

Neuronal Dysfunction in DM with Special Focus on Afferents

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Introduction

- Diabetic cystopathy is seen in 50% of patients with a 20-year history of DM (Thomas et al, 1993)
- Diabetic cystopathy is characterized by impaired sensation of fullness, increased bladder capacity, elevated residual urine volume (Ueda et al., 1997)
- Dysfunction of sensory and autonomic nervous systems is found in diabetic cystopathy
- The treatment modality for diabetic cystopathy is limited

Topics

- Time-dependent changes in bladder function (mechanoreceptive and nociceptive) in diabetic rats
- Time-dependent changes in nerve growth factor (NGF) levels in the bladder and bladder afferent pathways in diabetic rats
- Herpes simplex virus (HSV) vector-mediated NGF gene therapy for bladder dysfunction in diabetic rats.

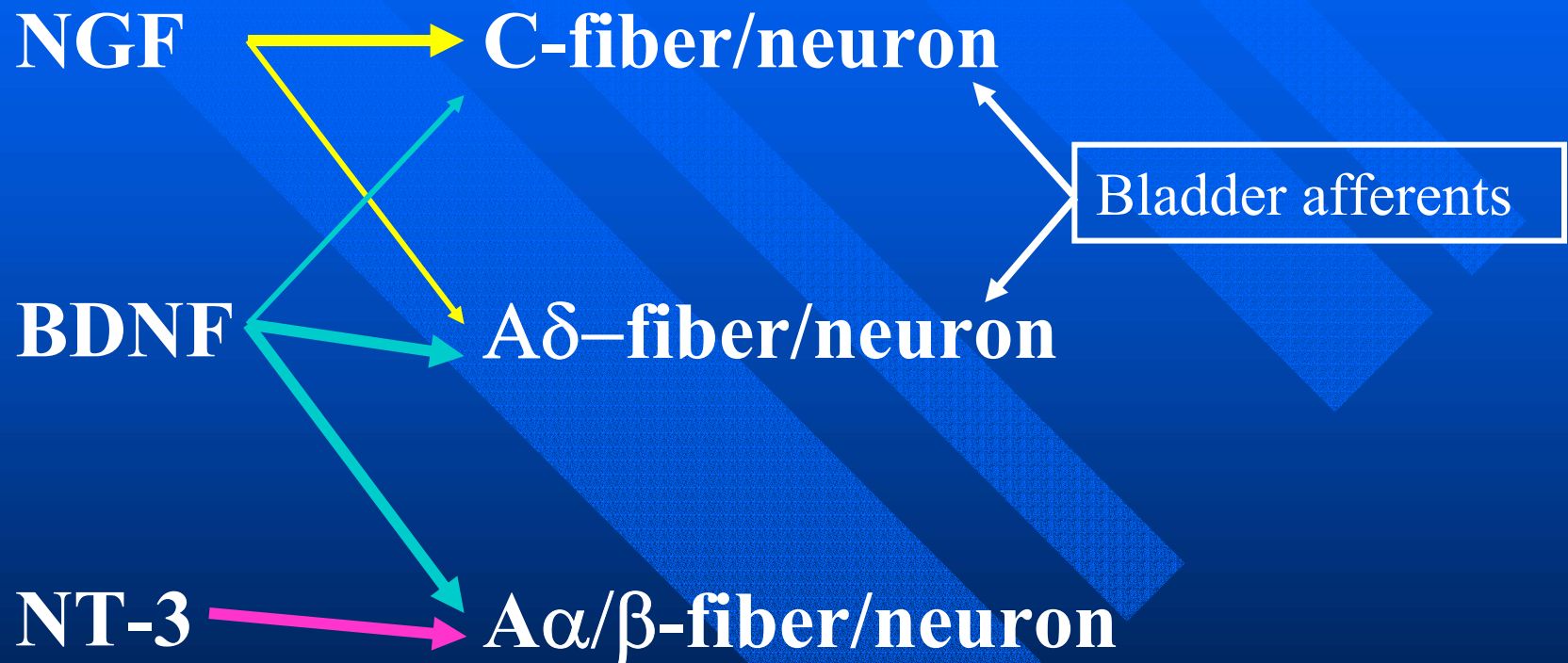
Neurotrophic factors

- Nerve growth factor (NGF)
- Brain-derived neurotrophic factor (BDNF)
- Neurotrophin 3 (NT-3)
- Neurotrophin 4/5 (NT-4/5)
- Glial cell line-derived neurotrophic factor (GDNF)

Nerve growth factor (NGF)

- NGF is one of members of neurotrophic factors which is necessary for maintaining normal function of matured sensory and sympathetic neurons
- NGF can rescue from the cell death of sensory and sympathetic neurons following various neurotoxic treatments (Goins et al, 1999)
- The possibility of treatment for neurodegenerative disease have been reported (Hefti 1991, Cho-Lundberg 1996, Springer 1993)
- Phase 2 trial of systemic administration of recombinant human NGF was performed with significant efficacy as treatment for diabetic polyneuropathy (Apfel et al, 1998)

