Interactive control of the lower urinary tract

CHAPTER 9

Impact

Involuntary urine loss and lower urinary tract dysfunction are major health problems and a burden to patients and their caregivers. The impact urinary incontinence has on the quality of life of patients and their self-reliance is so severe that it is one of the main reasons to move to institutionalized care for elderly people. The lack of a complete understanding regarding the central control of micturition limits our knowledge of the dysfunctional mechanisms associated with different types urinary incontinence, possible central compensatory mechanisms, and the extent to which we understand how certain interventions lead to their therapeutic effect. This severely hampers the care that can be offered to patients because it is not known what the most optimal therapeutic targets are and for many therapies predictive factors regarding effectivity are missing. The work discussed in this thesis will improve our understanding of the control of the lower urinary tract and will, thereby, help to fill this knowledge gap.

Some of the most significant shortcomings of current diagnostic and therapeutic approaches are the almost exclusive focus on the peripheral organs, the non-specific patient characteristics related to effectivity prediction, and a broad definition of the disease. This leads to treatment selections based on trial-and-error principles and step-up therapies. In some cases, up to 6 iterations of therapy selection are needed before finding an effective treatment. Most compounds that were evaluated for pharmacological treatments showed effectivity in animal research, however, numerous of these compound candidates have entered very costly clinical trials and showed no benefit in the human situation, wasting animals' lives, money, and above all impose unnecessary risks on human trial participants.

Currently existing therapies are not only insufficient in treating lower urinary tract symptoms, but also often cause severe side-effects which are frequently the reason for therapy discontinuation. Therefore, there is a high need to better optimize existing therapies and develop novel therapeutic approaches. The developments emerging from this project contribute to unravelling the mechanisms related to interaction between neuronal control systems and lower urinary tract functioning. As such, this work is expected to contribute to the development of novel, innovative therapeutic approaches. It will enable the discovery of predictive factors, and more optimally targeting of mechanisms involved in certain types of urinary incontinence and. This will help decrease the burden on patients by more efficient matching with effective therapies. During the past decades, modifying sensory information by pharmaceutical therapies or neuromodulation has more often become the target of therapies for lower urinary tract symptoms.

In the current project the structural and functional integrity of the bladder wall in rat models associated with lower urinary tract dysfunction was assessed. Furthermore, approaches to evaluate biomechanics of the pelvic floor associated with stress urinary incontinence and successful therapeutic intervention were developed. In addition, novel neuroimaging methods that help progress our understanding of central nervous system control of the lower urinary tract in human participants at the level of the brain stem were introduced. These developments pave the way towards a unified theory of visceral lower urinary tract sensation and control. In the near

future, these developments will be integrated with more widely used diagnostic tools (e.g. (mobile) urodynamic assessment, micturition diaries, patient reported bladder sensations, LUTS questionnaires, and momentary assessment tools) to investigate correlates between the different biometric modalities. The integration of different measurement models offers new insight into the diagnostic value of each tool on its own and will enable further optimization of the differentiation capacities of diagnostic procedures.