Antagonistic effects of 3 sesquiterpene lactones from *Atractylodes macrocephala* Koidz on rat uterine contraction *in vitro*

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KEY WORDS *Atractylodes macrocephala*; parasympatholytics; uterine contraction; acetylcholine; verapamil; oxytocin; calcium chloride; potassium chloride; diethylstilbestrol

ABSTRACT

AIM: To study the effects of three sesquiterpene lactones: atractylenolide Ⅰ (8, 9-dehydroasterolide, B), 4,15-epoxy-8β-hydroxyasterolide (C), and atractylenolide Ⅲ (8β-hydroasterolide, D) from *Atractylodes macrocephala* Koidz, on rat isolated uterus smooth muscle. METHODS: Rat isolated uteri bathed in De Jalon Ⅰ solution were used; acetylcholine (ACh), $CaCl_2$, and oxytocin (Oxy) were used to evoke the contraction of uterus. RESULTS: B, C, and D 28 or 56 $\mu mol \cdot L^{-1}$ inhibited the spontaneous movement of uterus, reducing their rest force, contractile force, and movement ability. B 28 or 56 $\mu mol \cdot L^{-1}$ also slowed down the frequency of uterus spontaneous contraction, but C or D did not. B, C, or D 28 and 56 $\mu mol \cdot L^{-1}$ inhibited the uterine spasm induced by Oxy and ACh. Likewise, Ver 0.28 $\mu mol \cdot L^{-1}$, B, C, and D 28 or 56 $\mu mol \cdot L^{-1}$ relieved the contraction mediated by $CaCl_2$ in high-KCl solution, but B, C, or D had not marked influence on the maximal response of uterus to $CaCl_2$. CONCLUSION: B, C, and D inhibit the movement of uterus smooth muscle, and the mechanism is related to the inhibition of cholinergic system as well as Ca^{2+} movement.

INTRODUCTION

The rhizome of *Atractylodes macrocephala* Koidz is known as a tonic herb, a nutrient for the vital energy, stomachic, and digestive disorder[1]. It is also used to release the quickening of womb and prevent abortion in traditional Chinese medicine[2]. Many researches about this herb or its constituents demonstrated the perfect effects on gastrointestinal movement[3-7]. We have extracted several novel compounds from *Atractylodes macrocephala*[7] and found their inhibitory effects on gastrointestinal movement.

The uteri of rat, guinea pig, and human are widely controlled by cholinergic nerve with M_2 receptors as a major regulator[8-10]. In guinea pig ileum, acetylcholine increases an inward cation current, inducing an action potential discharge[11]. M_2 and M_4 receptors directly activate the G protein to K^+ channel to open the K^+ and Ca^{2+} channels, evoking an inward calcium current[12]. The increase in $[Ca^{2+}]_i$ is mainly due to opening of L-type Ca^{2+} channel, and partly due to Ca^{2+} release and Ca^{2+} influx through nonselective cation channel, and Ca^{2+}-release activates Ca^{2+} influx pathway (CRAC), as well as the reverse mode of the Na^+-Ca^{2+} exchanger. Calcium released from the sarcoplasma reticulum (SR) also increases $[Ca^{2+}]_i$. The inhibitory effects of relaxants on the smooth muscle are realized via this proceeding: the relaxants block the binding of transmitter to the related receptors, or the relaxants reduce $[Ca^{2+}]_i$. Compared with the L-type Ca^{2+} channel blockers, the SR-inhibiting relaxants present poor antagonistic effects on the contraction e-

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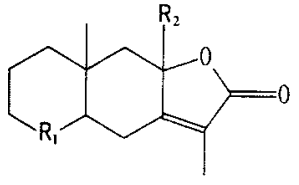
voked by high potassium or receptor agonists, suggesting that Ca^{2+} in SR does not play a crucial role in the contraction[13].

Since the smooth muscles of intestine and uteri have the similar mechanism of contraction, and few work has been done to illustrate the influences of *Atractylodes macrocephala* on uterus, we studied the effects of 3 sesquiterpene lactones from this herb on rat isolated uterus (RIU).



