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Hypotensive effect of tenuifolic saponin and its mechanism

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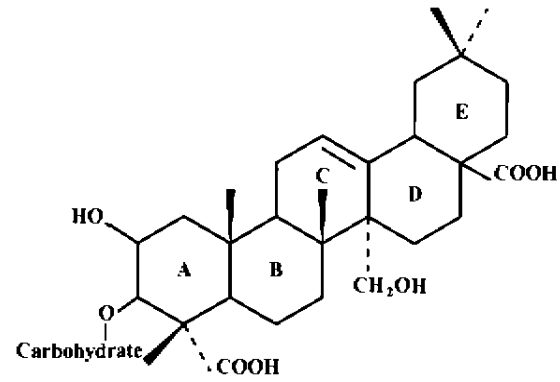
KEY WORDS tenuifolic saponin; blood pressure; renovascular hypertension; diphenhydramine; atropine; epinephrine

ABSTRACT

AIM: To study the effect of tenuifolic saponin (TS) on arterial pressure. **METHODS**: Mean arterial pressure (MAP) was recorded from left carotid artery in rat which was anesthetized with urethane and then injected iv gtt with a transfusion of NaCl 0.15 mol·L^{-1}. Systolic blood pressure (SBP) of conscious rat and renovascular hypertensive rat (RVHR) was measured by tail cuff method. **RESULTS**: TS 2, 4, 8 mg·kg^{-1} iv, 20 and 40 mg·kg^{-1} ig reduced the MAP by 31 %, 37 %, 50 %, 21 %, and 31 %, respectively. Bilateral vagotomy plus atropine (Atr) iv, or pretreatment with diphenhydramine hydrochloride (Dip) failed to influence TS effect. Lack of effect of TS on carotid-occlusion-induced- or epinephrine (Epi)-induced-hypertensive response was found. SBP in conscious rat and RVHR was suppressed, highest by 38.0 % and 26.8 % at 60 and 90 min, maintaining at least 2 and 3 h, respectively, after ig TS 40 mg·kg^{-1}. **CONCLUSION**: TS reduced the arterial pressure, not related to vagus excitation, ganglionic blockade, and peripheral α-adrenergic-, M-cholinergic-, and H_1-receptors.

INTRODUCTION

Tenuifolic saponin (TS, yellow powder, M_r 1304, mp 254-256 ℃) was isolated from *Polygala tenuifolia* Willd which is a Chinese traditional plant medicine for the treatment of insomnia, amnesia, and convulsion[1]. It was similar to the known saponin A-G of *Polygala tenuifolia* Willd in structure with the same sapogenin (presenegenin) and the different desmosides[2]. TS was a monodesmoside saponin but saponin A-G contained two desmosides. This monodesmoside, existing at C_3 of A ring, included glucose, *D*-arabinose, *D*-xylose, and *D*-rhamnose, while the connection among them was not defined. The present study was carried out to further study the effect of TS on blood pressure.



Tenuifolic saponin

MATERIALS AND METHODS

TS, spectrum pure, isolated by the Department of Chemistry, Sun Yat-Sen University, was dissolved in NaCl 0.15 mol·L^{-1} solution (pH 7.0). Histamine phosphate (His, National Institute for the Control of Pharmaceutical and Biological Products, Beijing). Diphenhydramine hydrochloride (Dip, Guangzhou Mingxing Pharmaceutical Factory, China). Atropine sulfate (Atr, Guangzhou Qiaoguang Pharmaceutical Factory, China). Epinephrine hydrochloride (Epi, Shanghai Tianfeng Pharmaceutical Factory, China). Acetylcholine chloride (ACh, Fluka, Switzerland).

