REVIEW

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Selective beta-adrenoceptor agonists, calcium antagonists and potassium channel openers as a possible medical treatment of the overactive bladder and urge incontinence

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Urinary incontinence affects millions of people worldwide and also represents a social problem. People of all ages suffer from urinary incontinence. The disease is found in about 30% of women aged 30 to 60 years. There are different types of incontinence. Urge incontinence is the most often pharmacologically treated type. The mainly used substances belong to the class of antimuscarinic drugs. Their use is limited by several side effects. Furthermore, in some patients anticholinergic medication is ineffective and antimuscarinics used as single medication do not lead to a sufficient therapeutic effect. Other possible pharmacological substances for treatment of overactive bladder (detrusor instability) associated with urge and urge incontinence are the selective β-adrenoceptor-agonists which are mainly responsible for the adrenergic mediated relaxation. It depends on the species, which β-adrenoceptor-subtype (the β2- and/or β3-adrenoceptor) mainly mediates the relaxation. Non selective β-adrenoceptor-agonists exhibit serious cardiovascular side effects like tachycardia or decrease of blood pressure by stimulating β1- and β2-adrenoceptors. These side effects should be decreased when using selective agonists. Additionally, substances whose targets are membrane channels of muscle cells could be interesting for treatment of overactive bladder. This group includes L-type calcium antagonists and potassium channel openers of ATP-sensitive potassium channels or BK channels. Especially the local use of the pharmacologically very potent calcium antagonists could be an interesting therapeutic approach, since systemic cardiovascular side effects were avoided. After chronic oral treatment with different calcium antagonists effects on the detrusor muscle were reduced or could not be detected, possibly due to an upregulation of 1,4-dihydropyridine-sensitive potassium channels. A very interesting approach is the use of potassium channel openers said to be selective for the urinary bladder. If there is a selectivity for the detrusor muscle, cardiovascular side effects were reduced. Possibly, the local use is a useful application form. Selective β-adrenoceptor agonists, calcium antagonists and potassium channel openers are pharmacological approaches, which are not yet available for clinical use.

1. Introduction

1.1. Urinary incontinence

Urinary bladder dysfunction is a widely spread disease. Older people and women are more often affected. The disease is found in about 30% of women aged 30 to 60 years. In an aging population, the urinary incontinence is also a social and economic problem. In Germany, the total cost of urinary incontinence was 1.2 billion marks per year (Hautmann und Huland 2001). In the USA, the overactive bladder affected 34 million individuals compared with 17 million with urinary incontinence during the year 2000. In the USA, the total cost of urinary incontinence and overactive bladder for year 2000 was 19.5 billion dollars and 12.6 billion dollars, respectively (Hu 2004). Urinary incontinence can be categorised into five classes (Badawi und Langbein 2005). Main types are the stress incontinence and the urge incontinence. There are also mixed types in which symptoms of both urge and stress incontinence are found.

1.2. Urge incontinence and overactive bladder

The urge incontinence is characterized by the involuntary loss of urine associated with a strong desire or urge to urinate which cannot be suppressed. Simplified there are two types of urge incontinence: One is associated with involuntary detrusor contractions leading to a loss of urine, the other is characterized by a hypersensitive bladder in which micturition reflexes are induced due to an in-

creased afferent activity. It is also important to distinguish between an idiopathic type of urge incontinence and a symptomatic type. Before diagnosis and treatment of an idiopathic type, causes of the secondary type like inflammation or tumours of the urethra, urinary bladder or prostate, bladder stones, foreign bodies and infravesical obstructions must be excluded.

An overactive bladder can be found in patients suffering from diabetes mellitus, apoplex, multiple sclerosis and after injuries of the spinal cord or congenital malformations of the spinal cord. Often it is found in patients with chronic infravesical obstructions, especially caused by benign prostate hyperplasia. Diagnostics is based on a careful medical history, clinical examination and an urodynamic evaluation used to show the involuntary detrusor contractions (Badawi and Langbein 2005). Under all incontinence types the urge incontinence is the most often pharmacologically treated type.

1.3. Pharmacological treatment of the overactive bladder and urge incontinence

Pharmacological substances for treatment of overactive bladder (detrusor instability) associated with urge and urge incontinence are rare. At present, antimuscarinic drugs like oxybutynin, trospiumchloride and tolterodine are the therapeutic agents mainly used for detrusor instability (Andersson 2000). Unfortunately, their use is limited by different adverse effects generated by the antimuscarinic action like extremely dry mouth, constipation and blurred vision (Yarker et al. 1995). Patients often have to discontinue the therapy because of side effects. Furthermore, antimuscarinics used as single medication often do not lead to a sufficient therapeutical effect. Therefore, drugs with other mechanisms of action are urgently needed.