Neurotrophic factors and sensory pathways



Over 80% of bladder afferent neurons express receptors (trkA) for NGF

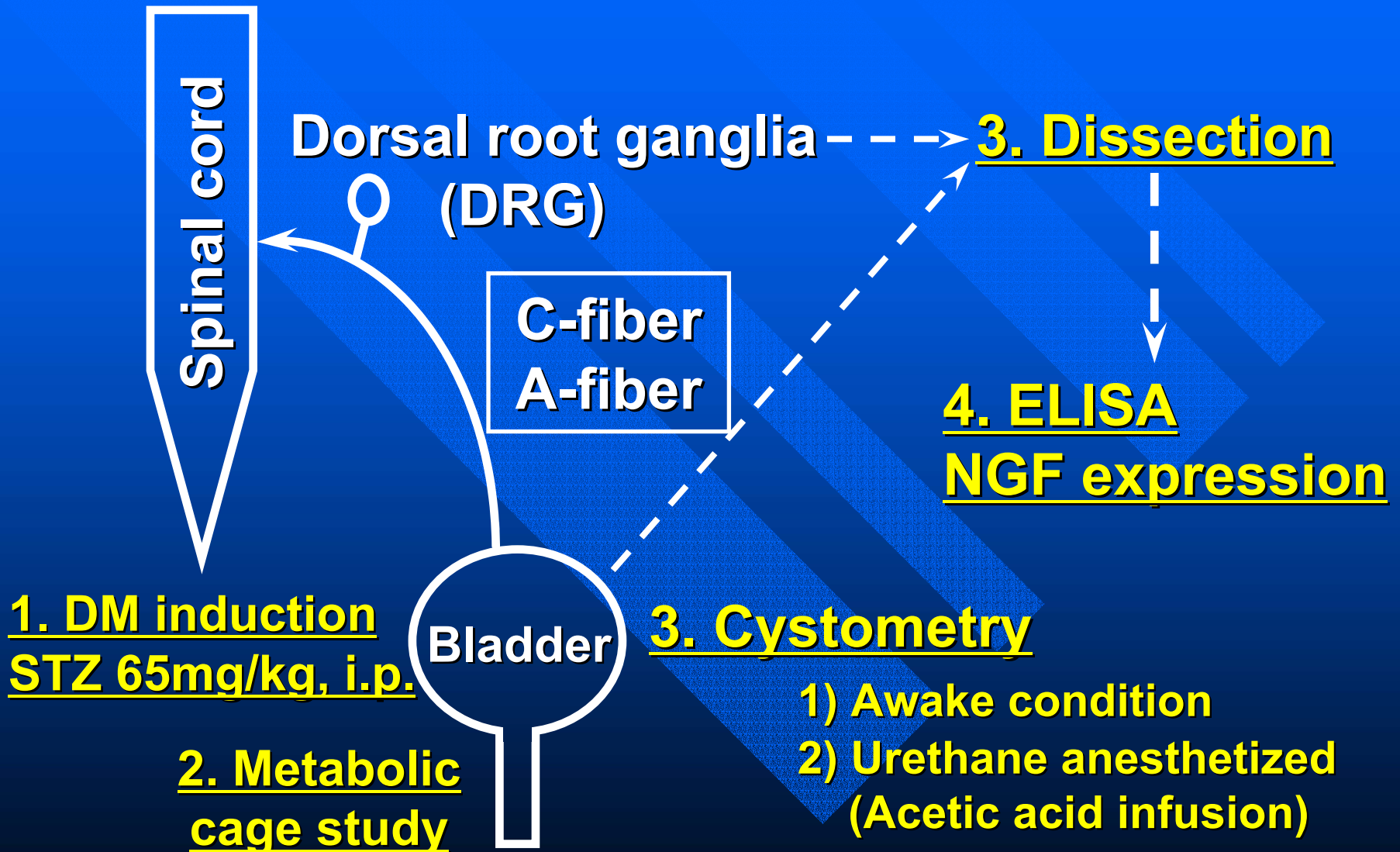
Hypothesis 1

- Changes in tissue NGF levels in the bladder and/or bladder afferent pathways could be involved in bladder dysfunction induced by peripheral neuropathy in DM

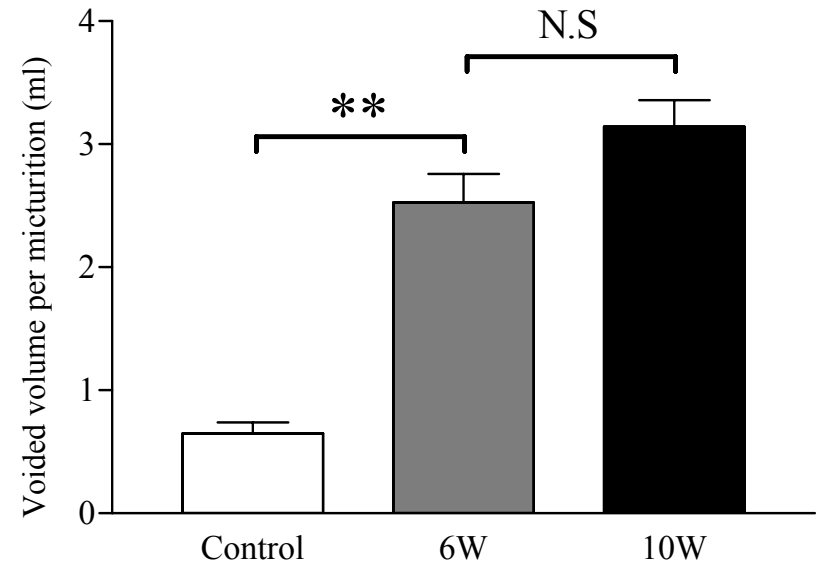
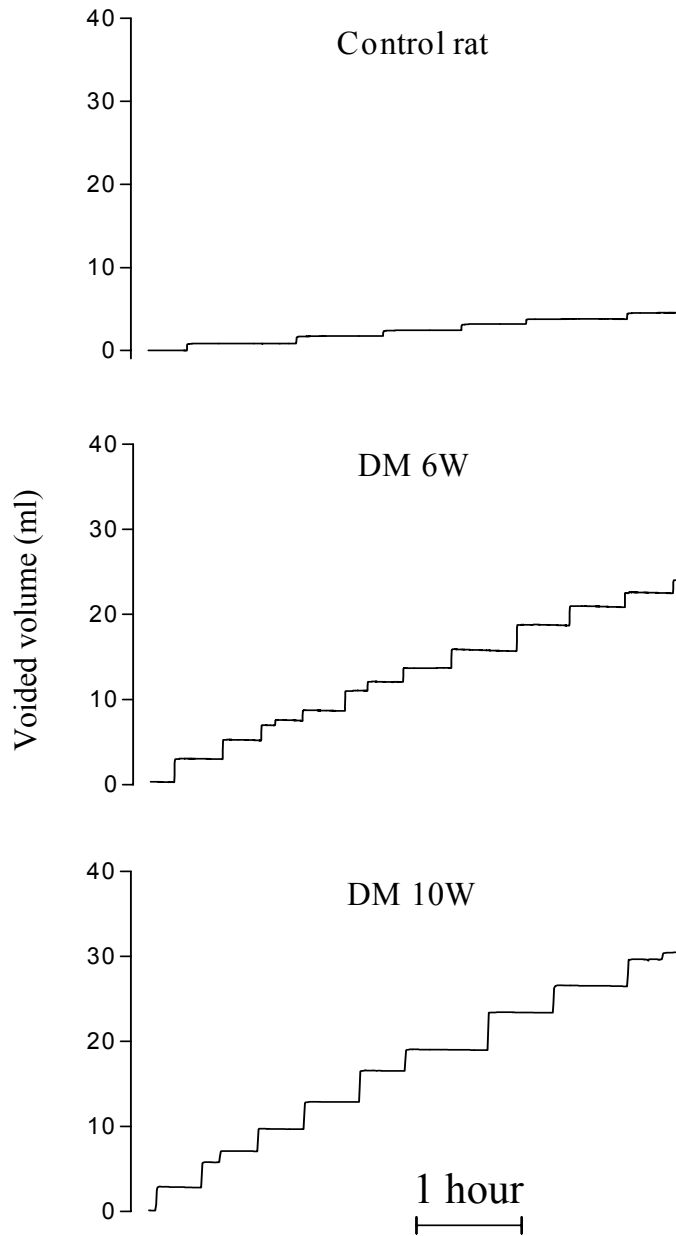
Objective

- We investigate whether bladder dysfunction progresses in parallel with the reduction of NGF levels in the bladder and bladder afferent pathways in streptozotocin induced DM rats

