의 最高減少量은 各各 60 및 39mmHg 였고, 弛緩期血壓의 最高減少量은 各各 56 및 27mmHg 였다. Ethanol 注入後 모든 쥐의 脈壓에는 有意한 變化가 없었다. 以上의 結果에서 ethanol은 收縮期나 弛緩期血壓을 비슷한 程度 減少시킴을 알 수 있다. Ethanol의 血壓 降下 作用은 正常血壓 쥐에서 보다 高血壓 쥐에서 더욱 顯著하게 나타났으며, ethanol 投與後 3時間 以上 繼續 維持되었다. 高血壓 쥐에서는 中等量이 大量의 ethanol 投與 때보다 有意하게 强한 血壓 降下作用을 나타내었다.

Introduction

Ethanol is generally considered as a peripheral vasodilator agent[1-4], and its cardiovascular effects are dose dependent. Ethanol in moderate dose increases blood flow to the skin but decreases the muscle blood flow[2,3]. In human,

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moderate dose of ethanol usually produces tachycardia and decreases blood pressure[1-7], but some investigators observed no changes in blood pressure, cardiac output and cardiac contractility[3,8,9]. Severe alcoholic intoxication produces the cardiovascular depression mainly due to central vasomotor factors and to the respiratory depression[10]. In the past, ethanol was used for the management of patients with coronary heart disease[10,11]. However clinical evidences showed that ethanol neither increases coronary blood flow nor helps release of the attacks of angina pectoris[5,6,12]. Recently, Klatsky and his associates[13] studied 83,947 men and women, and reported that people who took 3 or more drinks per day chronically had higher systolic pressure, diastolic pressure and substantially higher prevalence of hypertension. Several other epidemiologic studies[14-16] also suggest that clinically hypertension might be more prevalent among chronic heavy drinkers. Many people believe that alcohol has adverse effects on hypertensive patients, but little study has been conducted on it.

Although ethanol affects cardiovascular system generally, its dose-related responses and responses in hypertensive subjects have been rarely studied. Thus the present study was undertaken to determine the cardiovascular responses following moderate to severe doses of ethanol in normotensive and hypertensive rats.

Methods

Sprague Dawley rats were partially nephrectomized (PN) under anesthesia. The right kidney and both poles of the left kidney were removed with little blood loss by the method described by Muirhead et al[17]. By the surgery, approximately 70% of the renal mass were removed. Sham operations were performed by exposing and manipulating both kidneys. Rats were housed individually in eachcage, and food (Cheil Rat Chow) and tap water were allowed ad libitum during 5 days of recovery period. Thereafter, PN rats were given 100ml of 1% saline daily for drinking and got hypertensive within a week after substituting 1% saline for water. Sham operated rats were allowed to drink tap water throughout the experiment.

In order to examine changes in blood pressure after ethanol infusion in hypertensive and normotensive rats, the following experiments were performed at least 15 days after the surgery. On the day of the experiment, a rat was anesthetized with ether and catheterized in a femoral artery for direct arterial pressure measurement and in a femoral vein for ethanol infusion. The catheters were filled with heparin solution and were exteriorized at the back. The rat was placed in a restraining cage designed to prevent rat movements. The arterial catheter was connected to a pressure transducer (Narco RP-1500) and pulse pressure of mean arterial blood pressure was recorded on a physiograph (Narco MK--Ⅳ-P). After 2 hours of recovery from the surgery of cannulation, 30% of ethanol solution was infused at a rate of 0.2ml/min for either 5 or 10 minutes. Following the completion of ethanol infusion, blood pressure was recorded continuously for 3 hours. For the measurement of blood alcohol concentration by the enzymatic method (Sigma Kit No. 331--UV), approximately 300μl of blood from the arterial catheter was collected every hour.

Results

By the PN surgery, 70.4±1.0% of the renal mass was removed and 100% of the PN rats were survived. Body weight returned to the presurgical level 5 days after the surgery (Table 1). While PN rats drank 1% saline instead of water, they lost weight initially but gained much slowly thereafter than the sham operated rats.

The systolic blood prssure of the PN rats drank 1% saline over a week significantly increased to a hypertensive level, 180mmHg.

