

INCREASED BLADDER REFLEX ACTIVITY INDUCED BY CYSTITIS IS REDUCED AFTER NEUTRALIZATION OF BRAIN DERIVED NERVE FACTOR (BDNF). AN EXPERIMENTAL STUDY IN THE RAT.

Hypothesis / aims of study

It is widely accepted that Nerve Growth Factor (NGF) modulates bladder activity and sensory input during cystitis. The contribution of other neurotrophins is less clear. In particular, the role played by Brain Derived Nerve Factor (BDNF) in cystitis is still poorly understood. However, BDNF is the most abundant and widely distributed neurotrophin in the central nervous system. In primary sensory neurones, BDNF is present in small to medium sized predominantly peptidergic dorsal root ganglion cells. BDNF is anterogradely transported from the cell bodies of these cells to terminals in the spinal cord. BDNF binds to its specific TrkB receptor present in second order sensory neurones leading to activation of intracellular signalling pathways, including the Extracellular signal-Regulated Kinases 1 and 2 (ERK) cascade. In the present study we investigated the effects of a synthetic BDNF antibody on bladder reflex activity and spinal cord ERK phosphorylation in animals with chronic bladder inflammation.

Study design, materials and methods

Female rats (n=4/group) were injected with cyclophosphamide (200mg/Kg) and allowed to survive for 3 days. During that period, antibody against BDNF, sterile saline or unspecific IgG were injected daily in the tail vein under isoflurane anaesthesia (5% for induction, 2% for maintenance). As controls, non-manipulated intact rats were also used (n=4). On the 4th day, rats were anaesthetized with urethane (1.2g/Kg) and bladder function evaluated by cystometry. Two hours afterwards, animals were perfusion-fixed through the ascending aorta and the spinal cord segment L6 collected, post-fixed and immersed in sucrose overnight. Segments were then cut into 40 µm sections and immunoreacted against phosphoERK using the ABC-HRP method.

Results

In animals injected with cyclophosphamide the frequency of bladder reflex contractions was significantly increased in comparison with naïve rats (1.17 ± 0.16 versus 0.60 ± 0.08 , respectively; $p < 0.05$). The frequency of bladder contractions was significantly reduced in animals that received 100 µg (0.66 ± 0.13 ; $p < 0.05$ versus saline) and 200 µg of BDNF antibody (0.42 ± 0.31 ; $p < 0.01$ versus saline). In animals treated intravenously with unspecific IgG, there was no reduction in the frequency of bladder reflex contractions (1.15 ± 0.13). Lack of effects was obtained in inflamed animals that received intravenous saline instead of BDNF antibody. In what concerns ERK activation, a known downstream target of BDNF, preliminary data indicates a possible dose dependent reduction in phosphoERK levels in rats injected with anti-BDNF. As with bladder reflex activity, intravenous injection of unspecific IgG did not affect spinal levels of ERK phosphorylation.

Interpretation of results

Present results indicate that BDNF neutralization brings bladder reflex activity of rats with chronic cystitis to levels found in intact animals. Given the reduction of ERK phosphorylation levels observed in the same rats, it is likely that BDNF contributes to bladder hyperactivity via the MAPK intracellular pathway.

Concluding message

BDNF plays a significant and up to now unforeseen role in the regulation of bladder reflex activity in cystitis. This raises the possibility of using BDNF neutralization as a therapeutic tool to reduce bladder reflex activity in chronic bladder inflammatory conditions.

References

- 1- J. Comp. Neurol. (2004), 475:590-603.
- 2- Mol. Cell. Neurosci. (2002), 21:684-695.
- 3- Eur. J. Neurosci. (2005), 21:773-781.

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Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	Yes
Name of ethics committee	Zimmermann, M., 1983. Ethical guidelines for investigations of experimental pain in conscious animals. Pain 16, 109-110.