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Original Article

Effects of hydromorphone postconditioning on ischemia-reperfusion injury in isolated rat hearts and mitochondial permeability transition pore

Ying Zhang[1*], Qing Liu[1*], Miaoling Li[2], Qi Chen[1], Chang Liu[1], Li He[1], Xin Wang[1], Jie Zheng[1], Fengxu Yu[3]

[1]Department of Anesthesiology, Traditional Chinese Medicine Hospital of Southwest Medical University, Luzhou, China; [2]Key Laboratory of Medical Electrophysiology, Ministry of Education of China, Luzhou, China; [3]Department of Cardiothoracic Surgery, The Affiliated Hospital of Southwest Medical University, Luzhou, China. [*]Equal contributors.

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Abstract: To investigate the effects of hydromorphone postconditioning on ischemia/reperfusion injury in isolated rat hearts and mitochondial permeability transition pore (mPTP). Male SD rat hearts were harvested and then perfused in a Langendorff apparatus with K-H solution saturate. Rat hearts were randomly assigned into 4 groups (n = 10): Control group (group C), ischemia reperfusion group (group I/R), Hydromorphone postconditioning group (group H) and hydromorphone + Lonidamine postconditioning group (group HL). Group C was perfused continuously for 120 min; the rest groups were perfused for 30 min and treated by 30 min of ischemia followed by 60 min reperfusion to establish I/R injury model. Group H was received 10 min postconditioning treatment with 0.3 μmol/L hydromorphone after 30 min ischemia, group HL was received 0.3 μmol/L hydromorphone and 30 μmol/L Lonidamine for postconditioning at the same time. Compared with group C, LVDP, CF, +dp/dtmax and the fluorescence intensity of cardiomyocytes were significantly decreased in the rest groups, while LVEDP, LDH, CK-MB, Tn-T, NAD+, infarct size were significantly increased ($P < 0.05$). Compared with group H, LVDP, CF, ±dp/dtmax, HR and the fluorescence intensity of cardiomyocytes were significantly decreased in the group HL and group I/R, while LVEDP, LDH, CK-MB, Tn-T, NAD+, infarct size were significantly increased. There was no significant difference between group HL and group I/R except LDH ($P = 0.012$) and HR ($P = 0.034$). Hydromorphone can attenuate the I/R injury in isolated rat hearts, and 30 μmol/L Lonidamine (mPTP opener) can significantly abolished the effect of hydromorphone on myocardial protection.

Keywords: Hydromorphone, myocardial ischemia reperfusion injury, mitochondrial membrane transport proteins, postconditioning

Introduction

Ischemic heart diseases cause the 15% of global mortality, of which the myocardial ischemia reperfusion injury (MIRI) account for the largest proportion. The treatment of MIRI includes ischemia preconditioning (I-preC) and ischemia postconditioning (I-postC) [1]. Compared to I-preC, I-postC has more clinical practical value which works before ischemic myocardia reperfusion. In addition, I-postC can be divided into multiple sub-class, including drug postconditioning, remote ischemic postconditioning and delayed postconditioning [2].

The opioids, such as morphine, fentanyl and its derivatives, are opioid receptor agonists which were the important parts in clinical anesthesia and analgesia. Accumulating evidence indicates that opioids postconditioning can activate various survival signaling pathways to induce cardioprotection similar with I-postC [3-5]. However, as one of the morphine's derivatives, it is unclear that how hydromorphone postconditioning induces the cardioprotection.

During the MIRI, mitochondria were influenced by many factors. It is reported that increases of Reactive Oxygen Species (ROS) production or calcium overload can injury myocardial mitochondria so as to cause ATP synthesis disorder and even myocardial apoptosis [6]. Mitochondrial membrane transport pore (mPTP) permeates from mitochondrial inner to outer membranes, which is the main channel of exchange information and material for mito-

