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• *BASIC RESEARCH* •

Cholecystokinin octapeptide improves cardiac function by activating cholecystokinin octapeptide receptor in endotoxic shock rats

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Abstract

AIM: To explore the effect of sulfated cholecystokinin octapeptide (sCCK-8) on cardiac functions and its receptor mechanism in endotoxic shock (ES) rats.

METHODS: The changes of the mean arterial pressure (MAP), heart rate (HR), the left ventricular pressure (LVP) and the maximal/minimum rate of LVP ($\pm LVdp/dt_{max}$) were measured by using physiological record instrument in eight groups of rats. The expression of cholecystokinin-A receptor (CCK-AR) and cholecystokinin-B receptor (CCK-BR) mRNA of myocardium in ES rats was examined by reverse transcription polymerase chain reaction (RT-PCR).

RESULTS: (1) Low doses of sCCK-8 (0.4 μg/kg) caused tachycardia (441±27, normal control 391±22 s/min) and slight increase in MAP, LVP and $\pm LVdp/dt_{max}$ (16.96±1.79, 18.21±1.69 and +768.85±31.28/-565.04±27.71 kPa, respectively, all $P<0.01$), while medium doses (4.0 μg/kg) and high doses of sCCK-8 (40 μg/kg) elicited bradycardia and marked increase in MAP, LVP and $\pm LVdp/dt_{max}$ (17.29±1.63, 19.46±2.57 and +831.46±22.57/-606.08 ±31.32; 17.46±1.08, 19.83±2.91 and +914.52±35.95/ -639.15±30.23 kPa, respectively, all $P<0.01$). Proglumide (1.0 mg/kg), a nonselective antagonist of CCK-receptor (CCK-R), significantly inhibited the pressor effects of sCCK-8 (15.96±1.38, 17.36±0.66 and +748.18±19.29/-512.12±14.39 kPa, respectively, all $P<0.01$), whilst reversing the bradycardiac responses. (2) High doses of LPS (8 mg/kg) elicited marked decrease in MAP, LVP and $\pm LVdp/dt_{max}$. (7.16±0.59, 7.6±0.68 and +298.01±25.52/ -166.96±19.25 kPa, respectively, all $P<0.01$). Pretreatment with sCCK-8 (40 μg/kg) could reverse the decline of cardiac functions (10.71±0.45, 11.7±1.26 and +446.04±67.18/ -347.90±36.98 kPa, respectively, all $P<0.01$), while proglumide could cause further decline of cardiac function in ES rats (4.71±0.67, 5.58±1.25 and +226.48±15.84/ -142.83±20.23 kPa, respectively, all $P<0.01$). (3) CCK-A/BR mRNAs were expressed in myocardium of control rats. Gene expression of CCK-AR and CCK-BR significantly increased in myocardium of ES rats. The increase of CCK-AR mRNA induced by LPS began at 0.5 h, peaked at 2 h, kept a high level at 6 h and declined at 12 h, respectively. Similar to CCK-AR mRNA, the expression of CCK-BR mRNA peaked at 2 h and kept a high level at 6 h, but it did not change at the first 0.5 h and was stable at a high level at 12 h.

CONCLUSION: The above results indicate that endogenous and exogenous sCCK-8 may significantly improve cardiac function and intractable hypotension of ES rats, which was likely related to high expression of CCK-A/BR in myocardium induced by LPS.

Key words: Sulfated cholecystokinin octapeptide; Endotoxic shock

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INTRODUCTION

Lipopolysaccharide (LPS), the main component of bacterial endotoxin, can induce endotoxic shock (ES), which is very critical in clinic and leads to high mortality. ES is associated with cardiac dysfunction and intractable low arterial pressure[1]. We have shown previously that endogenous and exogenous cholecystokinin octapeptide (CCK-8) had anti-ES effect, such as reversing the fall in mean arterial pressure (MAP), preventing pulmonary artery hypertension (PAH), attenuating pathomorphological changes of main organs, and decreasing mortality[2,3]. In contrast, pretreatment with proglumide, the nonselective CCK-receptor (CCK-R) antagonist, could delay the recovery of blood pressure and increase mortality of ES rats[2,3]. However, the effect of CCK-8 on cardiac function and its mechanism remains unclear. Recently, our study showed that CCK-8 might

enhance cardiac function in a dose- dependent manner, which was likely induced by directly activating CCK-R in myocardium[4]. CCK-R was classified into two subtypes: CCK-AR and CCK-BR. CCK-AR was found predominantly in gastrointestinal tract and restricted areas of the brain, whereas CCK-BR was known to exist widely in brain and gastric glands[5]. At present, it is unknown whether sCCK-8 improves the cardiac function in ES rats and whether LPS induces the change of gene expression of CCK-R in myocardium. The aim of this study was to explore the effect of CCK-8 on cardiac function in ES rats and its receptor mechanism.

