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ROLE OF BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) IN NEUROGENIC DETRUSOR OVERACTIVITY (NDO)

Hypothesis / aims of study

Neurogenic detrusor overactivity (NDO) is a well known consequence of spinal cord injury (SCI) that emerges after a period of spinal shock during which the bladder is areflexic. The appearance and maintenance of NDO are dependent on profound plastic changes of the spinal neuronal pathways that regulate bladder function. It is generally assumed that neurotrophic factors (NFs) are major regulators of such neuroplastic changes. NFs are tissue-derived proteins and are divided in two main groups: the GDNF family ligands and neurotrophins (NTs). This latter group comprises several members, of which nerve growth factor (NGF) is the best studied in the bladder. Indeed, the role of NGF in NDO has already been established (1). Another very abundant neurotrophin is brain derived neurotrophic factor (BDNF) (2). Although it has been recently shown that BDNF, acting at the spinal cord level, is a key mediator of bladder dysfunction and pain during cystitis (3), it is presently unclear if BDNF is also important for NDO. Therefore, the present study aimed to clarify this issue.

Study design, materials and methods

Female Wistar rats (n=5 /group) were submitted to spinal cord transection (SCT) at T9 level and sterile gelfoam placed between the retracted ends. Animals were submitted to cystometry under urethane anaesthesia at 1 and 4 weeks after SCT, after which they were perfused through the ascending aorta. BDNF levels and GAP43, a marker of axonal growth, and CGRP expressions were quantified in the L6 spinal cord segment by immunohistochemistry.

In three other groups of animals, an intrathecal catheter was placed at the L6 spinal cord level for delivery of TrkB-Ig_2, a recombinant protein that effectively sequesters BDNF (3). In one group of animals, saline or the recombinant protein (20µg/day) were continuously delivered with an osmotic mini-pump connected to the catheter for seven days after SCT. At this time point, rats were anaesthetized and underwent cystometry. In another group, the catheter was left subcutaneously and externalized at 4 weeks after SCT. These rats were anaesthetized and submitted to cystometry, during which increasing amounts of saline or TrkB-Ig_2 (1µg, 10 µg and 20 µg) were intrathecally injected every 30 minutes. At the end of cystometries, as above, rats were perfused through the ascending aorta and BDNF levels and GAP43 expression analysed by immunofluorescence.

In a final experiment, dorsal root ganglia from non-treated SCT rats (1 and 4 weeks) and TrkB-Ig_2-treated SCT rats were freshly collected and cultured to assess growth ability.

Results

In the first week after SCT, bladder function was significantly altered ($p<0.05$ versus spinal intact animals). The frequency of bladder contractions decreased from 0.57±0.1/min, in spinal intact rats, to 0.13±0.1/min. At 4 weeks after SCT, NDO was obvious and the frequency of bladder contractions was 1.2±0.3/min.($p<0.05$ versus spinal intact animals). This was accompanied by a significant time-dependent increase in spinal BDNF and GAP43 expression ($p<0.001$ versus spinal intact animals).

BDNF sequestration with TrkB-Ig_2 during the 1st week resulted in a significant decrease in spinal BDNF, in comparison with non-treated SCT at the same time point ($p<0.001$). This was accompanied by a significant increase in the frequency and amplitude of bladder reflex activity was registered, the values being 1.6±0.1/min and 11.8±0.7 cm H_2O ($p<0.05$ versus one-week SCI animals treated with saline). These alterations in bladder function occurred together with an upregulation of GAP43 expression ($p<0.05$ versus spinal intact animals), which was observed in CGRP-positive fibres. Accordingly, cell culture experiments demonstrated that BDNF sequestration stimulated neurite outgrowth, as demonstrated by high neurite branching ($p<0.01$ versus all SCT rats, irrespective of the time point).

In four-week SCI-animals treated with TrkB-Ig_2, a dose dependent decrease in the frequency and amplitude of bladder contractions was observed, the maximum effect being observed with 20 µg. At this dose the frequency of bladder contractions was reduced from 1.8±0.4/min ($p<0.05$ versus intact animals) to 0.4±0.4/min ($p<0.05$ versus saline-treated SCI animals). The amplitude of bladder contractions was also reduced to 4.2±3.2 cm H_2O ($p<0.05$ versus SCI animals treated with saline).

Interpretation of results

The present results demonstrate a dual role for BDNF during the course of NDO caused by SCI. During spinal shock, BDNF seems to repress the growth of sensory afferents, an event classically linked to NDO. Accordingly, BDNF sequestration resulted in increased axonal growth and early bladder overactivity. This is supported by *in vivo* and *in vitro* observations. In rats with chronic NDO, BDNF is a positive inducer of NDO as its sequestration improved bladder function. The reasons underlying this dual role of BDNF are under investigation.

Concluding message

These findings suggest that BDNF may have a protective role during the spinal shock period. In contrast, in animals with established NDO, BDNF potentiates bladder dysfunction. Thus, BDNF is an attracting therapeutic target to be differentially manipulated at different stages of NDO establishment.

References

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Disclosures
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