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Effects of octreotide on gallbladder pressure and myoelectric activity of Oddi sphincter in rabbits

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Subject headings octreotide/pharmacology; gallbladder/drug effects; oddi sphincter/drug effects; electrophysiology; rabbits; somatostatin; electric stimulation

Abstract

AIM To observe the effect of octreotide (OT) and somatostatin (SS) on gallbladder pressure and myoelectric activity of SO in rabbits.

METHODS Male rabbits fasted for 15h-18h and anesthetized with urethane. The mean gallbladder pressure (GP) and myoelectric activity of SO were simutaneously measured with a frog bladder connected to a transducer and a pair of copper electrodes.

RESULTS After injection of OT (10 μg/kg, iv), the GP decreased in 2min and reached the lowest value in about 60min ($P<0.01$, $n=19$), and completely or partially returned to the normal level in 120min. The frequency of myoelectric activty of SO was reduced, even disappeared in 2min ($P<0.01$, $n=19$) and returned to normal in about 20min. Injection of SS (10 μg/kg, iv) also decreased GP and myoelectric activity of SO ($P<0.01$, $n=7$); Before and after injection of OT or SS, injection of CCK-8 (100ng or 200ng) caused similar increase in myoelectric activity of SO and GP ($P>0.05$). Before and after injection of OT, there were no significant differences in increases of myoelectric activity of SO and GP caused by electric stimulation of dorsal motor nucleus of vagus ($P>0.05$).

CONCLUSION OT and SS decreased GP and myoelectric activity of SO, demonstrating that effects of OT were similar to those of SS. Intravenous injection of OT did not affect the increase of myoelectric activity of SO and GP caused by CCK-8 or electric stimulation of dorsal motor nucleus of vagus.

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INTRODUCTION

Octreotide (OT) is an 8 amino acids synthetic analog of somatostatin (SS). Treatment with OT in acromegaly is effective but leads to gallstone formation. OT injections inhibit gallbladder contraction in acromegalic patients[1,2] and normal subjects[3], stimulating human sphincter of Oddi (SO) activity[4], which may impair bile evacuation. However, studies of SS, especially effect of OT on motor function of biliary system in animals are scarce and controversial. The aim of this study was to observe the effects of OT and SS on gallbladder pressure (GP) and myoelectric activity of SO in rabbits.

MATERIALS AND METHODS

Preparation of animals

Thirty-eight male rabbits, weighing 2kg-2.5kg were used. They were fasted for 15h-18h with free intake of water and then anesthetized with urethane (1.0g/kg, iv). A cannula was inserted into trachea and the unilateral femoral artery was cathered for the blood pressure measurement.

Measurement of GP and myoelectric activity of SO

A frog bladder perfused with saline was placed into the gallbladder and connected to a transducer (TP-200T). A pair of copper electrodes was inserted into subsera of SO. Blood pressure, GP and myoelectric signals of SO were simutaneously measured by a polygrapher (RM-6000, NIHON KHODEN).

Administration of drugs

OT, cholecystokinin octapeptide (CCK-8) and SS were injected through ear vein. SS and CCK-8 were products of Sigma Chemical Company (St. Louis, U.S.A.) and Pennisula Laboratories (Belmont, U.S.A.) respectively. OT was produced by the Sandoz Pharm Ltd (Besel, Switzerland).

Electric stimulation of dorsal motor nucleus of vagus (DMV)

The animal's head was fixed in a sterotaxic instrument (I-C model, Jiang Wan, China) A wire electrode was inserted into DMV for stimulation (0.2mA, 10Hz, 0.5ms duration, 1min) according to Messen's method. An indifferent electrode was placed on the skin tissure of skull.

Statistical analysis

The constant mean GP of each animal was taken as control level (i.e., basic GP served as 0kPa in place of the real value) and the frequency of myoelectric activity of SO was considered as normal value. The percentage of frequency changes=(effect value-normal value) ÷ normal value×100%. All values were expressed as $\bar{x}\pm s_{\bar{x}}$. Experimental data were treated statistically by Student's *t* test.