Methods

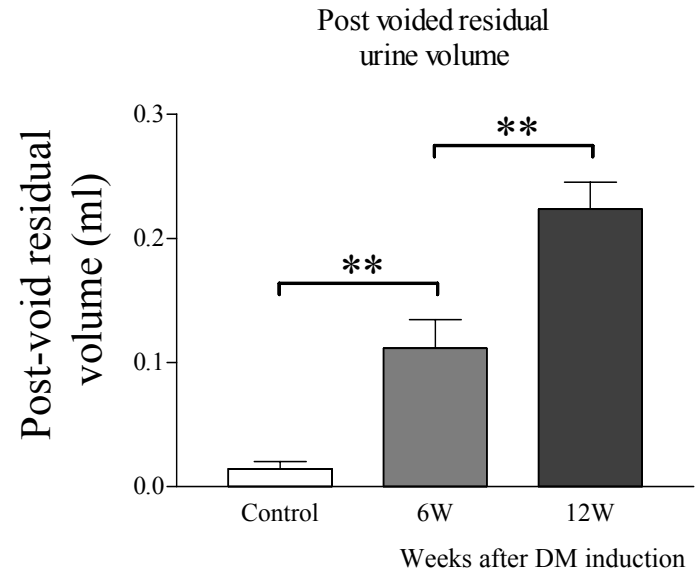
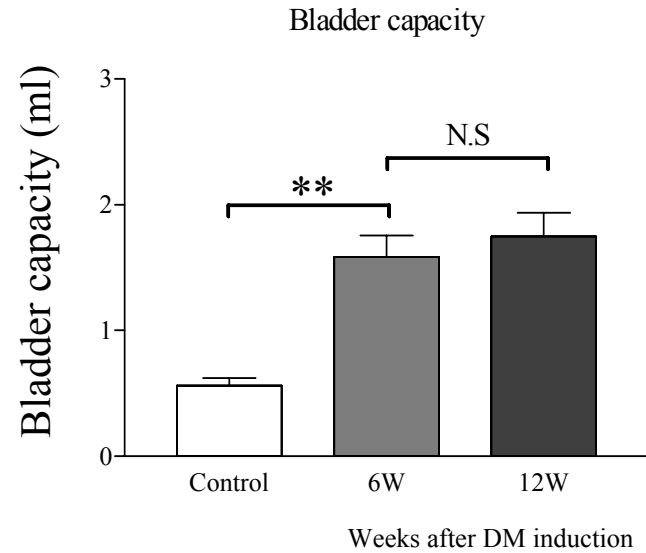
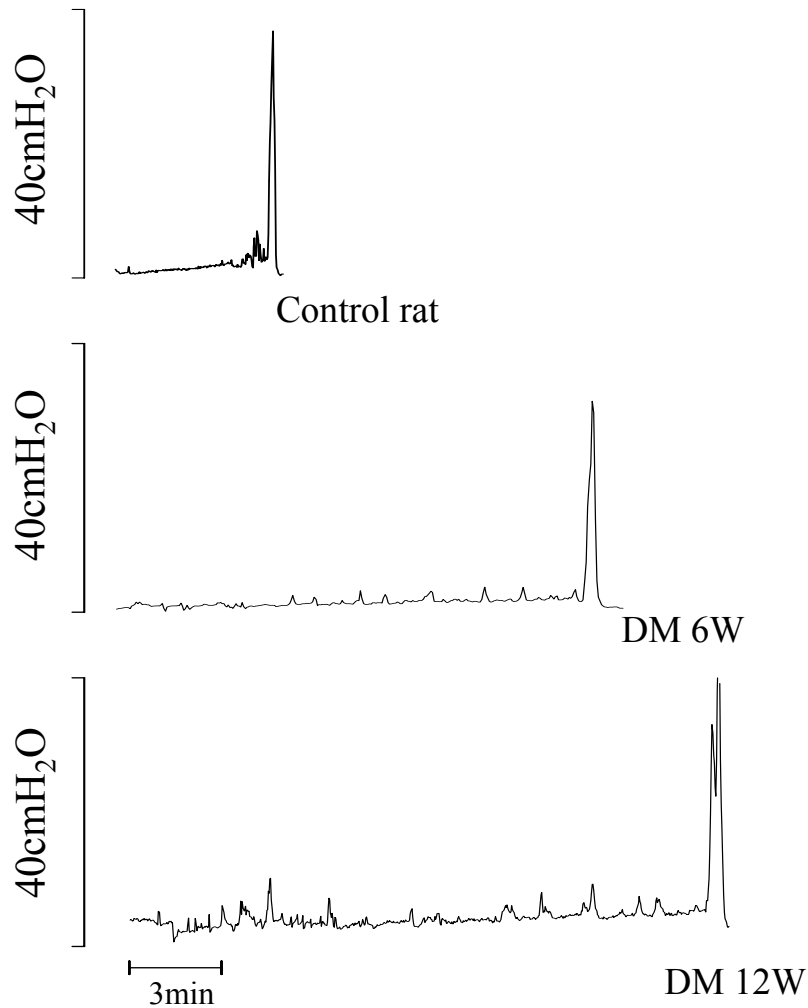


Metabolic Cage Study



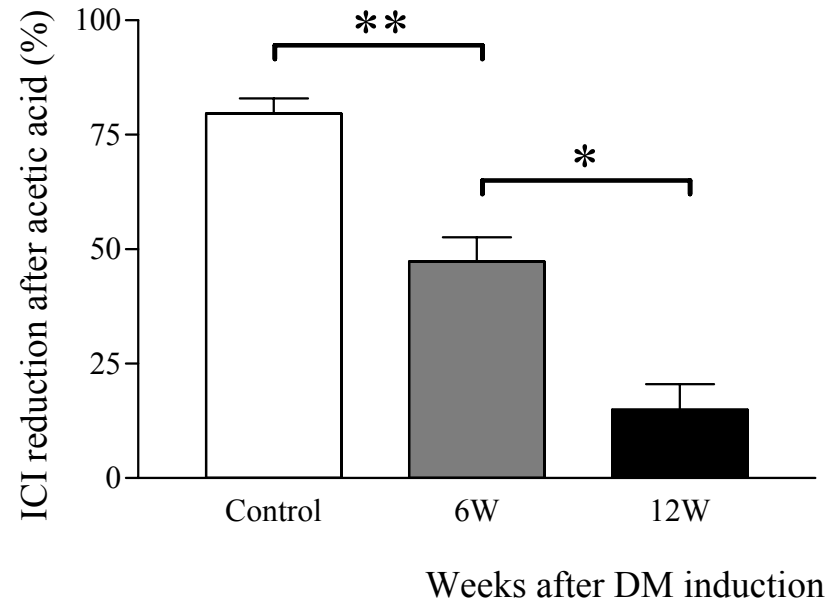
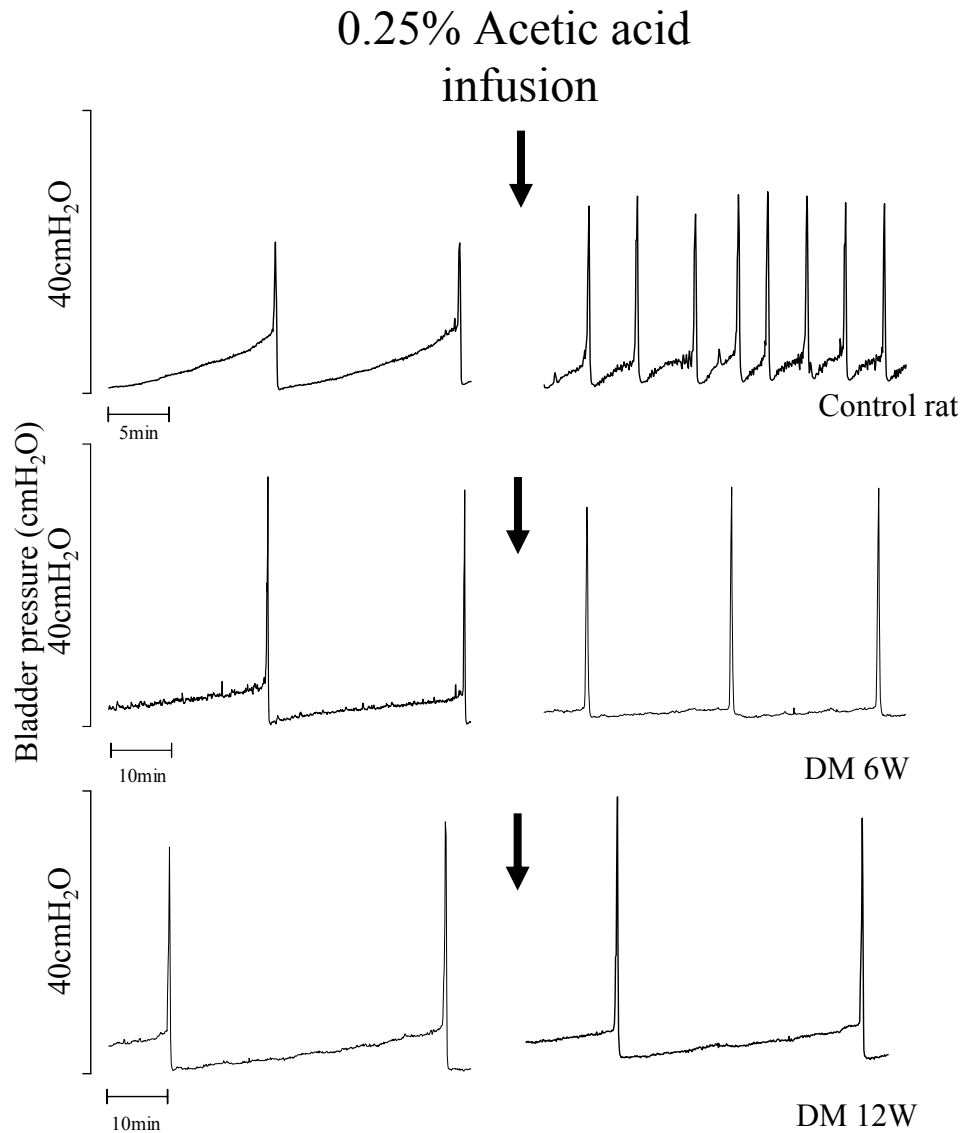
** $p < 0.01$ (unpaired t test)