MATERIALS AND METHODS

Materials

LPS (*E.coli* 0111: B4), sulfated CCK-8 (sCCK-8) and proglumide were obtained from Sigma (St. Louis, MO). Total RNA isolation system and access RT-PCR system were purchased from Promega Inc., Beijing. All the other reagents used were of analytical grade, purchased from Chinese Chemicals Co., Male, specific pathogen-free Sprague-Dawley rats (weighing 220-260 g) were obtained from Experimental Animal Center of Hebei Province.

Animal preparation

Forty-eight rats were randomly assigned to eight groups ($n = 6$ in each) and different agents were administered: (1) low-dose sCCK-8 group: the rats were given sCCK-8 (0.4 μg/kg); (2) medium-dose sCCK-8 group: the rats were given sCCK-8 (4.0 μg/kg); (3) high-dose sCCK-8 group: the rats were given sCCK-8 (40 μg/kg); (4) proglumide plus sCCK-8 group: sCCK-8 (4.0 μg/kg) was given 10 min after administration of proglumide (1 mg/ kg); (5) ES group: the rats were given LPS (8 mg/kg); (6) ES plus sCCK-8 group: sCCK-8 (40 μg/kg) pretreatment 10 min before LPS (8 mg/kg); (7) proglumide plus LPS group: proglumide (1 mg/kg) pretreatment 10 min before LPS (8 mg/kg); (8) negative control animals received saline.

General operation

The animals were anesthetized with urethane (1.0 g/kg, ip). The right carotid artery was exposed and a catheter was inserted into the left ventricle (LV). The arterial cannula was connected to a pressure transducer (AP-601G) for measurement of LV systolic pressure (LVP). The signal of LVP was introduced by a differentiator Amp (ED-601G) to record the maximal/minimum rate of LVP ($\pm LVdp/dt_{max}$). HR was measured with an HR counter (AT-600G) triggered by left ventricular pressure pulse. Another catheter was inserted into the femoral artery and connected to a pressure transducer (AP-601G) for measurement of MAP. The changes in MAP, LVP and $\pm LVdp/dt_{max}$ were recorded on a polygraph (RM-6000G, Nihon Kohden). The caudal vein was cannulated for intravenous administration of various agents. All of the operations were finished in 40 min. Following a 15 min stabilization period, MAP, LVP and $\pm LVdp/dt_{max}$ were recorded as the control, and the agents were administered intravenous injection in a bolus dose. The rats were killed at 2 h.

Gene expression of CCK-R in cardiac tissue

Fifteen rats were divided into five groups ($n = 3$), (1) control group; (2)-(5) LPS groups, the rats were given 8 mg/kg LPS and were killed at 0.5, 2, 6, and 12 h. The kidney sections were used as positive control. Total RNA was extracted from both the myocardial and kidney samples by guanidinium thiocyanate method. The concentration of RNA was determined by absorbance at 260 nm. The primers for CCK-AR, CCK-BR and β-actin were constructed according to the report of Monstein[6] as follows: CCK-AR (630 bp), 5'-CTC GCT CGC CCA GAA CTC TAC CAA GGA ATC AAA TTT GAT GC-3' (sense) and 5'-CTG GTT CGG CCC ATG GAG CAG AGG TGC TCA TGT GGC TGT AG-3' (antisense); CCK-BR (320 bp), 5'-CTC GCT CGC CCA GAA CTC TAC CTA GGA CTC CAC TTT GA-3' (sense) and 5'-CTG GTT CGG CCC ACG CAC CAC CCG CTT CTT AGC CAG CA-3' (antisense); β-actin (420 bp), 5'-GAGACCTTCAACACCCAGCC-3; (sense) and 5'-GCGGGGCATCGGAACCGCTCA-3'(antisense). All the primers were synthesized by Sangon Corporation (Shanghai).

