120

Honda K[1], Nomiya M[1], Shishido K[1], Yoshimura Y[1], Yamaguchi O[1]
1. Fukushima Medical University

MUTATION OF B 3-ADRENOCEPTOR GENE: A GENETIC MARKER FOR OVERACTIVE BLADDER

Hypothesis / aims of study

The β 3-adrecoceptor (AR) is the most abundant in human detrusor muscle. A miss-sense mutation in codon 64 of the β 3-AR gene, with a replacement of tryptophan (Trp) to arginine (Arg), occurs with am approximate frequency of 8% to 10% in the white population, 20% to 30% in the Japanese population, and 40% in Alaskan Eskimos.[1)] Because activation of the β 3-AR causes a relaxation of detrusor muscle during bladder filling, we hypothesized that mutation of the β 3-AR gene may be involved in idiopathic overactive bladder(OAB), leading to an insufficient relaxation of bladder during urine storage, decreasing bladder capacity, and favoring detrusor overactivity.

Thus, in order to explore this possibility, we investigated the mutation frequency of the β 3-AR gene in women with OAB as well as in healthy volunteer women without OAB.

Study design, materials and methods

This study involved 100 women with idiopathic OAB and 101 healthy control women without OAB. The mean age of OAB patients and normal controls was 64.8 years (range, 42-80 yr) and 62.1 years (range 47-80 yr), respectively. There was no difference between the above 2 groups in age distribution.

The diagnosis of OAB was made according to the ICS definition.[2)] The OAB patients with neurological diseases were excluded from this study. All control women were asked to answer the OAB questionnaire (OAB-q) to confirm that they had no OAB symptoms.

Hair root samples were obtained from all subjects and used for β 3-AR gene analysis. PCR-RFLP was performed to analyze a polymorphism in the gene of Trp64Arg.

Results

Of 100 women with OAB, 42 patients had the heterozygous mutation (Trp64Arg), 5 patients had the homozygous mutation (Arg64Arg), and 53 patients had the normal gene (Trp64Trp). On the other hand, of 101 normal control women, 78 had the normal gene, 21 had the homozygous mutation and 2 had the homozygous mutation. Thus, the overall mutation frequency in women with OAB was 47%, which was significantly higher ($p<0.01$) than the frequency of 22.8% found in non-OAB healthy women. (Table1)

Within the patients with OAB, there was no significant difference between women with mutation (heterozygous+ homozygous) and women without mutation in the number of micturition /day, the number of urgency episode /day respectively.

Interpretation of results

The present study demonstrated that approximately 50% of women with OAB had the mutation of the β 3-AR gene. This mutation frequency was shown to be significantly higher than that in non-OAB women. The above results may suggest that dysfunction of β 3-AR resulting from its gene mutation, at least party, contributes to the pathophysiology of OAB.

In the OAB patients who have the normal gene, factor other than dysfunction of β 3-AR may be involved in this disorder. Considering that multiple factors are involved in the pathogenesis of OAB, the β 3-AR gene mutation alone may not be correlated to severity of OAB symptoms, which was shown in this study.

Our study also showed that approximately 23% of non-OAB healthy women had the mutation of the β 3-AR gene. This implies that in non-OAB women with mutation, there may be mechanisms which have the compensatory effects on the insufficient relaxation of detrusor due to the β 3-AR gene mutation. Since the prevalence of OAB is known to increase with age, it is speculated that if such mechanisms depend on estrogens, these compensatory mechanisms would be downregulated with age, which may lead to late development of OAB in women with this mutation.

Concluding message

The Trp64Arg mutation of the β 3-AR gene may be a genetic marker for idiopathic OAB.

Reference

1. J Intern Med 1999;245:667-672,
2. Neurourol Urodyn. 2002; 21(2):167-78.

Table1 Mutation frequency of β 3-AR gene

Genotype	OAB (n=100)	Non-OAB (n=101)
mutation		
Arg/Arg	5 (5.0%)	2 (2.0%)
Trp/Arg	42(42.0%)	21(20.8%)
(Arg/Arg+Trp/Arg)	47 (47.0%)	23(22.8%)
normal		
Trp/Trp	53(53.0%)	78(77.2%)

□($p<0.01$) as compared to non-OAB

FUNDING: NONE
DISCLOSURES: NONE
HUMAN SUBJECTS: This study was approved by the Fukushima Medical University and followed the Declaration of Helsinki Informed consent was obtained from the patients.