Awake CMG



** p<0.01 (unpaired t test)

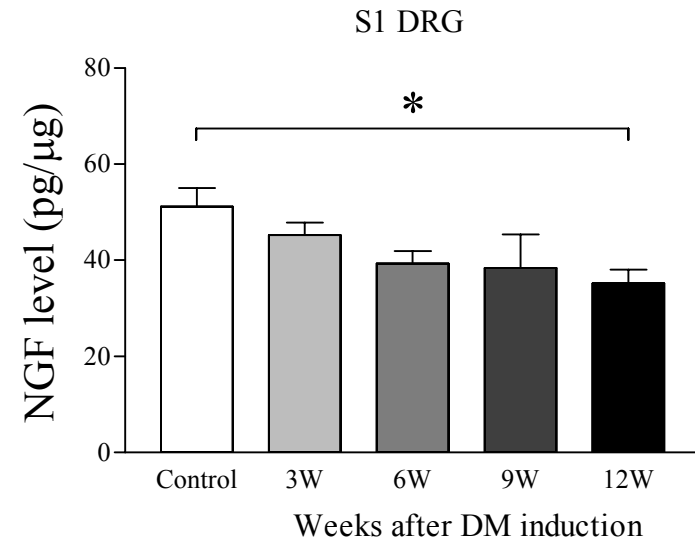
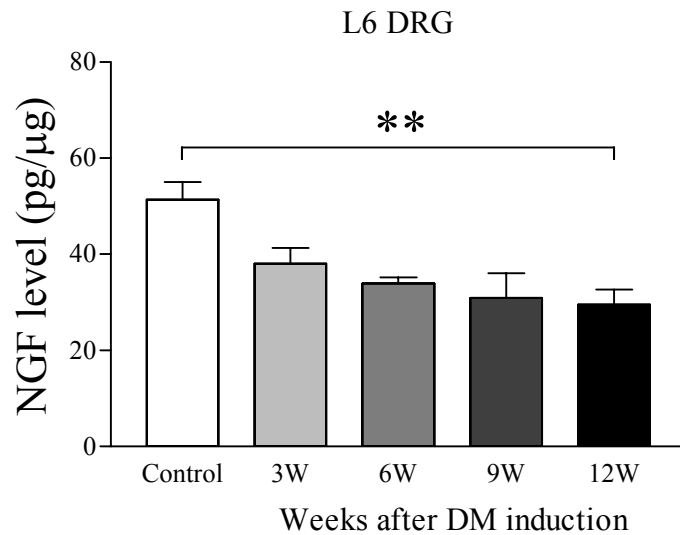
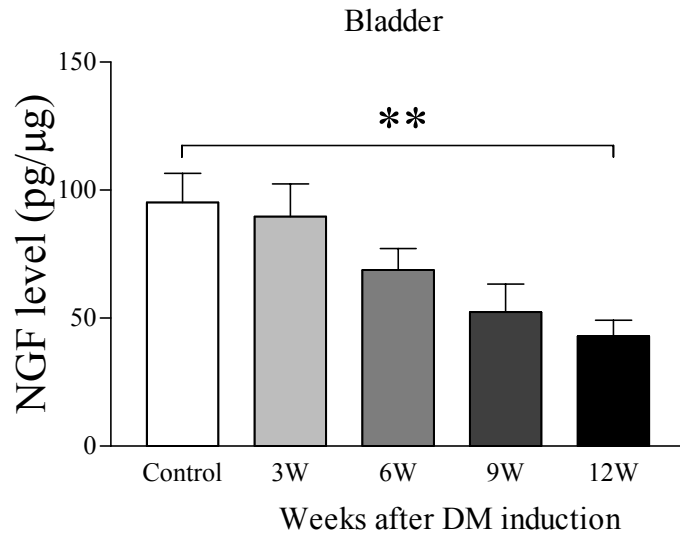
CMG (Urethane anesthesia) (Acetic acid infusion)



* $p < 0.05$ (unpaired t test)

