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The Diuretic Action of Eucommiae Cortex and Its Effects on Cardiovascular System

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ABSTRACT

The effect of aqueous extract of Eucommiae Cortex (ECAq) on cardiovascular system and diuretic action were evaluated in the studies. Intraperitoneal administration of ECAq decreased blood pressure, mean blood pressure and heart rate of the anesthetized rats at dose higher than 800 mg/kg. Effect of ECAq on coronary blood flow was examined by T-1824 method and the results showed ECAq increased coronary blood flow. It was observed that, Intraperitoneally administrated at dose of 200 mg/kg of ECAq, the increase of coronary blood flow was 8.4%; at 400 mg/kg, 11.9% and at 800 mg/kg, 15%. Tested with the method of Krawkow-Pissemiski, ECAq showed a dilation of rabbit ear vessels and a 22% increase in outflow and recovered within 6 min after administration of ECAq 100 mg. Saline saturated rats were employed to study the diuretic effects of ECAq. The result indicated that diuretic action of ECAq was mainly in the increase of urine flow, without change its electrolyte concentration and pH of urine flows within 30 min of ECAq (400 mg/kg) i.v. injection.

INTRODUCTION

Eucommiae Cortex is an ancient Chinese medicine and prescribed in treatment of the liver, renal and puerperal diseases and excessive perspirations[1,2,3]. Previous reports have suggested that[4,5,6]. Eucommiae Cortex can decrease the force of cardiac contraction and blood pressure, to dilate blood vessel and to relax smooth muscle. But, there is little information is available about the Eucommiae Cortex effect over renal functions. In the present study, the effects of Eucommiae Cortex on cardiovascular respiratory systems and diuretic action will be evaluated to explore the pharmacological nature of the ingredients.

METHODS

(1) Extraction of Eucommiae Cortex

The cortex of Eucommia ulmoides Oliver (Eucommiaceae) (Tu-Chung) was

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collected from the Chinese drug's market in Taipei and extracted with water. The extracted solution was concentrated under 40°C by vaccum and freezing dryer. The dry aqueous extraction dissolved in saline solution to the required concentration and adjusted to correct pH for experiment.

(2) Effect on blood pressure (BP), mean blood pressure (MBP), heart rate (HR) and respiration

Female Wistar rats weighing about 200 g were anesthetized by i.p. injection of sodium pentobarbital (40 mg/kg). The trachea was cannulated and the femoral artery was catheterized. The arterial pressure monitored with a Gould P23ID transducer, the heart rate was monitored with a Gould Biotach amplifier and the respiration was monitored with a Gould PM15ETC transducer. All recording were performed with a four-channel Gould 2400S polygraph. The ECAq was intraperitoneally administrated at a volume of 2ml/kg.

(3) Saline saturated method for determing diuretic action[7,8]

Female Wistar rats weighing about 200 g were anesthetized by i.p. injection of sodium pentobarbital (40 mg/kg). The ureter and vena femoralis were cannulated with a polyethylene tube (PE-50) and standard saline was injected into the rats through vena femoralis at the rate of 10 ml/hr, and within 2-3 hrs the urine flows were stabilized. The urine flows were collected for every 30 min and the concentration of sodium, potassium and chloride and pH of urine flows were examined. The pH was measured by digital pH meter HM-105, sodium and potassium by flame meter FLM-3 and chloride by $HgNO_3$

Table 1. Effects of Aqueous Extract of Eucommiae Cortex (ECAq) on Urinary Volume and Electrolyte Excretion in Saline Saturated Rats