Sprague Dawley rats weighing 250 g ± *s* 10 g of either sex, obtained from the Guangdong Experimental

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Animal Centre (Grade Ⅱ, Certificate № 96A02), bred in our laboratory, were anesthetized with ip urethane 1.0 g·kg^{-1}. NaCl 0.15 mol·L^{-1} solution was transfused iv gtt into the saphenous vein at 0.3 mL·kg^{-1}·min^{-1} during the whole experiment. Blood pressure, through a YL-2 pressure transducer in the left carotid artery, was measured in LMS-2B recorder. One-third of systolic pressure plus two-thirds of diastolic pressure was calculated as mean arterial pressure (MAP). The volume of drug injection was 0.6 mL·kg^{-1}. NaCl 0.15 mol·L^{-1} was used as control. Anesthetized rats underwent: 1) Receptor antagonist was given iv 15 min before TS. 2) Right carotid occlusion or iv Epi was injected immediately after the maximal response of MAP to TS. 3) The inter-injection interval was 2 min.

Systolic blood pressure (SBP) of conscious rat and renovascular hypertensive rat (RVHR) which was prepared by the method[3] was measured by tail cuff method using a MRS-Ⅲ recorder. The reported data were presented as $x \pm s$. Significant difference between groups was made by paired t test.

RESULTS

Acute toxicity Mice (n = 10) did not die within 7 d after TS 0.5 g·kg^{-1} iv or 2.0 g·kg^{-1} ig.

MAP and SBP Rat MAP was dose-dependently decreased by 31 %, 37 %, and 50 % after TS 2, 4, and 8 mg·kg^{-1} iv, respectively, and recovered quickly; TS 20 and 40 mg·kg^{-1} ig also reduced the MAP, highest by 21 % and 31 % at (22 ± 9) min after TS, respectively, lasting 40 – 60 min. Rat MAP was still lower, but not obvious 3 h after TS ig than that before TS. The effect of TS on systolic pressure was more significant than that on diastolic pressure. No marked change in MAP was observed when rat was dosed with NaCl 0.9 mol·L^{-1}. TS 40 mg·kg^{-1} ig suppressed the SBP of normal rat and RVHR, highest by 38.0 % and 26.8 % at 60 and 90 min, lasting at least 2 and 3 h, respectively (Tab 1).

Dip, or bilateral vagotomy plus Atr-pretreatment on TS effect Pretreatment of Dip 4 mg·kg^{-1} iv abolished the decrease in MAP induced by His 4 mg·kg^{-1} iv, but failed to influence hypotensive effect of TS; Bilateral vagotomy plus Atr 1 mg·kg^{-1} iv did not block the hypotensive response to either TS iv or TS ig (Tab 2).

Tab 1. Hypotensive effects of TS. $x \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* 0 min.

Time/min	Blood pressure/kPa			
	Mean arterial pressure (Anesthetized rats)			
iv mg·kg^{-1}	2	4	8	
n	13	13	12	
0	12.4 ± 1.2	12.8 ± 1.5	13.1 ± 2.0	
0.25	10.5 ± 1.6^b	10.0 ± 1.8^c	8.6 ± 1.4^c	
0.5	8.5 ± 1.5^c	8.1 ± 1.7^c	6.6 ± 1.3^c	
0.75	8.9 ± 1.4^c	8.3 ± 1.5^c	6.6 ± 1.0^c	
1.0	10.1 ± 1.6^b	9.7 ± 1.7^b	6.7 ± 1.5^c	
1.5	11.0 ± 2.0^a	11.1 ± 1.4^b	8.3 ± 1.8^c	
2.0	12.2 ± 1.7^a	13.0 ± 2.4^a	11.6 ± 2.1^a	
3.0	12.2 ± 1.5^a	12.8 ± 1.9^a	14.0 ± 3.5^a	
4.0			13.4 ± 2.6^a	

