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THE PROCESS OF CHROMIC ISCHEMIA-INDUCED BLADDER DYSFUNCTION IN WATANABE HERITABLE HYPERLIPIDEMIC (WHHL-MI) RABBITS

Hypothesis / aims of study

Watanabe heritable hyperlipidemic (WHHL) rabbits have atherosclerotic lesions, which are similar to human lesion. It has been reported that WHHL rabbits are good model to study the development and progression of atherosclerosis and the related pathological conditions. In previous study, we have presented that 24 month-old WHHL rabbits have detrusor overactivity, which may be caused by bladder ischemia, and that this rabbit is a useful animal model for evaluation of pathophysiology of overactive bladder. In the present study, to clarify the process of ischemia-induced bladder dysfunction, we evaluate the time-course of histological, physiological and pharmacological changes in bladder of WHHL rabbits.

Study design, materials and methods

Male WHHL rabbits in three age groups (6 months: 6 M. n=4, 12 months: 12 M. n=4 and 24 months: 24 M. n=) and the age and sex-matched Japanese white rabbits (n=6 in each age group: control group) were used in this experiment. After one week of control period, each rabbit was maintained in the metabolic cage, and was continuously measured the number of micturition and each micturition volume for 3 days. After pentobarbital anesthesia, To evaluate blood flow of bladder, tissue oxygenation was determined using PO_2 measurement probe. Then, catheters were inserted into bladder dome for filling cystometry. Micturition volume, micturition frequency, post-void residual urine were evaluated. After sacrifice, bladders were obtained for HE staining and immunohistochemical staings for S-100 protein and CGRP positive neurons. In addition, bladder smooth muscle strip was suspended in organ bath filled with Krebs-Henseleit solution, and tension development was recorded. The contractions induced by carbachol, KCl (80 mM) and electrical field stimulation (EFS; supramaximal voltage, 0.3 msec duration, 2.5 - 40 Hz and 3 sec train) were evaluated.

Results

Daily urine volumes increased with age, however, there were not significant different between groups. The number of micturition and voided volume in 6 M old WHHL rabbits was not significantly different from the control group. However, the number of micturition and voided volume of 12 and 24 M old WHHL rabbits were significantly higher and lower than that of the control, respectively. In the control groups, tissue oxygenation was gradually decreased. However, there was not significant difference among 3 age groups. In WHHL rabbits, there was significant age-related decrease in bladder tissue oxygenation. Cystometric findings in 12 M old WHHL rabbits showed the premicturition contractions, shorter interval micturition and lower micturition volume, as compared to the control group. The abnormal findings worsened in the 24 M old WHHL rabbits. In the functional study, the contractile responses induce by carbachol and EFS in bladder strips from 6 and 12 M old WHHL rabbits significantly increased, as compared with age-matched control groups. However, the responses significantly deceased in 24 M WHHL rabbits. There were not significant differences in bladder histology among 3 control groups. However, urothelium of WHHL rabbits became thinner with age, and the connective tissue area of smooth muscle layer in WHHL rabbits significantly increased with age. S-100 and CGRP positive neurons mainly exist in smooth muscle layer and suburothelial space, respectively. In WHHL groups, the density of S-100 protein positive neuron significantly decreased with age. While, the density of CGRP positive neurons significantly increased is 12 and 24 M old WHHHL rabbits (Fig.)

Interpretation of results

WHHL rabbits have heritable hyperlipidemic state and atherosclerotic lesions, which are similar to that of human. It has been reported that WHHL rabbits are good model to study the development and progression of atherosclerosis and the related pathological conditions. In the measurement of bladder tissue oxygenation, the data suggested that age-related decrease in bladder blood flow in WHHL rabbits. Therefore, the present study demonstrates the process of ischemia-induced bladder dysfunction. In the present study, decrease in the density of S-100 protein positive neurons suggest that partial denervation of motor neurons, and increase in the density CGRP-positive neurons may imply the increased activity of afferent C neurons, respectively.

Concluding message

The present study demonstrated the age-related progression of bladder dysfunction of WHHL rabbits. In the early phase of bladder ischemia, increased smooth muscle responsiveness due to partial denervation may contribute to detrusor overactivity. In the chronic phase, activation of afferent neurons may also be related with the detrusor overactivity. Furthermore, detrusor underactivity was caused by decreases in smooth muscle, mother neurons and responsiveness to neurotransmitters.

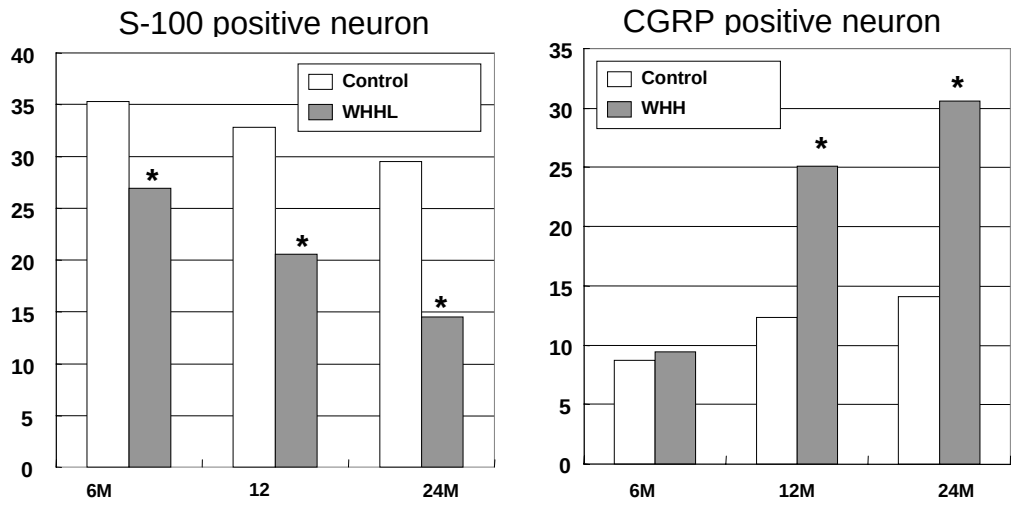

Fig. Comparison of mean nerve density score in WHHL and control rabbits
(* <0.05 as compared to the control)

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