RT-PCR was performed in 25 μL reaction volume. Cycling parameters for amplifying RT products were as follows: at 48 ℃ for 45 min, one cycle; at 94 ℃ for 2 min, one cycle; at 94 ℃ for 1 min, 55 ℃ for 45 s, 72 ℃ for 45 s, five cycles; at 94 ℃ for 45 s, 55 ℃ for 45 s, 72 ℃ for 1 min, 35 cycles; at 72 ℃ for 10 min, one cycle. PCR products were electrophoresed on 1. Five percent agarose gel, stained with ethidium bromide (0.5 μg/mL), and analyzed by Gel-Pro analyzer version 3.1 software (Media Cybernetics). The ratio of arbitrary unit (AU, $D_{area} \cdot D_{density}$) of target genes over β-actin was used for expressing the relative level of mRNA expression.

Statistical analysis

All data were expressed as mean±SD. Statistical significance was performed by one-way ANOVA followed by the paired t test for within group comparisons and the unpaired t test for between group comparisons. Statistical significance was accepted when $P<0.05$.

RESULTS

Changes in cardiac function after administration of sCCK-8

Low dose of sCCK-8 caused a tachycardia in 30-50 s ($P<0.01$). The change of HR restored to baseline after 10-15 min. Both medium and high doses of sCCK-8 elicited a bradycardia in 30-50 s ($P<0.01$). The change of HR restored to baseline after 10-15 min. Either low or high dose of sCCK-8 produced a dose-dependent marked increase in MAP, LVP and $\pm LVdp/dt_{max}$ in 30-50 s ($P<0.01$). Similar to the change of HR, these changes of MAP, LVP and $\pm LVdp/dt_{max}$ restored to baseline after 10-15 min. Pretreatment with proglumide could reverse the bradycardia induced by moderate dose of sCCK-8 to a tachycardia. The increases in MAP, LVP, and $\pm LVdp/dt_{max}$ also could be inhibited by administration of proglumide ($P<0.01$, Table 1).

Changes in cardiac function after administration of sCCK-8 in ES rats

LPS caused a variation in heart rate (HR)-a bradycardia

Table 1 Comparison of the cardiac functions after administration of sCCK-8 and proglumide (mean±SD; n = 6)

		CCK(μg)			
	Pre-administration	0.4 μg /kg	4.0 μg/ kg	40 μg /kg	Proglumide +CCK4.0 μg /k g
HR/bmp	391±22	441±27[b]	353±18[b]	340±21[b]	427±36[b,d]
MAP/kPa	14.07±1.68	16.96±1.79[b]	17.29±1.63[b]	17.46±1.08[b]	15.96±1.38[b,d]
LVP/kPa	16.48±2.56	18.21±1.69[b]	19.46±2.57[b]	19.83±2.91[b]	17.36±0.66[b,d]
LV$dp/dt_{max}$(kPa.S) $^{-1}$	634.43±32.88	768.85±31.28[b]	831.46±22.57[b]	914.52±35.95[b]	748.18±19.29[b,d]
LV$dp/dt_{min}$(kPa.S) $^{-1}$	429.82±18.95	565.04±27.71[b]	606.08±31.32[b]	639.15±30.23[b]	512.12±14.39[b,d]

[b]P<0.01 *vs* preadministration; [d]P<0.01 *vs* medium dose of sCCK-8 group.

following a tachycardia and rapid decrease of MAP, LVP, and ±LV$dp/dt_{max}$ (P<0.01). MAP declined to two bottoms at 30 and 75 min, while LVP and ±LV$dp/dt_{max}$ declined to two bottoms at 30 and 105 min. The rapid variation of HR and decline of MAP, LVP, and ±LV$dp/dt_{max}$ could be reversed by pretreatment with sCCK-8 in ES rats. The decrease of MAP, LVP, and ±LV$dp/dt_{max}$ were not inhibited by pretreatment with sCCK-8 at first 20 min, however, they were restored rapidly after 20 min, then they remained higher than ES rats at 120 min (P<0.01), but could not return to normal. Pretreatment with proglumide resulted in a further decline of MAP, LVP, and ±LV$dp/dt_{max}$ (P<0.01) in ES rats (Figures 1-3).

