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Urinary endothelin and endothelin pathway gene expression in overactive bladder

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Introduction and aim of the study: Endothelin is a potent constrictor of smooth muscle. Both endothelin A (EDRA) and endothelin B (EDRB) receptors are widely distributed in human bladder. A recent genome-wide association study identified a risk locus for urgency incontinence close to the endothelin 1 gene (EDN1). The aim of the study was to explore the role of endothelin in overactive bladder (OAB).

Materials and methods: Paired urine and blood samples were collected from 263 women. Genotyping for the rs34998271 single nucleotide polymorphism close to the EDN1 gene was performed using specific PCR. Urinary endothelin was tested using the ELISA kit. Bladder biopsies were collected directly into ice cold RNAlater.

Results: Urinary endothelin was present at a mean of 1.13 pg/ml. Urinary endothelin concentrations were significantly associated with OAB severity. The rs34998271 SNP was successfully typed for participants who provided DNA. The minor allele frequency was 4.29% (HWE $p > 0.05$), consistent with data from the 1000 Genomes project (5.1%). We found that the endothelin type A receptor (EDNRA) was more strongly expressed than type B (EDNRB) in bladder. There was statistically significant differential expression (OAB vs. controls), for 7 of 19 genes within the endothelin pathway.

Interpretation of results: We found that endothelin was expressed in human urine, with significantly less endothelin present for women with OAB. At least using these random midstream urine samples, the effect size was small, suggesting that endothelin is unlilkely to be a clinically useful biomarker for OAB. We found strong evidence for differential expression of genes in the endothelin pathway in OAB, suggesting the possibility of multiple drug targets.

Conclusions: Endothelin is significantly underexpressed in urine for women with OAB. Multiple genes within the endothelin pathway are differentially expressed in association with OAB, suggesting therapeutic potential for drugs that act in this pathway.

http://dx.doi.org/10.1016/j.ejogrb.2017.01.039

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Effect of simulated vaginal birth on urethral function and vaginal smooth muscle contractility

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Introduction and aim of the study: Vaginal childbirth is, next to age, an important risk factors for the development of pelvic floor disorders. Several animal models are being used to study the pathogenesis and develop preventive or therapeutic strategies. In a rat model we aimed to determine the effect of simulated vaginal delivery (SVD) on the urethral sphincter and vaginal smooth muscle layer. Because leak point pressure, a proxy for urethral resistance, is operator-dependent, and because electromyography of the urethral sphincter is invasive, we developed a technique using micro-ultrasound to assess urethral function. We use contractility testing of the vaginal smooth muscle as a proxy for vaginal function. This outcome measure has not yet been determined in the rat SVD injury model.

Materials and methods: 81 virgin Sprague-Dawley female rats (250–300 g) underwent either sham injury or vaginal distension (VD) and bilateral pudendal nerve crush (PNC) to establish simulated vaginal birth injury. Seven, 14, 21 or 42 days post-injury, micro-ultrasound was used to record high frequency oscillations (HFOs) during voiding were recorded. Another group of rats was euthanized at 7, 14, 21 or 42 days post-injury and full thickness circumferential strips of the middle rat vagina were assessed in organ bath experiments.

Results: Ultrasound of the urethral sphincter showed absence of HFOs in the rats at 7 days post-injury, yet with partial recovery at later time points. The half maximal effective concentration (EC50) for carbachol induced contraction was significantly different at 14, 21 and 42 days.

Interpretation of results: Simulated vaginal birth injury causes, next to other well characterised other effects, dysfunction of the urethral sphincter and increases the sensitivity of the vaginal smooth muscle layer to carbachol.

Conclusions: Simulated vaginal birth injury causes dysfunction of the urethral sphincter and increases the sensitivity of the vaginal smooth muscle layer to carbachol.

http://dx.doi.org/10.1016/j.ejogrb.2017.01.040