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The effect of urotensin II on calcium regulation during excitation-contraction coupling

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Introduction

Heart failure is characterized by left ventricular dysfunction due to aberrant Ca2+-regulation during excitation-contraction (E-C) coupling. Plasma levels of UII is elevated in patients with heart failure, and may be related to dysfunction of Ca2+ hemostasis. The aim of this study is to investigate influence of UII on E-C coupling and Ca2+-regulation.

Methods

The Langendorff perfused isolated rat heart was used to study effect of UII on left ventricular function. Adult Rat Ventricular Myocytes (ARVMs) were isolated from Wistar rats by enzymatic digestion. Percentage cell shortening of ARVMs was measured using the video-based edge detection system. Intracellular Ca2+ was measured in single freshly isolated ARVMs loaded with Fura-2 and sarcoplasmic reticulum Ca2+ content [Ca2+]SR was determined by rapid application of 10mM caffeine. Action potential was recorded using the whole cell patch clamp technique and resistance pipette value of the seal was (12-15MO).

Results

Exposure of rat heart to 50nM UII caused a 19.7 ± 2.5% reduction in left ventricular developed pressure (LVDP) (n = 8 hearts). The mechanical properties of ARVMs were assessed, the results show a significant reduction in the cell shortening from 12.6 ± 0.5% control to 10.9 ± 0.5% in UII-treated cells (n = 71 cells) (P<0.0001).

Superfusion of ARVMs with 200nM UII caused a reduction in systolic [Ca2+]i from 374.6 ± 19.9 in control to 304.7 ± 12.2 (P<0.0001) but had no effect on diastolic [Ca2+]i 54.5 ± 5.1 control and 55.9 ± 3.7 UII (n = 76 cells). Measurement of [Ca2+]SR show there was a reduction in the peak SR Ca2+ release from 440.8 ± 13.9 nM in normal Tyrode (NT) to 412.1 ± 14.7 nM in 200nM UII (n = 85 cells) (P<0.01). To determine the effects of UII on SR Ca-leak, AVRMs loaded with Fluo-3 were perfused with Ca2+ and Na+-free Tyrode (10mmol EGTA). The difference between the diastolic [Ca2+]i was measured in the presence and absence of tetracaine which blocks RyR, reflect SR Ca-leak through RyR. The data show that UII had no effect on this difference at 15.3 ± 2.6 nM in NT (n = 19 cells) and 17.1 ± 2 nM in UII (n = 25 cells) (P>0.05). To determine the effects of UII on electrical activity, the percentage change in action potential duration (APD30/50/90) was determined in response to UII (200nM). The data show APD30 was significantly reduced from 9.5 ± 1.4 ms in NT to 5.3 ± 0.9 ms in UII (P<0.01) and APD50 from 19.52 ± 2.1 ms in NT to 12.1 ± 1.6 ms in UII (n = 41 cells) (P<0.001). There was no significant change in APD90.

Conclusion

UII reduces LVDP and contraction of ARVMs. This reduction in contraction reflects a decrease in systolic [Ca2+]i, which may result from either the decline in SR Ca2+ content and/or a reduction in APD.
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