** $p < 0.01$ (unpaired t test)

Tissue NGF levels

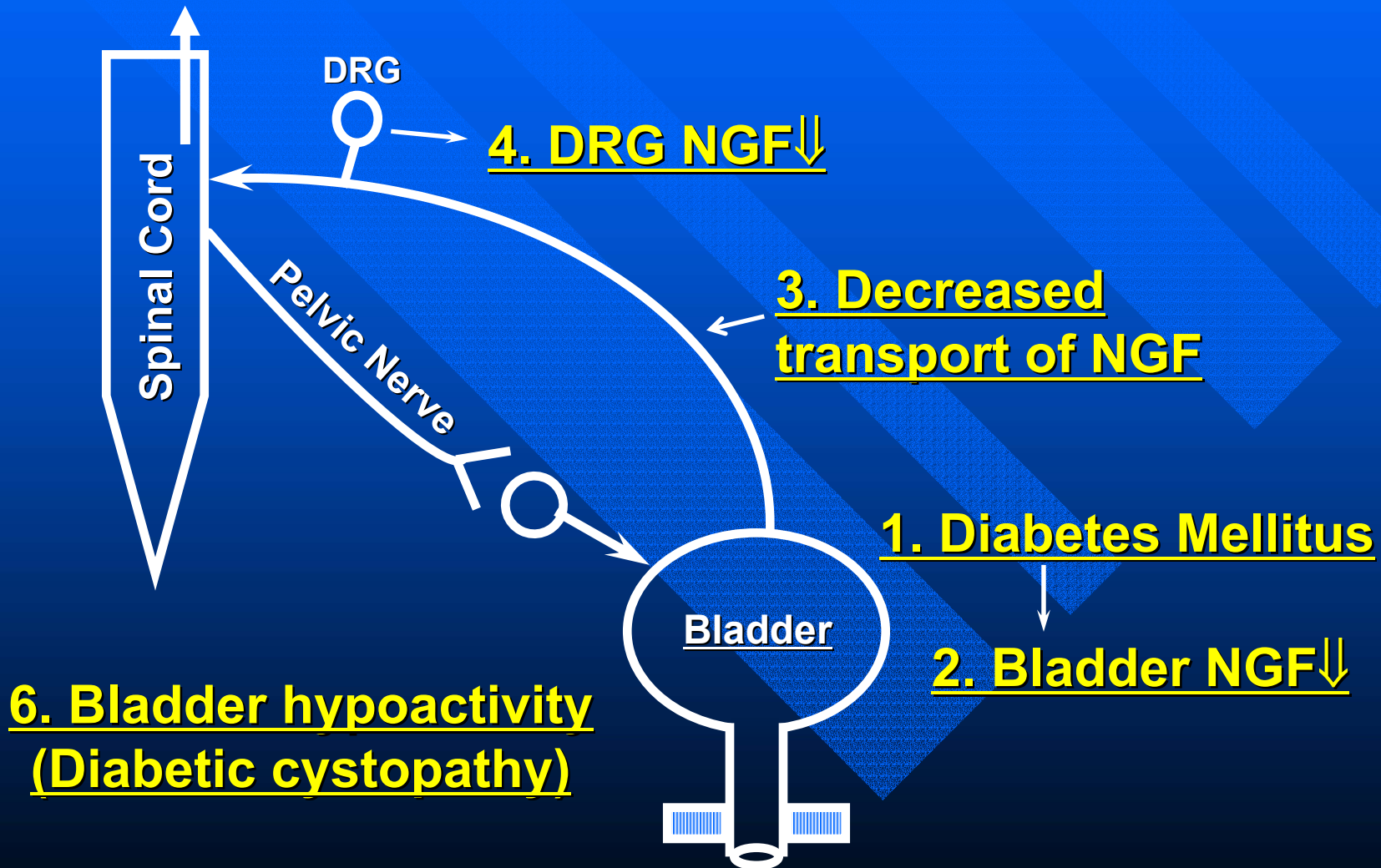


* $p < 0.05$ (ANOVA)

** $p < 0.01$ (ANOVA)

Conclusions 1

- 5. Bladder filling sensation (A δ -fiber afferent-dependent) ↓↓
- Bladder irritable response (C-fiber afferent-dependent) ↓↓

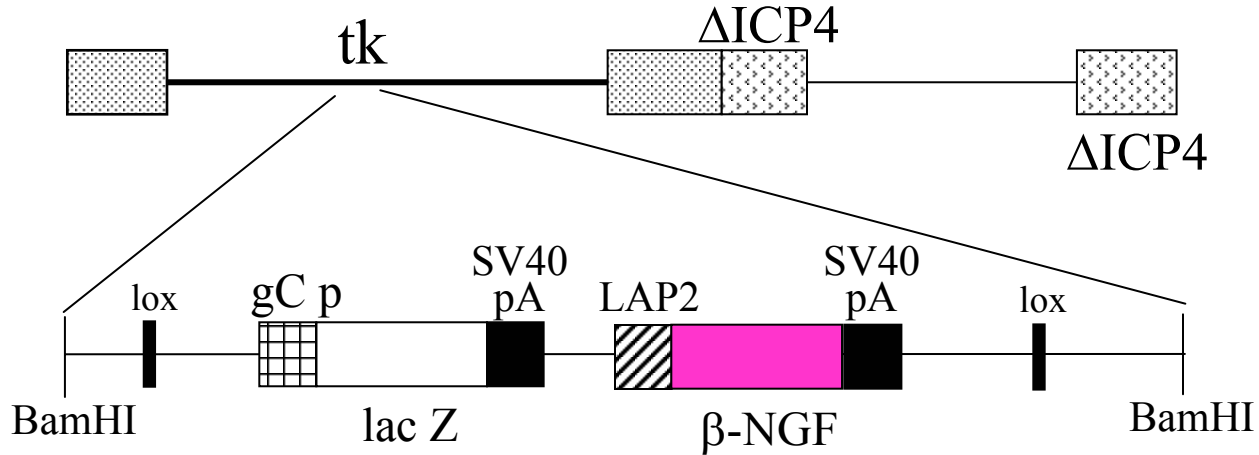


**NGF gene therapy mediated
by replication deficient HSV
in diabetic rats**

Hypothesis 2

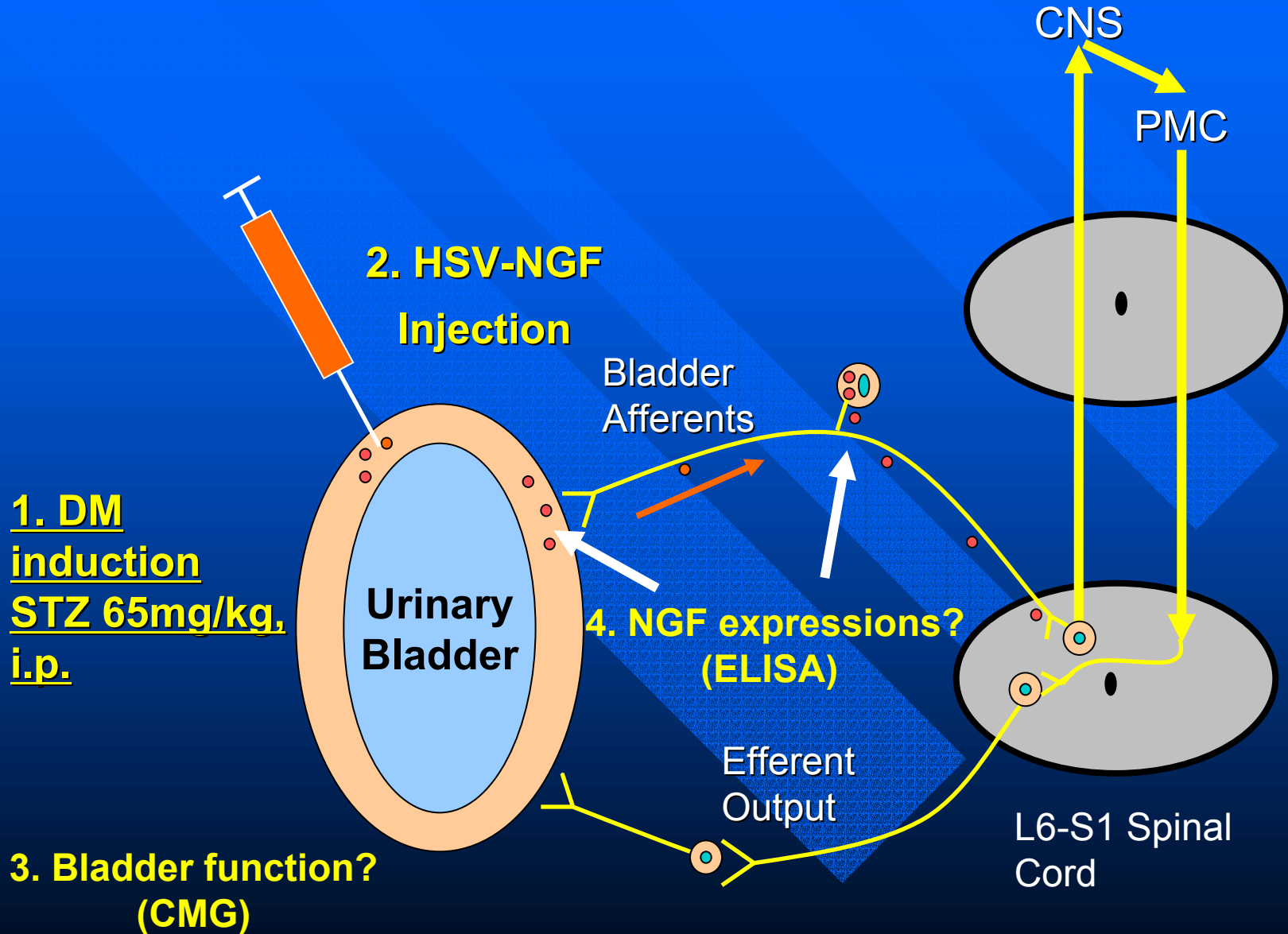
- Gene therapy with replication-deficient HSV-nerve growth factor (HSV-NGF) can restore bladder dysfunction in diabetic rats

