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NOVEL UNSTABLE BLADDER MODEL IN HYPERCHOLESTEROLEMIA RAT

Hypothesis / aims of study

Symptoms of unstable bladder, such as frequency and urgency, increase with aging. However, there is no adequate animal model of this kind of unstable bladder. Hypercholesterolemis has been shown to be closely related to aging and aging-related problems. We developed a new hypercholesterolemia rat model and want to demonstrate changes of the bladder with cystometrogram (CMG) and muscle strip studies.

Study design, materials and methods

We used twenty 12 week-old Sprague-Dawley rats. The plan of this study was reviewed and permitted in executive committee of the research institute in our hospital. Ten of them received the 1% cholesterol diet for 8 weeks. To induce endothelial dysfunction, which is essential to the development of atherosclerosis, L-NAME (1mg/ml) was added to the drinking water for first 2 weeks. The remaining ten served as the control and were fed a normal diet. The bladder muscle strips of each groups were evaluated for force development in response to electrical field stimulation, 5uM carbachol (CCh) and 60mM KCl, by an isometric transducer(n=7). By measuring the contractile response to field stimulation after adding 1uM atropine and 5uM α,β-methylene ATP, contributions of cholinergic and purinergic transmission were determined. The cystometrogram (CMG) in anaesthetized rats was recorded. Pathology of detrusor muscles was evaluated by hematoxylin and eosin (H&E) staining and Masson's trichromic staining for collagen.

Results

Compared to the normal control group, the mean serum cholesterol and body weight elevated significantly in the cholesterol group. Compared to the control, the cholesterol group showed a shorter voiding interval (377.6±205.4 vs 121.8±79.6sec., $p<0.01$) and smaller functional bladder capacity (1.4±0.7 vs 0.7±0.3ml, $p<0.05$) in CMG. There was no significant difference in basal pressure, threshold pressure and peak micturition pressure.

Compared to the control, the cholesterol group showed higher tension (0.078±0.033 vs 0.191±0.180g, $p<0.05$) in spontaneous activities. The cholinergic component was the main portion of electrically stimulated detrusor muscle strip. However, the cholesterol group showed an increase (12.7±5.3 vs 28.4±14.3%, $p<0.05$) in the proportion of purinergic components and a decrease (68.2±13.2 vs 48.4±22.5%, $p<0.05$) in the proportion of cholinergic components. Except stronger phasic contraction on sustained tonic contraction induced 5uM carbachol in the hypercholesterolemia group, there were no significant changes in results of contraction induced high concentration potassium solution (60mM KCl) and carbachol (CCh) between control and hypercholesterolemia group.

Histologically, the cholesterol group showed definite atherosclerosis in the aortic bifurcation and internal iliac artery. However, the muscle fibers of each group showed no significant difference.

Interpretation of results

The cholesterol group showed changes in detrusor activity, contractility and proportion in cholinergic and purinergic components. The results**,** such as shorter voiding interval and smaller functional bladder capacity in CMG and increased basal spontaneous activity, strongly support the possibility of bladder instability of hypercholesterolemia rat.

Concluding message

We do not have an adequate animal model of unstable bladder yet. Partial obstructed bladder models of rats or rabbits showed the similar data of the unstable bladder. However, it can explain the irritative symptoms of bladder outlet obstruction patients. Blood flow change and hypercholesterolemia always have the possibility of end-organ functional changes. Moreover, there are several reports which suggest that blood flow affected bladder detrusor function.

Compared to other hypercholesterolemia models, our model needs shorter time (8 weeks) to experiment and showed several clear data of bladder hyperactivity. The weakness of this study is that we did not demonstrate any pathologic changes in bladder itself. However, we are continuing more specific studies, such as protein and molecular level.

In conclusion, this novel rat model has clearly shown the possibility of usefulness for the study of unstable bladders.