	Mean arterial pressure (Anesthetized rats)		Systolic blood pressure (Normal rats)	(RVHR)
ig mg·kg^{-1}	20	40	40	40
n	13	11	10	8
0	12.8 ± 1.9	13.2 ± 2.4	14.2 ± 1.7	24.6 ± 3.5
10	12.6 ± 1.8^a	12.9 ± 2.0^a		
20	11.8 ± 2.2^a	11.5 ± 1.9^b		
30	9.9 ± 1.6^c	9.9 ± 1.7^c	12.0 ± 1.5^b	20.6 ± 3.5^b
40	10.9 ± 1.7^b	8.9 ± 1.5^c		
50	11.8 ± 1.7^a	10.5 ± 1.5^c		
60	12.3 ± 2.4^a	11.3 ± 1.8^b	8.8 ± 1.5^c	18.8 ± 3.0^c
90	12.3 ± 2.1^a	12.0 ± 2.6^a	9.2 ± 1.6^c	18.0 ± 2.4^c
120	12.1 ± 1.5^a	11.8 ± 2.2^a	11.7 ± 2.0^b	18.2 ± 2.7^c
150			13.5 ± 1.8^a	19.5 ± 3.7^c
180	12.2 ± 1.5^a	12.1 ± 1.8^a		20.1 ± 2.8^b
240			14.0 ± 1.5^a	22.4 ± 2.7^a
360			14.6 ± 2.1^a	24.6 ± 4.1^a

Effect of TS on carotid-occlusion- or Epi-induced pressor reflex There was little difference in the change of MAP induced by right carotid occlusion or Epi between normal and TS-treated rat (Tab 3).

Tachyphylaxis of TS on MAP The first administration of TS 2, 4, and 8 mg·kg^{-1} iv reduced the MAP by 33.5 %, 34.1 %, and 51.1 %, respectively. The second and the third administration of TS also produced such actions, with a higher potency at 2 and 4 mg·kg^{-1}, but a weakened potency at 8 mg·kg^{-1}. (Tab 4)

Tab 2. Effects of TS and histamine (His) 4 mg·kg^{-1} on MAP of anesthetized rats before and after pretreatment with bilateral vagotomy (BVt) plus atropine (Atr) 1 mg·kg^{-1} iv or with diphenhydramine (Dip) 4 mg·kg^{-1} iv. $n = 10$ rats. $\bar{x} \pm s$. $^aP > 0.05$, $^cP < 0.01$ *vs* Normal. $^dP > 0.05$ *vs* TS iv. $^gP > 0.05$ *vs* TS ig. $^lP < 0.01$ *vs* His.

	TS/ mg·kg^{-1}	MAP/kPa Normal	MAP/kPa Medication	Change/kPa
TS	4 iv	12.6±2.4	8.0±2.3^c	4.6±1.1
	20 ig	12.0±2.7	9.4±2.5^c	2.6±0.6
His		12.0±2.8	8.4±3.0^c	3.6±1.0
Dip + TS	4 iv	12.2±3.2	7.6±2.5^c	4.6±1.3^d
	20 ig	11.6±2.3	9.0±2.1^c	2.7±0.5^g
Dip + His		12.6±3.5	12.3±4.2^a	0.3±0.1^l
BVt + Atr + TS	4 iv	13.1±1.8	8.3±1.6^c	4.8±0.7^d
	20 ig	12.3±2.1	9.7±2.1^c	2.8±0.5^g

Tab 3. Hypertensive effect of carotid occlusion (CO) or epinephrine (Epi) 2 mg·kg^{-1} iv before (A) and after the anesthetized rats were dosed with TS 8 mg·kg^{-1} iv (B) or 40 mg·kg^{-1} ig (C). $n = 9$ rats. $\bar{x} \pm s$. $^aP > 0.05$ *vs* A.

Treatment		MAP/kPa Normal	MAP/kPa Treatment	Change/kPa
CO	A	11.6±2.3	14.9±4.8	3.3±0.9
	B	6.4±1.8	9.5±3.7	3.1±1.2^a
	C	8.3±2.6	11.4±4.2	3.1±1.4^a
Epi	A	12.7±2.3	17.0±3.5	4.3±1.0
	B	8.1±1.4	12.1±2.7	4.0±1.2^a
	C	8.7±1.9	12.9±3.3	4.2±1.5^a

DISCUSSION

Present study demonstrated that TS decreased all the blood pressure in normal, anesthetized, and hypertensive rats. The lasted time of this action on RVHR was 1.5 times as much as that on normal rat, although the hypotensive intensity in former was smaller than that in later, indicating that TS may be used as an oral antihypertensive drug, unlike saponin A – G.