Interesting substance classes which are not yet on the market for the treatment of special bladder dysfunctions are selective β-adrenoceptor-agonists and substances whose targets are membrane channels of muscle cells.

2. Selective β-adrenoceptor-agonists

β-Receptors play an important role in the relaxation of detrusor muscle via activation of adenylate cyclase. Both β2- and β3-receptors are suspected of mediating a major part of the relaxation via β-agonists. The β-receptor-subtype mediating relaxation of detrusor muscle is species-dependent (Li et al. 1992; Yamazaki et al. 1998). In rabbits the β2-receptor was shown to be mainly responsible for relaxation (Yamazaki et al. 1998), in cynomolgus monkey detrusor it was the β3-subtype (Takeda et al. 2003). Takeda et al. (2003) found in canine detrusor muscle that the relaxing potency of the β3-agonist CL 316 243 was bigger than that of the β2-agonist procaterol indicating a pronounced role of β3-adrenoceptors in dogs. Longhurst and Levendusky (1999) suggest that rat urinary bladder body contains β1-, β2- and β3-receptors, all of which mediate relaxation, whereas Yamazaki et al. (1998) suggest that both β2- and β3-receptors mediate relaxation in rats.

Some studies on the human detrusor muscle point to the β3-adrenoceptor subtype being the main one in the human bladder (Igawa et al. 1999; Takeda et al. 1999; Igawa et al. 2001; Yamaguchi 2002). Own studies on human detrusor muscle indicated that both β2- and β3-agonists relax human detrusor, concluding that both receptor subtypes are responsible for relaxation (Badawi et al. 2005). Non selective β-adrenoceptor-agonists exhibit serious cardiovascular side effects like tachycardia or lowering of blood pressure by stimulating β1- and β2-adrenoceptors. These side effects should be decreased when using selective agonists. This supposition is underlined by the clinical trials of Grueneberger (1984) and Grueneberger and Geier (1981). Clenbuterol, another β2-specific adrenergic agent, was successfully used to treat 20 women with motor urge incontinence (Grueneberger 1984). Ten women reported complete relief of symptoms and urge incontinence was reduced in five. The number of side effects was small. This implies that β-adrenergic agonists could be a good new therapy for bladder overactivity, possibly in combination with anticholinergic drugs. Nevertheless, they are not yet introduced on the market for the indication of bladder overactivity. However, bigger clinical trials are performed by the pharmaceutical industry.

3. Drugs using membrane channels as targets

3.1. Calcium antagonists

Calcium channels are membrane bound proteins that transport extracellular Ca^{2+} to the cytosol. Several types of calcium channels exist which differ in location and function. Included in the group of calcium channels are the N-type channels in neuronal tissue, P-type channels in Purkinje tissue, T-type channels, also known as low voltage-activated channels (LVA) and found in heart's natural pacemaker and vascular smooth muscle, and L-type channels (Abernethy et al. 1999).

The L-type channel, named for its long-lasting effect, is a voltage-gated, slowly-inactivating channel. It was first isolated from cardiac muscle and has been found in vascular and nonvascular smooth muscle as well as in noncontractile tissues. L-type channels as well as P- and N-type channels are part of the group of high voltage-activated channels (HVA). They first activate at relatively depolarized potentials and exhibit a high single-channel conductance (Tsien 1988). The increase of free Ca^{2+} ions within the cell initiates the process of contraction. Blockage of L-type channels in vascular smooth muscle results in relaxation.

Since the 1960s drugs called calcium antagonists or calcium-channel blockers have been used in clinical medicine mainly for the treatment of cardiovascular diseases like hypertension, angina pectoris, cardiac arrhythmias and left ventricular diastolic dysfunction, additionally for treatment of Raynaud's phenomenon, migraine and esophageal spasm. The blockage of calcium channels in vascular smooth muscle results in relaxation. Since L-type channels were also found in the smooth muscle of the urinary bladder, these channels could serve as a target for the treatment of bladder overactivity or detrusor instability.

