CONTRIBUTIONS OF DEHYDROEPIANDROSTERONE AT NEUROTRANSMITTER RECEPTORS IN THE CENTRAL NERVOUS SYSTEM ON BLADDER FUNCTION IN MALE RATS

Hypothesis / aims of study
Our clinical studies concerning lower urinary tract symptoms and serum levels of sex hormones revealed a significant correlation between storage symptoms and dehydroepiandrosterone (DHEA) in elderly men [1]. DHEA is the primary precursor of sex steroids and shows weak androgenic action. DHEA also acts as a kind of neurosteroid, synthesized in the brain, and modulates the activity of several neurotransmitter receptors such as dopamine, N-methyl-D-aspartate (NMDA), y-aminobutyric acid A (GABA_A), and/or sigma receptors. The aim of this study was to investigate the contributions of DHEA at neurotransmitter receptors in the central nervous system to bladder function in rats with DHEA deficiency.

Study design, materials and methods
Male Sprague-Dawley rats were divided into three groups: (1) a control group (C), (2) a DHEA deficiency group (DD), and (3) a DHEA replacement group (DR). After the DD and DR rats were bilaterally adrenalectomized, the DD rats received replacement treatment with deoxycorticosterone acetate (DOCA) (40 mg/kg/day), and the DR rats received replacement treatment with DOCA (40 mg/kg/day) and DHEA (15 mg/kg/day). The following experiments were performed 4 weeks after the adrenalectomy. First, serum levels of DHEA, corticosterone, aldosterone, adrenocorticotropic hormone (ACTH), and free testosterone were determined. Next, each rat was placed in a metabolic cage for 24 hours to assess voided volume per micturition. Cystometrography with fixed doses of SCH-23390 (a D1-selective dopaminergic receptor antagonist, 0.03 mg/kg iv), sulpiride (a D2-selective dopaminergic receptor antagonist, 0.3 mg/kg iv), or MK-801 (an NMDA glutamatergic receptor antagonist, 0.01 mg/kg iv) in cystometric study. SCH-23390, sulpiride, or MK-801 was repetitively administered at 1-h intervals. These doses were selected because they are known to produce no change in bladder activity [2].

Results
The serum DHEA level was significantly decreased in the DD rats compared with the C rats. The voided volume per micturition was significantly smaller in the DD rats than in the DR rats. In the C rats, there was no significant difference in cystometric parameters between ivc administration of DHEA and the vehicle. In the DD rats, the bladder contraction pressure was significantly increased, and the bladder contraction pressure was significantly decreased after ivc administration of DHEA. DHEA in combination with SCH-23390 did not change micturition reflex in the DD rats. DHEA in combination with sulpiride significantly increased the bladder contraction interval in the DD rats. In combination with MK-801, 30 nmol of DHEA produced a significant increase, but 100 nmol of DHEA produced a significant decrease in the bladder contraction interval in the DD rats. DHEA in combination with any drug did not change the bladder contraction pressure in the DD rats.

Interpretation of results
The results of our experiments suggest that DHEA may exert an inhibitory effect on bladder function via neurotransmitter receptors such as dopaminergic and/or glutamatergic receptors in the brain. However, how DHEA inhibits the micturition reflex via neurotransmitter receptors cannot be explained by our results. Recent research has demonstrated beneficial effects of DHEA on obesity, diabetes, cancer, atherosclerosis, enhancement of memory, psychiatric disorders, and viral infection. There is no data available that describe the effects on lower urinary tract symptoms. DHEA also modulates the activity of several neurotransmitter receptors in the brain by acting as a neurosteroid. Neurosteroids appear to act through both nuclear and nonnuclear receptor mechanisms. With respect to nonnuclear receptor actions, DHEA has been reported to act at dopamine, NMDA, GABA_A, and/or sigma receptors. DHEA may modulate the activity of the projection system of several neurotransmitters to the micturition center in the brain. The interaction between DHEA and neurotransmitter receptors needs to be evaluated in more detail in future experiments. The pathophysiology of overactive bladder syndrome (OAB) is complex. In fact, the proportion of idiopathic cases is high. There is a marked decrease in serum DHEA concentrations throughout adult life after a peak in early adulthood. Therefore, especially in elderly persons, OAB could be affected by serum DHEA level.

Concluding message
An animal model of DHEA deficiency was successfully constructed by subjecting bilaterally adrenalectomized rats to replacement treatment with DOCA and showed significant smaller voided volume per micturition than the DHEA replacement rats. DHEA may modulate the activity of the projection system of several neurotransmitters to the micturition center in the brain. However, further evidence of this interaction is needed.

References