Voiding Function and Dysfunction, Bladder Physiology and Pharmacology, and Female Urology

Re: Stress Urinary Incontinence and Endogenous Sex Steroids in Postmenopausal Women

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Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/26380958

Editorial Comment: These authors conclude that "within the postmenopausal range endogenous sex hormones may be associated with the presence of [stress urinary incontinence] in women not on menopausal hormone therapy." Their data showed that endogenous estradiol, and to a lesser extent Δ4-androstenedione, had a significant association with the presence of stress incontinence in 138 perimenopausal and postmenopausal women with stress incontinence matched 1:1 with continent women based on age and body mass index. The odds ratio of a patient to develop stress incontinence decreased by 11% when endogenous estradiol increased by 1 pg/ml. The effects of Δ4-androstenedione and sex hormone-binding globulin were significant but less pronounced (a decrease of 0.6% and 1.1%, respectively). The authors feel that these results support the role of a hormonal pathogenic mechanism in the development of stress urinary incontinence in postmenopausal women.[1–4]

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1. Cody JD, Jacobs ML, Richardson K et al: Oestrogen therapy for urinary incontinence in post-menopausal women. Cochrane Database Syst Rev 2012; **10:** CD001405.
2. Hendrix SL, Cochrane BB, Nygaard IE et al: Effects of estrogen with and without progestin on urinary incontinence. JAMA 2005; **293:** 935.
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4. Teleman PM, Persson J, Mattiasson A et al: The relation between urinary incontinence and steroid hormone levels in perimenopausal women. A report from the Women's Health in the Lund Area (WHILA) study. Acta Obstet Gynecol Scand 2009; **88:** 927.

Re: Long-Term Treatment with the Beta-3 Adrenocepter Agonist, Mirabegron Ameliorates Detrusor Overactivity and Restores Cyclic Adenosine Monophosphate (cAMP) Levels in Obese Mice

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Re: Impaired Contractility of the Circular Striated Urethral Sphincter Muscle May Contribute to Stress Urinary Incontinence in Female Zucker Fatty Rats

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Editorial Comment: Each of these articles discusses the effects of the creation of what is essentially an experimental model of the metabolic syndrome on different aspects of lower urinary tract function, potentially translatable to the human situation. Calmasini et al noted prior observed associations of benign prostatic hyperplasia and/or lower urinary tract symptoms with hypertension, visceral obesity, glucose intolerance and dyslipidemia. Male mice were fed a high fat diet that induces obesity for 12 weeks. These mice exhibited a significant increase in body weight, epididymal fat mass, fasting glucose and low density lipoprotein levels in comparison with control mice. Micturition in this group was irregular and characterized by significant increases in the frequency of voiding and nonvoiding contractions. The maximal responses to carbachol and potassium chloride were significantly greater in the bladders of the obese rats. Oral treatment with mirabegron normalized the higher amplitude of the stimulated contractions and restored the cystometric changes. The intracellular levels of cyclic AMP were reduced by 68% in the bladders of obese mice and treatment with mirabegron restored these. Mirabegron also reduced the epididymal fat, decreased low density lipoprotein and increased high density lipoprotein levels.

Calmasini et al succinctly describe the major pathway of the activation of beta receptors in the bladder. Agonists produce bladder relaxation through adenylate cyclase activation and higher levels of cyclic AMP, which in turn activates protein kinase A. The elevation of protein kinase A activates large conductance voltage and calcium activated potassium (BK) channels and attenuates spontaneous phasic contraction in detrusor smooth muscle. The increased transient, spontaneous outward (BK) current causes membrane hyperpolarization.

The article by Lee et al uses an obese female rat model (Zucker fatty female rats at 12 weeks old). This is considered a model for prediabetes, as characterized by a genetic defect in the leptin receptor, which results not only in obesity, but also in insulin resistance, hyperinsulinemia, hypertriglyceridemia and hypercholesterolemia. Urinary leakage from the external urethral orifice could be observed when light pressure was applied to the suprapubic area in these rats. With electrical field stimulation and caffeine stimulation the authors showed that these animals had significantly impaired contractile properties in the urethral striated sphincter, which suggested to them translationally that such urethral dysfunction could be an important contributor to stress incontinence in obese women. It would have been interesting to look at the urethral changes in the mice studied by Calmasini et al and the bladder changes in the rats studied by Lee et al. What would be more interesting would be to see whether the changes observed in the models could be reversed by correction of the metabolic changes without using pharmacological agents that affected either the bladder or the striated sphincter.

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Suggested Reading

Richter HE, Kenton K, Huang L et al: The impact of obesity on urinary incontinence symptoms, severity, urodynamic characteristics and quality of life. J Urol 2010; **183:** 622.

Subak LL, Richter HE and Hunskaar S: Obesity and urinary incontinence: epidemiology and clinical research update. J Urol, suppl., 2009; **182:** S2.