chondria. Studies showed that mPTP determined the cell survival or death [7]. If a large number of mPTP open, adverse event could be triggered, including the disequilibrium of mitochondrial permeability, uncoupling of oxidative phosphorylation, dissipation of the mitochondrial membrane potential, and cytochrome C (Cyt C) release into the cell plasma. Dysfunction of mPTP also causes cell apoptosis by increasing Bax and Caspase-3 [8]. In addition, the factor of ROS and calcium overload can induce the mPTP opening to cause the myocardial apoptosis [8], thus, mPTP is currently a hotspot in the field of MIRI [9]. Over the past decades, studies have shown that mPTP is one of the end effectors of the Opioids postconditioning. Opioids postconditioning was proved to inhibit cellular mPTP opening during reperfusion period by phosphorylating glycogen synthase kinase-3 beta (GSK-3β) by activating reperfusion injury salvage kinase (RISK), which included phosphoinositol 3-kinase (PI3K), protein kinase B (Akt) and extracellular regulated protein kinases (ERK1/2) [10-12]. However, it is unclear whether mPTP is an end effector of the hydromorphone postconditioning.

Accordingly, current study was focused on the effect of the mPTP in the hydromorphone postconditioning. With isolated perfused rat heart model, we evaluated cardioprotection of the hydromorphone postconditioning to explore changes of cardiac function, infarct size and myocardial enzymes, and investigated whether the mPTP opens after the hydromorphone postconditioning.

Materials and methods

This study was under approval of the Institutional Local Animal Care and Use Committee of the Southwest Medical University. Adult Dwaley-Sprangue male SD rats (age: 2-3 months; weighing 250-350 g) were purchased from the animal experimental center of Southwest Medical University. Rats were routinely fed for one week before experiment and were raised in temperature-controlled (24~26°C) cages with a 12-hour dark and 12-hour light cycle.

Heart perfusion

Langendorff perfusion system (ML176, Instruments AD, Australia) was used to establish the model of isolated perfused rat heart. Every rat heart was rapidly excised after intraperitoneal injection of 10% chloral hydrate (350 mg/kg) and heparin (1000 U/kg), and the aorta was separated in 4°C Krebs-Henseleit bicarbonate buffer (mmol/L: NaCl 118.0, KCl 4.7, KH_2PO_4 1.2, $NaHCO_3$ 25.0, $MgSO_4 \cdot 7H_2O$ 1.2, glucose 11.1, $CaCl_2$ 1.8, HEPES 10, pH 7.35~7.45) with 95% O_2 + 5% CO_2. Then isolated rat heart was connected on the cannula of Langendorff perfusion system via the aorta, and perfused with 37°C Krebs-Henseleit bicarbonate buffer (pH 7.35~7.45) with a constant perfusion pressure (60 mmHg).

After 30 min perfusion, the left atrial appendage of isolated hearts was snipped, and rest parts were inserted with a water-filled latex balloon into the left ventricle cavity. The balloon was connected to the pressure transducer (844-28, Memscap Instruments, France) and adjusted to 4~8 mmHg of initial pressure. Left ventricular systolic pressure (LVSP), left ventricular end diastolic pressure (LVEDP), left ventricular developed pressure (LVDP), the left ventricular diastolic pressure increased and decreased the maximum rate (±dp/dtmax), heart rate (HR) and Coronary flow (CF) were recorded and analyzed by Powerlab/8SP multichannel physiologic recorder (ML785, AD instruments, Australia) and Labchart 6 Pro software, respectively. The hearts were removed to global ischemia for 30 min, and then followed with 60 min of reperfusion. Hearts were abandoned if their HR < 200 times/min, LVSP < 75 mmHg or extrasystole > 2 times/min after 30 min perfusion.

Ischemia-reperfusion protocols for isolated hearts

40 isolated perfused rat hearts were randomly divided into 4 groups (n = 10): (1) Control group (Group C): 120 min of continuous perfusion; (2) Ischemia reperfusion group (Group I/R): 30 min perfusion, 30 min ischemia, and 60 min reperfusion; (3) Hydromorphone postconditioning (Group H): 30 min of perfusion, 30 min of ischemia, 10 min of hydromorphone postconditioning, 50 min of reperfusion; (4) Hydromorphone + Lonidamine postconditioning (Group HL): 30 min of perfusion, 30 min of ischemia, 10 min of hydromorphone + Lonidamine postconditioning, 50 min of reperfusion; The

Table 1. Left ventricular function comparison of isolated rat hearts in four groups (n=10, $\bar{x} \pm s$)

Group	LVDP (mmHg)			LVEDP (mmHg)		
	T0	T2	T3	T0	T2	T3
C	91±6	89±7	87±8	9.0±1.0	9.7±1.2	10.8±1.4
I/R	88±12	47±10[a]	43±14[a]	8.7±1.4	57.0±4.2[a]	55.5±4.7[a]
HL	91±11	50±5[a]	50±12[a]	7.9±1.5	56.6±3.9[a]	56.2±3.0[a]
H	90±13	76±7[a,b,c]	76±6[a,b,c]	7.9±1.1	17.0±2.1[a,b,c]	17.8±1.1[a,b,c]
	+dp/dtmax (mmHg/s)			-dp/dtmax (mmHg/s)		
	T0	T2	T3	T0	T2	T3
C	4249±368	4377±448	4395±513	2060±135	2101±220	1980±248
I/R	4333±521	1732±386[a]	1525±305[a]	2272±484	965±257[a]	1058±299[a]
HL	4211±525	1816±571[a]	1488±538[a]	2250±395	971±294[a]	1114±259[a]
H	4319±410	3927±232[a,b,c]	3737±373[a,b,c]	2345±396	1883±317[b,c]	1789±301[b,c]
	HR (beats/min)			CF (ml/min)		
	T0	T2	T3	T0	T2	T3
C	245±25	255±30	256±30	10.1±0.5	10.1±0.6	10.1±0.6
I/R	258±28	211±19[a]	224±29[a]	10.0±0.5	4.2±0.6[a]	4.9±1.0[a]
HL	257±37	248±39[b]	248±35[b]	10.5±0.4	4.2±0.6[a]	5.2±0.5[a]
H	258±26	241±32[b]	239±27[b]	10.0±0.7	7.3±0.4[a,b,c]	7.4±0.5[a,b,c]

Compared with group C, [a]$P < 0.05$; Compared with group I/R, [b]$P < 0.05$; Compared with group HL, [c]$P < 0.05$.

doses of hydromorphone and Lonidamine were 0.3 μmol/L and 30 μmol/L, respectively, which were determined by pre-experiment.

Examination of left ventricular function

Record and analyze LVSP, LVEDP, LVDP, ±dp/dtmax, HR and CF by Powerlab/8SP multichannel physiologic recorder and Labchart 6 Pro software at three time points, including 30 min of perfusion (T0), 30 min of reperfusion (T2) and 60 min of reperfusion (T3). All of the results were comprehensively analyzed within 20 s of the data in sinus rhythm.

Biochemical markers of myocardial ischemia

Two coronary outflows were collected at 30 min of perfusion (T0) and 60 min of reperfusion (T3). One of them was detected the content of LDH and CK-MB with full automatic biochemical analyzer (AU5800, Beckman Coulter Instruments, USA) immediately, the other was stored at -80°C for further assay of Tn-T content with ELISA.

Biochemical markers of mPTP opening

Collected liquid flowing from the coronary artery at 30 min of perfusion (T0) and 15 min of reperfusion (T1) and stored at -80°C for further assay of NAD+ content with ELISA.

Infarct size

Infarct size was assessed with routine protocol by 2,3,5-triphenylte trazolium chloride (TTC) staining after 60 min of reperfusion (T3) (n = 5 for every experimental group). Only preserved ventricle and cut off other tissues, weighed after drying with filter paper (G). Slice ventricle into five 1-2 mm cross every sections along with the short axis after 15 min of -30°C frozen. The slices were immediately incubated away from light for 15 min in 1% TTC buffer (1% TTC in 0.0IM PBS buffer, pH 7.4) at 37°C, and infarct size of the slices would turn pale. Calculate the pale area weighed after drying with filter paper (g) again, the infarct size = g/G × 100%.

Determination of mPTP opening with laser scanning confocal microscopy

According to the previous report [13], the rat heart was isolated with collagenase type II after 60 min reperfusion (T3) (n = 5 for every experimental group) and cultured with sodium bicarbonate buffered Medium 199. The amount of the mPTP opening was directly assessed by

Table 2. Biochemical markers of myocardial ischemia with comparison of isolated biochemical markers between four groups (n = 10, $\bar{x} \pm s$)

Group	LDH (U/L)		CK-MB (U/L)		Tn-T (pg/ml)	
	T0	T3	T0	T3	T0	T3
C	13.5±2.1	18.0±1.7	20.6±4.3	24.2±1.6	20±5	26±5
I/R	15.0±2.0	111.8±5.8[a]	23.3±3.3	81.0±7.1[a]	22±6	120±17[a]
HL	14.5±2.3	96.1±9.1[a,b]	24.0±3.0	82.9±6.4[a]	24±4	118±11[a]
H	14.5±2.1	41.8±3.0[a,b,c]	23.8±4.2	41.5±3.7[a,b,c]	24±4	42±3[a,b,c]

Compared with group C, [a]P < 0.05; Compared with group I/R, [b]P < 0.05; Compared with group HL, [c]P < 0.05.