		ECAq (400 mg/kg i.v.) ↓			
Time course (min)	-30 - 0	0 - 30	30 - 60	60 - 90	90 - 120
Saline					
Urine volume (ml/30 min)	4.58±0.21	4.90±0.25	5.16±0.28	5.09±0.26	5.11±0.25
Na output (μ mol/min)	23.52±1.34	29.44±3.02	27.32±1.50	28.62±1.40	30.11±1.34
K output (μmol/min)	2.97±0.21	3.07±0.22	2.91±0.14	3.00±0.15	3.16±0.32
Cl output (μ mol/min)	25.73±2.36	28.75±1.76	30.31±4.68	32.78±5.18	36.43±2.01
pH	6.20±1.19	6.13±1.21	–	–	–
ECAq (400 mg/kg i.p.)					
Urine volume (ml/30 min)	4.40±0.21	6.52±0.28**	5.58±0.31	5.19±0.28	5.12±0.33
Na output (μ mol/min)	23.50±1.49	29.35±2.39	27.29±2.39	24.01±3.04	27.39±1.91
K output (μ mol/min)	3.13±0.14	3.42±0.23	2.98±0.18	2.92±0.52	2.89±0.19
Cl output (μ mol/min)	25.49±1.50	31.94±2.11	29.02±2.70	28.52±2.01	29.57±1.37
pH	6.17±1.07	6.09±1.15	–	–	–

Results are given as Mean ± S.E. obtained from 10 animals.
t-test; significant differences from control are marked: ** ($P<0.01$)

titration method. The ECAq was intravenously administrated at a volume of 2 ml/kg.

(4) Effect on peripheral vessels[9]

Rabbit ear vessels were perfused with Locke-Ringer solution (pH 7.3) by the method of Krawkow-Pissemski. Solution of ECAq was injected into the arterial perfusion cannula at the rate of 0.1 ml per 10 sec, and the total amount given was 0.3 ml.

(5) Effect on coronary blood flow[10,11]

The amount of coronary blood flow was measured by T-1824 method. Male Wistar rats weighing about 200 g were used. 30 min after dosing with 200, 400 and 800 mg/kg (i.p.) of ECAq, exact amount of Evan's blue (50 mg/kg) was injected into the tail vein of rats. 5 min after the injection, the animals were decapitated and the heart were removed, opened, washed well, cut into small pieces and homogenized with 10 ml solution containing 1% sodium laurysulfate and 80% acetone. The homogenates were centrifuged at 3000 r.p.m. for 5 min. The dye concentration in the supernatant was measured at 620 mμ with a Beckman DU spectrophotometer. The 100% used as the amount of coronary blood flow of the control rat and all of the other obtained expressed as per cent of the control.

RESULTS

(1) Effect on blood pressure, mean blood pressure, heart rate and respiration

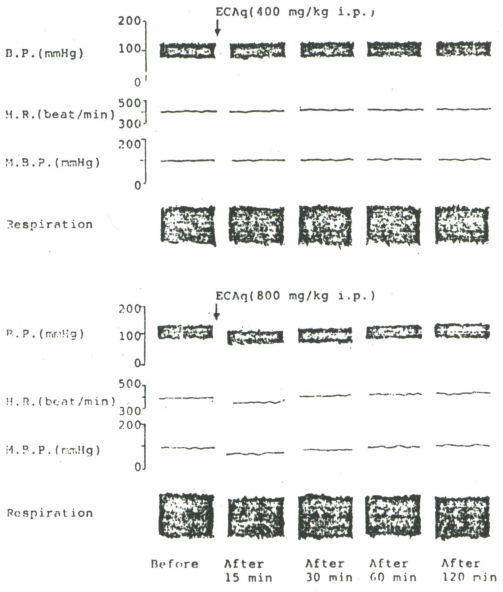

Fig. 1. Effect of aqueous extract of Eucommiae Cortex (ECAq) on blood pressure (B.P.), mean blood pressure (M.B.P.), heart rate (H.R.) and respiration in anesthetized rats (pentobarbital sod. i.p.).

As Fig. 1. indicated. With a dose of 400 mg/kg (i.p.) ECAq did not produce significant change on blood pressure, mean blood pressure, heart rate and respiration. But at a dose higher than 800 mg/kg (i.p.), ECAq showed a decrease in blood pressure, mean blood pressure and heart rate.

(2) Effect on urinary volume and electrolyte excretion in saline saturated rats

As Table 1. indicated. With i.v. administration of 400 mg/kg of ECAq the urine outflow volume was increased almost 33% within 30 minutes after administration but it did not produce marked effects on sodium, potassium and chloride output and pH of urine flows.

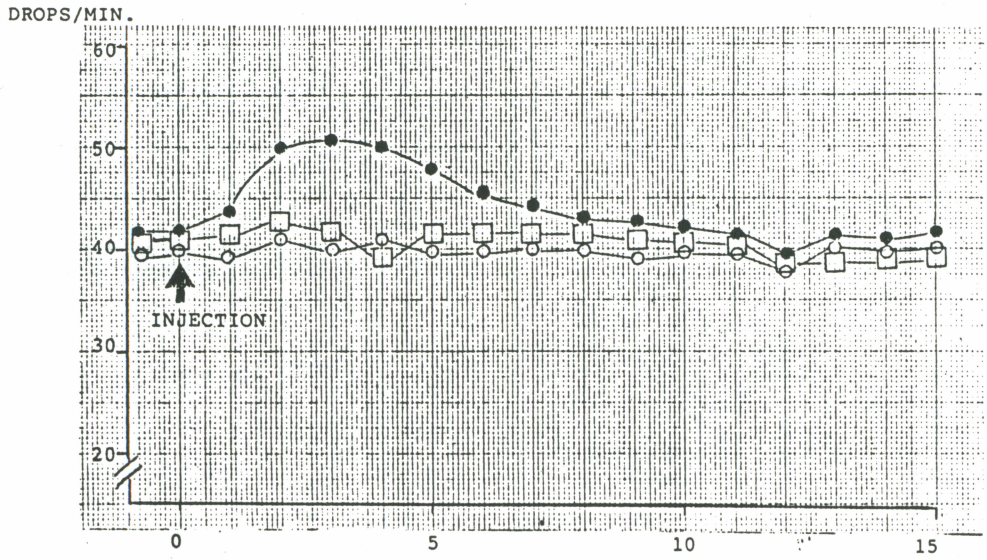

Fig. 2. Effect of aqueous extract of Eucommiae Cortex (ECAq) on the isolated rabbit ear vessels (average of 3 experiments)
●—●: ECAq 100mg
□—□: ECAq 40mg
○—○: Locke-Ringer solution

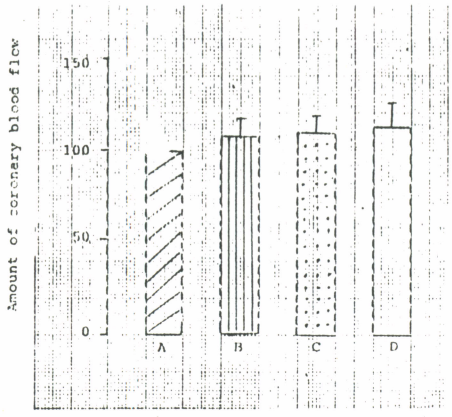

Fig. 3. The amount of coronary blood flow in rat 35 min after administration of 200, 400 or 800mg/kg (i.p.) of ECAq (n=6)
A: Control (As 100%).
B: ECAq 200mg/kg i.p.
C: ECAq 400mg/kg i.p.
D: ECAq 800mg/kg i.p.
B.C.D. expressed as per cent of the control.

(3) Effect of ECAq on peripheral vessel

Influence of ECAq on perfusion of the rabbit ear vessels with recording count of drops by Krawkow-Pissemisk's method. At a dose of 40 mg ECAq had no distinct effect on the outflow in the rabbit ear preparation but at dose of 100 mg, ECAq showed a dilatation of vessels and a 22% maximal increase in outflow and recovered within 6 min after administration as shown in Fig. 2.

(4) Effect of ECAq on coronary blood flow

As Fig. 3 shown, ECAq, with a intraperitoneally injected, caused an increase in the amount of coronary blood flow in rats. It was observed that, at a dose of 200 mg/kg of ECAq, the increase of coronary blood flow was 8.4%; at 400 mg/kg, 11.9% and at 800 mg/kg, 15%.

