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World J Gastroenterol 2006 August 28; 12(32): 5214-5218
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Effect of Fructus Psoraleae on motility of gallbladder isolated smooth muscle strips from guinea pigs

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Supported by Key Laboratory of Pre-clinical Study for New Drugs of Gansu Province and the Natural Science Foundation of Gansu Province, No.ZS021-A25-059-Y
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Received: 2006-02-15 Accepted: 2006-05-22

Abstract

AIM: To observe the effect of Fructus Psoraleae on motility of isolated gallbladder muscle strips of guinea pigs and its mechanism.

METHODS: Guinea pigs were hit to lose consciousness and the whole gallbladder was removed quickly. Two or three smooth muscle strips (8 mm × 3 mm) were cut along a longitudinal direction. The mucosa was gently removed. Every longitudinal muscle strip was suspended in a tissue chamber which was continuously perfused with 5 mL Krebs solution (37℃), pH 7.4, and aerated with 950 mL/L O_2 and 50 mL /L CO_2. The isometric response was recorded with an ink-writing recorder. After 2 h equilibration under 1 g-load, 50 μL Fructus Psoraleae (10, 20, 70, 200, 700, 1000 g/L) was added cumulatively into the tissue chamber in turn every 2 min to observe their effects on gallbladder muscle strips (cumulating final concentration of Fructus Psoraleae was 0.1, 0.3, 1.0, 3.0, 10.0, 20.0 g/L). The antagonists, including 4-DAMP, benzhydramine, hexamethonium, phentolamine, verapamil and idomethine were given 2 min before Fructus Psoraleae respectively to investigate the mechanisms involved.

RESULTS: Fructus Psoraleae dose-dependently increased the resting tension (r = 0.992, P < 0.001), decreased the mean contractile amplitude (r = 0.970, P < 0.001) and meanwhile increased the contractile frequency of the gallbladder muscle strip *in vitro* (r = 0.965, P < 0.001). The exciting action of Fructus Psoraleae on the resting tension could be partially blocked by 4-DAMP (the resting tension decreased from 1.37 ± 0.41 to 0.70 ± 0.35, P < 0.001), benzhydramine (from 1.37 ± 0.41 to 0.45 ± 0.38, P < 0.001), hexamethonium (from 1.37 ± 0.41 to 0.94 ± 0.23, P < 0.05), phentolamine (from 1.37 ± 0.41 to 0.89 ± 0.22, P < 0.01) and verapamil (from 1.37 ± 0.41 to 0.94 ± 0.26, P < 0.05). But the above antagonists had no significant effect on the action of Fructus Psoraleae–induced mean contractile amplitude (P > 0.05). Moreover, the increase of the contractile frequency due to Fructus Psoraleae was inhibited by 4-DAMP (decreased from 8.3 ± 1.2 to 6.8 ± 0.5, P < 0.01) and hexamethonium (from 8.3 ± 1.2 to 7.0 ± 0.9, P < 0.05). Idomethine had no significant effect on the Fructus Psoraleae-induced responses (P > 0.05).

CONCLUSION: Fructus Psoraleae enhances the motility of isolated gallbladder muscle strips from guinea pigs, in a dose-dependent manner. The effect of Fructus Psoraleae is partly related to M_3, N receptor, α receptor, H_1 receptor, Ca^{2+} channel, but not related to prostaglandin.

Key words: Fructus Psoraleae; Gallbladder smooth muscle strips; M_3, N, α, H_1 receptors; Ca^{2+} channel; Prostaglandin

Jin S, Li M, Lin ML, Ding YH, Qu SY, Li W, Zheng TZ. Effect of Fructus Psoraleae on motility of gallbladder isolated smooth muscle strips from guinea pigs. *World J Gastroenterol* 2006; 12(32): 5214-5218

http://www.wjgnet.com/1007-9327/12/5214.asp

INTRODUCTION

Fructus Psoraleae is the dry fruit of the leguminous plant *Psoralea corylifolia L.* In recent years, researchers from home and abroad have made extensive studies on its chemical composition and extraction[1-4]. Studies on the pharmacological action of Fructus Psoraleae have been focused on its therapeutic effect on leucopenia, uterine bleeding, chronic bronchitis and psoriasis[5-8]. However, reports of the effect and mechanism of Fructus Psoraleae on the gallbladder smooth muscle strips *in vitro* are rare. In this experiment, we observed the effects of Fructus Psoraleae on the gallbladder muscle strips from guinea pigs and studied the possible mechanisms involved.