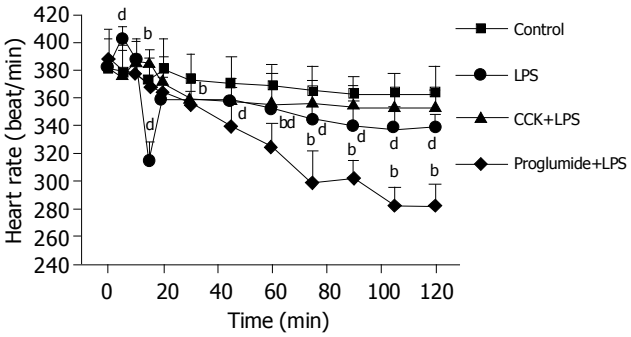

Figure 1 Changes of mean heart rate (HR) after intravenous injection of sCCK-8 or proglumide to ES rats. (mean±SD, n = 6). [b]P<0.01 *vs* control; [d]P<0.01 *vs* LPS group.

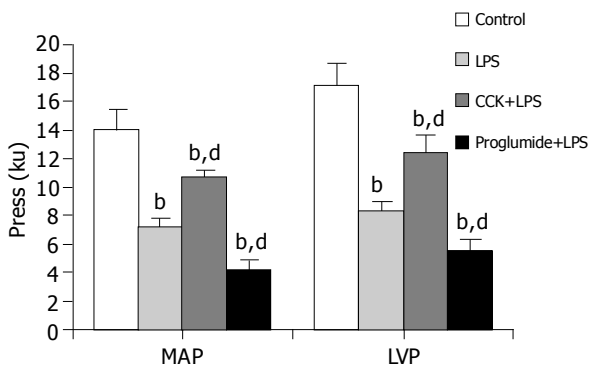

Figure 2 Changes in MAP and LVP after intravenous injection of sCCK-8 or proglumide to ES rats. (mean±SD, n = 6). [b]P<0.01 *vs* control; [d]P<0.01 *vs* LPS group.

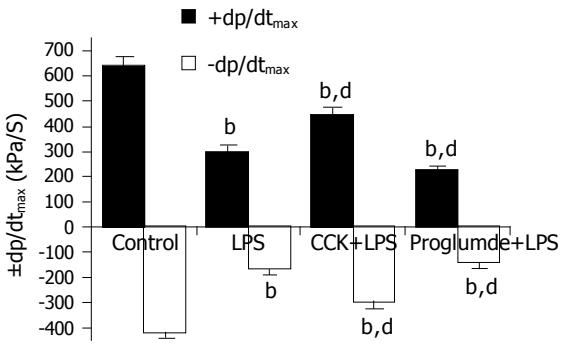

Figure 3 Changes in ±LV$dp/dt_{max}$ after intravenous injection of sCCK-8 or proglumide to ES rats. (mean±SD, n = 6) [b]P<0.01 *vs* control, [d]P<0.01 *vs* LPS.

Gene expression of CCK-R in myocardium of ES rats

Gene expression of CCK-A/ BR in myocardium of ES rats was up regulated by RT-PCR. The increase of CCK-AR mRNA induced by LPS began at 0.5 h, peaked at 2 h, kept a high level at 6 h and declined at 12 h, and they were 1.35, 2.23, 1.95, and 0.65 times that of control group, respectively. Similar to CCK-AR mRNA, the expression of CCK-BR mRNA peaked at 2 h and kept at a high level at 6 h, but it did not change at the first 0.5 h and was still at a high level at 12 h, and they were 0.944, 4.78, 2.79, and 2.67 times that of control group, respectively. The expression of housekeeping β-actin in different groups remained similar (Figure 4).

DISCUSSION

As a brain-gut peptide, cholecystokinin (CCK) exerts different physiological and pathophysiological actions[7]. Some previous studies suggested that sCCK-8, the predominant active form of endogenous CCK, might play an important role in adjusting the cardiac function and the effects were mediated by CCK-R. Marker *et al*[8], reported that CCK-8 added to the perfusion stream of isolated rat hearts produced an immediate bradycardia, which was abolished by using a CCK-R antagonist. Furthermore, Janssen *et al*[9], reported that CCK-8 elicited a dose-dependent increase in blood pressure and a variation in heart rate responses, that is, low doses of CCK-8 (0.5 μg/kg) caused tachycardia accompanied by renal, mesenteric and hindquarters vasoconstrictions, while high dose of CCK-8 (5 μg/kg) caused bradycardia accompanied by vasodilatation of the above arteries. To exclude the effect of central nervous system, a recent report by Gaw revealed that sCCK-8 caused

