228

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DOES CHRONIC BLADDER ISCHEMIA AFFECT RHOA/RHO-KINASE PATHWAY?

Hypothesis / aims of study

Recent studies suggest that lower urinary tract symptoms (LUTS), including overactive bladder, are a common condition in men and women in later life, and that chronic bladder ischemia induced by pelvic arterial occlusive disease such as atherosclerosis may be an important contributing factor in each gender. Currently, attention has focused on the role of RhoA/Rho-kinase (ROK) pathway in various pathologic conditions such as cardiovascular disease and bladder dysfunction. We previously reported that the alteration of RhoA/ROK pathway associated with bladder outlet obstruction (BOO) in the rat bladder smooth muscle.[1)] However, it has not been established whether arterial occlusive disease related chronic ischemia affects the RhoA/ROK pathway in the bladder. Therefore, we used a previously described rat model of chronic bladder ischemia[2)] to investigate the effect of chronic ischemia without BOO on RhoA/ROK pathway.

Study design, materials and methods

Adult Sprague-Dawley male rats (16-week old) were divided into two groups (arterial endothelial injury: AI, control). The AI group underwent balloon endothelial injury of the bilateral iliac arteries and received a 2 % cholesterol diet (n=10). The control group received a regular diet (n=9). After 8 weeks, bladder tissue was harvested, and the contractile responses to 80mM KCL, electrical field stimulation, carbachol(Cch) and 1mM ATP were recorded in the organ bath. Cch-induced contraction of bladder strips consisted of a phasic contraction followed by a tonic contraction. We measured the phasic contractions as the first contractile response to 1μM Cch and the tonic contractions as the magnitude of the sustained part of the response at 30 min after adding 1μM Cch. We also evaluated the effect of ROK inhibitor Y-27632 on the 1μM Cch-induced tonic contractions with concentration response curves.

Results

The body and bladder wet weight were not significantly different between two groups (control vs AI, body weight : 568 ± 17 g vs 559 ± 44 g, bladder wet weight : 0.242 ± 0.034 g vs 0.236 ± 0.034 g). Contractile responses of the bladder strips to KCL, electrical field stimulation, Cch and ATP were significantly less in the AI group than in the control group (Figure.1). In the control group, the tonic contractions significantly decreased as compared with the phasic contractions. On the other hand, there was no significant deference between the phasic contractions and the tonic contractions in the AI group (Figure.2). Y-27632 produced concentration-dependent decrease in Cch-induced sustained responses of bladder strips from both groups. The inhibitory effect of Y-27632 on the strips from the AI group significantly enhanced compared to the strips from the control groups (Figure.3).

Interpretation of results

Our results suggest that chronic ischemia leads to impaired detrusor contractility and causes the maintenance of contractile force of bladder smooth muscle, and ROK inhibitor attenuates tonic contraction produced by chronic ischemia as compared with a normal bladder.

Concluding message

It is possible that one source of bladder overactivity in the atherosclerosis-induced chronic bladder ischemia is sustained bladder contraction. And these results may imply that the chronic bladder ischemia can affect the ROK pathway.

Figure.1.The contractile responses to 80mM KCL, electrical field stimulation, carbachol(Cch) and 1mM ATP.

