The significance of the urine-blood-barrier for urge generation and possible changes in the aging bladder

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1. The aging bladder – an urgent problem

As a real challenge in current practice, urologists see a growing number of patients with age-related bladder symptoms. In a recent survey we found a 12.5% rate of functional bladder disorders among urology patients in the age group of 60–80, that increased to 34.5% for patients >80 years (Daha et al. 2002). But the frequency and importance of these problems is not yet reflected by an adequate number of research projects and publications. Only 3% of presentations throughout the last annual meetings of the American Urological Association (AUA) covered the topic of age-related changes to urological organ systems, with only a minimal share regarding the urinary bladder.

At least, three important statements on age-related changes to the bladder and micturition have been made.

1. The circadian rhythm of diuresis shows an increase of nocturnal diuresis in older patients. This may be consequent to hormonal or cardiovascular changes. The conclusion is that nocturia is a natural event in older people and less relevant as a symptom (Morgan et al. 2000).
2. Moderate detrusor ischemia may lead to detrusor hyperreflexia, and severe ischemia to detrusor fibrosis with hypercontractility (Azadzoi et al. 1999).
3. The basal release of acetylcholine, the main neurotransmitter in bladder contraction, is increased in older people and may contribute to age-related changes in bladder function and hyperreflexia (Yoshida et al. 2002).
Nocturia, better nocturnal polyuria, as well as detrusor hyperreflexia are the main urological symptoms affecting aging people. Various therapeutic regimens are available for the treatment of obstructive voiding disorders and incontinence but, in contrast to that, urgency and frequency are still a problem for patients and doctors, since common treatments are ineffective in a high proportion of cases. In the presence of global mobility, uncontrolled urgency and reduced functional bladder capacity result in the impossibility of leaving the home area and are extremely disabling and distressing to patients.

2. The physiology of urge generation and control

The base for treating age related urgency efficiently is a correct understanding of the physiological processes responsible for urge generation that are essentially related to the urine-blood-barrier (Hohlbrugger and Riedl 2000). While recent concepts favour a neuromechanical model for urge induction with mechanoreceptors stimulated by bladder distension, older concepts also included chemoceptive stimulation of the suburothelial C-fibres as responsible for urge sensation. Urgency in case of acute cystitis consequent to increased urothelial permeability as an inflammatory reaction is an excellent example for chemically induced C-fibre stimulation.

The present understanding of urge generation has to include both chemoceptive and neuromechanical concepts. The sensitive region for chemoception is the urine-blood-barrier, which morphologically consists of the urothelium (generally permeable for urinary compounds) and glycosaminoglycans (GAG-layer). Glycosaminoglycans are mucopolysaccharides consisting of hyaluronic acid, heparin, chondroitin sulfate, and dermatan sulfate (Parsons et al. 1990).

The high gradient of urinary compounds between urine, the suburothelial tissue, and blood (1:10 for potassium, 1:4.5 for urea) is a great challenge for this barrier. Maintenance of these gradients is of vital importance for body homeostasis and prevents recirculation of substances excreted by the kidneys. Very efficiently, a suburothelial microvascular countercurrent system (Fig. 1), similar to the one in the tubular system of the kidney, prevents penetration of transurothelially diffused urinary compounds, especially potassium, to deeper layers of the bladder wall. If potassium reached the detrusor this would result in immediate depolarisation and contraction of the detrusor smooth muscle cells. Via veno-arterial shunting the resorbed components of the urine recirculate in exchange for plasma water, and are thus diluted in the venous blood and retained in the suburothelial region (Steers 1998, Hohlbrugger 1995, Miodonski and Litwin 1999, Rosamilia et al. 1999). This effective vascular system is responsible for keeping potassium and hydrogen ions away from the chemoceptive suburothelial C-fibre endings. Under normal circumstances, the chemoceptive excitation of the C-fibres from potassium or hydrogen ions does not cross the threshold of the cerebral cortex as long as the integrity of the