Table 1 Effect of Fructus Psoraleae on resting tension (g) of isolated gallbladder muscle strip after pretreated with antagonists (means ± SD)

Resting tension (g)	Fructus Psoraleae (g/L)						
	0	0.1	0.3	1	3	10	20
Pso	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.04	0.09 ± 0.04	0.24 ± 0.08[a]	0.88 ± 0.35[d]	1.37 ± 0.41[d]
Ben + Pso	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.04	0.07 ± 0.06	0.14 ± 0.08[c]	0.29 ± 0.17[b,h]	0.45 ± 0.38[d,h]
Phe + Pso	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.04	0.07 ± 0.07	0.17 ± 0.08[b]	0.46 ± 0.11[d,h]	0.89 ± 0.22[d,f]
4-DAMP + Pso	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.04[f]	0.09 ± 0.07[f]	0.30 ± 0.18[d,h]	0.70 ± 0.35[d,h]
Hex + Pso	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.05 ± 0.08	0.16 ± 0.14[a]	0.42 ± 0.20[c,h]	0.94 ± 0.23[c,d]
Ido + Pso	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.02	0.09 ± 0.06	0.21 ± 0.12[a]	0.71 ± 0.23[d]	1.31 ± 0.41[d]
Iso + Pso	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.03[f]	0.10 ± 0.06[f]	0.38 ± 0.19[c,h]	0.94 ± 0.26[c,d]

[a]$P < 0.05$, [b]$P < 0.01$, [d]$P < 0.001$ *vs* control (under 1-g initial load the gallbladder spontaneous contraction when Fructus Psoraleae was 0 g/L). The resting tension of each strip in control was 0 ($n = 8$). [c]$P < 0.05$, [f]$P < 0.01$, [h]$P < 0.001$ *vs* Fructus Psoraleae (the resting tension of adding each concentration of Fructus Psoraleae) ($n = 8$). Pso: Fructus Psoraleae; Ben: Benzhydramine; Phe: Phentolamine; Hex: Hexamethonium; Ido: Idomethine; Iso: Verapamil.

MATERIALS AND METHODS

Materials

Fructus Psoraleae was ground into coarse powder, boiled, filtered and made into (1000 g/L) extract (the drug was prepared and tested by Gansu Institute for Drug Control), and then diluted to 10, 20, 70, 200, 700, 1000 g/L solutions respectively. The antagonists are as follows: 4-DAMP (1 μmol/L) (Sigma Chemicals Company), hexamethonium (10 μmol/L) (Sigma Chemicals Company), phentolamine (1 μmol/L) (Beijing No 13 Pharmaceutical Factory), verapamil (0.05 μmol/L) (Lanzhou Pharmaceutical Factory), idomethine (1 μmol/L)(Beijing Two-bridge Pharmaceutical Factory), and benzhydramine (1 μmol/L) (Jiangsu Taicang Pharmaceutical Factory). Guinea pigs of either sex, weighing between 350 and 450 g [purchased from Animal Center of Lanzhou Veterinary Institute, laboratory animal certificate FCXK (Gan2004-0005)]. The following equipments were used: JZ-BK external isometric force transducer (BK Company), LMS-ZB two channels recorder (Chengdu Equipment Factory, China).