Table 1. Body weight in partially nephrectomized (PN) and Sham-Operated rats

	Pre-	Post-Operation			
		5#	8	15	20days
PN	220±7(n=19)	222±8(n=19)	215±9⁺(n=18)	233±5⁺(n=18)	236±8⁺(n=5)
Sham	218±7(n=15)	227±7(n=15)	242±8⁺(n=15)	269±7⁺(n=15)	287±8⁺(n=7)

Values are Mean±S. E.
*$p<0.01$, pre vs. post operation.
⁺$p<0.01$, PN vs. sham-operated rats.
#PN rats began to drink 1% saline thereafter.

Systolic pressure over 160mmHg was regarded as hypertensive[17]. Blood ethanol concentrations 1 hour after 5 or 10min infusion of 30% ethanol were 132.6±13.0 or 302.4±19.7mg%, respectively (Table 2). Immediately after the ethanol infusion, bloodpressure of the rats was not changed significantly (Table 2, Fig. 1–3). However, during 3 hours after the ethanol infusion, arterial pressures of both normotensive and hypertensive rats were decreased significantly ($p<0.01$). In normotensive rats, both systolic and diastolic pressures began to decrease 30 minutes after ethanol infusion and remained low during the 3 hour experimental period. Maximum decreases of systolic and diastolic pressures following both low and high doses of ethanol were about 15mmHg. In PN-salt hypertensive rats, systolic and diastolic pressures were sharply decreased at 15 minutes after ethanol infusion and decreased further throughout the experiment. Following low and high doses of ethanol infusion into hypertensive rats, maximum decreases of systolic pressure were 60 and 39mmHg and those of diastolic pressures

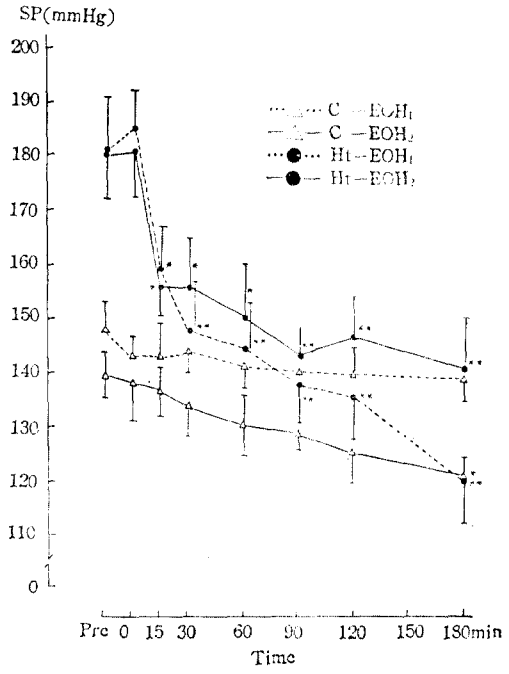

Fig. 1. Effect of low and high doses of ethanol (EOH_1, EOH_2) on systolic pressure (SP) in hypertensive (Ht) and normotensive (C) rats.

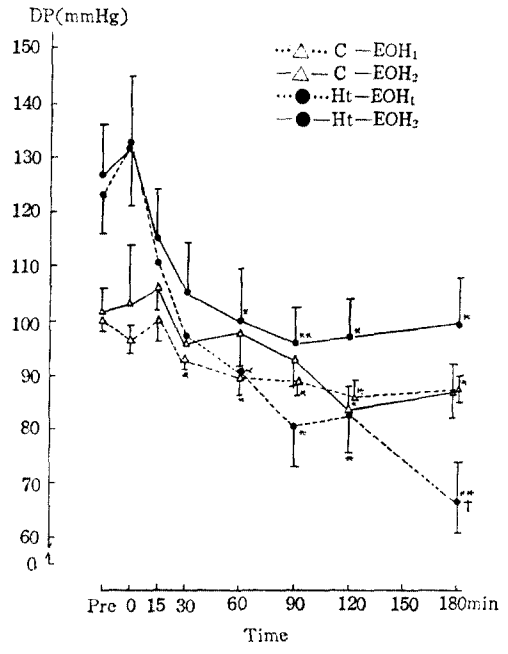

Fig. 2. Effect of low and high doses of ethanol (EOH_1, EOH_2) on diastolic pressure (DP) in hypertensive (Ht) and normotensive (C) rats.

