499

Gill B[1], Dissaranan C[1], Jiang H[1], Balog B[1], Lin D[2], Goldman H B[1], Damaser M[1]
1. *Cleveland Clinic Foundation, Cleveland, Ohio, USA,* ***2.*** *Research service,Louis Strokes VA Medical Center, Cleveland, Ohio, USA*

EFFECTS OF NEUROTROPHIN SUPPLEMENTATION ON FUNCTIONAL RECOVERY OF THE PUDENDAL NERVE FOLLOWING SIMULATED CHILDBIRTH INJURY

Hypothesis / aims of study

Pudendal nerve (PN) injury, associated with vaginal birth trauma, has been implicated as a major mechanism in the pathogenesis of stress urinary incontinence (SUI). Specifically, this injury produces an impairment of the neuromuscular continence mechanism consisting of the PN and external urethral sphincter (EUS). Following peripheral nerve injury, upregulation of brain-derived neurotrophic factor (BDNF) has been observed in target organs and axons distal to injury [1]. BDNF is required for neuroregeneration and local administration to injury sites reduces motorneuron death following transection [2]. BDNF is upregulated in the EUS following pudendal nerve crush (PNC). However, compared to PNC alone, markedly lower BDNF upregulation occurs after PNC with concurrent EUS trauma induced by vaginal distention (VD) [3]. The present study investigates whether continuous, local administration of exogenous BDNF can improve PN neuroregeneration as well as functional recovery of the EUS following simulated childbirth injury consisting of PNC and VD.

Study design, materials and methods

Female, virgin, Spraque-Dawley rats (200-225g) were divided into 3 groups: PNC & VD with BDNF treatment (N=11), PNC & VD with sham (saline) treatment (N=9), and an untreated, sham injured group (N=10). VD was performed by inserting a modified 10Fr. Foley catheter into the vagina and inflating the balloon to 3 ml for 4 hours. PNC was performed bilaterally by crushing the PN within the ischiorectal fossa twice, for 30 seconds. Immediately following injury, two subcutaneous, osmotic pumps containing the specified treatment were implanted dorsally with catheters to provide localized treatment secured near the site of PNC bilaterally.

Outcomes were tested 2 weeks after injury and treatment and consisted of simultaneous leak point pressure (LPP), EUS electromyography (EMG), and PN electroneurography (ENG) testing. The bladder was filled and intravesical pressure was recorded via a urethral catheter while PN motor branch ENG and EUS EMG were recorded both at rest and while the exposed bladder was gradually compressed to induce leakage and generate a neuromuscular continence reflex. Analysis of LPP consisted of subtracting baseline from leak point pressure. Electrophysiological signals from EMG and ENG were electronically processed to remove noise and the average frequency and amplitude of 1-second intervals at baseline and leak point were measured. Power, the time-based integral of the electrophysiological signal or area under the curve, was also assessed for both EMG and ENG data. Statistical comparisons of each measure for treatments and sham injury were made using One-Way ANOVA and appropriate post-hoc paired analyses. For all tests, $p < 0.05$ indicated statistical significance.

Results

LPP in the sham injury and BDNF treatment groups were significantly higher than that in the sham-treated group, but were not significantly different from each other (Figure 1). EUS EMG frequency at rest and EUS EMG amplitude both at rest and during LPP testing were significantly decreased after PNC & VD with sham treatment compared to sham injury. In contrast, the same outcomes were not significantly different after PNC & VD with BDNF treatment compared to sham injury. Power of EUS EMG was significantly decreased after PNC & VD with sham treatment compared to sham injury both at rest and during LPP testing. There were no differences in either PN amplitude or frequency among the 3 groups at rest or during LPP testing.

Interpretation of results

Continence, as assessed by LPP, recovered 2 weeks after simulated childbirth injury when treated with BDNF but not with a sham treatment. Furthermore, the improvement in continence with BDNF treatment was statistically significant compared to sham-treated animals. Previous studies have shown continence recovers approximately 3 weeks following PNC & VD [3]. Therefore, it appears BDNF treatment may shorten the time required for recovery of LPP after simulated childbirth. Functionality of the EUS recovered 2 weeks following PNC & VD when treated with BDNF but not when sham-treated, as evidenced by significantly reduced EUS activity with sham treatment but not with BDNF treatment, compared to sham injury. We conclude that BDNF accelerates the restoration of EUS function following injury leads to improved recovery of continence. Current work investigating molecular markers of PN neuroregeneration is underway.

Concluding message

Local administration of exogenous BDNF after simulated childbirth injury enhanced functional recovery of the neuromuscular continence mechanism consisting of the PN and EUS. Postpartum administration of BDNF may provide an effective agent for reducing the incidence of SUI after childbirth injury.

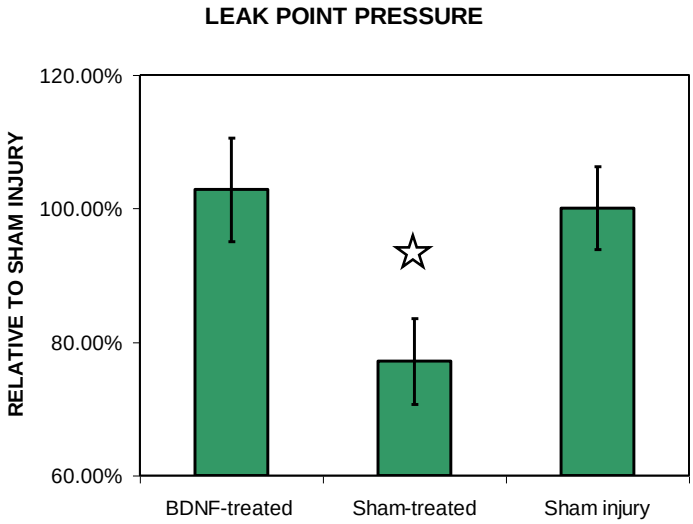

Figure 1. LPP 2 weeks after injury and treatment showing significantly improved recovery with BDNF treatment compared to placebo. Data is presented as mean ± standard error of the mean of animals in each group, expressed as a percentage of the mean LPP of the sham-injured group. The star indicates a statistically significant difference compared to both BDNF-treated and sham injured groups.

References

1. Funakoshi H, Frisen J, Barbany G, et al. Differential expression of mRNAs for neurotrophins and their receptors after axotomy of the sciatic nerve. J Cell Biol. 1993;123:455.
2. Sendtner M, Holtmann B, Kolbeck R, et al. Brain-derived neurotrophic factor prevents the death of motoneurons in newborn rats after nerve section. Nature. 1992;360(6406):757.
3. Pan H, Kerns J, Lin D, et al. Dual simulated childbirth injury delays anatomic recovery. Am J Physiol Renal Physiol. 2009;296(2):277.

Specify source of funding or grant	**This study was funded by NIH Grant RO1 HD38679-10 and the Cleveland Clinic**
Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**Cleveland Clinic Institutional Animal Care and Use Committee and all experiments were performed with strict adherence to the approved protocol.**