Arab Journal of Urology

ISSN: (Print) 2090-598X (Online) Journal homepage: https://www.tandfonline.com/loi/taju20

Inhibitory effects of the ATP-sensitive potassium channel openers cromakalim, pinacidil and minoxidil on the carbachol–response curve in porcine detrusor muscle

Jasmin Katrin Badawi, Ruth Kirschner-Hermanns & Andrea Ding

To cite this article: Jasmin Katrin Badawi, Ruth Kirschner-Hermanns & Andrea Ding (2012) Inhibitory effects of the ATP-sensitive potassium channel openers cromakalim, pinacidil and minoxidil on the carbachol–response curve in porcine detrusor muscle, Arab Journal of Urology, 10:2, 207-215, DOI: 10.1016/j.aju.2011.12.009

To link to this article: https://doi.org/10.1016/j.aju.2011.12.009

Arab Journal of Urology (2012) **10**, 207–215

Arab Journal of Urology
(Official Journal of the Arab Association of Urology)

www.sciencedirect.com

UROSCIENCE

ORIGINAL ARTICLE

Inhibitory effects of the ATP-sensitive potassium channel openers cromakalim, pinacidil and minoxidil on the carbachol–response curve in porcine detrusor muscle

Jasmin Katrin Badawi [a,*], **Ruth Kirschner-Hermanns** [b], **Andrea Ding** [a]

[a] *Department of Urology, University Hospital of Mannheim, Medical Faculty of the Ruprecht Karls-University Heidelberg, Germany*
[b] *University Hospital of Aachen, Centre for Continence, Aachen, Germany*

Received 26 October 2011, Received in revised form 13 December 2011, Accepted 14 December 2011
Available online 3 March 2012

KEYWORDS

Pig;
Bladder smooth muscle;
Detrusor overactivity;
Potassium-channel opener;
Carbachol-induced contraction

ABBREVIATIONS

CRC, concentration–response curve; DO, detrusor overactivity;

Abstract ***Aims:*** ATP-sensitive potassium channels represent promising drug targets for treating specific bladder diseases. The inhibitory effects of ATP-selective potassium channel openers (PCOs) on the carbachol–response curve in porcine detrusor muscle were examined.

Materials and methods: Each of the three substances used in the study represent one prototype of a different class of PCO: cromakalim belongs to the benzopyran series, pinacidil is a cyanoguanidine derivative, and minoxidil represents a pyrimidine derivative. The porcine detrusor muscle represents one of the best models for human detrusor. Experiments were conducted on muscle strips of porcine detrusor muscle suspended in a tissue bath. Concentration–response curves of carbachol were constructed after pretreatment with cromakalim at 10^{-7}, 10^{-6} and 10^{-5} M, and with pinacidil and minoxidil at 10^{-6}, $10^{-5.5}$ and 10^{-5} M, respectively. Each muscle strip was only used to examine one concentration of one substance.

Results: Cromakalim had the greatest inhibitory effect, significantly suppressing the carbachol–response curve at 10^{-6} and 10^{-5} M. Pinacidil showed a significant inhibitory

* Corresponding author. Address: Department of Urology, University Hospital of Mannheim, Medical Faculty of the Ruprecht Karls-University Heidelberg, Theodor-Kutzer-Ufer 1–3, D-68167 Mannheim, Germany. Tel.: +49 178 62 42 973/+41 41 210 11 39/+41 77 4716981.
E-mail address: jasmin-katrin.badawi@gmx.de (J.K. Badawi).

Peer review under responsibility of Arab Association of Urology.
doi:10.1016/j.aju.2011.12.009

Production and hosting by Elsevier

PCO, potassium channel opener; OAB, overactive bladder; DMSO, dimethyl sulphoxide

effect at $10^{-5.5}$ and 10^{-5} M, which was smaller than that of cromakalim. Minoxidil did not significantly inhibit the contractions at all examined concentrations.

Conclusions: The examined ATP-sensitive PCOs belonging to the benzopyrans and cyanoguanidines significantly suppressed detrusor contractions. The development of derivatives of these prototypes could open new possibilities for the pharmacological treatment of selected bladder diseases.

