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ALTERATIONS IN CAVEOLAE-MEDIATED SIGNALING IN OVERACTIVE BLADDERS FROM SPONTANEOUS HYPERTENSIVE RATS

Hypothesis / aims of study

Sarcolemmal caveolae have been shown to mediate the contractile response to several agonists in bladder smooth muscle[1]. Furthermore, caveolins, the principal protein component of caveolae, appear to be responsive to physiologic challenge, suggesting that altered caveolae or caveolin expression could lead to bladder dysfunction. In spontaneously hypertensive rats (SHR), an animal model of bladder overactivity, expression of caveolin proteins is significantly reduced in vascular and cardiac tissues[2,3]. We hypothesized that a similar caveolar deficiency may occur in bladder smooth muscle of SHR, resulting in dysregulation of specific receptor-mediated signaling processes, and thus leading to detrusor overactivity. Therefore, the aim of this study was to determine whether caveolae-mediated contractile responses are altered in overactive bladders from SHR.

Study design, materials and methods

Longitudinal bladder strips without urothelium were prepared from SHR, placed in organ baths and stretched to 1.5 grams. Normal bladders from age-matched normotensive rats (WKY) were similarly processed and used in parallel as control for all experiments. Contractile responses to physiologic agonists previously shown to be negatively regulated by caveolae in normal bladders, bradykinin (BK) and phenylephrine (PE), were measured. Stimulation with agonists was repeated after disruption of caveolae achieved by depleting membrane cholesterol with methyl-ß-cyclodextrin (mßcdx), as well after caveolae restoration as a result of cholesterol replenishment. In addition the amplitude of spontaneous activity and the contractile response induced by carbachol (Cch), and KCl were similarly measured.

Results

Baseline contractile responses to phenylephrine (PE) and bradykinin (BK) were significantly greater in SHR compared to WKY. Moreover responses to PE and BK in SHR were significantly less affected by mßcdx-induced disruption of caveolae and less sensitive to caveolae restoration by cholesterol replacement compared with WKY. KCl-induced contractions were not affected by disruption of caveolae in either SHR or WKY suggesting that contractile elements were not impaired by mßcdx treatment. The amplitude of SA in SHR was significantly higher than in the WKY control rats. However SA in WKY bladders was more sensitive to disruption of caveolae than in SHR where mßcdx had no significant effect. In SHRs, the contractile response to Cch was similar at baseline to the response in WKY and was not altered by caveolae disruption, indicating that caveolae-mediated signaling is agonist specific.

Interpretation of results

The augmented baseline contractile responses to PE and BK as well as the increased amplitude of SA and the diminished sensitivity to mßcdx in SHR compared with WKY are consistent with a decreased negative regulation of receptor activated signalling in SHR.

Concluding message

These data suggest that bladder overactivity may be associated with functional aberrations in caveolae mediated signaling.

References

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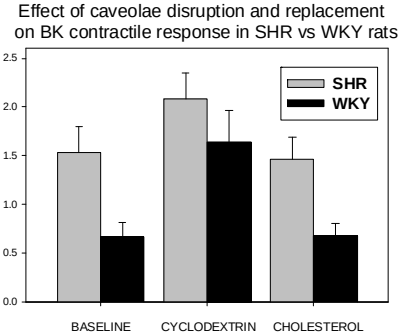
3: Cardiovasc Res. 51(4):709-16 2001



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