R_1	R_2	
$=CH_2$	-H	Atractylenolide I (B)
-4,15-epoxy	-OH	4,15-Epoxy-8 β -hydroasterolide(C)
$=CH_2$	-H	Atractylenolide III (8 β -hydroasterolide, D)

MATERIALS AND METHODS

Drugs B, C, and D were extracted and purified from the dry root of *Atractylodes macrocephala* bought from Guangzhou Medicine Co. All the sesquiterpene lactones were in spectrum-purity with mp 123 ℃, 164 ℃, and 198 ℃. C is a new sesquiterpene lactone. ACh was a product of Sigma Co (lot № 23H0078). Verapamil (Ver) was purchased from Jiangsu Lianyun Port Pharmaceutical Factory (lot № 971104). Atropini sulfatis (Atr) was from Guangdong Jiangmen Pharmaceutical Factory (lot № 970606). Diethylstilbestrol was produced by Guangzhou Mingxing Pharmaceutical Factory (lot № 961210-1). Injectio Oxytocini (Oxy), a product of Shanghai Biochemical Pharmaceutics Factory (lot № 970905). Tetrandrine (Tet) was from Zhejiang Jinhua Pharmaceutics (lot № 960819). B, C, and D were firstly solved in Me_2SO with TW-80 as the solubilizer, and diluted with normal saline to the needed concentrations when used. The final concentration of Me_2SO was <0.1 % and TW-80 <0.2 %. Other drugs were dissolved in normal saline.

Rats Sprague-Dawley rats ♀, weighing 200 −250 g were supplied by Guangdong Medical Experimental Animal Center (Certificate № 97A017, grade Ⅱ).

Measurement of spontaneous movement of rat isolated uteri (RIU) Two days before the experiments, diethylstilbestrol 0.1 mg·kg^{-1} was sc injected to rats once a day to sensitize the uterus. The uteri were prepared and put into De Jalon Ⅰ solution aerated with 95 % O_2 + 5 % CO_2 at 37 ℃[14]. A g force was given as the basic physiological burden. After the tissue contracted frequently, which could be recorded with physiologic recorder (LBS-2B), B, C, D, Ver, and their solvent were dropped in. After 10 min, the changes of the spontaneous movement of uteri were recorded. The data recorded included: rest force, contractile force, and frequency per min.

Contraction induced by Oxy and ACh RIU were pretreated with B, C, D, Tet, and their solvent in De Jalon Ⅰ solution for 10 min and then stimulated with Oxy or ACh.

Contraction induced by $CaCl_2$ RIU were bathed in De Jalon Ⅰ solution without calcium for 30 min before they were transferred into the non-calcium De Jalon Ⅰ solution with potassium 100 mmol·L^{-1} in which concentration the uteri were depolarized. Ten min later, $CaCl_2$ in final concentration of 50, 100, 200, 500, and 1000 μmol·L^{-1} was added into the solution, so that the uteri would contract and the dose-response curves could be drawn.

Contraction of RIU in Oxy 1 U·L^{-1} solution without or with $CaCl_2$ 1 μmol·L^{-1}[15] The uterus samples were bathed in De Jalon Ⅰ solution at 32 ℃ for equibrillum, then the solution was replaced with non-calcium De Jalon Ⅰ solution with KCl 100 mmol·L^{-1} and the tissues were bathed for 0.5 h, and after that, Oxy 1 U·L^{-1} was added. When the uteri contracted and reached the platform, $CaCl_2$ 1 μmol·L^{-1} was added to stimulate another contraction of uteri. The stimulated uteri were washed with normal De Jalon Ⅰ Solution to recover. After the samples retrieved, B, C, D, Ver, and their solvent were applied to pretreat the uteri for 10 min before another activation of these tissues.

RESULTS

Effects of B, C, D, and Ver on spontaneous movement of RIU B, C, D 28 or 56 μmol·L^{-1}, and Ver 0.28 μmol·L^{-1} inhibited the spontaneous movement of uteri *in vitro*. B, C, D 56 μmol·L^{-1} and Ver 0.28 μmol·L^{-1} reduced the rest and contractile force as well as movement ability markedly. B 28 or 56 μmol·L^{-1} and Ver 0.28 μmol·L^{-1} also slowed down the frequency

of the spontaneous movement of uterus ($P<0.01$), while C or D could not ($P>0.05$) (Tab 1).

