Investigation on the cardio-protective effect of Xin Su Ning on ischemia-reperfusion induced injury in isolated heart.

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Introduction: We previously reported that Xin Su Ning (XSN) prolongs action potential duration (APD) of isolated cardiac myocytes¹². In this study we aimed to identify the cardio-protective effect of XSN in Ischemia-reperfusion (I/R) induced injury in isolated heart.

Methods: CHL cell line stably transfected human NaV1.5 channel were used for electrophysiological assay using Axopatch 200B patch clamp system with external and internal solutions prepared as previously described³. For isolated hearts study, male Sprague-Dawley rats (280 ~ 320g) were divided into control, I/R, XSN 0.05 g/L and 0.1 g/L groups. The hearts were isolated and perfused in retrograde mode at constant pressure of 60 mmHg at 37°C as previously reported³. The extracts of XSN in the form of frozen dried power were administrated by dissolving in the perfusing solution. The measurements used to evaluate XSN’s effects were: Left ventricular developed pressure (LVDP), the rate of pressure development and rate of relaxation (max/min dP/dt), and heart rate (HR). Rate pressure product (RPP) was calculated by multiplying LVDP by HR. The differences between control and other groups were tested using Student’s t-test.

Results: XSN blocks human NaV1.5 channel in a dose dependent manner with an IC₅₀ = 0.184±0.017 g/L. XSN at 0.1 g/L produced the significant recovery of LVDP during 60 min reperfusion as shown in Figure 1. Max dP/dt, min dP/dt and HR after 60 min perfusion with vehicle and difference concentrations of XSN were shown in Table 1.
Fig. 1 (A) Dose response curve of XSN on human NaV1.5 channel (n=5); (B) Experimental protocol of contractile function of I/R perfused rat heart; (C) percent rate of LVDP of rat hearts with/without XSN treatment after reperfusion 0, 5, 10, 20, 30, 40, 60 min (n=5). The data were presented as mean±SEM. * p<0.05, ** p<0.01, *** p<0.001 vs. I/R group.

Table 1 Myocardial contractile function measured ex vivo in a rat I/R heart (mean±SEM, n=5).

<table>
<thead>
<tr>
<th>% pre-ischemia</th>
<th>LVDP</th>
<th>max dP/dt</th>
<th>min dP/dt</th>
<th>HR</th>
<th>RPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/R</td>
<td>48.11±2.18</td>
<td>56.82±4.91</td>
<td>48.06±3.67</td>
<td>97.61±5.80</td>
<td>46.82±3.06</td>
</tr>
<tr>
<td>XSN 0.05 g/L</td>
<td>61.28±6.08</td>
<td>57.50±7.82</td>
<td>58.07±6.05*</td>
<td>79.15±4.34</td>
<td>48.85±6.43</td>
</tr>
<tr>
<td>XSN 0.1 g/L</td>
<td>87.36±4.34***</td>
<td>93.39±4.53**</td>
<td>90.27±4.25***</td>
<td>75.56±3.94*</td>
<td>70.57±5.38**</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01, *** p<0.001 vs. I/R group.

Conclusions: XSN blocked NaV1.5 channel dose dependently, and together with the APD prolongation which could be the cellular electrophysiological mechanisms of the anti-tachyarrhythmic effect of XSN. XSN improved cardiac systolic function on ischemia-reperfusion injured rat heart by increasing LVDP, RPP, max dP/dt and min dP/dt, the protective effect may contribute to the anti-arrhythmic effect of XSN on ischemic heart.
References: