Stimulation of Oxytocin Receptor during Early Reperfusion Period Protects the Heart against Ischemia/Reperfusion Injury: the Role of Mitochondrial ATP-Sensitive Potassium Channel, Nitric Oxide, and Prostaglandins

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Abstract- Postconditioning is a simple and safe strategy for cardioprotection and infarct size limitation. Our previous study showed that oxytocin (OT) exerts postconditioning effect on ischemic/reperfused isolated rat heart. The aim of this study was to investigate the involvement of OT receptor, mitochondrial ATP-sensitive potassium channel (mKATP), nitric oxide (NO) and cyclooxygenase (COX) pathways in OT postconditioning. Isolated rat hearts were divided into 10 groups and underwent 30 min of regional ischemia followed by 120 min of reperfusion (n =6). In I/R (ischemia/reperfusion) group, ischemia and reperfusion were induced without any treatment. In OT group, oxytocin was perfused 5 min prior to beginning of reperfusion for 25 min. In groups 3-6, atosiban (oxytocin receptor blocker), L-NAME (N-Nitro-L-Arginine Methyl Ester, non-specific nitric oxide synthase inhibitor), 5-HD (5-hydroxydecanoate, mKATP inhibitor) and indomethacin (cyclooxygenase inhibitor) were infused prior to oxytocin administration. In others, the mentioned inhibitors were perfused prior to ischemia without oxytocin infusion. Infarct size, ventricular hemodynamic, coronary effluent, malondialdehyde (MDA) and lactate dehydrogenase (LDH) were measured at the end of reperfusion. OT perfusion significantly reduced infarct size, MDA and LDH in comparison with I/R group. Atosiban, 5HD, L-NAME and indomethacin abolished the postconditioning effect of OT. Perfusion of the inhibitors alone prior to ischemia without oxytocin infusion had no effect on infarct size, hemodynamic parameters, coronary effluent and biochemical markers as compared with I/R group. In conclusion, this study indicates that postconditioning effects of OT are mediated by activation of mKATP and production of NO and Prostaglandins (PGs).

Keywords: Oxytocin; Postconditioning; mKATP; NO; Cyclooxygenase; Isolated heart

Introduction

Rapid reperfusion of the ischemic myocardium is a valuable approach to decrease infarct size. However, reperfusion by itself leads to reversible and irreversible injuries in the ischemic myocardium (1-2). To decrease reperfusion injuries in the ischemic myocardium, postconditioning, as a cardioprotective phenomenon, is induced at the end of ischemia and early reperfusion by using the repetitive short periods of ischemia/reperfusion (I/R) or by administration of pharmacological agents (3-4).

Myocardial infarct-limiting effects of postconditioning have been reported to be sensitive to inhibition of the NO-cyclic GMP (cGMP)-dependent protein kinase G (NO-cGMP-PKG) signaling pathway which has protective role against I/R injuries (5). Recently it has been reported that nitric oxide (NO) is involved in cardiac postconditioning (6). Administration of L-NAME prior to the onset of nitric oxide (NO) is involved in cardiac postconditioning (6). Administration of L-NAME prior to the onset of nitric oxide (NO) is involved in cardiac postconditioning (6). Also, the role of NO was reported in the heart failure and left ventricular remodeling (7). In a previous study, we showed that oxytocin-induced preconditioning was mediated by NO (8). It has also been shown that postconditioning leads to release of endogenous ligands...
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and activates G-protein-coupled receptor and then stimulates intracellular signaling pathway that may terminate on mitochondrial ATP-sensitive potassium channel (mKATP) and permeability transition pore (mPTP) (9-10). At mitochondria, PKG can open the mKATP via protein kinase C-ε (PKC-ε) (9). Postconditioning has an antioxidant effect and can decrease oxidative stress by reduction of the superoxide (11). It also induces activation of guanylyl cyclase; activate the reperfusion injury signaling kinase (RISK), extracellular regulated kinase-1 (ERK1/2), and PI3k/Akt signaling pathways (12,13). Postconditioning also increases expression and activation of the phosphorylated endothelial nitric oxide synthase (p-eNOS). Activation of NOS through the production of cGMP and activation of PKG could open mKATP and leads to cardioprotection (14).

Prostaglandins (PGs) have a putative role in cardioprotection and reduction of myocardial injuries such as infarct size in the rat model of myocardial I/R injury (15). Also, there were increased cardiac I/R injuries in COX-1 and COX-2 knockout mice in coronary artery ligation model (16-17). Then, it suggests that COX-1 and COX-2 signaling pathways may be involved in the cardioprotection (16-18). Birnbaum showed that PGs are essential for mediating cardioprotective effects of atorvastatin (15). Berti (19) and Rossoni (20) also reported indomethacin and aspirin can increase ischemia-induced ventricular dysfunction in perfused rabbit hearts, therefore this effect was related to inhibition of prostacyclin (PGI2) synthesis in the myocardium. PGI2 production is increased during the early 5–10 min of reperfusion and then declined during more reperfusion (21). In addition, it is reported that administration of opioids or anesthetic agents through COX-2 up-regulation leads to cardioprotection (22). It has been shown that activation of OT receptor can lead to PGs production (23-24), and decrease I/R injuries.

Oxytocin (OT) as a cardiovascular hormone is synthesized and released in the heart, and large vessels, and systemic administration of exogenous OT shows some cardiovascular functions (25-26). Some experiments showed that atosiban (a blocker of oxytocin receptor) can inhibit OT effects on heart function (27-28). Recently we reported that infusion of OT at the end of ischemia and early reperfusion period, postconditioned the isolated rat heart against I/R injury (29). It has been shown that in the cardiovascular system, OT receptor can activate atrial natriuretic peptide (ANP) and NO-eGMP signaling pathways (30). OT can also activate PKC in cardiomyocytes (31). On the other hands, PKC activation promotes mKATP channels opening in rat heart and induces cardioprotection (32).

The aim of this study was to determine the possible role of oxytocin receptor, mKATP channel, nitric oxide and prostaglandins in the postconditioning effects of oxytocin in the ischemic/reperfused isolated rat heart.

Materials and Methods

Experimental animals and ethical approval

Male wistar rats weighing 250–300g were housed in an animal room with 12h light/dark cycle at 22 ± 2°C and free access to food and water. Animals were adapted for at least seven days before the experiments. The experimental protocol was approved by the institutional care and use committee of Tehran University of Medical Sciences (Tehran, Iran).

Preparation of isolated hearts

The animals were anesthetized with sodium pentobarbital (50mg/kg, i.p.) and given heparin sodium (500IU). The hearts were excised quickly and placed in an ice-cold buffer, then attached to Langendorff apparatus for their perfusion. Hearts were perfused with modified Krebs–Henseleit bicarbonate buffer containing: NaHCO3 25; KCl 14.7; NaCl 118.5; MgSO4 1.2; KH2PO4 1.2; glucose 11; CaCl2 2.5 (in mmol/l) and gassed with 95% O2, 5% CO2 (pH 7.35–7.45 at 37°C). Heart temperature was kept constant during the experiment with a water-jacketed closed system. A fluid-filled latex balloon was inserted into the left ventricle via the left atrium and connected to a pressure transducer (Harvard). Left ventricular systolic and diastolic pressures and heart rate were measured throughout the experimental protocols via a custom designed chart recorder (Oscillograph Monitor, Biomed, Tehran, Iran). The left ventricular end-diastolic pressure (LVEDP) was adjusted to 5-10 mmHg by filling the balloon with water and was not changed afterward.

A 6-0 silk suture was passed below the origin of the left anterior descending coronary artery (LAD), and the ends of the suture were passed through a pipette tip to form a snare. Regional ischemia was accomplished by pulling the snare. Reperfusion was performed by releasing the ends of the suture. Hearts were allowed to beat spontaneously during the experiments. Left ventricular developed pressure (LVDP) was calculated as left ventricular systolic pressure minus left ventricular end diastolic pressure (LVDP=LVSP–LVEDP). Left ventricular function was assessed by rate pressure product (RPP=HR×LVDP). Coronary effluent was...
collected for assessment of lactate dehydrogenase (LDH) and malondialdehyde (MDA) at the end of reperfusion.