Effects on Oxy- and ACh-induced contraction B, C, D, and Tet inhibited the response of uterus to Oxy and ACh, with the dose-response curves shifted to the right (Tab 2, 3). The antagonistic indices pD'_2 of B, C, D 28 and 56 $\mu mol \cdot L^{-1}$ to Oxy were 3.854, 3.546, and 3.731, and 3.870, 3.606, and 3.808, respectively. And the pD'_2 of Tet 100 $\mu mol \cdot L^{-1}$ to Oxy was 3.842.

The antagonistic indices pD_2 of B, C, D 28 and 56 $\mu mol \cdot L^{-1}$ to ACh were 4.197, 3.985, and 4.031, and 4.052, 3.818, and 3.976, respectively.

Effects of B, C, and D on contraction induced by $CaCl_2$ in rat uterus *in vitro* Compared with the control group, B, C, D, and Ver inhibited the contraction induced by Ca^{2+} in K^+-depolarized RIU. Except Ver, a calcium channel blocker, B, C, or D, did not markedly reduce the maximal response induced by addition of $CaCl_2$ 1 $mmol \cdot L^{-1}$. The effects of B, C, and D were obviously dose-dependent (Tab 4).

Effects of B, C, and D on Ca^{2+}-related contraction of uteri After RIU were pretreated with B 28 or 56 $\mu mol \cdot L^{-1}$, C, D 56 $\mu mol \cdot L^{-1}$, or Ver 0.28 $\mu mol \cdot L^{-1}$, Oxy (1 $U \cdot L^{-1}$)-evoked contraction was inhibited (Tab 5). In the control group, the uterus contracted again when $CaCl_2$ 1 $\mu mol \cdot L^{-1}$ was added into the solution after the Oxy-induced contraction reached the platform. Ver obviously inhibited this contraction but B, C, or D did not. The order of inhibitory rate was: B>D>C.

Tab 1. Influences of B, C, D, and Ver on the spontaneous movement of rat isolated uteri. $n=5$ strips from 3 rats. $\bar{x} \pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* control.

Group	Concentration/ $\mu mol \cdot L^{-1}$	Rest force/g	Contractile force/g	Frequency per min	Ability/ $g \cdot min^{-1}$
Control	–	1.02±0.05	2.3±0.3	0.97±0.06	2.3±0.4
Solvent	–	0.99±0.07[a]	2.26±0.28[a]	0.97±0.07[a]	2.17±0.21[a]
B	28	0.94±0.10[a]	1.8±0.4[b]	0.87±0.02[c]	1.47±0.16[c]
	56	0.83±0.07[c]	1.4±0.4[c]	0.82±0.07[c]	1.19±0.20[c]
C	28	0.95±0.13[a]	1.92±0.28[a]	0.97±0.06[a]	1.86±0.19[a]
	56	0.91±0.09[b]	1.8±0.3[b]	0.88±0.10[a]	1.61±0.28[b]
D	28	0.95±0.21[a]	1.90±0.14[b]	0.90±0.11[a]	1.71±0.24[b]
	56	0.88±0.09[b]	1.65±0.29[c]	0.87±0.09[a]	1.43±0.27[c]
Ver	0.28	0.62±0.10[c]	0.84±0.11[c]	0.50±0.09[c]	0.43±0.08[c]

Tab 2. Influences of B, C, D, and Tet on Oxy-evoked contraction of rat uteri *in vitro*. $n=5$ strips from 3 rats. $\bar{x} \pm s$ (g). $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* control.