Table 3. Content of NAD+ (pg/ml) and comparison of isolated rat hearts between four groups (n=10, $\bar{x} \pm s$)

	C	I/R	HL	H
T0	22±3	23±4	23±3	23±4
T1	26±3	110±5[a]	110±8[a]	46±9[a,b,c]

Compared with group C, [a]P < 0.05; Compared with group I/R, [b]P < 0.05; Compared with group HL, [c]P < 0.05.

15 min of co-loading with calcein AM (2 μM) and $CoCl_2$ (4 mM) in the standard incubator atmosphere of 5% CO_2, and then rinsed by PBS (free of calcein AM and $CoCl_2$) before scanning with confocal microscope (LSM 510, Carl Zeiss, Germany).

Excitation and emission wave lengths for calcein AM were 488/500-540 nm (λex/λem), observed 5 rod-shaped cardiomyocytes with clear myocardial striation randomly and the fluorescence intensity of cardiomyocytes was calculated and analyzed by image pro plus 6.0.

Data analysis

All data are presented as the form of mean ± SD. Statistical analysis was performed with one-way ANOVA and followed by LSD test analysis for multiple comparisons to investigate statistical significance of differences between groups. P < 0.05 was considered statistical significance.

Results

40 isolated perfused rat heart models were successfully established in this study and all data of 40 isolated rat hearts were used for statistical analysis.

Effects on left ventricular function

There were no differences at baseline of left ventricular function among groups. Compared with Control group (Group C), the left ventricular function of other three groups decreased with different degrees at 30 min of reperfusion (T2) and 60 min of reperfusion (T3) (P = 0.019). However, left ventricular function of hydromorphone postconditioning (Group H) was significantly improved than Ischemia reperfusion group (Group I/R) and hydromorphone + Lonidamine postconditioning (Group HL) after reperfusion (P = 0.023). And there was no significant difference between Group HL and Group I/R (P = 0.152) **Table 1**.

Effects on biochemical markers of myocardial ischemia

Compared with Control group (Group C), the biochemical markers of myocardial ischemia of other three groups increased at 60 min of reperfusion (T3) (P = 0.009). However, 10 min of 0.3 μmol/L hydromorphone postconditioning significantly reduced the content of LDH, CK-MB and Tn-T compared with Ischemia reperfusion group (P = 0.011). Moreover, the biochemical markers of Group HL increased significantly again compared with Group H and Group C (P = 0.024) **Table 2**.

Effects on mPTP opening

Compared with Control group (Group C), the content of NAD+ of other three groups increased at 15min of reperfusion (T1) (P = 0.003). Hydromorphone postconditioning decreased the content of NAD+ compared with Ischemia reperfusion group (P = 0.042). The content of NAD+ of Group HL increased again compared with Group H and Group C (P = 0.037) (**Table 3**).

The fluorescence intensity of cardiomyocytes showed that Group C was 168.94±7.69, Group I/R was 65.38±8.67, Group HL was 72.42±7.15 and Group H was 124.96±9.34. Compared with Group C, the fluorescence intensity of

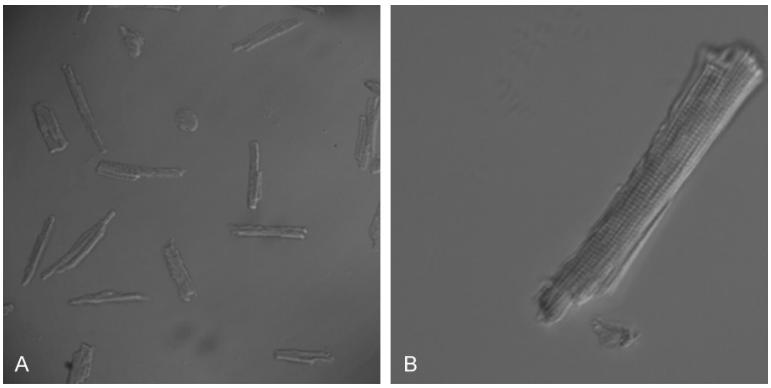

Figure 1. A: Cardiomyocytes of adult rat heart under 20 × microscope. B: Cardiomyocytes of adult rat heart under 200 × microscope.

