Peripheral pharmacological targets to modify bladder contractility

Valorisation

Lower urinary tract dysfunctions are a major global health issue. The studies presented in this thesis have aimed to identify new treatment targets. Detailed knowledge of urinary bladder signalling is of utmost importance when new treatment targets have to be identified. Until now, it is not fully known how the different signalling systems, involved in regulation of micturition and continence, interact with each other. Two important bladder dysfunctions have been discussed in this thesis i.e. the overactive bladder syndrome and detrusor underactivity. These two dysfunctions will be elaborated to elucidate the societal impact of the presented research.

The overactive bladder syndrome (OAB) is defined as urgency, usually with frequency and nocturia, with or without urgency urinary incontinence[1,2]. It is a highly prevalent condition with almost 100 million people affected in the western world, 33 million in the United States[3] and 66 million in the European Union[4]. The impact on patients' quality of life is enormous and even higher than the impact on quality of life associated with diabetes[5-8]. Furthermore, the economic costs and burden of OAB are comparable to those of rheumatoid arthritis and asthma[9]. The pathophysiology is multifactorial and the patient group shows a high heterogeneity. Therefore, optimal therapy remains challenging. To optimize bladder function in those patients, two aspects are of importance: the heterogeneity of OAB needs to be taken into account. Furthermore we need to more knowledge about symptomatology-related physiological processes taking place at bladder level. Concerning the heterogeneity of OAB, patient subgroups have to be identified and the pathological functional and morphological derivatives have to be investigated for each subgroup. Concerning the aspect on bladder physiology, the question to put forward is: How do the different signalling systems interact with each other and what will be the effect of bladder dysfunction on those interactions? Answering these questions will enable us to identify new, more specific treatment targets for OAB.

Currently, antimuscarinic drugs are widely used to treat patients suffering from OAB. However, the effect has been shown to be small compared to placebo, with a high prevalence of side effects[10]. This signifies the need for new pharmacological treatment targets. The question is: Can we use other signalling systems, which are active in the bladder to modify excitation–contraction coupling? In studies presented in chapter 4 and 5, the prostanoid system was identified to be a potential candidate for the modulation of muscarinic induced contractions.

Future research can elaborate on our data and might help to identify new treatment targets with less side effects for the patients.

The second bladder dysfunction that may benefit from the results of this thesis, is detrusor underactivity. In older women, the prevalence of detrusor underactivity ranges from 12%-45%. In males, a prevalence between 9% and 45% has been identified dependent on population and diagnostic criteria[11]. One of the causes of detrusor underactivity is bladder outlet obstruction, which will induce a cascade of morphological and functional changes within the bladder wall. At a later stage, these changes can lead to detrusor underactivity. The most frequently occurring cause of bladder outlet obstruction in men, is prostate enlargement due to Benign Prostatic Hyperplasia. In addition, functional neurogenic and even psychogenic causes may also underlie the detrusor underactivity[12]. Detrusor underactivity and the subsequent bladder distension give rise to residual urine after voiding in males and females resulting, in a significant burden: Chronic urinary tract infections, increased antibiotic resistance of microorganisms, reduced quality of life and high costs for care, especially in the institutionalised elderly.

Currently, there is no treatment option for detrusor underactivity with good long-term results. The current management includes life-long intermittent catheterisation, which is the only option to prevent urinary tract morbidity. Unfortunately, performing intermittent catheterisation has a large impact on the quality of life[13]. It is of utmost importance to understand the pathophysiological processes, which lead to detrusor underactivity. This thesis contains a literature review on detrusor underactivity, that identifies potentially new treatment targets and could serve as a base for future research. Current knowledge is presented, on possible changes in physiological processes that may lead to detrusor underactivity. To find new treatment modalities, more basic and clinical research is needed. Patient subgroups have to be identified, and pathophysiological processes involved in the development of detrusor underactivity have to be elucidated. Hereby, novel treatment strategies can be developed, improving patients' quality of life.

The studies presented in this thesis focussed on the interaction of signalling systems. The prostanoid system was identified as a potential target system when searching for new therapeutical strategies. Therefore, a first step was provided towards new therapeutical approaches using pharmacological modulators of the prostanoid system for the treatment of bladder dysfunctions.

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