Introduction

ATP-sensitive potassium channels represent promising drug targets for treating bladder diseases based on detrusor overactivity (DO). Potassium channel openers (PCOs) relax smooth muscle cells and could be useful therapeutic agents in the treatment of specific neurogenic bladder dysfunctions, types of urinary incontinence or idiopathic DO. Urinary incontinence affects millions of people worldwide and represents a major social problem. The main goal of the present study was to examine the inhibitory effects of different PCOs on contractions of the detrusor muscle in relation to using the PCOs as additional pharmacological therapy for bladder dysfunction based on involuntary detrusor contractions. Substances mainly used for the pharmacological treatment of such diseases are antimuscarinics, e.g. oxybutynin, trospium and tolterodine. Unfortunately, their use is limited by various adverse effects and patients often have to discontinue the therapy [1]. Furthermore, in some patients anticholinergic medication is ineffective and antimuscarinics used as a single medication do not lead to a sufficient therapeutic effect. Also, the placebo effect is very high, as shown in studies comparing an antimuscarinic drug and a placebo [2]. The advantage of examining new drugs during *in vitro* experiments, as in the present study, is that the placebo effect often found in clinical studies is eliminated [2], making the *in vitro* experiments very helpful for choosing potent substances before conducting clinical trials. Urinary incontinence is a common disease in elderly patients. As the percentage of elderly people is increasing, the incidence of urinary incontinence is also increasing. Therefore, the development and examination of alternative drugs for treating urge incontinence are also very important for this older population. In this context the disease pattern of overactive bladder (OAB), which is characterised by frequency, urgency and/or urge incontinence is important, as drugs for treating DO could also be used to treat such forms of OAB based on DO.

The ICS describes urgency (a sudden compelling desire to void), with or without urge incontinence, usually with frequency and nocturia, as the OAB syndrome, urge syndrome or urgency–frequency syndrome. This combination of symptoms is often based on urodynamically demonstrable DO, but can also be due to other forms of urethro-vesical dysfunction. The term 'OAB syndrome' should be only used if there is no confirmed infection or other obvious pathology like bladder cancer. DO is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase. DO incontinence means incontinence due to an involuntary detrusor contraction. DO can also be qualified according to the cause as neurogenic DO, when there is a relevant neurological condition, or idiopathic DO, when there is no defined cause. The OAB syndrome is very common; in the USA an OAB affected 34 million people, compared to 17 million with urinary incontinence, during the year 2000 [3]. It also represents a social and economic problem. In the USA the total cost of urinary incontinence and OAB for the year 2000 was $19.5 billion and $12.6 billion, respectively [3]. An overactive detrusor can also be the reason for bladder dysfunction due to neurological disorders, e.g. Parkinson's disease, cerebral apoplexy, multiple sclerosis or transverse spinal cord syndrome. Patients who have to use intermittent self-catheterisation often have involuntary loss of urine due to involuntary detrusor contractions occurring during the intervals between successive self-catheterisations. In this patient group, drugs inhibiting the contractions of the detrusor muscle could be used locally.

Beside antimuscarinics, other possible pharmacological substances for the treatment of DO are substances that target membrane channels of muscle cells, including L-type calcium antagonists [4] and PCOs. Potassium channels are important in regulating the membrane potential. Opening of the potassium channels [5] by PCOs leads to a hyperpolarisation of the cell membrane of smooth muscle cells [6]. It also reduces the opening probability of ion channels that are necessary for membrane depolarisation [7]. Among the different classes of potassium channels, ATP-sensitive channels are interesting for their use as targets for treating bladder overactivity. Each of the three substances used in the present study represents one prototype of a different subclass of ATP-sensitive PCOs; cromakalim belongs to the benzopyran series, pinacidil is a cyanoguanidine derivative. The atypical PCO minoxidil is clinically known to treat high blood pressure [8] and topically used as a hair-growth stimulant, and is a pyrimidine derivative.

The porcine detrusor muscle was used because it is one of the best models for the human detrusor muscle,

e.g. it has similar adrenoceptor expressions [9]. Therefore, examination of porcine detrusor muscle might allow conclusions about human detrusor and can facilitate the choice of interesting drugs which should be tested *in vivo*. In the present study we continued our previous *in vitro* experiments on porcine detrusor muscle, again using the three different prototypes of ATP-sensitive PCOs [10], focusing on their inhibitory effect on the carbachol–response curve.

Materials and methods

Urinary bladders of female pigs (German Landrace) obtained from the abattoir in Mannheim were examined. After the pigs had been slaughtered, the bladders were removed immediately and placed in a sodium Krebs solution (composition, mM: sodium chloride 119, potassium chloride 4.6, sodium bicarbonate 15, calcium chloride 1.5, magnesium chloride 1.2, sodium dihydrogen phosphate 1.2, glucose was 1.98 g/L). *N* represents the number of different pigs and *n* the number of strips.

Smooth muscle strips were cut from the posterior wall of the bladder body, and the mucosa and serosa were removed while in sodium Krebs solution. The tissues were mounted in a 7-mL organ bath containing sodium Krebs solution, which was maintained at 37 °C and continuously gassed with 95% O_2 and 5% CO_2.