Schematic representation of replication-deficient HSV-NGF (SLN)



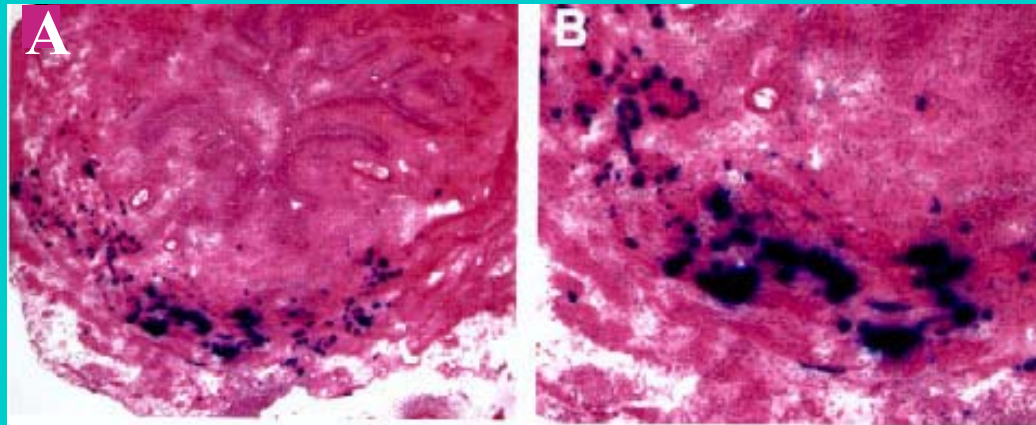
Modified from
Goins, et al. J.
virol, 1999

Methods of HSV-NGF gene therapy

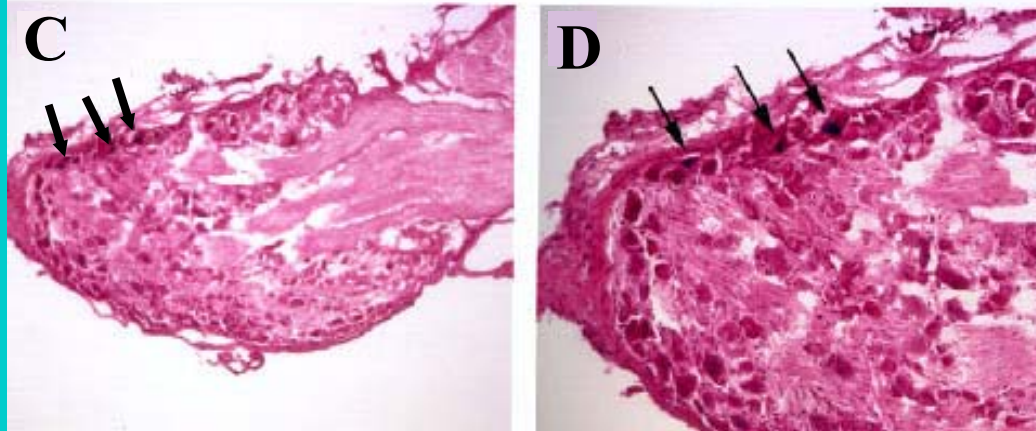


HSV vector-mediated β -gal expression localizes in bladder smooth muscle and L6 DRG.

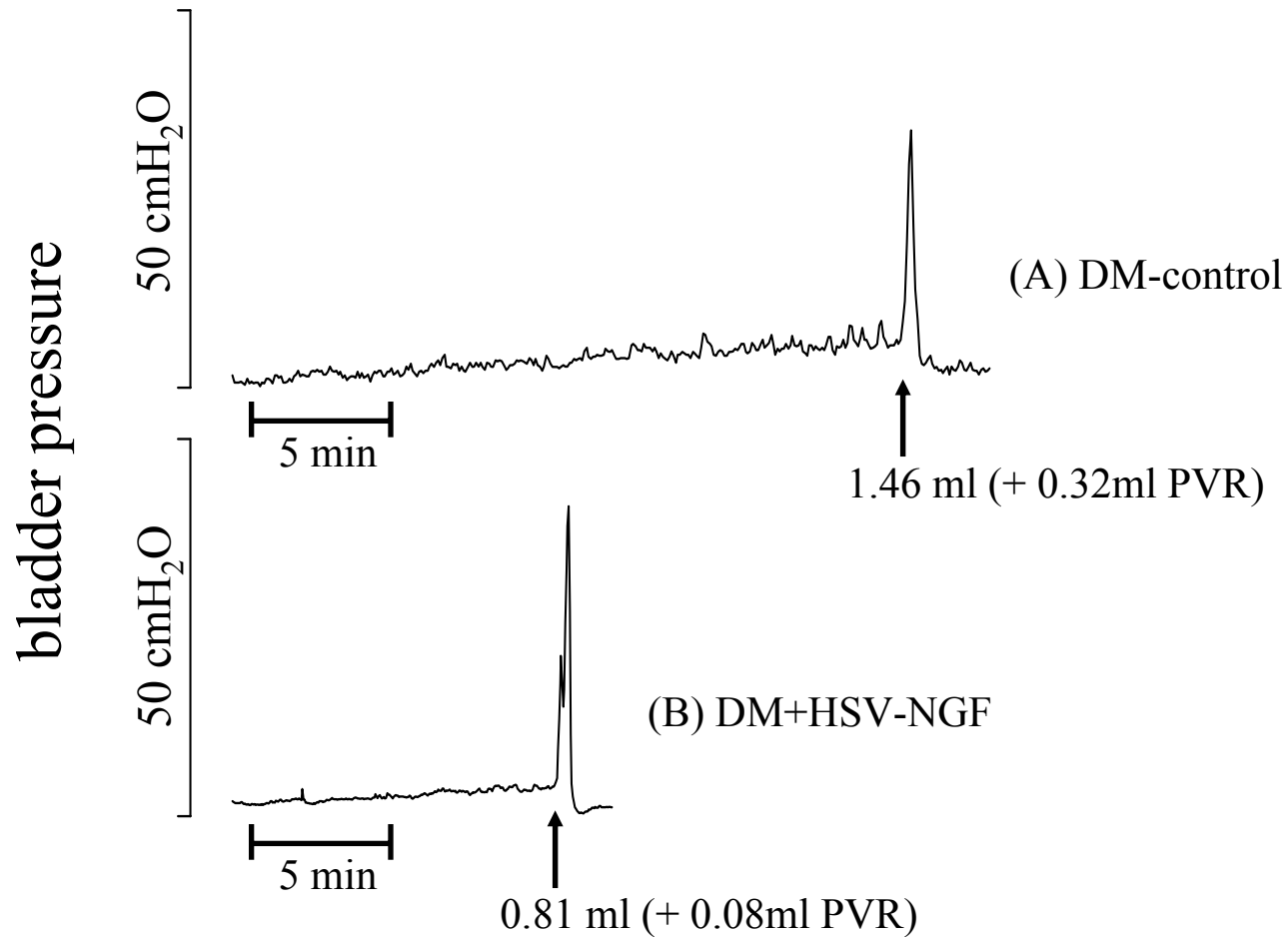
Bladder →



L6 DRG →

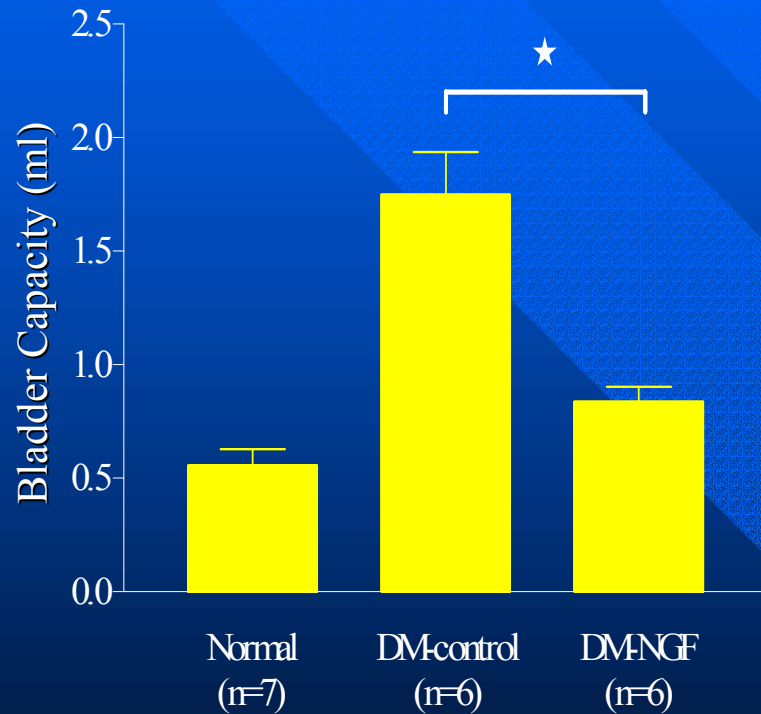


Awake cystometograms

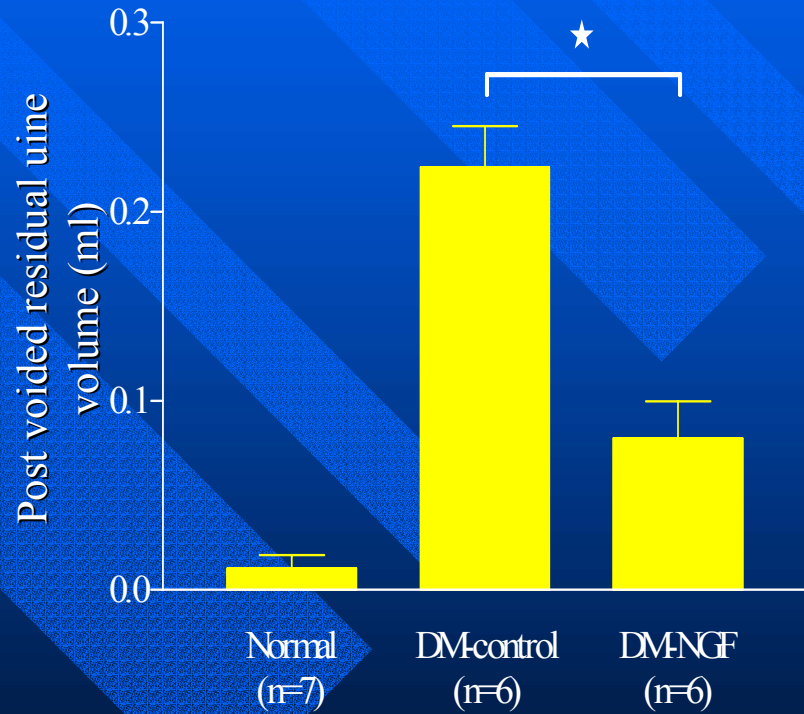


Awake cystometrogram after gene therapy

(A) Bladder capacity

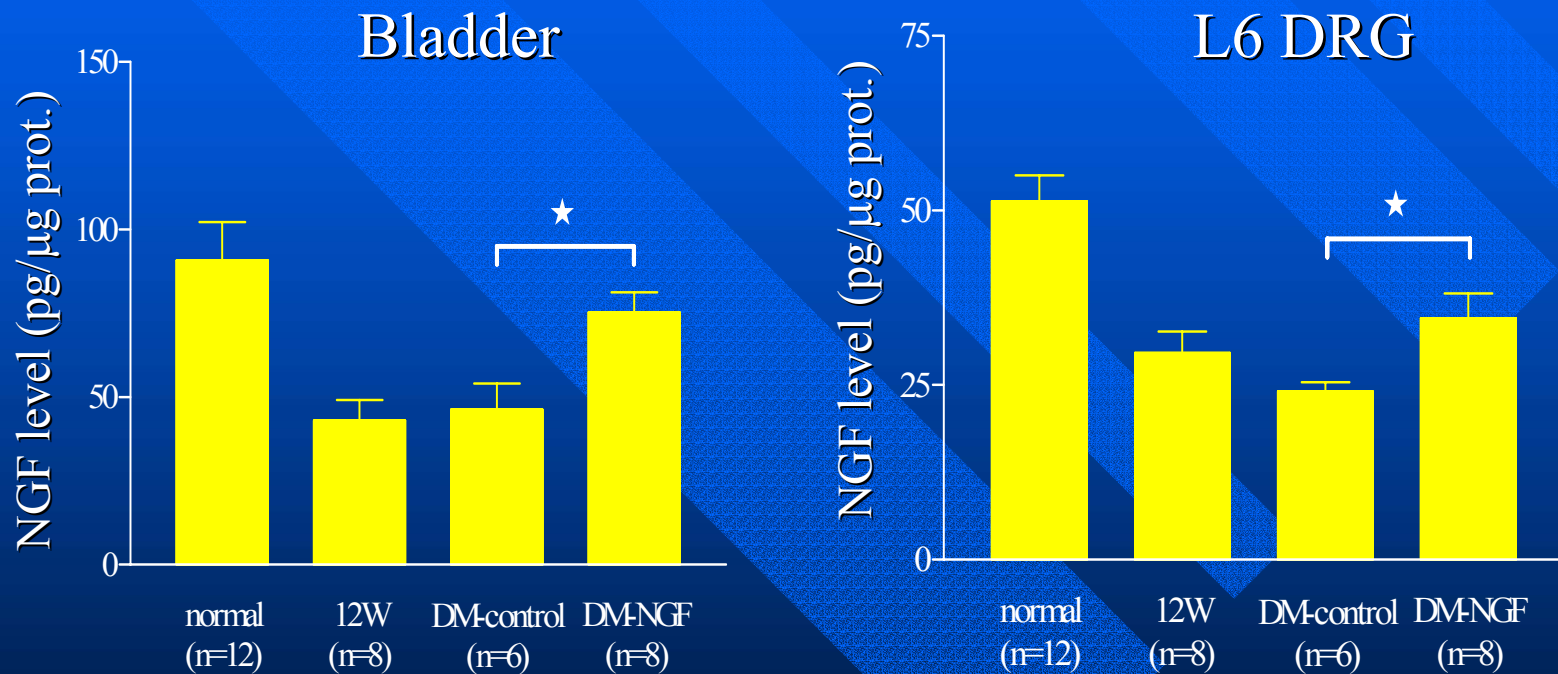


(B) Post voided residual urine volume



