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BLADDER DYSFUNCTION IN A NEW ANIMAL MODEL OF INCREASED LEVELS OF SUPEROXIDE IONS

Hypothesis / aims of study

Nitric oxide (NO) released from postganglionic parasympathetic neurons mediates urethral smooth muscle relaxation during reflex micturition. There are evidences that the NO pathway may be also involved in the control of detrusor activity. Impaired urethral relaxation and increased detrusor activity were described in mutant mice lacking nNOS and cGKI. (1,2) Using a transgenic insertional mutagenesis strategy, we generated a mouse with a mutation in the inner mitochondrial membrane peptidase 2-like (*Immp2l*) gene. This mutation leads to high superoxide ion levels, a consequent decrease in the bioavailability of NO and an increase in oxidative stress. We used this model to study bladder function in old and young animals.

Study design, materials and methods

Using an ear biopsy, homozygote mutation for the Immp2l gene was proved by PCR and Western blot analysis. Young male mutants (4-6 months), old female mutants (18 months) and healthy age-matched controls (wild-types) were used in this study. Detrusor contractile response to carbachol and electrical field stimulation (EFS) was tested in isolated detrusor strips in organ baths (n=5 per group). To evaluate the bladder function *in vivo*, the animals had their bladder catheterized and underwent conscious cystometry 3 days later (n=5 per group).

Results

Urodynamically the young male mutants showed significant lower micturition and higher residual volumes. These animals had pronounced difficulties in initiating micturition and massive straining was seen before voiding. This could be objectified by measuring the time between the first raise in bladder pressure till the maximal pressure during micturition. The contractile responses of the detrusor to carbachol and EFS were similar between mutants and wild-types. The old female mutant mice exhibited lower bladder capacity and micturition volume, higher micturition frequency and bladder/body weight ratio. In the *in vitro* study, detrusor strips from mutants showed a lower maximum response to carbachol.

Interpretation of results

These results suggest that Immp2l mutant mice exhibit bladder dysfunction mainly characterized by emptying abnormalities in the young male, and increased detrusor activity in the old female. Detrusor function was preserved in the young males and impaired in the old females. The mechanism of urethral relaxation is probably deficient in the young animals, which could be explained by the lower bioavailability of NO. The mechanisms underlying the changes seen in the old animals may include the chronic exposition to higher superoxide, lower NO levels, and the elevated outflow resistance.

Concluding message

Mice with a mutation in the *Immp2l* gene, which leads to high superoxide ions production exhibit bladder dysfunction. These animals are a natural model of oxidative stress and low bioavailability of NO and, therefore, represent interesting tools to evaluate the role of these conditions on bladder dysfunction.

References

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