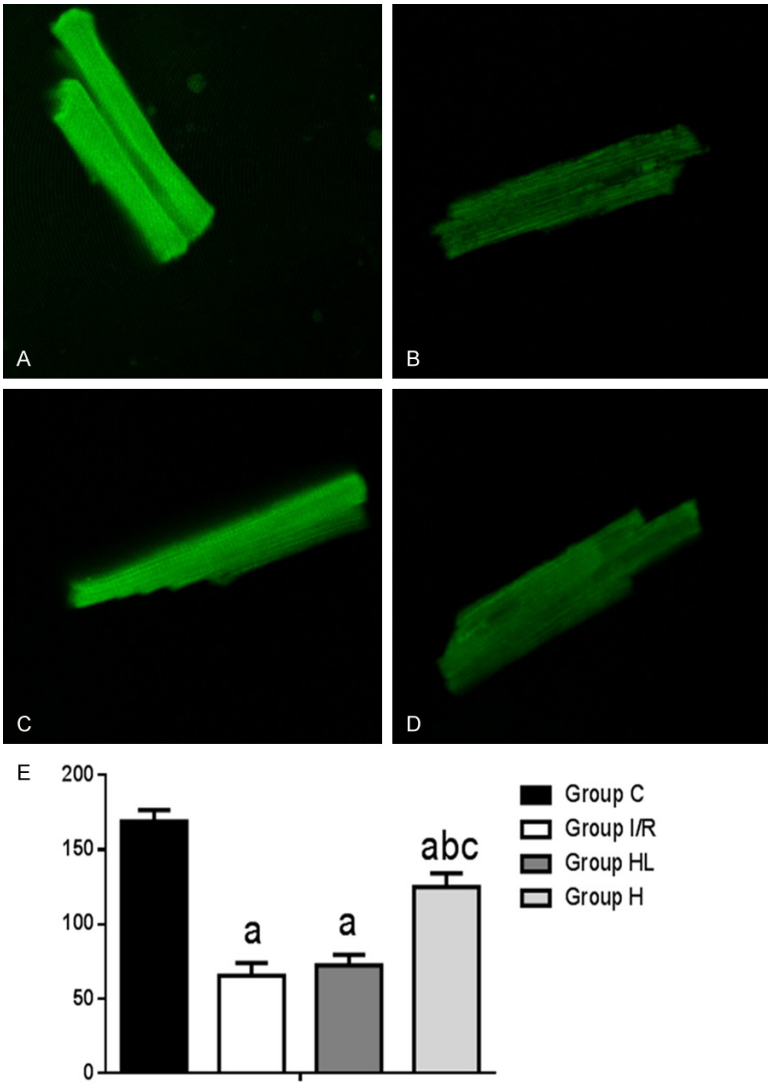

Figure 2. Fluorescence intensity of cardiomyocytes under 200 × laser scanning confocal microscopy with λex/λem = 488/500-540 nm. A: Group C; B: Group I/R; C: Group H; D: Group HL; E: Compared with group C, aP < 0.05; Compared with group I/R, bP < 0.05; Compared with group HL, cP < 0.05.

cardiomyocytes of other three groups increased (P = 0.034). Hydromorphone postconditioning could increase the fluorescence intensity when compared with Group I/R (P < 0.05). And the fluorescence intensity of Group HL decreased again when compared with Group H and Group C (P = 0.029) (**Figures 1** and **2**).

Effects on myocardial infarct injury

The infarct injury: Group C was (10.9±2.1)%, Group I/R was (61.4±6.7)%, Group HL was (64.8±6.1)% and Group H was (23.4±3.4)%. Compared with Group C, the infarct injury of other three groups increased (P = 0.007). Hydromorphone postconditioning could decrease the infarct injury when compared with Group I/R (P < 0.05). The infarct injury of Group HL increased again when compared with Group H and Group C (P=0.015).