Table 2. Effect of Low and High doses of Ethanol (EOH_1, EOH_2) on Systolic Pressure (SP), Diastolic Pressure (DP), Mean Arterial Pressure (MAP), and Pulse Pressure (PP) in Partial Nephrectomy-Salt Hypertensive (Ht) and Normotensive (C) Rats

		Pre	Post- EOH Infusion						
			0	15	30	60	90	120	180min
BEC, mg%	EOH_1					132.6± 13.0		63.8± 7.5	35.2± 4.3
	EOH_2					302.4±19.7		213.9±10.8	153.6±10.7
SP, mmHg	C-EOH_1[a]	148.0±5.0	143.1± 3.5	142.8± 6.3	144.2± 3.6	141.7± 4.8	140.5± 3.3	140.3± 4.7	139.5± 5.1
	C-EOH_2[b]	139.2±4.2	138.3± 6.9	137.2± 4.9	134.4± 5.3	130.6± 5.1	129.2± 3.0	126.2± 8.3	121.7± 2.9**
	Ht-EOH_1[c]	181.3±9.8	185.3±15.5	158.9±10.0*	147.7± 9.5**	145.3± 8.1**	138.1± 7.3**	136.2± 8.1**	121.1± 7.6**
	Ht-EOH_2[d]	180.2±8.0	180.9± 8.4	157.9±10.8*	155.6±10.7*	149.7±10.9*	143.7± 6.5**	147.1± 7.2**	141.0± 9.5**
DP, mmHg	C-EOH_1	100.9±2.0	96.4± 2.1	100.1± 4.1	93.1± 1.5*	89.5± 2.9*	89.1± 3.1*	86.4± 2.1*	88.1± 1.8*
	C-EOH_2	102.5±4.5	103.8±10.3	106.5± 7.3	96.1± 5.0	97.9± 6.6	92.9± 5.3	84.2± 3.7*	87.3± 6.1
	Ht-EOH_1	123.5±7.1	132.9± 8.2	110.8±10.7	97.3±10.3*	90.4± 8.9*	80.8± 7.5*	82.9± 8.7*	67.2± 6.5**
	Ht-EOH_2	126.9±9.3	131.6±10.3	115.2± 9.8	105.2± 9.8*	100.0± 9.7*	95.6± 6.7**	97.1± 7.2*	99.9± 9.0**
MAP, mmHg	C-EOH_1	121.2±2.2	113.6± 2.3*	117.2± 3.3	114.6± 1.8*	110.9± 2.9**	110.3± 3.3**	108.4± 2.7**	109.3± 3.1**
	C-EOH_2	117.2±4.0	121.0± 6.4	123.7± 6.6	115.6± 5.0	109.8± 2.6	108.3± 3.6	104.0± 5.7	103.0± 5.4*
	Ht-EOH_1	147.7±6.3	150.4±13.1	126.7± 9.0*	114.1±10.0*	108.7±12.9*	99.9±11.6**	100.7±12.7*	85.2± 6.8**
	Ht-EOH_2	144.7±8.8	148.1±10.9	129.4± 9.6	122.0±10.3	116.6± 7.9*	111.6± 6.6**	110.0± 7.0*	113.6± 9.6**
PP, mmHg	C-EOH_1	47.5±2.4	46.6± 3.1	43.2± 3.5	48.2± 3.0	49.8± 3.5	51.4± 4.2	52.2± 3.8	49.9± 5.2
	C-EOH_2	36.8±3.2	34.5± 3.8	40.7±10.4	32.9± 9.7	32.6± 6.2	36.3± 4.3	42.0± 9.6	36.8± 5.5
	Ht-EOH_1	57.8±5.3	52.3± 4.1	48.1± 1.9	50.4± 3.2	54.9± 3.3	57.3± 4.7	53.3± 3.8	53.9± 2.3
	Ht-EOH_2	53.2±3.5	49.3± 3.9	42.7± 7.0	50.4± 4.4	49.7± 9.5	48.2± 1.2	48.1± 3.5	41.1± 3.4

Values are Mean±S.E.

*$p<0.05$, **$p<0.01$ pre vs. post-ethanol infusion.

C-EOH_1; n=8, C-EOH_2; n=7, Ht-EOH_1; n=9, Ht-EOH_2; n=9.