The composition of the K^+ solution, pH 7.4, was (in mM): potassium chloride 124, sodium bicarbonate 15, calcium chloride 1.5, magnesium chloride 1.2, sodium dihydrogen phosphate 1.2; glucose 1.98 g/L).

The following drugs were used: carbamylcholine chloride (carbachol, molecular weight 182.65); cromakalim (286.3) and pinacidil (245.3), from Sigma–Aldrich Chemie GmbH (Taufkirchen, Germany), and minoxidil sulphate (289.3) from Alexis Biochemicals (Qbiogene-Alexis GmbH, Grünberg, Germany). Substances were dissolved as follows: cromakalim (10^{-2} M) and pinacidil (10^{-2} M) in ethanol, 100%. Minoxidil sulphate (10^{-1} M) was dissolved in dimethyl sulphoxide (DMSO). Carbachol was dissolved in 0.9% NaCl solution (10^{-1} M) and subsequently diluted in bath solution. Subsequent dilutions of these drugs were prepared in bath solution. The reported concentrations are the calculated final concentrations in the bath solution.

We assessed the inhibitory effect of the PCOs cromakalim, pinacidil and minoxidil on the carbachol–response curve. During the equilibration period of 1 h the muscle strips were placed under a tension of ≈1 g. The bath solution was changed every 30 min. The muscle strips were then contracted with 124 mm potassium solution. After maximum contraction had developed, preparations were washed four times until a steady resting level of tension was attained. This maximum potassium-induced contraction was defined as 100% (peak contraction minus baseline before the contraction) and used as the reference. Then tissue was allowed to equilibrate for 30 min. The bath solution was changed again and the appropriate drug or vehicle was added as control in the appropriate concentration to the Krebs solution. Each muscle strip was only used for one concentration of the PCO, or it was used as a control strip where only vehicle was added.

For pinacidil and minoxidil the concentrations assessed were 10^{-5}, $10^{-5.5}$ and 10^{-6} M. For cromakalim the concentrations were 10^{-5}, 10^{-6} and 10^{-7} M. In the preliminary experiments [10] we found that cromakalim had a significant inhibitory effect at lower concentrations than pinacidil and minoxidil. Therefore we chose different concentrations for cromakalim than for pinacidil and minoxidil. The equilibration time was 10 min for all substances, and then the concentration–response curves (CRCs) for carbachol were constructed with no change of solution. In the associated control group only the 'vehicle' was added without the PCO. The vehicle was the solvent (ethanol or DMSO) in which the PCO was dissolved, equivalently diluted compared to the pretreated group. In this way, in each control group, the concentration of the solvent was identical to the concentration in the associated pretreated group, so that the possible influence of the solvent was excluded when the two groups were compared. The CRCs for carbachol were obtained by increasing the concentration from 10^{-9} to 10^{-4} M in a stepwise manner in 0.5 log unit increments after the response to the previous concentration had reached a plateau. Each preparation was used for only one CRC, as previous experiments showed a reduction of the contractions when several CRCs were assessed on the same muscle strip, possibly because of tachyphylaxis.

The results are expressed as the mean (SEM). When assessing the carbachol–response curve the maximum potassium-induced contraction evoked before adding the agent was defined as 100% (peak contraction minus baseline before the contraction) and used as the reference. The contraction evoked by one concentration of carbachol was compared to the equivalent value in the control group using a Student's unpaired two-tailed *t*-test. Also, the maximum carbachol-induced contraction after treatment with the PCO was determined for each concentration of one examined drug. The *P*-values calculated by Student's *t*-test are shown, and $P < 0.05$ was taken to indicate significance.

Results

The CRCs for carbachol are shown in Fig. 1 after pretreatment with cromakalim at 10^{-7} M (A), 10^{-6} M (B) and 10^{-5} M (C). The CRC was significantly suppressed at 10^{-6} and 10^{-5} M. When using cromakalim at 10^{-5} M for pretreatment there was an undulating pattern of tension after each addition of carbachol. The recorded tension undulated around a mean value changing