Experimental protocol
Before 15 min baseline period, each heart was allowed to stabilize for 20 min. The hearts in all groups were subjected to 30 min of regional ischemia followed by 120 min of reperfusion. Atosiban (oxytocin receptor blocker), L-NAME (N-Nitro-L-Arginine Methyl Ester, non-specific nitric oxide synthase inhibitor), 5-HD (5-hydroxydecanoate, nKATP inhibitor) and indomethacin (cyclooxygenase inhibitor) were used in this study. The hearts were randomized into one of ten groups (n=6): 1) ischemia/reperfusion (IR) group; hearts subjected to 30 min of regional ischemia followed by 120 min of reperfusion without any treatment. 2) OT group; Oxytocin (10-11M, optimum dose of OT was achieved by our previous study (29)) was perfused 5 min prior to reperfusion for 25 min; 3) ATO group; Atosiban (10-8 M) was perfused 10 min before ischemia for 10 min; 4) ATO+OT group; Atosiban was perfused 35 min before OT perfusion; 5) 5HD group; 5-HD (10-6 M) was perfused 10 min before ischemia for 10 min; 6) 5HD+OT group; 5HD was perfused 35 min before OT perfusion; 7) L-NAME group; L-NAME (10-6M) was perfused 10 min before ischemia for 10 min; 8) L-NAME+OT group; L-NAME was perfused 35 min before OT perfusion; 9) INDO group; Indomethacin (10-6M) was perfused 10 min before ischemia for 10 min; 10) INDO+OT group; Indomethacin was perfused 35 min before OT perfusion (Figure 1).

Measurement of infarct size
After 120 min of reperfusion, LAD was re-occluded, and Evans blue dye (2%) was infused through the aorta to differentiate the ischemic area from the non-ischemic area. Hearts were frozen at -20°C for 24h and then sliced into 2 mm transverse sections. Slices then incubated in 1% 2, 3, 5 triphenyl tetrazolium chloride (TTC in 0.1M phosphate buffer, pH 7.4) for 15-20 min at 37°C. TTC reacts with the viable tissue, producing a red formazan derivative, which is distinct from the white necrotic area when placed in 10% formalin for several days. The area at risk (ischemic zone) and infarcted area were calculated by Photoshop program (Ver. 7.0, Adobe System, San Jose, CA, USA). The area at risk was expressed as a percentage of the left ventricle (AAR/LV), and infarct size was expressed as a percentage of area at risk (IS/AAR).

Measurement of LDH and MDA
LDH and MDA levels were measured in coronary effluent at the end of 120 min reperfusion. LDH (a marker of myocyte necrosis) was determined with LDH Kit (Pars Azmoon, Teheart ratean, Iran), using an autoanalyzer (Roche Hitachi Modular DP Systems; Mannheim, Germany). MDA (a marker of lipid peroxidation) was assessed by a thiobarbituric acid (TBA) method. In brief, 1.5ml of perfusate fluid was

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**Figure 1.** Schematic illustration of experimental groups
IR, Ischemia/Reperfusion; OT, Oxytocin; ATO, Atosiban; 5HD, 5-hydroxydecanoic acid; INDO, Indomethacin
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added to 0.5 ml of a solution containing 30% trichloroacetic acid, 0.75% TBA, and 0.5 NHCl, and then incubated in a 100°C for 20 min. After cooling, the samples were centrifuged, and MDA level was read by spectrophotometer at 532 nm (33).

Drugs and reagents

Oxytocin, atosiban, 5-HD, L-NAME, indomethacin, 2, 3, 5 triphenyl tetrazolium chlorides (TTC) and Evans blue were obtained from Sigma Chemical Co.

Statistical analyses

Data are expressed as means ± SEM. Statistical comparison of means between groups was made by one-way ANOVA and a subsequent Tukey test for infarct size ratio and biochemical parameters. Statistical analysis of hemodynamic data within and between groups was performed with Two-way ANOVA. Statistical significance was defined as \( P<0.05 \).

Results

Hemodynamic function

Table 1 shows HR, RPP and LVDP changes during the experiments. LVDP and RPP were expressed as a percentage of their baseline. HR, RPP, and LVDP were decreased significantly in all groups at the end of ischemia and reperfusion compared to their baseline \( (P<0.05) \), but not significant differences were shown between experimental groups at baseline, end of ischemia and reperfusion.