Methods

Guinea pigs were fasted with free access to water for 24 h. They were hit on the head to become unconscious. The whole gallbladder was removed, quickly transferred to Krebs solution and rinsed. The wall of the gallbladder was incised from the end of the cystic duct to the base to make two or three longitudinal smooth muscle strips (8 mm × 3 mm). The mucosa was gently removed with forceps. Every longitudinal muscle strip was suspended in a tissue chamber which was continuously perfused with 5 mL Krebs solution (37℃), pH 7.4, and aerated with 950 mL/L O_2 and 50 mL /L CO_2. One end of the strip was fixed to a hook on the bottom of the chamber. The other end was connected to an external isometric force transducer (JZ-BK, BK). The strip was subjected to 1 g load tension and washed with 5 mL Krebs solution every 20 min. Motility of gallbladder strips in tissue chambers was simultaneously recorded by electrophysiolograph (LMS_ZB, Chengdu), including the resting tension, the mean contractile amplitude, and the contractile frequency[9]. After 2 h equilibration, 10, 20, 70, 200, 700, 1000 g/L Fructus Psoraleae was added cumulatively in turn every 2 min to observe their effects on contractility of gallbladder. The 4-DAMP (1 μmol/L), benzhydramine (1 μmol/L), hexamethonium (10 mol/L), phentolamine (1 μmol/L), verapamil (0.05 μmol/L) and idomethine (1 μmol/L) were added 2 min before Fructus Psoraleae was added to investigate whether the actions of Fructus Psoraleae were mediated *via* M_3, N receptor, α receptor, H_1 receptor, Ca^{2+} channel and prostaglandin(PG).

Statistical analysis

The data were presented as mean ± SD and analyzed with one-way ANOVA and correlation. $P < 0.05$ was considered statistically significant.

RESULTS

Effect of Fructus Psoraleae and antagonists plus Fructus Psoraleae on the resting tension of gallbladder muscle strips

Fructus Psoraleae dose-dependently increased the resting tension of gallbladder muscle strips *in vitro* ($r = 0.992$, $P < 0.001$). The 4-DAMP (1 μmol/L), benzhydramine (1 μmol/L), hexamethonium (10 μmol/L), phentolamine (1 μmol/L), verapamil (0.05 μmol/L) and idomethine (1 μmol/L) had no significant effects on the resting tension of gallbladder muscle strips. But when given 2 min before the administration of Fructus Psoraleae (0.1, 0.3, 1.0, 3.0, 10.0, 20.0 g/L), 4-DAMP, benzhydramine, hexamethonium, phentolamine and verapamil partly blocked the enhancing action of Fructus Psoraleae on the resting tension of gallbladder muscle strips. However, idomethine had no significant action on the increasing effect of Fructus Psoraleae on resting tension (Table 1).

Effect of Fructus Psoraleae and antagonists plus Fructus Psoraleae on the mean contractile amplitude of gallbladder muscle strips

Fructus Psoraleae dose-dependently decreased the mean contractile amplitude of gallbladder isolated smooth muscle strips ($r = 0.970$, $P < 0.001$). The 4-DAMP (1 μmol/L), benzhydramine (1 μmol/L), hexamethonium (10 μmol/L), phentolamine (1 μmol/L), verapamil (0.05 μmol/L) and idomethine (1 μmol/L) had no significant effects on the mean contractile amplitude of gallbladder muscle strips. When

Table 2 Effect of Fructus Psoraleae on the contractile amplitude (mm) of isolated gallbladder muscle strip after pretreated with antagonists (means ± SD)

Amplitude (mm)	Fructus psoraleae (g/L)						
	0	0.1	0.3	1	3	10	20
Pso	4.54 ± 0.64	4.23 ± 0.78	4.24 ± 0.84	4.07 ± 0.72	3.71 ± 0.59[a]	2.36 ± 0.77[d]	1.72 ± 0.74[d]
Ben + Pso	4.70 ± 0.57	4.43 ± 0.80	4.19 ± 0.88	4.09 ± 0.97	3.93 ± 0.97	3.55 ± 0.93[a]	2.37 ± 0.83[d]
Phe + Pso	4.71 ± 1.37	4.47 ± 1.42	4.64 ± 1.32	4.49 ± 1.35	4.17 ± 1.41	3.36 ± 1.43[a]	2.15 ± 0.65[d]
4-DAMP + Pso	4.91 ± 0.60	4.58 ± 0.71	4.23 ± 0.60	4.27 ± 0.84	3.84 ± 0.81[a]	3.70 ± 1.28[b]	2.34 ± 1.07[d]
Hex + Pso	5.48 ± 1.57	5.13 ± 1.64	5.34 ± 1.60	4.86 ± 1.63	4.80 ± 1.46	3.43 ± 1.10[b]	1.93 ± 1.02[d]
Ido + Pso	5.40 ± 1.30	5.01 ± 1.37	4.83 ± 1.33	4.62 ± 1.42	4.16 ± 1.29	3.39 ± 1.48[b]	2.24 ± 1.25[d]
Iso + Pso	4.47 ± 1.23	4.42 ± 1.37	4.60 ± 1.56	4.29 ± 1.32	4.00 ± 1.08	3.98 ± 1.74	2.80 ± 1.57[b]

[a]$P < 0.05$, [b]$P < 0.01$, [d]$P < 0.001$ *vs* control (under 1-g initial load the gallbladder spontaneous mean contraction amplitude when Fructus Psoraleae was 0 g/L) ($n = 8$).

