LONG-TERM CALORIC RESTRICTION MAY PREVENT IN VIVO LOWER URINARY TRACT DYSFUNCTION ASSOCIATED WITH AGEING IN MALE RATS

Hypothesis / aims of study
A recent study using in vitro investigations revealed that ageing causes an impaired detrusor contractility, decreased expression of M3 muscarinic receptors and bladder wall fibrosis in male rats (1). Furthermore, interestingly, long-term caloric restriction (CR) prevented these age-related changes (1). Several groups have evaluated age-related changes in rodent bladder function but only a few used in vivo cystometry (CMG) to characterize the changes (2, 3). In addition, to date, the impact of long-term CR on in vivo bladder function has not been investigated. In this study, we aimed to clarify the age-related changes in in vivo lower urinary tract function, and impact of CR on the age-related changes by using conscious CMG measurements.

Study design, materials and methods
Fischer 344 male rats were divided into three groups: young (6 months-old, Y: N = 7), old (26-28 months-old) fed fully ad libitum with normal food (O+AL: N = 7) or calorie restriction (O+CR: N = 8). The O+CR group has been fed the same normal food only days (Monday, Wednesday and Friday) a week since 6 weeks-old. Three days after a cather-implantation through the bladder dome, single CMG measurements were performed with saline-instillation at a rate of 6 mL/hour under a conscious and restraint condition. At the end of each micturition, the residual volume was precisely measured by collecting naturally dripping of post-void residual through the bladder catheter for 10 minutes. After stable and reproducible recordings were obtained, 4 micturition cycles were averaged and the following parameters were analysed: basal pressure, threshold pressure, maximum pressure, non-voiding contractions (NVCs), voided volume, residual volume, bladder capacity, mean flow rate, voiding efficacy, and bladder compliance. Non-voiding contractions (NVCs) were defined as bladder contractions of which amplitude was more than 3 cmH2O observed during the filling phase.

Results
The O+AL group had higher body weight than the other two groups, and the O+CR group had lower body weight than the other groups. In contrast, there were no significant differences in the mean bladder weight among the three groups (Table 1). The O+AL group showed higher threshold pressure, lower bladder compliance and the increased numbers of NVCs compared with Y group. The O+AL group also showed increased residual volume and decreased voiding efficiency compared with the O+CR as well as Y group. The remaining other parameters investigated were not significantly different among the three groups (Figures 1 and 2).

Interpretation of results
Although maximum pressure did not change with ageing, increased residual volume and decreased voiding efficiency were observed in the O+AL group and these changes were not observed in the O+CR group. These results suggest that ageing impairs the voiding function and long-term CR has a preventative effect on the age-related voiding dysfunction. These present in vivo findings support the previous in vitro findings that ageing caused an impaired detrusor contractility (1). Higher threshold pressure and lower bladder compliance observed in the O+AL group may be linked to the previous report (1) that ageing causes fibrotic changes in the bladder wall. In addition, the O+AL group showed frequent NVCs. These parameters did not differ from the O+CR group, suggesting that ageing also causes the storage dysfunction, but a preventative effect of CR on these age-related storage dysfunctions may be limited.

Concluding message
The present in vivo CMG investigations demonstrated the age-related voiding and storage dysfunctions in the rat and also that long-term CR may have preventative effects on the age-related voiding dysfunction rather than the storage dysfunction.

Table 1. The body weights and bladder weights in each group

<table>
<thead>
<tr>
<th></th>
<th>Y (N=7)</th>
<th>O+AL (N=7)</th>
<th>O+CR (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>366.86 ± 4.89##</td>
<td>402.85 ± 13.46*##</td>
<td>252.63 ± 5.96**</td>
</tr>
<tr>
<td>Bladder weight (mg)</td>
<td>155.86 ± 9.71</td>
<td>162.71 ± 10.29</td>
<td>148.38 ± 17.92</td>
</tr>
</tbody>
</table>

The numerical values are expressed as mean ± SEM.

* p<0.05, ** p<0.01: significant differences from Y (Tukey's test)

## p<0.01: significant difference from O+CR (Tukey's test)
Figure 1. Representative tracings of intravesical pressure and voided volume during CMG with constant saline instillation (6.0 ml/hour) taken from a young rat (Y), an old rat fed with normal food (O+AL) and an old rat with caloric restriction (O+CR).

VV: Voided Volume, RV: Residual Volume

Figure 2. Comparative results of CMG parameters among the three groups.
The values are expressed as mean ± SEM.
Y: young rats, O+AL: old fed with normal food, O+CR: old with caloric restriction
NVCs: Non-voiding contractions
*p<0.05, **p<0.01: significant differences between two groups (Tukey’s test)

References

Disclosures
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