Infarct size and area at risk

Statistical analysis showed that there were no significant differences in the ratio of the area at risk to the total left ventricular area \( (AAR/LV \%) \) between the hearts in all groups. The ratio of infarct size to area at risk \( (IS/AAR \%) \) significantly decreased from 36.35 ± 0.48 in I/R group to 11.68±0.86 \( (P<0.05) \) in OT group (Figure 2).

Administration of atosiban in ATO+OT group, 5HD in 5HD+OT group, L-NAME in L-NAME+OT group and Indomethacin in INDO+OT group increased infarct size to 32.27 ± 2.8, 31.19 ±3, 32.36±1.2 and 27.23±1.76, respectively in comparison with OT group \( (P<0.05) \).

Atosiban, 5HD, L-NAME, and INDO alone had no significant effect on infarct size. There were no significant differences in ATO+OT, ATO, 5HD+OT, 5HD, L-NAME+OT, L-NAME, INDO+OT and INDO groups compared to IR group.

Biochemical analysis

The levels of LDH and MDA in coronary effluent were used to monitor the damages of the myocardium. LDH level in coronary effluent significantly decreased in OT group \( (53.14±10.97) \) compared to IR group \( (232.125±21.5) \) \( (P<0.05 \text{ Figure 3} \)).

Administration of ATO in ATO+OT group, 5HD in 5HD+OT group, L-NAME in L-NAME+OT group and Indomethacin in INDO+OT group significantly increased LDH levels.
(172.125±22.6, 169.125±13.301, 186.75±8.6 and 171.5±16.5 respectively) in comparison with OT group ($P<0.05$). There were no significant differences in ATO+OT, ATO, 5HD+OT, 5HD, L-NAME+OT, L-NAME, INDO+OT and INDO groups compared to IR group.

Figure 3. Levels of LDH in coronary effluent at the end of reperfusion period in different groups (n=6)
IR, Ischemia/Reperfusion; OT, Oxytocin; ATO, Atosiban; 5HD, 5-hydroxydecanoic acid; INDO, Indomethacin. Data are presented as mean±SEM. *$P<0.05$ vs. IR group and $P<0.05$ vs. OT group.

MDA levels in coronary effluent significantly decreased in OT group (1.27±0.299) in comparison with IR group (5±0.37) ($P<0.05$ Fig.4). Administration of ATO in ATO+OT group, 5HD in 5HD+OT group, L-NAME in L-NAME+OT group and Indomethacin in INDO+OT group increased MDA (4.7±0.51, 5.375±0.744, 4.82±0.45 and 5.3±0.67 respectively) compared to OT group ($P<0.05$ Fig.4). There were no significant differences in ATO+OT, ATO, 5HD+OT, 5HD, L-NAME+OT, L-NAME, INDO+OT and INDO groups compared to IR group.

Figure 4. Levels of MDA in coronary effluent at the end of reperfusion period in different groups (n=6)
IR, Ischemia/Reperfusion; OT, Oxytocin; ATO, Atosiban; 5HD, 5-hydroxydecanoic acid; INDO, Indomethacin.
Data are presented as mean±SEM

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**Discussion**

Postconditioning is an easy and safe strategy which provides a new method to protect organs from I/R injury, such as heart and liver (34). Our previous study demonstrated that OT has a postconditioning effect on the isolated rat heart. OT administration at the end of ischemia and the beginning of reperfusion dose dependently protected isolated rat heart from I/R injury (29).

In this study, administration of OT had no significant effect on hemodynamic parameter (such as; HR, LVDP, and RPP) compared to IR group and it seems that cardioprotective effect of OT is not related to changes in hemodynamic parameters. In the other hand, OT significantly decreased infarct size, LDH, and MDA level compared to IR group. These cardioprotective effects were abolished by administration of atosiban, as a non-selective OT-receptor antagonist, 5HD, as an mKATP channel blocker, L-NAME, inhibitor of NO production, and indomethacin as an inhibitor of PGs production. According to current findings, it seems that OT postconditioning can occur through stimulation of oxytocin receptor, PGs release, NO production and opening of mKATP channel and leads to cardioprotection against ischemia/reperfusion injury.