RESULTS

Effect of intravenous injection of OT on GP

Intravenous injection of OT caused dose-dependent decrease of GP. After injection of OT (10 μg/kg, iv), the GP decreased in 2min (-0.142kPa±0.029kPa, $P<0.01$) and reached the lowest value in 60min (-0.257kPa±0.065kPa, $P<0.01$), and completely or partially returned to the normal level in 120min. Small dose of OT (5 μg/kg, iv), also decreased GP ($P<0.01$) but the effect was slight. No change in GP was found after injection of 1ml of 0.9% saline ($P>0.05$). The differences were significant ($P<0.01$) (Figure 1, Table 1) between the two groups of OT.

Effect of intravenous injection of OT on myoelectric activity of SO

After injection of OT (10 μg/kg, iv), the frequency of myoelectric activity of SO was reduced, even disappeared in 2min (-83.1%±8.0%, $P<0.01$) and returned to normal in about 20min. At the dose of 5 μg/kg of OT, frequency of myoelectric activity of SO also decreased (-54%±6.1%, $P<0.01$). In contrast to OT 10 μg/kg group, the effect is weak ($P<0.05$). Injection of the same volume of 0.9% saline influenced neither GP nor myoelectric activity of SO (Figures 1, 2, Table 2).

Effect of iv injection of SS on GP and myoelectric activity of SO

After injection of SS (10 μg/kg, iv) in 7 rabbits, GP and myoelectric activity of SO were decreased. These changes were similar to those in OT ($P>0.05$) (Figure 3, Tables 1, 2).

Effect of iv OT and SS on changes in GP and myoelectric activity of SO caused by CCK-8

Ten minutes before and 15 minutes after injection of OT (10 μg/kg, iv), and CCK-8 (100ng) there was a marked increase in GP and myoelectric activity of SO. Before and after injection of SS (10 μg/kg), and CCK-8 (200ng) greatly increased GP and myoelectric activity of SO. These responses to CCK-8 showed no significant differences between pre- and post-injection of OT or SS ($P>0.05$), (Figure 4, Table 3).

Table 1 Effect of OT and SS on gallbladder pressure

Groups	*n*	Changes in gallbladder pressure (basic pressure=0kPa)							
		2	10	20	40	60	80	100	120min
NS	5	-0.024	-0.000	-0.013	-0.013	-0.010	-0.010	-0.012	-0.020
		±0.020	±0.024	±0.024	±0.032	±0.024	±0.024	±0.024	±0.040
OT	6	-0.074[a]	-0.097[b]	-0.068	-0.135	-0.101	-0.120	-0.068	-0.052
(5 μg/kg)		±0.012	±0.023	±0.024	±0.050	±0.062	±0.052	±0.038	±0.031
OT2	19	-0.142[bc]	-0.196[bd]	-0.184[a]	-0.154[a]	-0.257[a]	-0.145	-0.104	-0.040
(10 μg/kg)		±0.020	±0.052	±0.034	±0.052	±0.065	±0.048	±0.036	±0.042
SS(10 μg/kg)	7	-0.143[b]	-0.122[a]	-0.071	-0.021	0.029			
		±0.034	±0.037	±0.021	±0.036	±0.028			

[a]$P<0.05$, [b]$P<0.01$ *vs* NS group; [c]$P<0.05$, [d]$P<0.01$, *vs* group 1 OT.

Table 2 Effect of OT and SS on frequency of myoelectric activity of SO

Groups	*n*	Changes in frequency of myoelectric activity of SO (%)							
		2	10	20	40	60	80	100	120min
NS	5	-8.0	-4.0	-2.0	0.0	4.0	-3.0	-1.0	-2.0
		±8.2	±6.5	±5.0	±11.0	±6.0	±6.0	±8.2	±5.0
OT1	6	-51.4[b]	-42.3[a]	-18.5	-5.0	-4.0	5.0	-2.0	4.0
(5 μg/kg)		±6.1	±11.9	±9.0	±10.0	±6.0	±6.5	±4.5	±5.3
OT2	19	-83.1[bd]	-65.0[a]	-21.5	5.0	3.5	-4.0	-4.0	-3.5
(10 μg/kg)		±8.0	±11.3	±9.3	±6.2	±9.1	±7.0	±5.0	±8.5
SS	7	-86.7[b]	-78.5[a]	-48.9	-10.0	7.0			
(10 μg/kg)		±11.0	±14.0	±14.0	±18.8	±9.0			

[a]$P<0.05$, [b]$P<0.01$ *vs* NS group; [c]$P<0.05$, [d]$P<0.01$, *vs* OT 1 group.

Table 3 Comparision of effects of iv CCK-8 and electric stimulation of DMV on gallbladder pressure and myoelectric activity of SO after

Group	*n*	Changes of frequency of myoelectric activity of SO (%)		Changes in gallbladder pressure (basic pressure = 0kPa)	
		Before	After	Before	After
DMV OT	10	283.8±69.6	285.8±75.8	0.128±0.046	0.123±0.031
CCK-8 (100ng) OT	12	346.8±79.2	275.8±37.7	0.363±0.113	0.321±0.112
CCK-8(200ng) SS	4	485.8±78.9	426.4±59.0	1.795±0.468	1.955±0.340

Before, before injection of TO or SS; After, after injection of OT or SS.

Effects of iv OT on changes of GP and myoelectric activity of SO caused by electric stimulation of DMV

Ten minutes before and after injection of OT (10 μg/kg, iv), electric stimulation of DMV increased GP, frequency and amplitude of myoelectric activity of SO, the effects being similar (P>0.05), (Table 3).

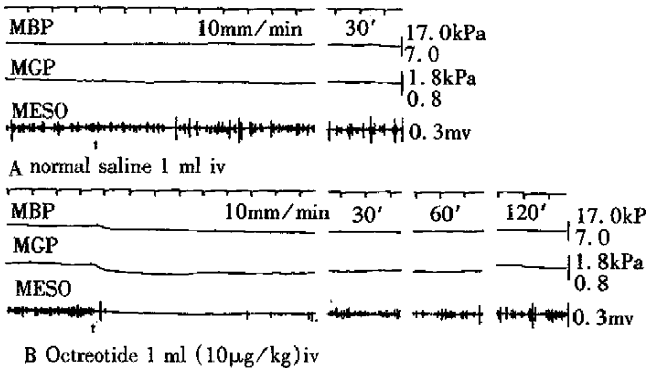

Figure 1 Effect of iv octreotide on gallbladder pressure and myoelectric activity of SO. A, injection of normal saline; B, injection of OT; MBP, mean blood pressure; MGP, mean gallbladder pressure; MESO, myoelectric activity of SO. ↑, intravenous injection mark.

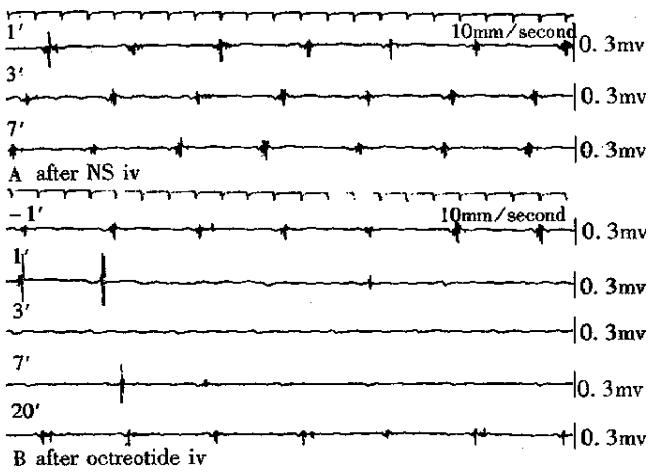

Figure 2 Effect of octreotide on myoelectric activity of SO. A, injection of normal saline; B, injection of OT (10 μg/kg, iv)