Since detrusor myocytes show a high density of L-type calcium channels which are suspected to be necessary for increasing the intracellular calcium concentration between successive contractions (Fry et al. 2002), L-type calcium channels could be a good target for the treatment of the overactive bladder. Well known L-type calcium antagonists of the first generation are the 1,4-dihydropyridine nifedipine, the phenylakylamine verapamil and the benzothiazepine diltiazem. Using calcium antagonists *in vivo* to inhibit the contractile response, Elliott et al. (1996) found in rats that the dihydropyridine antagonist nimodipine was effective after a single oral dose, but had no significant effect after 8 day's treatment. This loss of effect

after chronic oral treatment was possibly caused by an up-regulation of the 1,4-dihydropyridine-sensitive channels. Similar results were shown by the clinical trial of Naglie et al. (2002), who treated older patients with detrusor instability and urge incontinence with nimodipine 30 mg twice daily. No significant improvement of incontinent episodes was found. Nevertheless, an interesting therapeutic approach to treat bladder dysfunctions with such potent pharmacological agents is their intravesical instillation Kato et al. (1989) showed in a rabbit whole bladder model two hours after instillation an inhibition of the contractile response to bethanechol and EFS by 85% and 81% for verapamil and 47% and 39% for diltiazem, respectively. A significant increase in bladder capacity was shown in rabbits after *in vivo* application of verapamil on the bladder of rabbits with a multiple-sclerosis-like disease (Hassouna et al. 1986). Gotoh et al. (1987) also report on good results after intravesical instillation of verapamil in the bladder of rabbits. In patients with detrusor hyperreflexia verapamil produced a significant increase of the bladder capacity, but not in patients with detrusor instability (Mattiasson et al. 1989), showing that the neurogenic or non-neurogenic origin of the detrusor hyperactivity was important.

Besides the systemic application, local use by intravesical instillation to avoid side effects and possible up-regulation of the L-type channel with loss of effectiveness may be a good alternative to conventional therapies.

3.2. Potassium channel openers

A high density of potassium channels is found in the cell membrane of myocytes. Under the different classes of potassium channels ATP-sensitive channels and large conductance channels (BK channels) are interesting with regard to using them as targets for the treatment of bladder overactivity. Potassium channels play an important role for the membrane potential. Opening of the potassium channels, for example by potassium channel openers (Masuda et al. 1995), leads to a hyperpolarization of the cell membrane of smooth muscle cells (Foster et al. 1989). It also reduces the opening probability of ion channels which are necessary for membrane depolarization (Andersson 1992). In this way, they lead to relaxation of the muscles or inhibition of the contractility (Barany 1996).

BK channels (voltage- and calcium-activated channels) are activated by increasing of the intracellular calcium concentration and depolarization of the membrane potential (Cox et al. 1997; Herrera et al. 2000; Meredith et al. 2004 Herrera et al. 2002). Meredith et al. (2004) showed that spontaneous and nerve-induced contractions as well as frequency were increased in genetically abnormal mice with loss of these channels. BK channels seem to play an important role in the function of the detrusor muscle.

Openers of ATP-sensitive potassium channels may also be an interesting pharmacological approach for the treatment of bladder overactivity. The effects of this substance class were shown to be species-dependent. Rizk et al. (2001) performed *in vitro* experiments with the potassium channel openers pinacidil und cromakalim. They showed different effects of both potassium channel openers compared to the anticholinergic substance oxybutynin in different species. Depending on the examined species and the type of contraction, oxybutynin exhibited in some cases a smaller pharmacological potency than the potassium channel openers. Lynch et al. (2003) showed that several newly developed potassium channel openers of ATP-sensitive potassium channels inhibit detrusor instabilities of obstructive rats. Authors showed that the potassium channel opener A-278637 exhibited effective pharmacological effects. A-278637 was also shown to inhibit unstable bladder contractions of the porcine detrusor muscle. A-278637 was shown to be more selective for the urinary bladder compared to potassium channel openers of the first generation (Brune et al. 2002).

Knowledge about different potassium channel openers concerning their effects on the detrusor musle of different species is small. Since this substance class relaxes the vascular smooth muscle, some drugs were clinically used as antihypertensive medication, for example minoxidil (Criddle and de Moura 2000). Potassium channel openers have not yet been introduced on the market to treat urinary bladder dysfunctions. Substances recently developed are said to be selective for the urinary bladder. They could be an interesting pharmacological approach (Brune et al. 2002). If they were selective for the detrusor muscle, cardiovascular side effects, especially lowering of the blood pressure (Komersova et al. 1995), would be reduced. In this case this substance class could be clinically used. Side effects were also reduced using the potassium channel openers locally by intravesical application (Weiss et al. 2002).

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