It has been shown that ROS play a crucial role in the I/R injury. After ischemia, ROS were produced at the onset of reperfusion (34-35). In the present study, OT administration prevented the MDA level raise and it appears that OT by reducing oxidative stress attenuates myocardial injury. OT reverses the increased level of MDA to a considerable extent, that confirms its antioxidant effect on I/R injury. Biyikli et al., reported that OT attenuates oxidative renal damage in pyelonephritic rats through its antioxidant effect (36). NO can activate antioxidant defense via formation of intracellular antioxidants (37) and decrease ROS release via inhibition of NADPH oxidase activity (34). NO is involved in the cardioprotection induced by postconditioning (6, 9, 34, 38). It has been shown that NO acts as a postconditioning trigger in ischemic/reperfused heart (5, 9, 34). cGMP is the downstream signaling target of NO, which by activating of PKG and opening of the mKATP channel leads to reducing post-ischemic Ca2+ overload (5, 9, 13, 39). Different cellular effects of NO may depend on its concentration, site of release and duration of action. Low levels of NO may have protective effects, but high levels may be detrimental. In I/R injury, NO may have a dual function. In one hand, it reacts with superoxide anions and converts to the cytotoxic oxidant peroxynitrite. On the other hand, NO can decrease neutrophil infiltration, reduce infarct size and decrease coronary vascular endothelium damages (6, 13, 38, 40). Current findings support the role of endogenous NO, in OT protection specifically during the early reperfusion period. In this regard, Burley and Baxter showed that administration of B-type Natriuretic Peptide (BNP) during the early phase of reperfusion decreases infarct size and the cardioprotective effect of BNP is likely due to endogenous NOS/N0 activity (39). Krolkowski et al., reported that eNOS but not iNOS or nNOS mediates cardioprotection by isoflurane during the early phase of reperfusion (41). It has also been reported that OT have renal protective effect against I/R injury with reduction of lipid peroxidation that is mediated by NO production (42). Postconditioning can reduce the free radical formation, and consequently postconditioning-Table1. Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>End of ischemia</th>
<th>End of reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (Beats/min)</td>
<td>LVDP (Baseline/min)</td>
<td>RPP (Baseline/min)</td>
</tr>
<tr>
<td>IR</td>
<td>205±3.7</td>
<td>155.3±11*</td>
<td>74.7±4.5*</td>
</tr>
<tr>
<td>OT</td>
<td>221±9.8</td>
<td>172±17*</td>
<td>69.5±8.2*</td>
</tr>
<tr>
<td>ATO-OT</td>
<td>212±17</td>
<td>176.5±16*</td>
<td>72.9±3.5*</td>
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<tr>
<td>ATO</td>
<td>241±20</td>
<td>169±12*</td>
<td>69.4±3.5*</td>
</tr>
<tr>
<td>5HD-OT</td>
<td>222.5±12</td>
<td>156±10*</td>
<td>68.8±2.6*</td>
</tr>
<tr>
<td>5-HD</td>
<td>245±16</td>
<td>170±21*</td>
<td>68.9±3.5*</td>
</tr>
<tr>
<td>L-NAME-OT</td>
<td>237±13.2</td>
<td>176±8±9.1*</td>
<td>73.9±3*</td>
</tr>
<tr>
<td>L-NAME</td>
<td>239±31.4</td>
<td>173±6;11.2*</td>
<td>67.2±3.6*</td>
</tr>
<tr>
<td>INDO-OT</td>
<td>208±5.6</td>
<td>152±8±15.6*</td>
<td>70.12±4.5*</td>
</tr>
<tr>
<td>INDO</td>
<td>245±21</td>
<td>185±14*</td>
<td>61.1±4*</td>
</tr>
</tbody>
</table>

HR, Heart Rate (Beats/min); LVDP, Left Ventricular Developed Pressure; RPP, Rate Pressure Product; IR, Ischemia/Reperfusion; OT, Oxytocin; ATO, Atosiban; 5HD, 5-hydroxydecanoic acid; INDO, Indomethacin. Data are presented as mean±SEM.