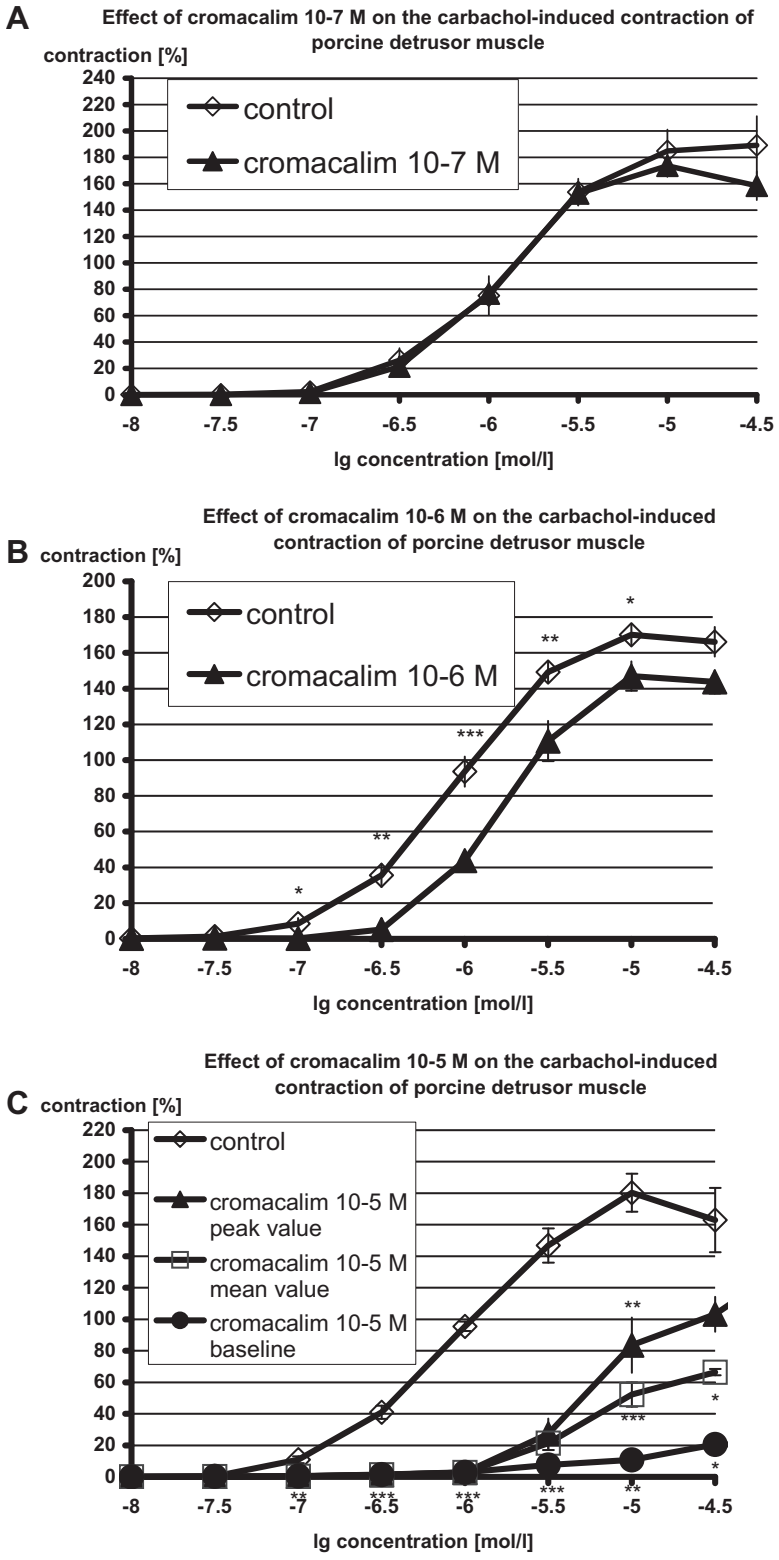

Figure 1 The mean cumulative CRCs of carbachol after pretreatment with cromakalim at 10^{-7} M (A: $n = 4$–6, $N = 3$–5; control group N, $n = 3$–4), 10^{-6} M (B: n, $N = 5$–7, control group n, $N = 9$) and 10^{-5} M (C: n, $N = 4$–5, control group: n, $N = 4$–5). As the recorded tension showed an undulating shape after using cromakalim at 10^{-5} M, the peak value as well as the baseline of the tension after adding carbachol at one concentration was determined for each curve and are shown together with the calculated mean value of the peak value and the baseline in C. Values are the mean (SEM). Appropriate values were compared with those of the control group (only treated with vehicle) in an unpaired Student's two-tailed t-test. $P^{*} < 0.05$, $^{**} < 0.01$, $^{***} < 0.001$. 100% was defined as maximum peak of the same muscle strip induced by high-concentration KCl solution.

repetitively from a baseline value to a peak value. Fig. 1C shows not only the mean value of the tension after adding one concentration of carbachol, but also the peak value (maximum value) and baseline value (minimum value). The undulation of the tension could be related to the strong hyperpolarising effect of cromakalim at the highest concentration interfering with the internal regulation of the transport of calcium, including the calcium 'sparks'. The maximum carbachol-induced contraction after pretreatment with cromakalim in the different concentrations and the corresponding value of each control group in which only the solvent was present is shown in Table 1. The unpaired two-tailed Student's *t*-test showed no significant difference in the maximum carbachol-induced contraction of the two groups.