Figure.1

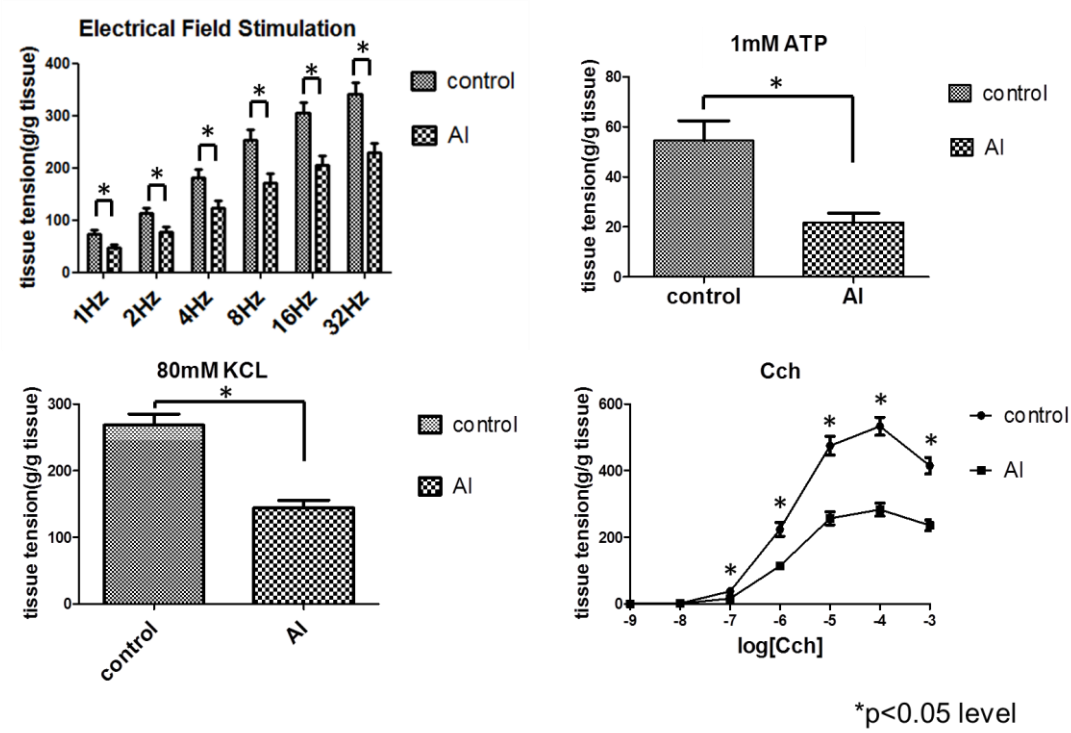


Figure.2. Cch-induced contraction of bladder strips consisted of a phasic contraction followed by a tonic contraction. Bladder strips from the AI group maintained the magnitude of tonic contraction compared with control group.

Figure.2

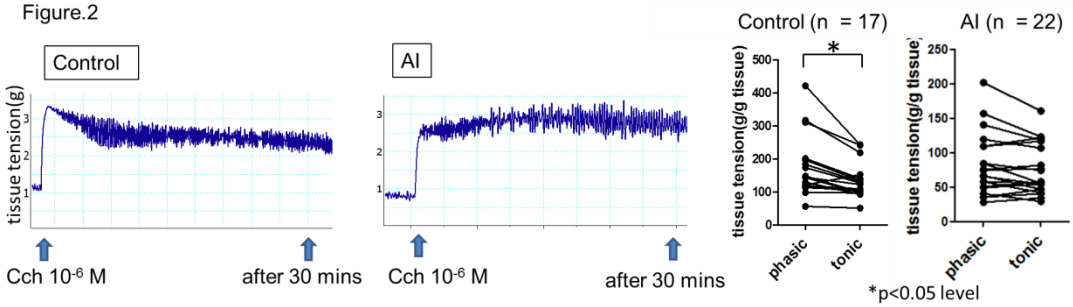
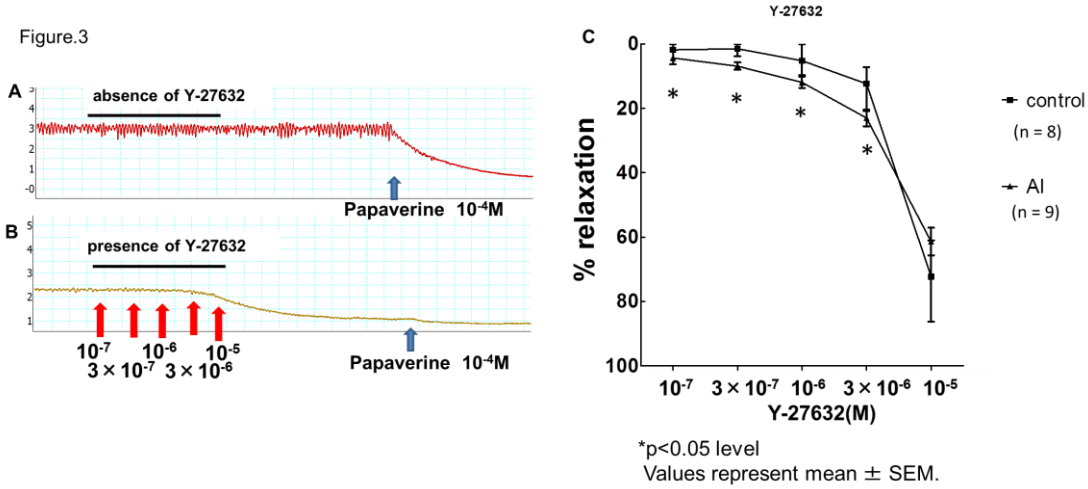


Figure.3. The effect of ROK inhibitor Y-27632 on the Cch 1μM - induced tonic contractions. **A**: 1μM Cch-induced tonic contraction. **B**: Concentration response curves produced by Y-27632. **C**: Summary data for the effects of Y-27632.

Figure.3



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Disclosures

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