Group	Concentration/ $\mu mol \cdot L^{-1}$	Oxy/ $U \cdot L^{-1}$ 0.1	0.5	1.0	2.0	5.0	10.0	20.0
Control	–	0.71±0.17	7.7±0.5	10.31±1.18	11.6±1.4	13.7±1.3	14.6±2.4	15.6±1.1
B	28	0.47±0.09[a]	5.6±0.7[c]	7.0±0.6[c]	8.4±0.8[c]	10.4±1.8[b]	11.0±1.3[b]	13.0±2.2[b]
	56	0.31±0.03[c]	3.54±0.19[c]	4.2±0.4[c]	7.4±0.5[c]	8.7±0.7[c]	10.4±1.2[c]	11.0±1.8[c]
C	28	0.59±0.08[a]	1.43±0.22[c]	8.5±1.0[b]	9.7±1.0[b]	12.0±1.6[a]	12.2±1.5[a]	14.2±2.5[a]
	56	0.49±0.04[a]	5.4±1.0[c]	7.0±0.6[c]	8.0±1.6[c]	9.5±1.2[c]	11.7±1.6[a]	12.7±1.5[c]
D	28	0.55±0.04[a]	6.2±0.3[c]	8.3±0.7[c]	9.2±1.3[b]	10.6±0.9[c]	11.5±1.3[b]	13.6±1.4[b]
	56	0.41±0.05[c]	4.5±0.4[c]	5.3±0.4[c]	7.8±0.6[c]	9.0±1.1[c]	10.8±0.9[b]	11.5±1.2[c]
Tet	100	0.35±0.08[c]	3.9±0.4[c]	5.1±0.8[c]	7.8±0.3[c]	8.9±0.8[c]	10.5±0.4[c]	11.2±0.9[c]

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Tab 3. Effects of B, C, D, and Atr on dose-response relationship of ACh-induced rat uterus contraction *in vitro*. $n=5$ strips from 3 rats. $\bar{x}\pm s$ (g). $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* control.

Group	Concentration/ μmol·L^{-1}	ACh/ − lg mol·L^{-1} 9.0	8.0	7.0	6.0	5.0
Control	−	1.36±0.20	2.89±0.21	3.36±0.16	3.93±0.24	5.2±0.3
B	28	0^c	0.53±0.09^c	1.38±0.15^c	2.34±0.26^c	3.63±0.17^c
	56	0^c	0^c	0.74±0.12^c	1.87±0.25^c	3.2±0.3^c
C	28	0.39±0.07^c	1.30±0.24^c	1.97±0.27^c	2.99±0.18^c	4.12±0.32^c
	56	0^c	0.79±0.10^c	1.6±0.4^c	2.18±0.22^c	3.83±0.28^c
D	28	0.19±0.03^c	0.91±0.12^c	1.67±0.29^c	2.65±0.17^c	4.03±0.23^c
	56	0^c	0.63±0.13^c	0.94±0.18^c	1.91±0.23^c	3.4±0.3^c
Atr	0.2	0.46±0.17^c	0.91±0.15^c	1.32±0.11^c	2.20±0.15^c	4.66±0.25^b

Tab 4. Effects of B, C, D, and Ver on the contraction induced by addition of $CaCl_2$ on K^+-depolarized rat uteri *in vitro*. $n=5$ strips from 3 rats. $\bar{x}\pm s$ (g). $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* control.

Group	Concentration/ μmol·L^{-1}	$CaCl_2$/μmol·L^{-1} 50	100	200	500	1000
Control	−	0.81±0.15	1.80±0.24	3.8±0.6	5.3±1.4	6.2±1.5
Solvent	−	0.81±0.13^a	1.83±0.10^a	3.6±1.0^a	5.2±1.1^a	6.1±1.2^a
B	28	0.55±0.07^b	1.40±0.28^b	2.80±0.27^a	4.8±1.1^a	5.3±1.3^a
	56	0.30±0.09^c	0.78±0.08^c	1.73±0.12^c	3.2±0.6^b	4.8±0.9^a
C	28	0.70±0.07^a	1.53±0.11^b	3.3±1.0^a	5.0±1.3^a	6.0±1.4^a
	56	0.56±0.05^b	1.42±0.26^b	2.6±0.7^a	3.8±1.0^b	5.8±1.0^a
D	28	0.62±0.09^a	1.51±0.26^a	3.0±0.6^a	5.0±1.2^a	5.5±1.3^a
	56	0.55±0.14^b	1.21±0.09^c	2.4±0.7^b	3.3±0.4^b	4.9±1.1^a
Ver	0.28	0^c	0^c	0.11±0.04^c	0.23±0.09^c	0.34±0.12^c