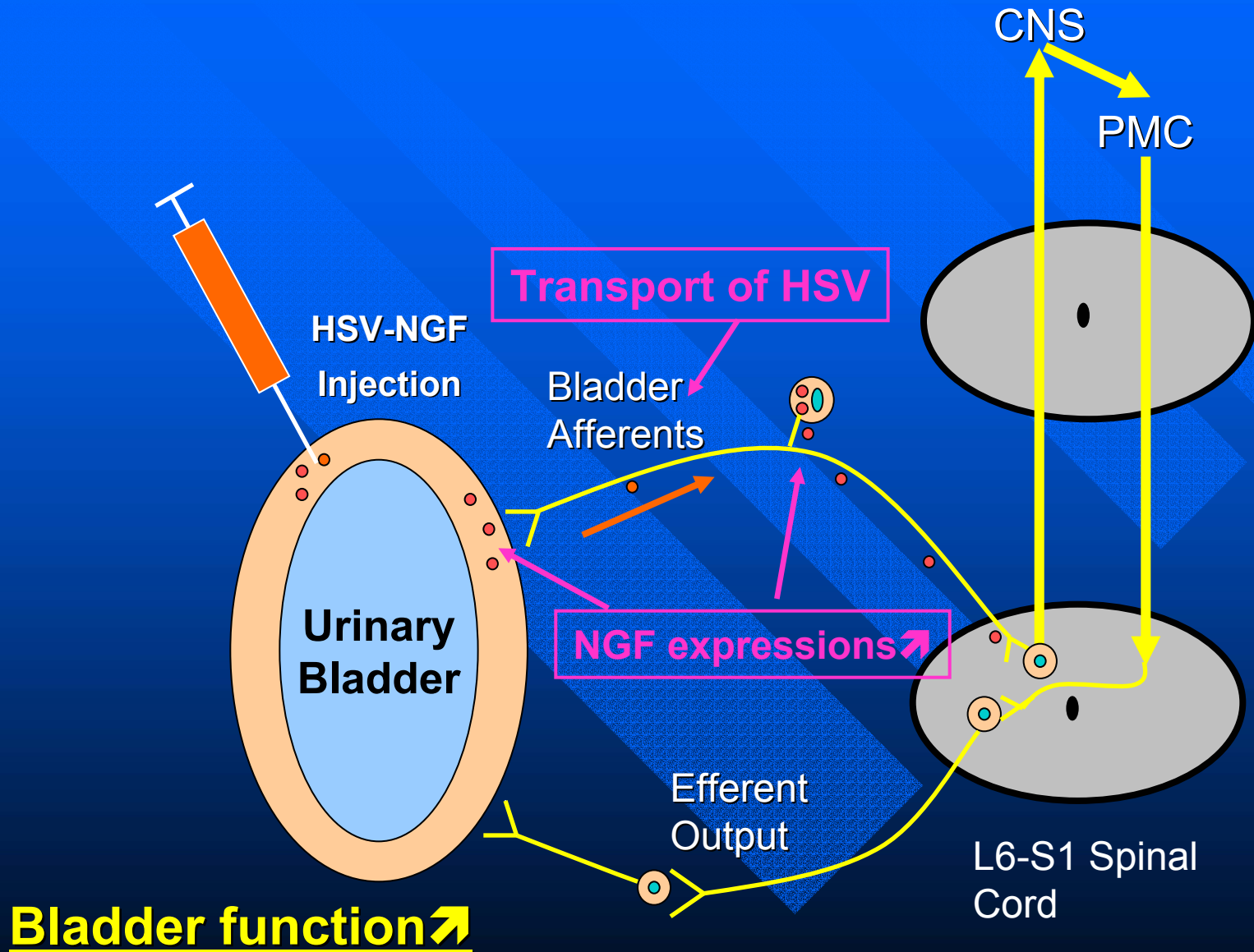
★ $p < 0.05$
(unpaired t test)

Effects of HSV-NGF gene therapy on NGF levels

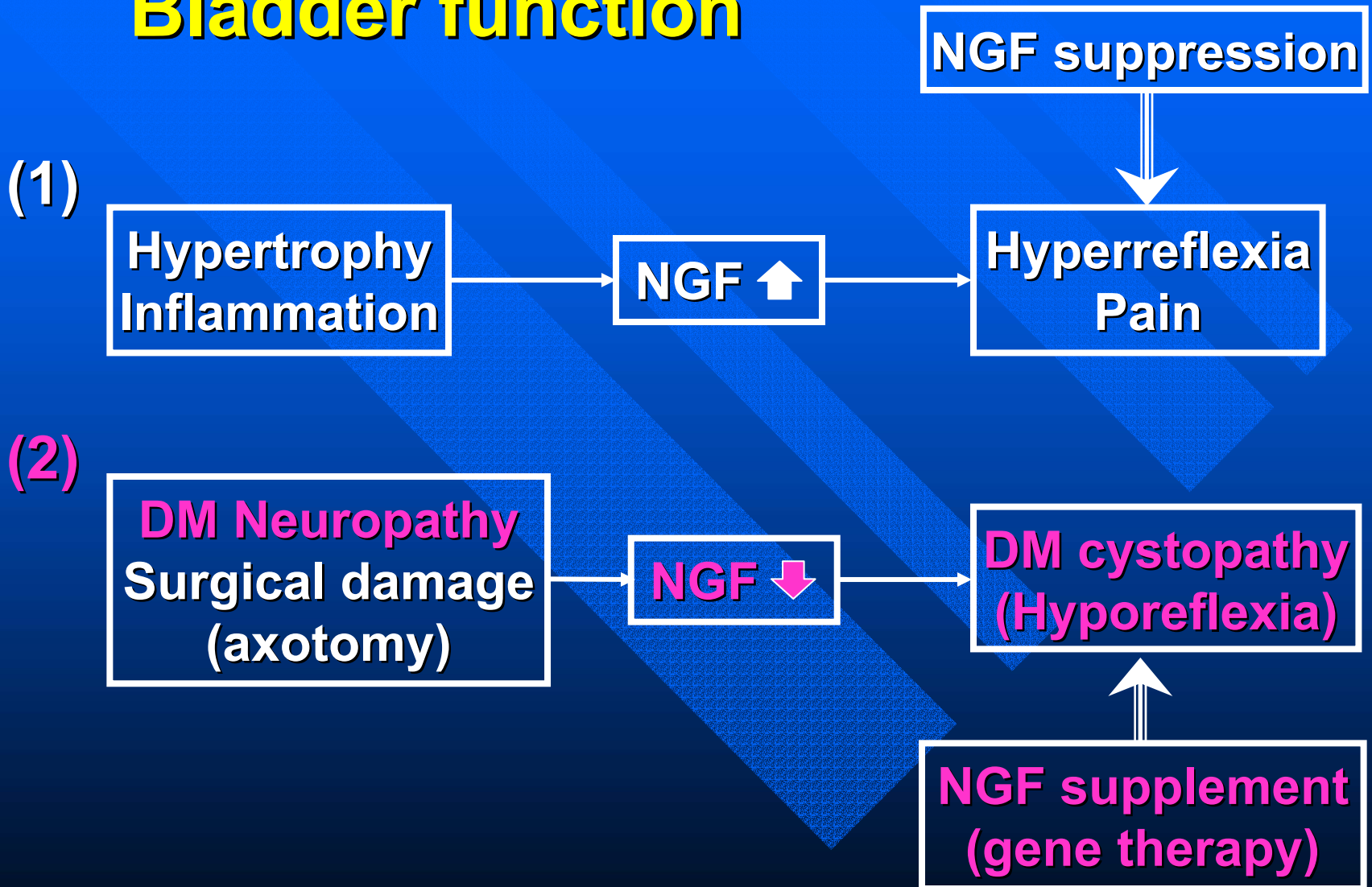


★ $p < 0.05$
(unpaired t test)

Conclusions 2



Conclusions: NGF and Bladder function



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