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LEVELS OF mRNA FOR BRAIN-DERIVED NEUROTROPHIC FACTOR ARE UP-REGULATED IN THE URETHRA OF DIABETIC RATS

Aims of Study
Diabetic neuropathy is often accompanied with neurogenic voiding dysfunction (NVD). NVD in diabetic patients is caused by peripheral neural impairment of the bladder (diabetic cystopathy) as well as the urethra. However, diabetic cystopathy has been the main focus of investigations and few studies have been done on the etiology of diabetic urethral dysfunction. On the other hand, the neurotrophic factors are essential for the development and functions of nerve cells, and are considered to regulate the organs innervated by the relevant nerves. To elucidate the molecular mechanisms of diabetic urethral dysfunction, we examined quantitative changes in various neurotrophic factors in the urethra of diabetic rats.

Methods
Male Sprague-Dawley rats were made diabetic with streptozotocin at the age of 8 weeks. Vehicle treated rats fed with or without 5% sucrose water from the age of 8 weeks were also obtained as control. Rats were sacrificed to extract total RNA from the urethra after 2, 4, 6, and 8 weeks of diabetic induction. RNase protection assay was employed to quantitate the levels of mRNA for NGF, BDNF, GDNF, CNTF, NT-3, and NT-4.

Results
NGF-, CNTF- and NT-3-mRNA levels were up-regulated at 2 weeks of diabetic induction and then, down-regulation was observed at 8 weeks. However, these changes remained in rather small range (10-50% of control). GDNF- and NT-4-mRNA levels were very low and no obvious changes were observed. On the other hand, BDNF-mRNA levels were up-regulated dramatically in diabetic rats from 6 weeks. BDNF-mRNA levels reached 9 times as much as those of control rats at 6 weeks and 12 times at 8 weeks.

Conclusions
Up-regulation of BDNF-mRNA, and concomitant down-regulation of NGF- and NT-3-mRNA in skeletal muscle of diabetic rats were previously reported elsewhere. Our results are compatible with these reports, because substantial part of the male rat urethra is composed of striated muscle. The changes in urethral neurotrophic factors observed in the present study may represent an endogenous protective and/or reparative response of the muscle induced by diabetes mellitus. Although detrusor-sphincter dyssynergia and urethral denervation supersensitivity have been documented in clinical studies as the pathophysiology of NVD in diabetic patients [1-3], there are few basic studies investigating the etiology of diabetic urethral dysfunction. Our study demonstrated novel urethral neurotrophic changes in diabetic rats that may be relevant to the molecular mechanisms of the development of neurogenic urethral dysfunction seen clinically in diabetic patients.

References:
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