Table 3. Effect of Low and High Doses of Ethanol (EOH_1, EOH_2) on Duration of Systole (DS), Diastole (DD) and One Cardiac Cycle (DC), and Heart Rate (HR) in Partial Nephrectomy-Salt Hypertensive (Ht) and Normotensive (C) Rats

		Pre	Post-EOH Infusion						
			0	15	30	60	90	120	180min
HR, (Beat/min)	C-EOH_1	415.8± 2.9	408.9±10.9	432.9± 7.7	425.1±10.3*	437.5± 9.3	435.7± 8.3*	442.3± 7.5*	416.0± 7.4
	C-EOH_2	383.1±14.1	359.9±22.2	431.7±22.0	417.4±14.6*	436.1±18.7	413.8±20.2	408.7±18.2	417.2±28.1
	Ht-EOH_1	442.7±10.6	413.6±16.4	409.8±19.2	395.1±17.6*	370.6±20.3	381.9±24.7*	372.2±23.9*	365.4±18.8*
	Ht-EOH_2	424.9± 5.8	430.0±15.3	448.9±14.7	430.0±19.4	431.1±18.1	433.5±13.8	438.1±11.3	433.3± 9.2*
DS, (mSec)	C-EOH_1	68.3± 4.2	70.1± 3.4	70.7± 4.0	68.6± 3.8	70.0± 2.7	69.4± 2.8	70.9± 4.1	78.3± 3.3
	C-EOH_2	83.5± 2.3	95.3± 5.7	85.4± 7.9	79.6± 3.9	84.8± 4.4	83.2± 3.7	85.5± 4.4	85.8± 3.1
	Ht-EOH_1	72.1± 4.8	69.6± 5.1	72.8± 3.9	69.7± 2.5	72.7± 4.4	76.8± 5.1	72.3± 4.9	72.5± 4.9
	Ht-EOH_2	72.8± 2.7	69.3± 2.1	64.7± 3.8	64.7± 2.7*	66.2± 2.1	64.3± 2.1*	62.7± 1.9**	66.5± 2.3
DD, (mSec)	C-EOH_1	73.5± 3.6	77.2± 1.8	68.6± 3.2	71.6± 2.1	67.7± 1.9	70.3± 3.2	65.8± 2.8	69.8± 3.1
	C-EOH_2	73.2± 5.4	71.0± 1.6	54.1± 4.4**	62.8± 6.5	51.9± 4.6**	64.9± 2.2	61.5± 7.7	58.3± 8.9
	Ht-EOH_1	73.9± 5.2	76.6± 4.6	73.8± 6.7	83.6± 7.4	87.4± 9.2	84.8±12.4	86.0±11.2	89.3± 8.1
	Ht-EOH_2	70.7± 3.8	71.2± 4.8	72.8± 4.8	77.3± 5.3	74.3± 3.7	73.2± 2.3	74.2± 3.1	72.7± 2.9
DC, (mSec)	C-EOH_1	141.8± 5.2	147.3± 4.8	139.3± 3.2	140.2± 4.2	137.7± 4.3	137.7± 3.8	135.7± 4.7	147.3± 4.6
	C-EOH_2	156.7± 5.7	172.3± 7.2	139.5± 3.7**	142.4± 5.7	136.7± 2.7**	148.1± 5.3	147.0± 3.7	144.1± 3.8
	Ht-EOH_1	146.0± 7.2	146.1± 5.9	150.0± 2.5	154.7± 6.6	166.1± 8.7	161.7± 8.5	158.3± 8.3	166.8± 7.7*
	Ht-EOH_2	143.5± 2.1	140.5± 4.7	137.5± 6.2	142.0± 7.4	140.5± 5.7	137.5± 3.6	136.8± 3.7	139.2± 2.6

Values are Mean±S.E.

*$p<0.05$, **$p<0.01$, pre vs. post ethanol infusion.

C-EOH_1; n=8, C-EOH_2; n=7, Ht-EOH_1; n=9, Ht-EOH_2; n=9.

were 56 and 27mmHg, respectively. In hypertensive rats, lower dose of ethanol produced significantly greater decrease in blood pressure than the higher dose of ethanol. The hypertensive rats produced significantly greater decrease in blood pressure following ethanol infusion than the control rats. The pulse pressure was not significantly altered following ethanol infusion either in normotensive and hypertensive rats.