The CRCs for carbachol are shown in Fig. 2 after pretreatment with pinacidil at 10^{-6} M (A), $10^{-5.5}$ M (B) and 10^{-5} M (C). The CRC was significantly suppressed at $10^{-5.5}$ and 10^{-5} M. The maximum carbachol-induced contraction after pretreatment with pinacidil in the different concentrations and the corresponding value of each control group in which only the solvent was present is shown in Table 1. The unpaired two-tailed Student's *t*-test showed no significant difference in the maximum carbachol-induced contraction.

The CRCs for carbachol are shown in Fig. 3 after pretreatment with minoxidil at 10^{-6} M (A), $10^{-5.5}$ M (B) and 10^{-5} M (C). The CRCs for carbachol were not significantly suppressed at all concentrations except one after pretreatment with minoxidil at $10^{-5.5}$ and 10^{-5} M, respectively. The maximum carbachol-induced contraction after pretreatment with minoxidil in the different concentrations and the corresponding value of each control group in which only the solvent was present is shown in Table 1. The unpaired two-tailed Student's *t*-test showed no significant difference in the maximum carbachol-induced contraction.

Table 1 The mean and SEM of the maximum carbachol-induced contraction (C_{max}) after pretreatment with the PCOs at different concentrations. The maximum potassium-induced contraction evoked before adding the agent was defined as 100% and used as the reference.

Group, concentration (M)	C_{max} (%)	SEM (%)	*n*/*N*
Control			
Cromakalim 10^{-7}	185	16	4/4
Cromakalim 10^{-7}	174	8	6/5
Cromakalim 10^{-6}	174	8	9/9
Cromakalim 10^{-6}	152	8	7/7
Cromakalim 10^{-5}	168	16	5/5
Cromakalim 10^{-5}	127	15	5/5
Pinacidil 10^{-6}	195	11	10/9
Pinacidil 10^{-6}	198	13	8/8
Pinacidil $10^{-5.5}$	173	12	5/5
Pinacidil $10^{-5.5}$	169	19	5/5
Pinacidil 10^{-5}	184	10	7/6
Pinacidil 10^{-5}	155	19	6/5
Minoxidil 10^{-6}	155	11	7/6
Minoxidil 10^{-6}	156	7	10/9
Minoxidil $10^{-5.5}$	181	9	10/9
Minoxidil $10^{-5.5}$	162	9	15/11
Minoxidil 10^{-5}	162	8	5/5
Minoxidil 10^{-5}	155	10	6/5

Discussion

We examined the inhibitory effects of three different ATP-sensitive PCOs on the CRC of porcine detrusor muscle strips. Cromakalim had the greatest inhibitory effect, significantly suppressing the CRC at 10^{-6} and 10^{-5} M. Pinacidil had a significant inhibitory effect at $10^{-5.5}$ and 10^{-5} M, which was smaller than that of cromakalim. Minoxidil did not significantly inhibit the contractions at all examined concentrations.

Rizk et al. [11] compared the inhibitory effects of cromakalim and pinacidil on detrusor muscle stimulation with those of oxybutynin in guinea pigs and rabbits. When using carbachol as stimulating agent they found the following order of potency of inhibition: oxybutynin > pinacidil > cromakalim in guinea pigs and oxybutynin > cromakalim > pinacidil in rabbits. Their experiment shows a species dependence. When using electrically induced contractions in guinea pigs, Rizk et al. [11] found the following potencies: pinacidil > cromakalim > oxybutynin. In rabbits, it was cromakalim > oxybutynin > pinacidil. These results also showed that the type of contraction used can be important. In our previous experiments [10] we examined the inhibitory effects of the three PCOs used in this study for inhibiting electrically evoked contractions of porcine detrusor muscle. Contrary to the study of Rizk et al. [11] in guinea pigs and rabbits, the rank order of potency of the used PCOs was the same in porcine detrusor muscle when inducing the contractions by electrical field stimulation. We found that cromakalim had the greatest inhibitory effect, being significant at 10^{-5} and 10^{-6} M. Pinacidil only showed a significant inhibitory effect at 10^{-5} M, smaller than that of cromakalim. At 3×10^{-6} M only a very small effect occurred at 1 Hz. Minoxidil did not inhibit the electrically evoked contractions at both examined concentrations except for a very small effect at 1 Hz. Vijayakumar et al. [12] showed, in goat detrusor muscle, similar results to our study, i.e. contractile responses induced by agonist or electrical field stimulation were more potently inhibited by cromakalim than pinacidil.

