

THE EFFECTS OF AGING ON NITRIC OXIDE AND NORADRENALINE RELEASE IN ISOLATED RABBIT PROSTATE

Hypothesis / aims of study

The prostate is innervated by sympathetic nerves, and noradrenaline (NA) released from adrenergic nerves induces prostatic smooth muscle contraction. In addition, there is increasing evidence showing that nitric oxide (NO) is a neurotransmitter substance for nitrinergic nerve-mediated relaxation of smooth muscle in the prostate. Thus, a balance between the amounts of NA and NO released from these intrinsic nerves would determine the tone of prostatic smooth muscle, which provides a functional mechanism for the bladder outlet obstruction (BOO) observed in patients with clinical benign prostatic hyperplasia (BPH). However, there is no direct evidence to support the above hypothesis. The present study attempted to determine whether aging alters adrenergic and nitrinergic neurotransmission in the prostate. Thus, we investigated the amounts of NA and NO release in response to transmural electrical stimulation in the prostate of both the young and the old rabbits.

Study design, materials and methods

Young (about 3 months old) and old (2-3 years old) Japanese white male rabbits were used for this experiment. The prostatic tissue strips were suspended in 25 ml organ baths containing Krebs solution. The resting tension was set at 1 g at the commencement of each experiment. Electrical field stimulation (EFS; supramaximum voltage, 0.5 msec duration and 5-20 Hz frequency for 5 sec) was performed with the muscle strips. The effects of pretreatment with tetrodotoxin (TTX, 1µM) on the electrically evoked responses were also examined. The magnitude of contraction was expressed as a percentage of that induced by 80 mM KCl. Two microdialysis probes were inserted through each strip. The probes were continuously perfused with Krebs solution at a constant flow rate of 2.0 µl/min. Then, EFS (supramaximum voltage, 0.5 msec duration and 5-20 Hz frequency for 3 min) was applied to the strips and dialysate obtained during EFS was collected for the measurement of NO and NA. The stable final NO degradation products were evaluated as NOx (NO₂⁻+NO₃⁻). Increase in NOx in the dialysate fraction was measured by using NO₂⁻/NO₃⁻ analyzing system based on the Griess reaction. In the same way, NA was assayed by using high-performance liquid chromatography assay system. The effects of TTX on the NO and NA release were also evaluated. EFS-induced NO and NA release were measured at the same time. Data are expressed as the mean ± SEM. Comparisons between the two groups were done using unpaired t-test. Statistical significance was considered at p<0.05.

Results

The contractile responses of prostatic strips increased with an increase in frequency of stimulation in both the young and the old groups (Fig. 1). TTX completely abolished these responses. Contractile responses of prostatic strips from the old rabbits were significantly higher than those from the young rabbits at frequencies of stimulation from 5 to 20 Hz (Fig. 1). Similar to the contractile response, NO and NA release from nerve fibers also increased with the increase in stimulation frequency in prostatic strips from the two groups (Fig. 2 and 3). TTX also suppressed the EFS-induced NO and NA release. The amount of NO released from nerves was significantly lower in prostatic strips from the old rabbits than in those from the young rabbits at all frequencies of stimulation (5, 10 and 20Hz). However, at each stimulation frequency, the amount of NA release was significantly higher in the old prostatic strips than those in the young prostatic strips.

Interpretation of results

Our findings showed that as a result of aging, NO released from nitrinergic nerves decreased while NA released from adrenergic nerves increased. These results indicate that the decrease in NO release and the increase in NA release can contribute at least to a significant increase in the contractile response of the old prostate to nerve stimulation. Taken together, it is suggested that NO deficiency and a strengthened α₁-adrenergic stimulation further increase the tone of prostatic smooth muscle, which may lead to BOO in patients with BPH.

Concluding message

In this context, the use of phosphodiesterase inhibitors in combination with α₁-adrenoceptor antagonists has been suggested to be a potential pharmacotherapy for men with BPH.

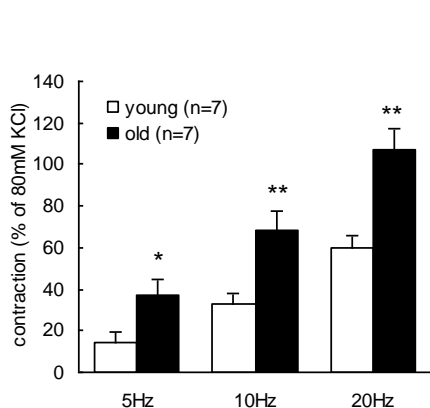


Fig. 1. Influence of aging on EFS-induced contraction, ** p<0.01, * p<0.05 vs. young

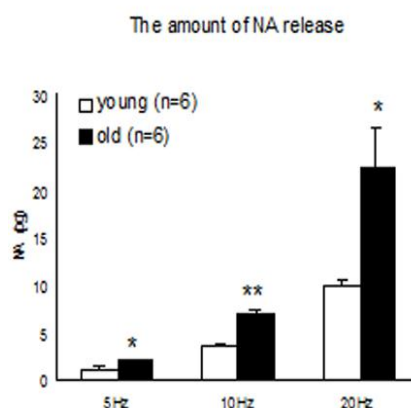


Fig. 2. Influence of aging on the amount of NO release ** p<0.01, * p<0.05 vs. young

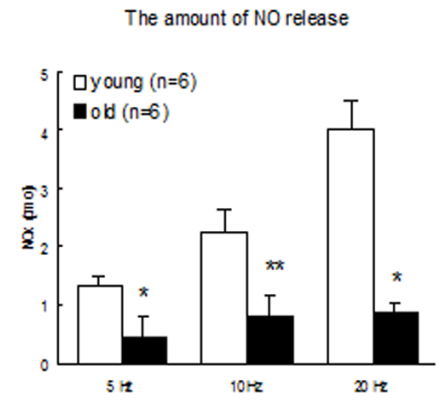


Fig. 3. Influence of aging on the amount of NA release ** p<0.01, * p<0.05 vs. young

References

1. Prostate 48:40-46 (2001)
2. J Urol 170:659-663 (2003)

<i>Specify source of funding or grant</i>	No
<i>Is this a clinical trial?</i>	No
<i>What were the subjects in the study?</i>	ANIMAL
<i>Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?</i>	Yes
<i>Name of ethics committee</i>	the Animal Ethics Committee of Fukushima Medical University