Tab 5. Effects of B, C, D, and Ver on the two components of Oxy (1 U·L^{-1})-evoked contraction of rat uteri *in vitro* in De Jalon Ⅰ solution with or without $CaCl_2$ **1 μmol·L^{-1}**. n **= 5 strips from 3 rats.** $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ ***vs* control.**

Group	Concentration/ μmol·L^{-1}	Rest force/ g	Contractile force/g Ca^{2+} free	Inhibition/%	$CaCl_2$ 1 μmol·L^{-1}	Inhibition/%
Control	−	1.04±0.03	0.54±0.10	−	4.5±0.9	−
Solvent	−	0.99±0.25^a	0.55±0.08^a	−	4.5±0.8^a	−
B	28	0.82±0.25^a	0.31±0.01^c	42.9	4.0±0.8^a	11.8
	56	0.80±0.20^b	0.16±0.04^c	70.9	3.6±0.8^a	21.4
C	28	0.92±0.24^a	0.48±0.08^a	11.2	4.4±0.8^a	3.3
	56	0.86±0.18^a	0.32±0.09^b	40.5	4.4±0.5^a	3.0
D	28	0.86±0.27^a	0.45±0.08^a	18.5	4.1±0.8^a	9.1
	56	0.80±0.18^b	0.32±0.08^b	41.6	4.4±0.8^a	2.4
Ver	0.28	0.55±0.11^c	0.07±0.02^c	86.7	0.16±0.04^c	96.4

DISCUSSION

It has been reported that the petrol ether extract, alcohol extract, and water extract of *Atractylodes macrocephala* inhibited the spontaneous contraction of uteri *in vivo* and *in vitro* with the lipid-soluble parts as the active constituents[16]. This report demonstrates that sesquiterpene lactones are the active compounds for the effects of *Atractylodes macrocephala* on uterus. In addition, our studies on the inhibitory effects of B, C, and D on rat isolated ileum demonstrated that they inhibited the muscarinic system and antagonized with Ca^{2+} move-

ment. The inhibitory effects of B, C, and D on the $CaCl_2$-induced contraction of rat isolated uteri were not so strong as they acted on ileum which could be estimated by pD'_2. They could obviously inhibit the Ca^{2+}-induced contraction of uterus smooth muscle but not markedly decrease the maximal response. This may be due to the complex mechanisms of the contraction of uterus. In the dose that B, C, and D produced obvious antagonistic effects to ACh, B, the most potent one, partly inhibited the high K^+-induced spasm of rabbit isolated aorta with inhibitory rate of 18.4 %. However, Ver showed inhibition to the Ca^{2+}-evoked contraction of rat isolated ileum, of uterus, and of rabbit isolated aorta. This suggested that Ver blocked the potential-dependent calcium channel (PDC) and the release of Ca^{2+} from the SR of the cell, while B, C, and D inhibited the intracellular Ca^{2+} release only. Moreover, all these three compounds are non-competitive antagonists to ACh.

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三种白术倍半萜烯内酯拮抗大鼠离体子宫收缩

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关键词 白术；抗副交感神经药；子宫收缩；乙酰胆碱；维拉帕米；缩宫素；氯化钙；氯化钾；乙烯雌酚

目的：研究白术内酯Ⅰ（B），4，15-环氧羟基白术内酯（C），白术内酯Ⅲ（D）对子宫平滑肌活动的影响. 方法：离体大鼠子宫模型. 结果：B，C，D 28，56 $\mu mol \cdot L^{-1}$能明显降低子宫平滑肌的静息张力、收缩力和运动能力；抑制由 Oxy、ACh 介导的子宫痉挛 抑制高钾去极化下 $CaCl_2$ 引起的子宫收缩，但对子宫的最大反应没有明显的影响；抑制无 Ca^{2+} 溶液中催产素引起的子宫收缩，但对胞外 Ca^{2+} 的内流没有显著抑制；B 可降低子宫自发运动的发放频率，但 C 和 D 没有显著作用（$P > 0.05$）. 结论：B、C 和 D 可显著地抑制大鼠离体子宫平滑肌运动，其作用与胆碱能系统的抑制及 Ca^{2+} 的运动有关.

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