Effects of hydromorphone post-conditioning on myocardial infarct size

The infarct size in Group C, Group I/R, Group HL and Group H respectively was (10.9±2.1)%, (1.4±6.7)%, (64.8±6.1)% and (23.4±3.4)%. Compared with the Group C, the infarct size significantly increased in the rest groups. Compared with Group H and Group C, the infarct size significantly increased again in Group HL (**Table 4**).

Discussion

In the present study, we hypothesized that hydromorphone postconditioning could

Table 4. Comparison of infarct size (ratio) of hearts between four groups (n=10, $\bar{x} \pm s$)

	C	I/R	HL	H
Infarct size	(10.9±2.1)%	(1.4±6.7)%[a]	(64.8±6.1)%[b,c]	(23.4±3.4)%

Compared with group C, [a]P < 0.05; Compared with group I/R, [b]P < 0.05; Compared with group H, [c]P < 0.05.

reduce the ischemia/reperfusion injury in isolated rat hearts via inhibiting the mPTP opening during reperfusion.

To prove this hypothesis, we firstly establish ischemia reperfusion model of isolated rat heart using Langendorff system according to the previous report [14]. We observed that, after 30 min global ischemia, left ventricular dysfunction occurred; LDH, CK-MB and Tn-T in coronary outflow increased; Infarct size of isolated rat heart increased during reperfusion. We selected 0.3 μmol/L Hydromorphone postconditioning 10 min after 30 min global ischemia. We observed that 0.3 μmol/L hydromorphone postconditioning could promote left ventricular function recovery; decrease LDH, CK-MB and Tn-T in coronary outflow and prevent from myocardial infarct. These results illustrated that 0.3 μmol/L hydromorphone postconditioning 10 min could alleviate myocardial reperfusion injury which was consistent with other opioids postconditioning results [15-18]. In addition, considering the progress of ischemia-reperfusion injury, we observed phenotype in different time points (T0, T2 and T3) according to previous reports [16, 17, 19].

We observed that the content of NAD+ in coronary outflow increased at 15 min reperfusion in ischemia reperfusion group, and 0.3 μmol/L Hydromorphone postconditioning 10 min could decrease the content of NAD+. Furthermore, after treatment of 30 μmol/L Lonidamine postconditioning 10 min, the content of NAD+ in coronary outflow increased. We also observed that 30 μmol/L Lonidamine postconditioning 10 min could reduce the cardioprotection of the hydromorphone postconditioning. These results illustrated that cardioprotection of the hydromorphone postconditioning was related to inhibition of mPTP opening. We also confirmed this result by laser scanning confocal microscopy.

Hydrophobicity of calcein AM is greatly enhanced due to AM's esterification which can freely diffuse into cytoplasm and mitochondria, and then calcein AM can be catalyzed into calcein by non-specific esterase and remain in the cytoplasm and mitochondria. $CoCl_2$ can freely diffuse into cytoplasm and quench fluorescence of calcein but cannot diffuse into mitochondria, so co-loading with calcein AM and $CoCl_2$ can quench fluorescence of cytoplasm without affecting the fluorescence of mitochondria [20, 21]. But when mPTP opened, calcein in mitochondria can release and be quenched by $CoCl_2$, therefore, the change of fluorescence of mitochondria reflect the degree of mPTP opening [22].

We observed that fluorescence intensity of cardiomyocyte weakened after ischemia-reperfusion injury; Hydromorphone postconditioning could increase the fluorescence intensity; but added Lonidamine postconditioning could decrease the fluorescence intensity again. These results illustrated that Hydromorphone postconditioning could inhibit the mPTP opening.

Conclusion

Hydromorphone postconditioning can alleviate myocardial reperfusion injury in rats and the mechanism relate to inhibition of mPTP opening. Hydromorphone could a potential target to prevent myocardial ischemia/reperfusion injury.

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Disclosure of conflict of interest

None.

Address correspondence to: Fengxu Yu, Department of Cardiothoracic Surgery of The Affiliated Hospital of Southwest Medical University, 25 Taiping Street, Luzhou 646000, China. Tel: 0086-830-3165471; Fax: 0086-830-2392753; E-mail: yishujiuq@sina.com

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