TS effect in anesthetized rat was not affected by bilateral vagotomy plus administration of Atr, which revealed that it was not related to peripheral M-receptor and the activation of vagus. In addition, the effector of carotid-occlusion-pressor reflex is generally believed

Tab 4. Effects of 3-repeated administrations of TS iv within 4 min on anesthetized rat MAP. $n = 11$ rats. $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* First of the same dose.

Dose/ mg·kg^{-1}	iv	MAP/kPa Normal	MAP/kPa Medication	Change/kPa
2	First	12.6±2.1	8.6±1.6	4.0±0.7
	Second	12.8±2.4	8.5±1.8	4.3±0.8^a
	Third	12.6±2.0	8.2±2.0	4.4±0.8^a
4	First	12.8±2.0	8.4±2.1	4.4±0.8
	Second	12.6±1.8	7.4±1.9	5.2±1.1^a
	Third	12.2±1.7	6.5±1.7	5.7±1.1^c
8	First	12.9±2.3	6.2±1.5	6.7±1.4
	Second	13.0±2.7	6.9±1.5	6.1±1.2^a
	Third	12.5±2.2	7.7±1.9	4.8±1.0^b

to be sympathetic nerve existing in the autonomic nervous system. Either ganglionic- or sympathetic adrenergic-receptor blocker inhibited this reflex[4]. According to the result that TS did not influence this reflex and also did not block α-receptor, it was not quite possible for TS to be a ganglionic blocker.

His dilatates the vascle and increases the blood flow so as to reduce the blood pressure[5]. Dip almost abolished this effect but did not change the response of MAP to TS. These facts, together with the lack of effect of TS on Epi-induced pressor reflex which was mainly produced by the stimulation of α-adrenergic receptor[6], showed that TS decreased the MAP by means of neither the release of His nor the blockade of α-receptor.

The response of blood pressure to calcium antagonist in hypertensive rat was more sensitive than that in normal one[7]. TS reduced MAP in normal rat with a higher potency than what it did in RVHR, although the persistent time of the former was shorter than that of the later. This simply suggested that TS effect did not involve calcium blockade.

Small dose of TS possessed a hypotensive effect without tachyphylaxis, different from big dose of TS, like the result observed in nicorandil which decreased the blood pressure mainly by opening potassium channel when its small dose but together by increasing cGMP when its big dose[8]. Potassium opener is effective to inhibit the heart[9]. This inhibition by TS was also found in our other study and present work which

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showed that TS decreased the systolic blood pressure with a more obvious action than diastolic one. It is of value to further investigate whether TS effect is related to potassium channel and cGMP.

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远志皂苷的降压作用及其机制

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关键词 远志皂苷; 血压; 肾性高血压; 苯海拉明; 阿托品; 肾上腺素

目的: 研究远志皂苷(tenuifolic saponin, TS)对血压的影响. **方法**: 大鼠麻醉后左颈总动脉记录平均动脉压(MAP). 尾袖法测定清醒大鼠和肾性高血压大鼠(RVHR)收缩压. **结果**: TS 2, 4, 8 mg·kg^{-1} iv, 20 和 40 mg·kg^{-1} ig 分别使 MAP 降低 31 %, 37 %, 50 %, 21 %和 31 %; 40 mg·kg^{-1} ig 使清醒大鼠和 RVHR 的血压分别于给药后 60 和 90 min 降低 38.0 %和 26.8 %, 并至少维持 2 和 3 h. Dip 或切除双侧颈迷走神经合并 Atr iv 均不影响 TS 的作用; TS 不改变 Epi 或结扎右颈总动脉所引起的升压反射. **结论**: TS 有降压作用, 此作用与迷走神经兴奋、神经节阻断、以及外周 α-肾上腺能, M-胆碱能和 H_1 受体无关.

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