Table 3 Effect of Fructus Psoraleae on the contractile frequency(waves/min) of isolated gallbladder muscle strip after pretreated with antagonists (means ± SD)

Frequency (w/min)	Fructus psoraleae (g/L)						
	0	0.1	0.3	1	3	10	20
Pso	3.3 ± 0.5	3.3 ± 0.7	3.3 ± 0.6	3.8 ± 0.9	4.6 ± 0.7[b]	7.3 ± 1.2[d]	8.3 ± 1.2[d]
Ben + Pso	3.4 ± 0.5	3.6 ± 0.4	3.6 ± 0.4	3.7 ± 0.4	4.6 ± 0.4[d]	6.3 ± 0.5[d]	7.3 ± 0.8[d]
Phe + Pso	3.5 ± 0.7	3.9 ± 0.8	3.9 ± 0.8	4.4 ± 1.0	5.1 ± 0.8[b]	7.1 ± 1.2[d]	9.1 ± 1.1[d]
4-DAMP + Pso	3.5 ± 0.4	3.5 ± 0.4	3.6 ± 0.6	3.9 ± 0.7	4.2 ± 0.5[a]	5.1 ± 0.9[d,h]	6.8 ± 0.5[d,f]
Hex + Pso	3.3 ± 0.5	3.5 ± 0.8	3.5 ± 0.5	3.9 ± 0.8	4.8 ± 1.0[d]	6.0 ± 0.7[c,d]	7.0 ± 0.9[c,d]
Ido + Pso	3.4 ± 0.5	3.4 ± 0.6	3.6 ± 0.7	3.8 ± 0.7	4.4 ± 0.7[a]	6.9 ± 1.4[d]	8.4 ± 1.1[d]
Iso + Pso	3.4 ± 0.5	3.4 ± 0.8	3.5 ± 0.8	3.8 ± 0.9	5.2 ± 1.4[b]	6.3 ± 1.2[d]	8.8 ± 1.6[d]

[a]$P < 0.05$, [b]$P < 0.01$, [d]$P < 0.001$ *vs* control (under 1-g initial load the gallbladder spontaneous contraction frequency when Fructus Psoraleae was 0 g/L) ($n = 8$). [c]$P < 0.05$, [f]$P < 0.01$, [h]$P < 0.001$ *vs* Fructus Psoraleae (contraction frequency of adding each concentration of Fructus Psoraleae) ($n = 8$).

added 2 min before administration of Fructus Psoraleae (0.1, 0.3, 1.0, 3.0, 10.0, 20.0 g/L), none of the above antagonists showed significant action on the decreasing effect of Fructus Psoraleae on the mean contractile amplitude (Table 2).

Effect of Fructus Psoraleae and antagonists plus Fructus Psoraleae on the contractile frequency of gallbladder muscle strips

Fructus Psoraleae dose-dependently increased the contractile frequency of gallbladder muscle strips from guinea pigs *in vitro* ($r = 0.965$, $P < 0.001$). The 4-DAMP (1 μmol/L), benzhydramine (1 μmol/L), hexamethonium (10 μmol/L), phentolamine (1 μmol/L), verapamil (0.05 μmol/L) and idomethine (1 μmol/L) had no significant effects on the contractile frequency of gallbladder muscle strips. When given 2 min before the administration of Fructus Psoraleae (0.1, 0.3, 1.0, 3.0, 10.0, 20.0 g/L), 4-DAMP and hexamethonium partly inhibited the action of Fructus Psoraleae on contractile frequency of gallbladder muscle strips; nevertheless, the other antagonists had no significant effects on the action of Fructus Psoraleae on the contractile frequency (Table 3).

