Methods: To simulate lower urinary tract behaviour, mechanical properties of the lower urinary tract and its neural control are modelled (figure 1). The mechanical part describes the properties of the detrusor and the urethra with its striated sphincter. The neural control is described by a number of blocks and connecting lines. The blocks represent anatomical structures where neural interaction is assumed to take place. The lines between these blocks represent connections that are assumed to be involved in lower urinary tract control. The blocks and connections that are used in our model are as much as possible based on anatomical structures that were shown to be important in lower urinary tract control.

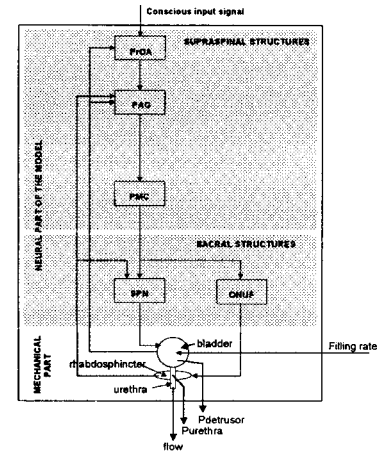

Figure 1: Schematic representation of the model. The model has two input signals and three output signals. The output signals are the detrusor pressure (Pdetrusor), the urethral pressure (Purethra) and the flow. The dashed lines represent the afferent signals. Other neural connections are characterised with solid lines.

Specific anatomical structures, both sacral and supraspinal structures, are described to be involved in the neural control of the lower urinary tract. The supraspinal control in our model consists of three blocks: the pontine micturition centre (PMC), the periaquaductal gray (PAG), and the preoptic area (PrOA). These structures are assumed to be involved in the 'unconscious' control of storage and micturition. We assume that the other centres known to be involved in lower urinary control affect the 'conscious' control of the lower urinary tract. Although the difference between conscious and unconscious control is not very distinct in vivo, we assume that under normal circumstances the conscious part only initiates micturition. The conscious control is represented by an input signal to the PrOA-block.

The sacral part of the neural control comprises two blocks that represent the sacral parasympathetic nucleus (SPN) and the nucleus of Onuf (ONUF). The SPN-block is assumed to have two input signals. The first input is connected to the PMC-block and the other input signal depends on the urethral stretch. The ONUF-block, like the SPN-block, is assumed to be connected to the PMC-block. The output of the ONUF-block represents the somatic nerves to the rhabdosphicter.

Results: With this rather simple model, which includes afferents related to bladder wall tension and urethral stretch, behaviour that resembles normal lower urinary tract behaviour was simulated. Every 100 sec a pressure of 10 cmH_2O was added to the detrusor pressure. These disturbances in the detrusor pressure did not cause micturition or leakage. The effect of these disturbances depends on the volume in the bladder. Due to a larger volume in the bladder, urethral pressure decreases more severely. At 550 sec the applied disturbances cause a decrease in urethral pressure as well as a detrusor contraction. Due to the assumption that urethral afferents have an excitatory effect on the SPN and an inhibitory effect on the PAG, at the start of micturition the input from the PrOA to the PAG is very important. If the inhibition of the PAG by the PrOA is still large enough, due to the increase in afferent signal from the urethra, micturition is inhibited although already some detrusor contraction has occurred.

Conclusion: One of the most important assumptions included in the present model is that afferent signals from the urethra are involved in the neural control on both sacral and supraspinal level. By including this assumption, behaviour that resembles normal lower urinary tract behaviour can be simulated. Besides normal behaviour also behaviour that resembled detrusor overactivity was simulated after disturbances were added to the model.

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PLASMA ELASTASE REGULATION IN STRESS URINARY INCONTINENCE

Aims of Study: Stress urinary incontinence (SUI) is the involuntary leakage of urine due to weakened support of the urnary bladder and urethra. Although the etiology of SUI is unknown, factors such as aging and

multiple childbirths are thought to play a role. Reduction in the elastin content of the connective tissues that support the bladder and urethra would weaken and reduce the elasticity of these supportive structures and contribute to the development of SUI. The maintenance of elastin content is dependent on the balance of protease/anti-protease activity. We recently developed a method of determining elastase activity in plasma and elastase inhibitory capacity of plasma. The aims of this study were to determine (1) whether net elastase activity is lower in the plasma of women with SUI compared to women without SUI and (2) whether the capacity to inhibit elastase is lower in the plasma of women with SUI compared to women without SUI.