In the models of spinal cord injury it was shown that subcutaneous infusion of the PCO ZD0947 decreased detrusor hyperreflexia and, when given orally, was actually more effective than the antimuscarinic tolterodine in this respect [13].

Pinna et al. [14] examined the effects of pinacidil and the new generation PCO ZM226600 on cystometric

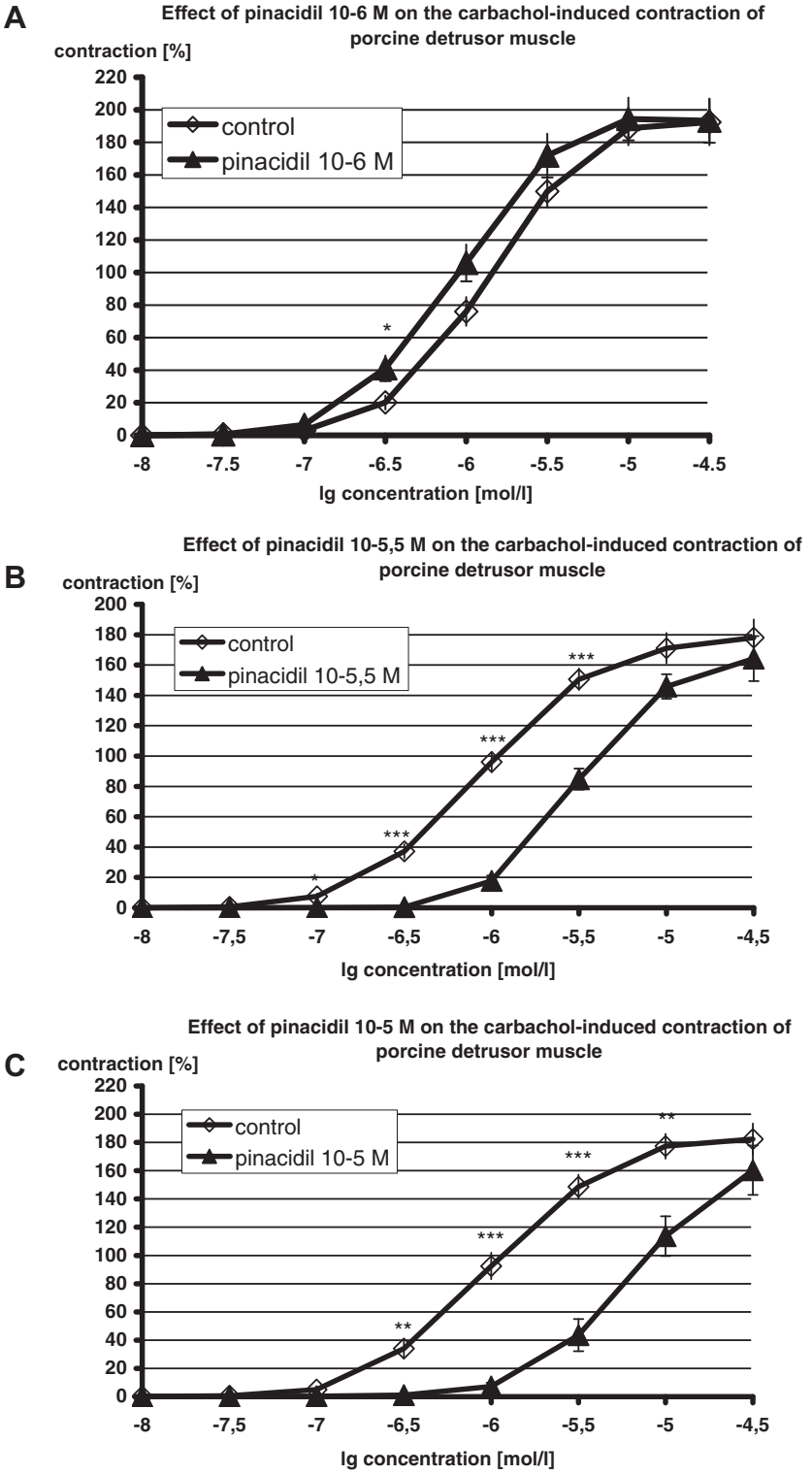

Figure 2 The mean cumulative CRCs of carbachol after pretreatment with pinacidil at 10^{-6} M (A: n, $N = 8$, control group $n = 10$, $N = 9$), $10^{-5.5}$ M (B: n, $N = 5$, control group n, $N = 5$–6) and 10^{-5} M (C: $n = 5$–6, $N = 5$, control group: $n = 7$–8, $N = 6$–7). Details as Fig. 1.