DISCUSSION

The present results showed that with a high dose of ECAq (800 mg/kg i.p.) can cause a decrease in BP, MBP and HR of the

anesthetized rats, but, there were little effect on these physiological parameters at a dose of 400 mg/kg (i.p.). ECAq also dilated the peripheral vessels and coronary vessels according to experimental results. The key to regulate cardiovascular function lies in the reciprocal relationships between vagal tone and sympathetic efferent activity. The changes induced by ECAq may be attributed to enhance the vagus tone and/or to attenuate the sympathetic activity which leads to decrease vascular tone, BP, MBP and HR. Further experiments are needed to assess the possible mechanism by which Eucommiae Cortex modifies cardiovascular function in rats.

Most diuretics generally work by inhibiting solute reabsorption by the renal tubular epithelial cells; since solute and water transport are intimately linked, the inhibition of solute reabsorption constrains osmotic water reabsorption, and diuresis ensures. The so-called osmotic diuretics, represented by mannitol, are impermeant solutes and hence act by inhibiting passive water reabsorption. In order to evaluate the diuretic effect of ECAq, urine samples are tested for their pH, sodium, potassium and chloride ion content and from this information and the rate of production of urine, it is possible to calculate the rates of excretion of sodium, potassium and chloride ions. Since different diuretics work on different segments of renal tubules with different mechanism of actions, the urination activities such as urinary excretion of salt and water, urine flow rate and pH can provide the informations regarding the different nature and site of their renal actions of diuretics. As shown in results, ECAq caused a 33% increase in the urine outflow volume but exert no effect over electrolytes output and pH of urine flows within 30 minutes after the administration of 400 mg/kg (i.v.) in saline saturated rats. There were reports indicated potassium contained in ECAq may play a role in the diuretic action of ECAq, but in our preliminary studies indicated that saline saturated rats received same amount of potassium contained in the ECAq, did not cause the same diuretic action shown in ECAq administration. Compared the diuretic nature of ECAq to the well established diuretics, i.e., osmotic diuretics, organomercurial diuretics, carbonic anhydrase inhibitors, loop diuretics and potassium-sparing agents[7,12,13,14,15,16], it is unlikely ECAq acts on segments of renal tubule to induce diuresis. Since the electrolytes output, osmolarity and pH being rather stable after ECAq administration, the diuretic nature of ECAq may be caused by increase of glomerular filtration rate (GFR) and then increase urine outflow. Furthermore, the experimental data indicated ECAq caused vasodilation effectively, it may also induced vasodilation of renal vessels to increase renal blood flow and rise the GFR. Direct evidence for the conclusion required further investigation.

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杜仲的利尿作用及其對心臟血管之影響

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本實驗之主要目的，係探討杜仲水抽物的利尿作用，及其對心臟血管之影響。

(A)杜仲水抽物在劑量高於 800 mg/kg，由腹腔注射時，有降低血壓、平均血壓，及抑制心跳等作用。

(B)以膀胱導尿法來探討杜仲水抽物的利尿作用；杜仲水抽物以400 mg/kg的劑量，由靜脈投予於 Saline Saturated 的大白鼠，則大白鼠於杜仲水抽物投予後 30 分鐘內，呈現有意義地增加尿量，但尿中鈉、鉀、氯等電解質的排泄濃度，及 pH 值，並無明顯改變的現象。

(C)以色素稀釋法（T-1824），來檢測杜仲水抽物對冠狀血管血流量之作用；杜仲水抽物由腹腔投與後 35 分鐘，在劑量爲 200 mg/kg 時，可增加冠狀血管血流量 8.4 %，在劑量 400 mg/kg 時，增加 11.9 %，在劑量 800 mg/kg時，增加 15.0 %。

(D)利用Krawkow-Pissemski 的方法，以離體兎耳來檢測，杜仲水抽物對末稍血管的作用；杜仲水抽物 100 mg，可有效地擴張末稍血管，而使灌流液流出量，約增加 22 %。

台北醫學院生理學科

民國七十四年十二月九日受理