DISCUSSION

Cholelithiasis is a common disease worldwide and many epidemiological studies have shown that the incidence of cholelithiasis has been on a rapid increase in some regions of the world since the last decade. Motor dysfunction of the gallbladder plays an important role in cholelithiasis and cholecystitis[10-12]. According to the literature, traditional Chinese medicine, western medicine and surgical management have been employed to treat cholelithiasis at home and abroad[13-16]. Herbal medicine is characterized by having few side effects and good curative effects, which is gradually accepted by people over the world. Zhou[17] reported that Fructus Psoraleae extract excited the intestinal canal *in vivo* and *in vitro*, and relaxed the uterus of guinea pigs. In the present study, we observed that Fructus Psoraleae significantly increased the resting tension and contractile frequency; meanwhile decreased the mean contractile amplitude of isolated gallbladder muscle strips of guinea pigs.

All smooth muscles in the gallbladder are involuntary and the nerves are controlled by both extrinsic and intrinsic nervous systems. Von Schrenck *et al*[18] reported that gallbladder smooth muscle cells possess muscarinic receptors of the M_3 type, which mediate contraction. Chen *et al*[19] reported the M_3 receptors are preferentially associated with the activation of phospholipase C, intracellular Ca^{2+} release and the calmodulin-dependent pathway. It has been identified that cholinergic N-receptor exists on the membrane of nerve ganglion cells of gallbladder smooth muscle. Our results showed that M_3

antagonist (4-DAMP) and hexamethonium(nicotinic cholinergic antagonist) partly blocked the enhancing action of Fructus Psoraleae on the resting tension and contractile frequency of gallbladder muscle strips, but not that of the contractile amplitude of the strips. These results suggested that Fructus Psoraleae excited gallbladder muscle strip *via* M_3 and ganglion N receptors.

Moreover, there were some relevant reports about histamine and histamine receptors. Jennings *et al*[20] proposed that histamine is distributed in the guinea-pig gallbladder and it could regulate contractile activity *via* activation of H_1 and H_2 but not H_3 receptor. Gallbladder muscle possesses stimulatory H_1 receptors and inhibitory H_2 receptors[21]. The depolarization and associated contraction of gallbladder smooth muscle represent the net effect of activation of both H (1) (excitatory) and H (2) (inhibitory) receptors, with the H (2) receptor-mediated response involving the activation of K (ATP) channels[22]. In this experiment, we observed that H_1 antagonist-benzhydramine partly inhibited the enhancing action of Fructus Psoraleae on the resting tension, but had no effect on the mean contractile amplitude and contractile frequency of gallbladder muscle strip. The results showed the excitatory action of Fructus Psoraleae on gallbladder muscle strip was possibly mediated *via* H_1 receptor. Yanaura *et al*[23] reported that contractions and relaxations produced by sympathomimetic amines are mediated by alpha-excitatory and beta-inhibitory adrenoceptors in the biliary system (gallbladder, common bile duct and sphinctor of Oddi) of guinea-pigs. We also observed that adnephrin antagonist-phentolamine partly inhibited the enhancing action of Fructus Psoraleae on the resting tension, but had no effect on the mean contractile amplitude and contractile frequency of gallbladder muscle strip, and the results revealed that the excitatory action of Fructus Psoraleae on gallbladder muscle strip was possibly mediated *via* α receptor. Ca^{2+}, which participates in excitation contraction coupling plays an important role in the contraction process of smooth muscle. The action potential in gallbladder smooth muscle (GBSM) is caused by Ca^{2+} entry through voltage-dependent Ca^{2+} channels (VDCC), which contributes to the GBSM contraction[24]. Shimada[25] believed the L-type Ca^{2+} current is dominant in gallbladder smooth muscle cells and may contribute to excitation-contraction coupling. In addition, our data showed that verapamil partly inhibited the exciting action of Fructus Psoraleae on the resting tension, suggesting that Fructus Psoraleae-induced gallbladder contraction was related to the Ca^{2+} channel. Verapamil is an L-type calcium channel blocker which inhibited the exciting effect induced by Fructus Psoraleae; whereas idomethine (prostaglandin enzyme suppressor) had no significant effects on the action of Fructus Psoraleae, indicating that the exciting action of Fructus Psoraleae on gallbladder smooth muscle strips was not related to prostaglandin (PG).

In summary, results from this study provide us new insights into the mechanisms underlying gallbladder motility and will be useful for further understanding of biliary dyskinesia diseases and the treatment.

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