variables in rats with OAB due to ligature-intact, partial urethral obstruction. Both ZM226600 and pinacidil instilled into the bladder (10^{-7} M) or after systemic administration almost completely abolished bladder overactivity and improved the residual volume and frequency of micturition. Pinacidil affected arterial pressure more than ZM226600, even when used locally. It decreased the mean arterial pressure after intravesical

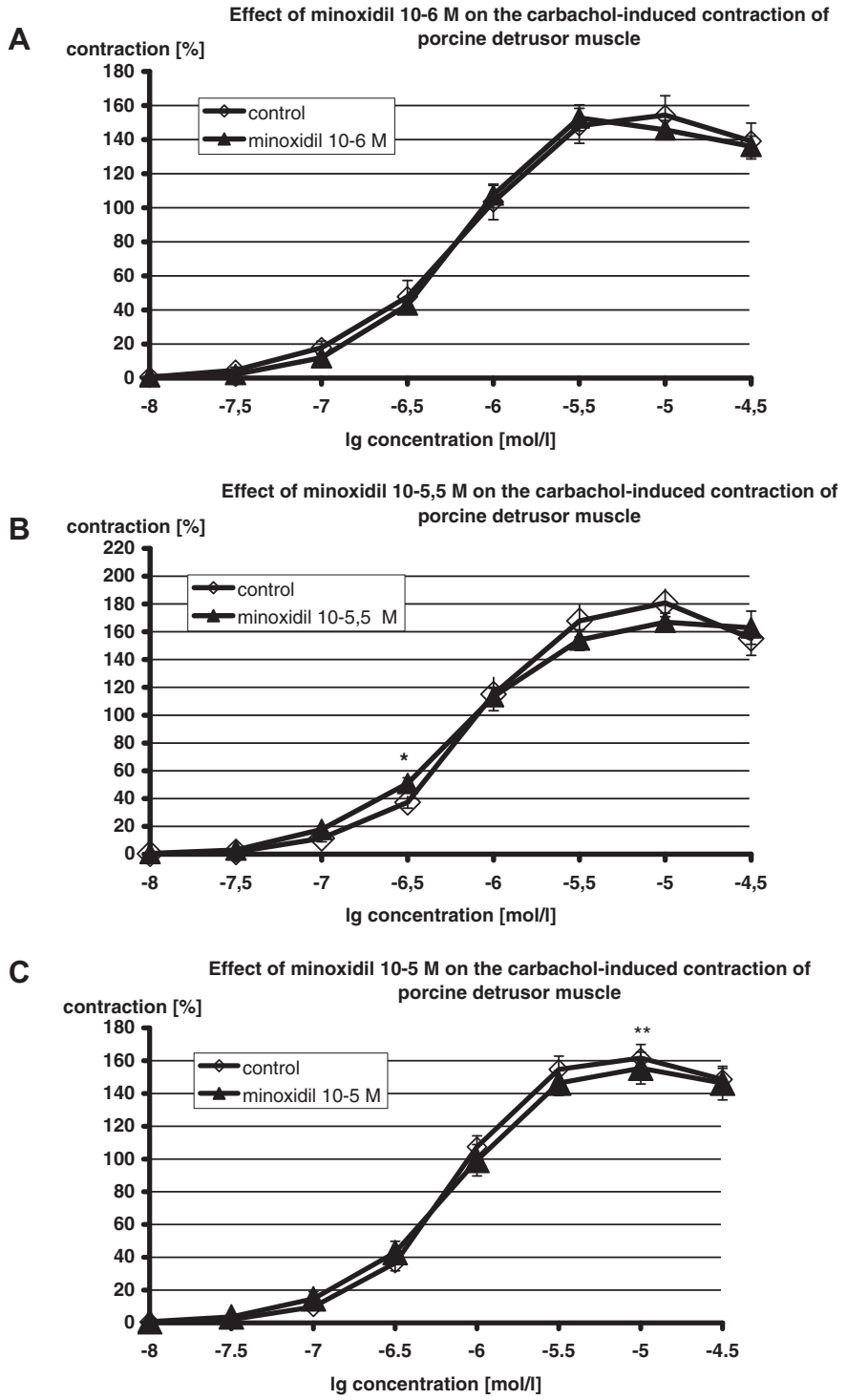

Figure 3 The mean cumulative CRCs of carbachol after pretreatment with minoxidil at 10^{-6} M (A: $n = 8$–11, $N = 7$–9, control group: $n = 5$–7, $N = 4$–6), $10^{-5.5}$ M (B: $n = 8$–16, $N = 7$–11, control group: $n = 5$–10, $N = 5$–9) and 10^{-5} M (C: $n = 6$, $N = 5$, control group: n, $N = 5$). Details as Fig. 1.

instillation by ≈ 12% and 26% at 10^{-7} and 10^{-5} M, respectively. Intravenous administration of pinacidil had more pronounced and persistent effects on mean arterial pressure than ZM226600.