Methods: Plasma was prepared from blood taken from women with SUI (n=30) and age matched control women (n=30). Diagnoses of SUI were made by physical and urodynamic evaluation. Plasma (10 µl) was added to an assay mixture containing succinylated elastin substrate to initiate the elastase reaction, in order to measure plasma elastase activity (reported as U/ml ± SEM. In order to measure inhibition of elastase, plasma (10 µl) was added to an assay mixture containing succinylated elastin substrate and the reaction was initiated by the addition of purified porcine pancreatic elastase. Elastase activity in the presence of plasma was compared to that determined in the absence of plasma. Data is reported as percent of elastase activity in the absence of plasma.

Results: The elastolytic activity in the plasma of women without SUI was 4.5±1.5 U/ml, while that of age matched women with SUI was 16.3 ± 3.5 U/ml ($p<0.01$). Thus the elastolytic activity in plasma of women with SUI was threefold the elastolytic activity in plasma of women without SUI. Purified porcine pancreatic elastase was inhibited by unidentified plasma components. The purified elastase activity measured in the presence of 10 µl plasma from normal women was 13.3 ± 1.6% of that in the absence of plasma. However, purified elastase activity measured in the presence of 10 ul plasma from women with Sui was two-fold higher (25.5 ± 2.2%, $p<0.001$).

Conclusions: These data suggest that SUI patients have significantly (threefold) elevated plasma elastolytic activity compared to age-matched women without SUI. At least part of this elevated elastolytic activity can be attributed to a reduced level of certain components in their plasma that control elastase activity, resulting in higher activity of this enzyme. The elevated elastolytic activity in these women may result in increased elastin degradation in cnnective tissues supporting the bladder and urethra and, thus, contribute to the development of SUI.

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COLLAGENASE ACTIVITY IS ELEVATED IN CONDITIONED MEDIA FROM FIBROBLASTS OF WOMEN WITH PELVIC FLOOR WEAKENING.

Aims of Study: Stress urinary incontinence (SUI), the loss of urine during episodes of increased abdominal pressure, is a result of weakened support of the urinary bladder and urethra. The primary structure supporting the bladder and urethra is the collagen-rich endopelvic fascia. A reduction in collagen would be expected to weaken its function in bladder support. A major objective of this study was to determine if weakened support of the bladder and urethra is associated with altered collagen metabolism and to determine if these changes are local or the result of systemic metabolic changes.

Methods: Skin and endopelvic fascia biopsies were obtained from women undergoing vaginal surgery. The experimental group included women with videourodynamic evidence of SUI undergoing bladder neck suspension surgery (n=21). The age matched control group consisted of continent women without evidence of pelvic floor weakening undergoing laparoscopic-assisted vaginal hysterectomy for symptomatic uterine fibroids, endometrial cancer, or benign ovarian pathology (n=11). Biopsies of the lower abdominal skin and endopelvic fascia were taken at the time of surgery, transferred to sterile tissue culture media, and fibroblasts cultured by standard methods. Collagenase activity was determined in the serum-free four-day conditioned media obtained from cultured fibroblasts, by soluble lysis assay. Immunoreactive matrix metalloproteinase 1 (MMP1) levels were determined by ELISA (Biotrak). The capacity for cultured fibroblasts to incorporate [3H]-proline into procollagen was determined.

Results: Mean collagenase activity in the conditioned media from skin was more than 6 fold higher in the SUI group (30.26 U/mg protein) compared to the control group (4.65 U/mg protein). Collagenase activity in the conditioned media from endopelvic fascia fibroblasts was also higher in the SUI group (8.28 U/mg protein) compared to the control group (6.44 U/mg protein), but this difference was not statistically significant. The specificity of the soluble lysis assay for collagenase was confirmed in representative samples by SDS-PAGE fluorography. Immunoreactive MMP1 was more than 10 fold higher in the conditioned media from skin fibroblasts from SUI women (948.9 ng/mg protein) compared to controls (86.72 ng/mg protein). Immunoreactive MMP1 was more than 5 fold higher in the conditioned media from