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INSULIN-LIKE GROWTH FACTOR-1 (IGF-1) ACCELERATES RECOVERY FROM STRESS URINARY INCONTINENCE IN RATS WITH SIMULATED CHILD BIRTH TRAUMA INJURY THROUGH AKT SIGNAL TRANSDUCTION PATHWAY

Hypothesis / aims of study
Insulin-like growth factor-1 (IGF-1) plays an important role in cell proliferation, survival and regeneration in various tissues. However, the therapeutic potential of IGF-1 for stress urinary incontinence (SUI) has not been explored. We therefore examined the effect of IGF-1 in a rat model of SUI induced by simulated child birth trauma injury.

Study design, materials and methods
Simulated birth trauma was induced by vaginal distension (VD) with an inflated balloon catheter for 4 hrs in the vagina of female SD rats. Human recombinant IGF-1 (hrIGF-1) (50 and 150μg/kg/day) or vehicle (saline) was continuously delivered from 1 day before VD using subcutaneous osmotic pumps. At 4 and 7 days after VD, the effect of hrIGF-1 was examined by functional and molecular biological analyses. Urethral function was assessed by measuring leak point pressure (LPP), urethral baseline pressure (UBP) and urethral responses during passive elevation in intravesical pressure. Western blotting and histological analyses of urethral tissues were performed to evaluate phosphorylation of Akt and IGF-1-mediated anti-apoptotic and cell proliferative effects.

Table 1: Study design

preoperative	Operation	4 days post operation	7 days post operation
✓ Osmotic pump implantation (vehicle or hrIGF-1; 50 & 150μg/kg/day)	✓ VD	✓ LPP, UBP and urethral closure reflex responses ✓ ELISA ✓ Western blotting ✓ Histological examination	✓ LPP, UBP and urethral closure reflex responses

Results
Functional analyses
The IGF-1–treated group showed significant improvements in LPP, UBP and urethral responses, which were reduced significantly 4 and 7 days after VD in the vehicle-treated group (Figures 1 and 2).
Phosphorylation of Akt
After VD, there was a decrease of phosphorylated Akt in the urethral tissues of vehicle-treated groups, whereas IGF-1 treatment increased Akt phosphorylation as compared to the IGF-1-untreated group (Figure 3).
Anti-apoptotic and cell proliferative effects
In Western blot analysis, IGF-1 treatment decreased caspase-3 expression, which was increased in the vehicle-treated group after VD (Figure 3). In urethral tissues from the IGF-1 group, the percentage of TUNEL positive cells was significantly lower than that of t vehicle-treated group after VD (Figure 2). On the other hand, cell proliferating nuclear antigen Ki-67 positive cells was significantly higher in IGF-1 group compare to the vehicle-treated group after VD (Figure 4).

Interpretation of results
The present results indicate that systemic hrIGF-1 administration accelerates the recovery process of urethral continence function following simulated child-birth injury-induced SUI, increases phosphorylation of Akt in urethral tissues, and enhances cell proliferation (shown by increased Ki-67 expression) and suppress apoptotic changes (evidenced by reductions of caspase-3 and TUNEL positive cells) in damaged urethral tissues in VD rats.

Figure 1 LPP and UBP after IGF-1 treatment. (* P < 0.05, ** P < 0.01)

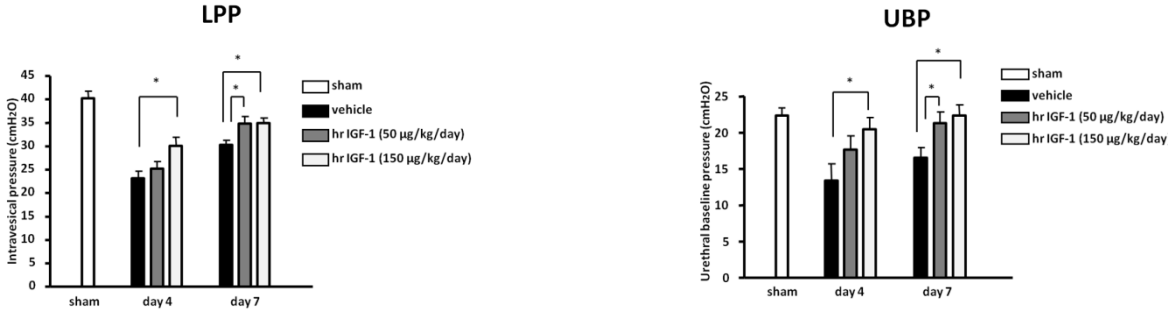


Figure 2 Urethral responses during passive elevation of intravesical pressure.

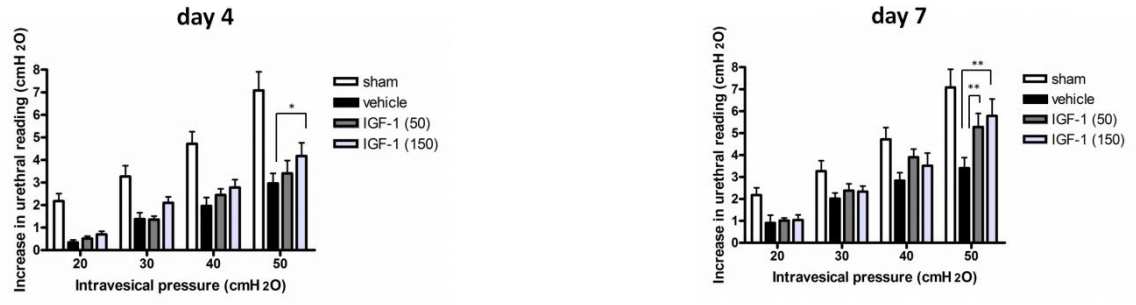
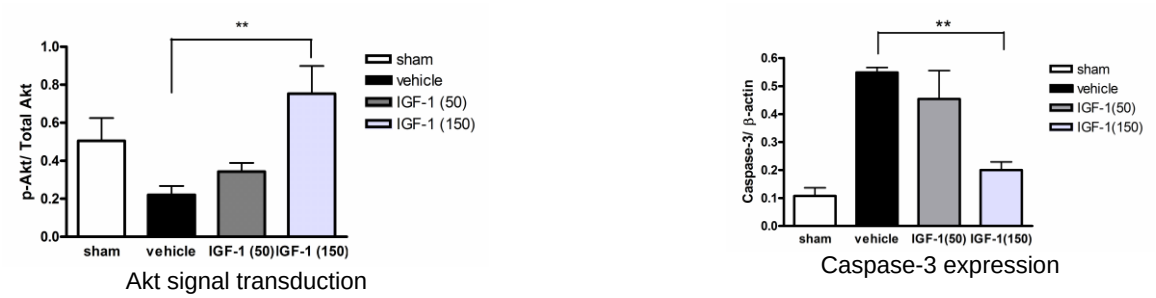


Figure 3 Phosphrylation of Akt and caspase-3 expression in urethral tissues.



Akt signal transduction

Caspase-3 expression

Figure 4 TUNEL staining and Ki-67 immunostaining in urethral tissues.

Apoptosis index

Ki-67 immunostaining

Concluding message

IGF-1 treatment accelerates recovery from SUI induced by stimulated child birth trauma in rats. These therapeutic effects are associated with increased cell proliferation and reduced apoptotic changes, which are possibly induced by activation of the Akt signal transduction pathway. Thus, IGF-1 is likely to have an important therapeutic role in the recovery from childbirth-related SUI.

Disclosures

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