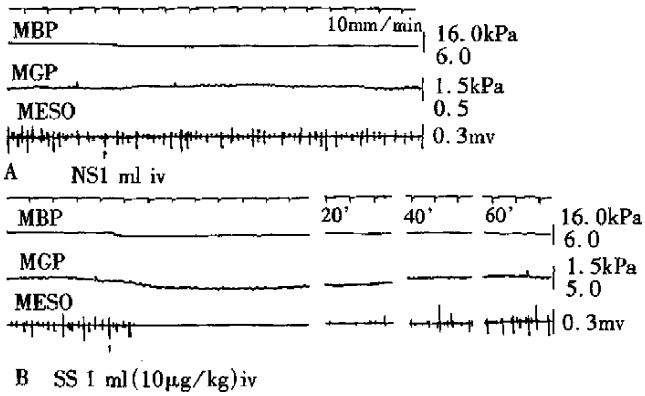

Figure 3 Effect of iv SS on gallbladder pressure and myoelectric activity of SO. A, injection of normal saline; B, injection of SS; MBP, mean blood pressure; MGP, mean gallbladder pressure; MESO, myoelectric activity of SO; ↑, iv injection mark.

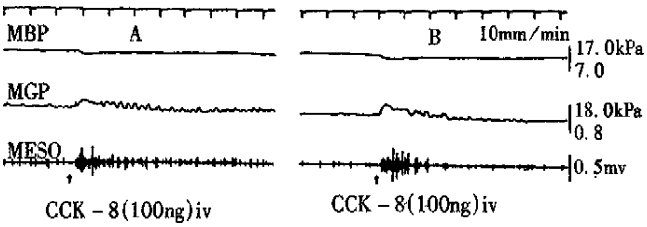

Figure 4 Effect of iv CCK-8 on gallbladder pressure and myoelectric activity of SO after injection of octreotide. A, before injection of OT; B, After injection of OT.

DISCUSSION

Several studies of SS effect on biliary motility have been reported but the results are different. SS has no effect on contraction of gallbladder smooth muscle strips in guinea pigs, dogs[5] and rabbits[6], but inhibits gallbladder motility in human[7] and

dogs[5] in vivo. SS has been reported to either stimulate or inhibit the SO of dogs[8,9]. In the present study, SS decreased both GP and myoelectric activity of SO. The latter response was similar to the inhibitory SS effect on SO in rabbits reported before[10]. OT, a long-acting analog of SS, has been found to inhibit human gallbladder motility and to stimulate SO contraction which may impair bile evacuation with a risk of gallstone formation[1,2,4]. The animal experiment of OT effect was only conducted on prairie dogs in which OT decreased the motility index of SO, but did not affect the gallbladder pressure[11]. In the present study, OT decreased GP and myoelectric activity of SO in rabbits. These results were consistent with those of SS, demonstrating that inhibitory effect of OT is similar to that of SS. The diverse effects of SS and OT on motility of SO and gallbladder may be explained by the species difference.

The motility of gallbladder and SO is regulated by both autonomic nervous system and intestinal hormones. CCK is an important hormone for mediating motility of biliary tract. In the experiments on dogs, SS inhibits contraction of gallbladder strips induced by electric stimulation and decreased GP by CCK-8 in vivo probably through suppressing Ach release by the intrinsic cholinergic neurons, but does not affect contraction of gallblader strips intiated by Ach or CCK[5]. Intravenous injection of SS inhibits contraction of human gallblader in response to CCK[7]. In our study, injection of CCK-8 markedly raised GP and increased myoelelctric activity of SO in rabbits. After injection of OT or SS, and CCK-8 resulted in increases of GP and myoelectric activity of SO, indicating that SS and OT do not affect the stimulatory effect of CCK-8 on gallbladder and SO. It is reported that electric stimulation of DMV raises GP and increases myoelectric activity of SO through a cholinergic mechanism of vagal nerve. In this study, before and after injection of OT, electric stimulation of DMV caused similar increases in GP and myoelectric activity of SO. These results imply that OT did not inhibit the increase in motility of gallbladder and SO caused by DMV stimulation. The mechanisms of OT effect on motor function of biliary tract require further investigations.

In conclusion, OT and SS decrease GP and myoelectric activity of SO, demonstrating that the inhibitory effect of OT is similar to that of SS in rabbits. Before and after injection of OT and SS, and CCK-8 injection or electric stimulation of DMV similar increases are caused in GP and myoelectric activity of SO, suggesting that OT and SS do not affect the increases in motility of gallbladder and SO caused by CCK-8 and electric stimulation of DMV.

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