Signal transduction underlying the control of urinary bladder smooth muscle tone
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Citation for published version (APA):
CHAPTER I

c. Introduction and research questions
Introduction and research questions

A better understanding of the physiology and patho-physiology of the bladder smooth muscle and the signalling mechanisms in controlling the smooth muscle tone is essential, as it may provide information for the identification of possible targets for a more efficacious treatment of bladder dysfunction. Against the background described in chapters Ia and b, this thesis aimed to address the following questions.

1. **Signalling mechanisms of M₃ receptors in mediating bladder contraction**

   At the time of design of the present study, a controversy existed with regard to the involvement of PLC in muscarinic receptor-mediated contraction. Therefore, this particular study was performed to re-investigate the involvement of PLC in muscarinic receptor-mediated bladder contraction.

2. **Signalling mechanisms of β-adrenoceptor in mediating bladder relaxation**

   At the time of design of the present study, several studies of smooth muscle tissues, other than in the bladder, had questioned the major role of cAMP and implicated the presence of cAMP-independent pathways in β-adrenoceptor signalling pathways. Therefore, this study was designed to investigate the role of cAMP-dependent and –independent pathways in β-adrenoceptor-mediated bladder relaxation, specifically a role for various types of potassium channels.

3. **Association between risk factors of bladder dysfunction with β-adrenoceptor functions**

   Gender, age and hypertension have been linked to bladder dysfunction. Previous studies showed that the bladder dysfunction associated with these risks factors cannot be explained by the alterations of the muscarinic receptor-mediated control of bladder contractility (Spitsbergen, et al., 1998; Clemow, et al., 1997; Ordway, et al., 1986; Schneider, et al., 2005a; Kories, et al., 2003; Rajasekaran, et al., 2005; Schneider, et al., 2005b; Afiatpour, et al., 2003; Pagala, et al., 2001). Therefore, a study was conducted to investigate whether any gender, age or hypertension alter the β-adrenoceptor-mediated relaxation of the detrusor.

4. **An alternative signalling molecule contributes to muscarinic receptor-mediated contraction in hypertrophic conditions**

   Sphingolipid metabolism has been shown to be involved in the regulation of cellular growth and smooth muscle tone (Spiegel, et al., 1998; Hemmings,
Moreover, it is possible that growth-induction could also affect the smooth muscle tone and/or its regulation by autonomic receptors. Therefore, a study was performed to investigate a possible role of sphingolipid signalling in muscarinic receptor-mediated bladder contraction under normal circumstances and hypertrophic conditions.

5. Possible agonism of nebivolol at β3-adrenoceptor

Nebivolol is a β1-adrenoceptor selective blocker which has vasodilating properties (Van de Water, et al., 1988). It has been proposed that the nebivolol-induced vasodilation may be mediated by agonism at β3-adrenoceptors (de Groot, et al., 2003). However, it has not been studied directly whether nebivolol indeed is a β3 agonist. Moreover, if it was a β3 agonist, this may have implications for the urinary bladder. Therefore, a study was designed to directly test possible β3-adrenoceptor agonism by nebivolol in CHO cells stably transfected with the human β-AR subtypes and specifically whether nebivolol can cause relaxation of human or rat urinary bladder.
References