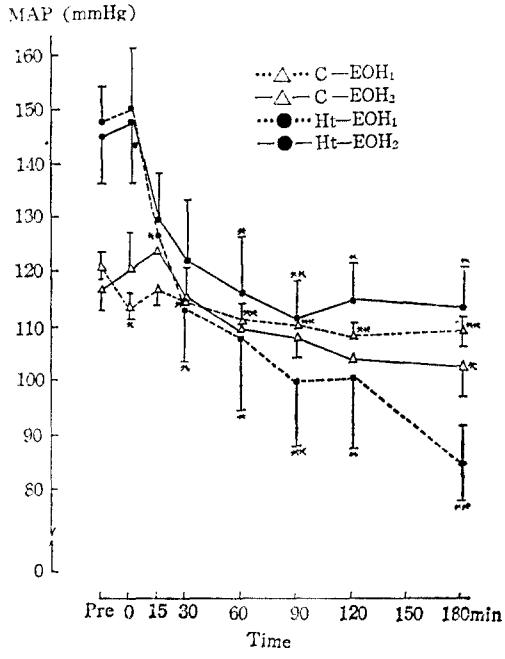

Fig. 3. Effect of low and high doses of ethanol (EOH_1, EOH_2) on mean arterial pressure (MAP) in hypertensive (Ht) and normotensive (C) rats

Table 3 shows changes in heart rate and durations of systole, diastole and one cardiac cycle following ethanol infusion. A pattern of changes in heart rate following different doses of ethanol was not consistent in the hypertensive and normotensive rats. In the normotensive rats, heart rate tends to decrease immediately after ethanol infusion, but increased from 15 minutes and stayed at high levels throughout the experimental period. On the other hand, the low dose of ethanol in hypertensive rats produced a marked decrease in heart rate throughout the experimental period, but the high does of ethanol did not alter the heart rate significantly. Durations of systole, diastole and one cardiac cycle did not show any significant alterations by ethanol in either group.

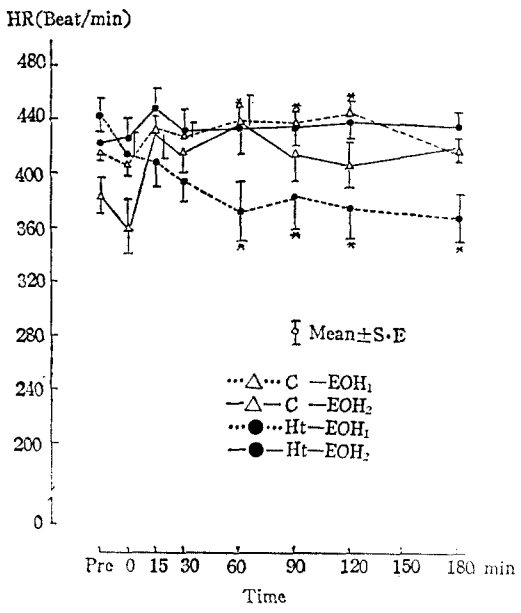

Fig. 4. Effect of low and high doses of ethanol (EOH_1, EOH_2) on heart rate (HR) in hypertensive (Ht) and normotensive (C) rats

Discussion

In the present experiment, ethanol lowered systolic and diastolic pressures similar degrees both in hypertensive and normotensive rats. Cardiovascular responses to the same dose of ethanol were remarkably stronger in the hypertensive rats than normotensive rats. Decrease in blood pressure following ethanol infusion was significantly greater in the hypertensive rats than normotensive rats. Furthermore, in the hypertensive rats the low dose of ethanol produced significantly greater decrease in blood pressure than the high does of ethanol. However, in normotensive rats both low and high doses of ethanol produced same degree of decrease in blood pressure.