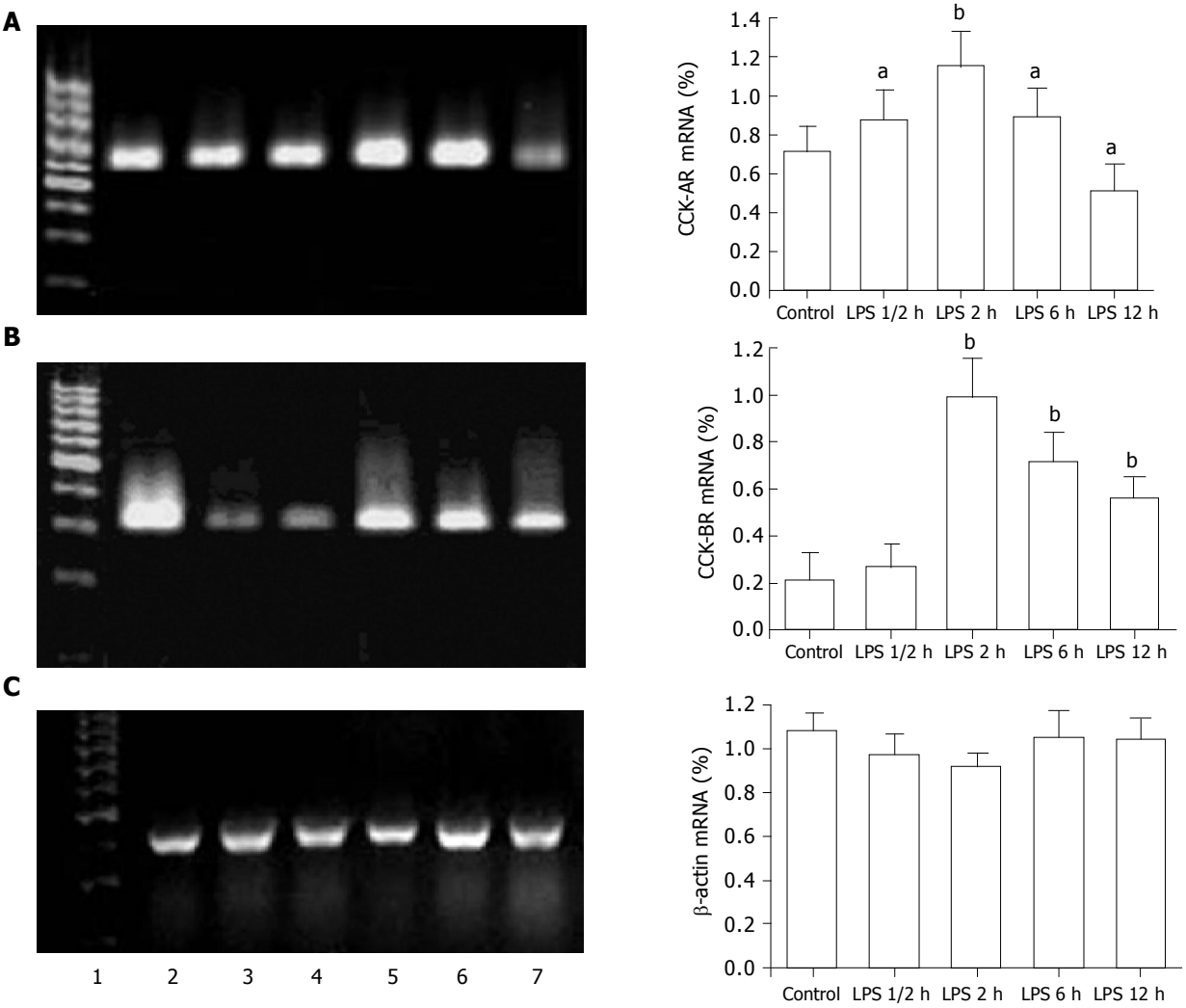

Figure 4 Expression of CCK-A/BR and β-actin mRNA of RT-PCR in the myocardium of ES rats. (mean±SD, n = 3) $^{a}P<0.05$ *vs* control, $^{b}P<0.01$ *vs* control. **A**: Representative pictures of CCK-AR (630 bp); **B**: representative pictures of CCK-BR (320 bp); **C**: representative pictures of β-actin (420 bp). Lane 1: DNA marker, lane 2: products expressed from kidney tissue as a positive control, lane 3: products expressed from control-saline-treated, lanes 4-7: products expressed from LPS-treated at 0.5, 2, 6, and 12 h, respectively.

