Editorial comments to paper published in this issue on pgs. 128–133

The article: "The calpain system as a potential target for pelvic muscle reinforcement"
Calpains and urinary incontinence

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The knowledge surrounding the molecular basis of urinary incontinence (UI) has improved in recent years and novel targets for treating UI are desperately being sought. However, the armamentarium of the urologist is still lacking and this serves as a drive to find novel targets through the elucidation of molecular pathways.

Recently the calpain system has been considered as a potential target for urinary incontinence. Calpains are calcium activated proteolytic enzymes with a homology to the protease domain of the papain family of cysteine proteases (papain, caspases, and cathepsin B, L, and S) [1, 2]. They are ubiquitously expressed in almost all tissues of the human and they are known to catalyze smooth muscle actins, SM-1 and SM-2 myosin heavy chains, vinculin, desmin, heavy caldesmon, α-tropomyosin, and calponin [3, 4]. This broad spectrum of smooth muscle protein substrates is catalyzed into stable fragments rather than a complete proteolytic digestion at a neutral pH, causing significant reorganization of the cytoskeleton. Calpain is also involved in signal transduction pathways and cell apoptosis. These factors are thought to affect the integrity of the connective and muscle tissue in the sphincteric and structural support system in various subgroups of urinary incontinent patients.

The expression of calpain-1 and calpain-2 in vaginal walls of women with and without uterovaginal prolapse show a marked reduction. Additionally these patients also present with either a marked change in the morphology of vaginal connective tissues or have anterior vaginal laxity [3]. In other studies of patients with urinary incontinence and uterovaginal prolapse, calpain-2 is overexpressed while the expression of the calpain inhibitor calpastatin is reduced [3]. In pathological states that lead to the elevation of cytosolic calcium, this can accelerate the degradation of various cytoskeletal structures and ultimately the integrity of the tissue structures [1]. Moreover, collagen fragments I and III, produced by extracellular matrix metalloproteinase activity, have been implicated in the activation of smooth muscle cell apoptosis by calpain-mediated inactivation of anti-apoptotic proteins such as X-chromosome-linked inhibitor of apoptosis (xIAP) [5, 6].

The possibilities of manipulating the calpain-calpastatin system are now considered, but significant research is required in this area. The involvement of calpains in cytoskeletal remodeling, cellular signaling and apoptosis suggest that its manipulation may have toxic consequences and the ubiquitous expression may also present complications for systemic treatment. However, this presents a novel opportunity as urologists have the advantage of local intravesical administration with minimal invasive techniques, thus reducing the potential of systemic side effects.

The greater number of publications in continence related studies with the calpain pathway should support an increased interest in this potential pathway and provide the urologist with an effective treatment tool.

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