* P<0.05 vs. IR group and $ P<0.05 vs. OT group
induced cardioprotection is related to oxidative stress reduction (14).

mKATP channels are the end-effectors of myocardial protection in postconditioning (32). When these channels are activated, they may reduce the action potential duration, decrease Ca2+ influx and cellular Ca2+ overload and increase myocyte survival during ischemia (32,43-44). Recent studies have suggested that mKATP channels play a pivotal role in postconditioning (32). Yang et al., indicated that non-selective KATP channel inhibitor, glibenclamide and the putatively selective mKATP channel inhibitor, 5HD abolished postconditioning protection in the rabbit heart (6). In the present study, we showed that OT can induce the postconditioning cardioprotective effect in rat heart and 5HD abolished the cardioprotective effects of OT, which indicates the contribution of mKATP channel opening in OT postconditioning. We showed that 5HD administration prior to OT infusion could increase infarct size; LDH and MDA levels compared to the OT group, but could not induce significant changes in hemodynamic parameter. Some studies showed that the signaling pathway initiated by G-protein coupled receptor activates the PKG, then activates the mitochondrial PKC-ε and leading to mKATP channel opening at postconditioning (32,45-46). The actual mechanism leading to mKATP channel opening is unclear. PKG and PKC activators, NO, and pharmacological agents have been identified as mKATP channel activators (47-48). The relation between NO and the mKATP channel modulation was seen in the various studies (49-50). Sasaki et al., indicated that NO itself can modulate the opening of the mKATP channel (51). Since current results showed that OT postconditioning effect occurs via NO production, therefore NO release may have a pivotal role in mKATP channel activation through OT receptors and by this mechanism, it may protect the heart against I/R injury.

Interactions exist between NO and PGs. NO can increase COX-1 and COX-2 activation. Endogenous NO and NO donors could increase PGs production. On the other hand, COX activation modulates NO pathway (52-53). Recently, genetic and pharmacological studies showed that COX enzymes and their metabolites participate in the cardioprotection against I/R injuries. Ischemic injuries in COX-1 and COX-2 null mice hearts were increased, and this suggests that endogenous PGs might cause cardioprotection (17). It is also reported that ischemic postconditioning results in a rapid increase in COX-2 and myocardial contents of PGE2 and PG12 (54-55). The cardioprotective mechanism of increased COX-2 activity is probably in part due to the increased levels of prostacyclin (18,54-55). The COX enzymes that involve in the cardiovascular system have complex and controversial roles. There is much clinical attention about COX pathways in myocardial infarction, and some studies propose that the increased level of COX-2 and its products have a cardioprotective role in the ischemic preconditioning. In response to I/R, prostacyclin, released from cardiac tissue, which is synthesised partly, from COX-2 (21). Some studies have been reported that synthesis of PG12 is increased especially during the 5–10 min of early reperfusion and then decreases quickly in the undefended myocardium (21). It was shown that bradykinin (BK) induced postconditioning can cause protection, and may allow COX activity and PG12 formation in the late phase of reperfusion; therefore it can decrease reperfusion injury. In this study, we proposed that protection by OT postconditioning is likely due to increased COX activity. Iloprost induces cardioprotection during early reperfusion, which this protective role attributes to the production of PGs (21). However, a little knowledge is available about the actions of endogenous prostaglandins in the protective effect of OT postconditioning. Therefore, we evaluated, using indomethacin, whether prostaglandins are involved in the cardioprotection induced by OT postconditioning. Our results showed that indomethacin abolished the protective effects of OT completely, because there were no significant differences between INDO+OT group and I/R group. These data suggest that endogenously produced COX metabolites have protective role in OT postconditioning against I/R injury. The present study substantiates the concept that PGs are involved in cardioprotection. Since PGs can reduce infarct size via activation of PKC and KATP channels opening (56), and the interactions between NO and PGs and their effects on cardioprotection, it seems that OT via NO, PGs and mKATP channels opening could induce postconditioning cardioprotection. This study shows that postconditioning by OT can attenuate cardiac ischemia/reperfusion injury which readily is abolished by atosiban, 5HD, L-NAME and indomethacin. Thus, it may be concluded that the cardioprotective effects of OT is closely related to the activation of mKATP channel and increasing concentrations of endogenous NO and COX metabolites during reperfusion period in the isolated ischemic rat heart.
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References

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