a dose-dependent bradycardia and increase in MAP in pithed rats. Both the pressor response and bradycardia elicited by CCK-8 were reduced by selective CCK-AR antagonists, while the selective CCK-BR antagonists did not inhibit the effects of CCK-8[10]. Many other evidences for the involvement of CCK-AR in the effects of sCCK-8 in cardiovascular regulation[9,10]. In our experiment, administration of sCCK-8 resulted in a dose-dependent increase of cardiac function, leading to increase of MAP. The bradycardia was induced by medium and high doses of sCCK-8, while low dose of sCCK-8 caused a tachycardia. The effects of CCK-8 on cardiac functions were significantly inhibited by nonselective CCK-R antagonist - proglumide. Another study on single cardiomyocyte showed that sCCK-8 could increase [Ca(2+)](i) via activating the receptor-operated Ca(2+) channel and eliciting the influx of Ca(2+) in isolated guinea-pig cardiomyocyte[11]. The above results provided further evidence that the effect of CCK-8 on cardiovascular system might be mediated by the activation of CCK-R in myocardium.

Previous studies indicated the sustained improvement of the cardiovascular function induced by injection of sCCK-8 into rats bled to invariably fatal hemorrhagic shock[12]. Riepl's report that the level of sCCK-8 in serum was increased in endotoxemia of rats attracted our great interest[13]. The study in our department showed that endogenous and exogenous sCCK-8 had anti-ES effect, and that sCCK-8 had the ability to reverse the fall in mean arterial pressure, which was related with decreased clearance of sCCK-8 by lung in ES[14]. Recently, our study indicated that administration of sCCK-8 prevented increase of TNF-α gene and protein expression induced by LPS in spleen and lung, and decreased the levels of TNF-α, IL-1β, and IL-6 in serum, lung and spleen in ES rats. The study about its upstream signal mechanisms demonstrated that sCCK-8 inhibited LPS-induced NF-κB activity, I-κB degradation, TNF-α release and gene expression in PIMs, which was abrogated by proglumide[16]. Furthermore, CD14 on PIMs which was induced by LPS and its receptor could be downregulated by sCCK-8 *in vitro*[17]. These results suggested that sCCK-8 had anti-inflammatory effect to some extent, and sCCK-8 could clearly lessen the inflammatory lesions in lung, spleen and liver tissues in ES rats[2,14]. Our study

showed that sCCK-8 could remit the variation of HR and increase of both MAP and contractility of myocardium, then exert anti-ES effect, which were likely related to activation of CCK-R on myocardium.

CCK receptors have been pharmacologically classified into two subtypes: CCK-A receptor (CCK-AR) and CCK-B receptor (CCK-BR) according to their affinity for the peptide agonists CCK and gastrin[5]. CCK-AR is highly selective for sulfated analogs of CCK and the antagonist L-364 718, whereas CCK-BR has similarly high affinity to both sulfated and nonsulfated peptide analogs of CCK/gastrin peptides and the antagonist L-365 260[5]. CCK-AR is found principally in gastrointestinal tract and selective areas of the CNS, while CCK-BR is found principally in CNS and selective areas of the gastrointestinal tract, on pancreatic acinar cells and parietal cells[17,18]. CCK binds to CCK-AR present in a variety of gastrointestinal target tissues including pancreatic acini, islets, gastric mucosa and gallbladder to induce pancreatic enzyme secretion, insulin secretion, release of pepsinogen and gallbladder contraction[19]. CCK-BR in CNS regulates feeding, anxiety and memory, *etc*.[17]. CCK-AR and CCK-BR are also expressed in neoplastic cells such as pancreatic cancer cells[20,21], gastric cancer cells[23,24], colonic cancer cells[24] and small cell lung cancer cells[25-27] where they may stimulate cell growth. In addition, CCK-R is also related with brain injury[28], cortical infarct[29] and gastric ulceration[30]. We first detected CCK-AR and CCK-BR mRNA expression successfully not only in lung tissue, but also in heart tissue of rats[4]. Our data also demonstrated, for the first time that the expression of CCK-AR and CCK-BR mRNA were increased when induced by LPS, while other researchers found the expression level of CCK-AR was related to CCK-8 itself[31]. These data suggested that both CCK-AR and CCK-BR were widely distributed in various kinds of tissues and their presence provided the structural basis for CCK to exert a broad array of physiological action, including improving cardiac function by CCK-8 in ES rats.

In summary, the above results indicate that endogenous and exogenous sCCK-8 may markedly improve the cardiac function and hypotension of ES rats, which is likely related to high expression of CCK-A/BR on myocardium induced by LPS.

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