The mechanism of blood pressure lowering effect of ethanol has long been believed due to vasodilation[1-4]. Responses to oral or intravascular administration of ethanol were different in healthy man. Ethanol drinking produced a marked increase in skin blood flow but decrease in muscle blood flow[2,3]. On the other hand, while ethanol was infused into brachial artery, both skin and muscle blood flow decreased, but skin blood flow began to increase 5 minutes after the intra-arterial infusion of ethanol was ceased[3]. These results suggest that ethanol perse constrict the smooth muscle of the arterial walls in skin and muscle but its metabolites (i.e., acetaldehyde) may produce vasodilation. In the present experiment, blood pressure was not changed significantly during or immediately after the intravenous infusion of ethanol but was decreased 15 to 30 minutes after the infusion (Table 2, Fig. 1). Therefore, it seems that lowered blood pressure is due to ethanol metabolites but not ethanol itself. In the sympathectomized subjects, responses of the blood vessels to ethanol are not consistent. In sympathectomized subjects, Gillespies[2] reported an increased skin blood flow after whisky drinking, but Fewings et al[3] observed no changes in blood flow in skin or skeletal muscle. Further studies are required to understand the mechanism of cardiovascular responses to ethanol and the involvement of the autonomic nervous system. Hypertensive rats showed not only a dose related cardilovascular responses to ethanol, but also stronger responses to ethanol than normal rats (Table 2). Removal of 70% renal mass (PN) and subsequent salt loading produces hypertension within a week[18-21]. Since excretory function of the kidney in the PN animals are reduced dramatically, salt loading produces an expansion of body fluid and thus hypertension[21]. When water[21-23] or ethanol[24] was administered instead of salt into the PN-salt hypertensive animals, their blood pressure returns to normal level on the next day by excreting extra salt and water. Therefore, the PN-salt hypertension is known as a volume dependent hypertension, and diuretics are very effective to lower the blood pressure in this type of hypertension. Ethanol is a very strong diuretic[24-26], but blood pressure lowering effect in the present experiment does not seem to be due to the diuretic action of ethanol because blood pressure was significantly decreased already at 15 minutes after the cessation of ethanol infusion. In a PN dog, salt loading elevated blood pressure that was initiated by increases in cardiac output but that was sustained by elevation of peripheral resistance[23]. When taken together, acute effects of ethanol seem to dilate the blood vessels, decrease the peripheral resistance and lowers the blood pressure of hypertensive animals to normal level. However, contribution of diuretic action of ethanol to lower pressure acutely is not clear. Low to medium doses of ethanol seem to be beneficial to lower the hypertensive blood pressure to normotensive level promptly and maintain at low level for several hours. However, its effect was studied only 3 hours in the present experiment and thus a pattern of recovery of blood pressure thereafter is not known. Etiology of development and maintenance of different types of hypertension is different. Therefore, further studies are necessary to understand whether ethanol lowers blood pressure effectively in other types of hypertension and chronic effects of ethanol on cardiovascular system both in normal and hypertensive subjects.

Summary

Cardiovascular responses to ethanol were examined in hypertensive and normotensive rats. Hypertension was produced by reducing renal mass 70% and substituting 1% saline for drinking water from 5 days after the surgery. A subsequent salt loading for over a week led to a marked increase in arterial pressures to hypertensive levels (systolic pressure: 181±7mm Hg, diastolic pressure: 125±5mmHg). On the experimental day catheters were placed in fem-

oral artery for arterial pressure measurement and in femoral vein for ethanol infusion. Arterial pressure was recorded continuously for 3 hours after the infusion of 30% ethanol at a rate of 0.2ml/min for either 5 or 10 minutes.

One hour after 5 or 10 minutes infusion of ethanol, blood alcohol concentrations reached 132.6±13.0 and 302.4±19.7mg%, respectively. Blood pressure of the normotensive rats began to decrease 30 miuutes after the ethanol infusion and remained significantly low during 3 hour experimental period. Both low and high doses of ethanol produced maximum decreases in systolic and diastolic pressures approximately 15 mmHg. In partial nephrectomy-salt hypertensive rats, arterial pressure sharply decreased at 15 minutes after ethanol infusion and decreased further throughout the experimental period. Maximum decreases of systolic pressure after low and high doses of ethanol in the hypertensive rats were 60 and 39mmHg, respectively, and those of diastolic pressure were 56 and 27mmHg, respectively. Pulse pressure was not changed significantly following ethanol infusion either in normotensive or in hypertensive rats.

The above results show that ethanol produced decreases both in systolic and diastolic pressures approximately by the same degrees. In hypertensive rats the low dose of ethanol produced significantly higher decrease in blood pressure than the high dose of ethanol but not in normotensive rats. Blood pressure lowering effets of ethanol was significatly stronger in hypertensive rats than normotensive rats.

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