The effects of the PCOs pinacidil and cromakalim in normal and hypertrophied rat detrusor were investigated *in vitro* by Malmgren et al. [15]. Both drugs suppressed spontaneous contractile activity and induced a relaxation of normal and hypertrophied detrusor preparations. In both types of preparation the contractions, independent of how they were evoked, were suppressed in the presence of the PCOs. The authors suggested that

PCOs might be effective in the treatment of bladder instability secondary to outlet obstruction.

Conclusions from normal detrusor muscle can be drawn in relation to the OAB. There was no significant difference between the potency of PCOs in normal and hyper-reflexic human detrusor muscle [16] when comparing the effects of levcromakalim and YM934 in isolated detrusor muscle from normal and hyper-reflexic bladders. The authors suggested that there were no appreciable changes in sensitive potassium channel function in the unstable bladder. Oger et al. [17] showed that pinacidil at 10^{-5} M markedly inhibited the spontaneous contractile activity of detrusor strips from normal patients and from patients with neurogenic DO. In a double-blind, crossover study the effect of pinacidil at 25 mg/day was studied in 10 patients with detrusor instability and BOO [18]. Pinacidil was not effective at the dosage given. Elzayat et al. [19] investigated the effect of the PCO WAY-133537 on the OAB of spinalised rats. The results were promising; neurogenic DO disappeared in half the rats that received WAY-133537 at 0.3 mg/kg for 1 week, and the frequency of DO decreased. After 2 weeks of treatment, DO was not apparent in two-thirds of the rats, with an even further reduction in the frequency of DO.

Abdel-Karim et al. [20] also reported promising results when testing the efficacy of the two ATP-dependent PCOs ZD6169 and ZD0947 on detrusor hyperreflexia after spinal cord injury in rats. Three weeks after this injury detrusor hyperreflexia developed in all control paraplegic rats; the detrusor hyperreflexia resolved in two-thirds of the rats that received ZD6169 for 1 week at either dose. All rats that received 3 mg/kg ZD0947 daily for 1 week showed no detrusor hyperreflexia, while at 0.3 mg/kg daily 83% showed no detrusor hyperreflexia. Each drug produced better urodynamic results when given for 2 weeks. The results of both studies suggest that PCOs are an effective treatment for detrusor hyperreflexia after spinal cord injury. PCOs represent an interesting pharmacological approach. If substances are selective for the detrusor muscle, cardiovascular side effects, especially lowering of blood pressure, are reduced [14] after systemic administration. In this case this substance class might also be used systemically. Side-effects should also be reduced using the PCOs locally by intravesical application [14]. More clinical studies should focus on these interesting pharmacological substances.

In conclusion, available data on the inhibitory effects of different prototypes of PCOs on the contractility of the detrusor muscle are very rare. The present study is of great clinical interest, as it gives insights into a special pharmacological substance class until now not clinically used. It confirms our previously published first results concerning PCOs, which suggested that cromakalim and pinacidil are strong inhibitory substances on bladder smooth muscle. Cromakalim had a stronger significant inhibitory effect than pinacidil on the carbachol–response curve of porcine detrusor muscle. Minoxidil was not a good inhibiting agent. ATP-sensitive PCOs could be an interesting pharmacological substance class for treating neurogenic and idiopathic DO and special types of urge incontinence or urge syndrome. Local instillation especially seems to be an alternative to the cheap and sometimes ineffective injection of botulinum toxin, as well as for the treatment of DO refractory to anticholinergic treatment for patients who have to use intermittent self-catheterisation. Local application might also allow the clinical use of non-bladder-selective PCOs. The results of the present study show significant, strong inhibitory effects of the benzopyran cromakalim and the cyanoguanidine pinacidil. The development of derivatives of these subclasses could open new possibilities in the pharmacological treatment of relevant bladder diseases.

Acknowledgements

We are grateful to Prof. Peter Alken (Mannheim, Germany) for giving us the opportunity to do research. Many thanks to Prof. Maurice-Stephan Michel (Mannheim, Germany) for constantly supporting our research projects. We are also very grateful to Prof. Lothar Schilling (Neurosurgical Research, Mannheim, Germany) for his excellent scientific advice and practical information. Many thanks to Prof. Karl-Erik Andersson (Lund, Sweden/North Carolina, USA) for sharing his uro-pharmacological knowledge about organ-bath techniques, and very helpful scientific advice. Special thanks to Ms. Elizabeth Dickmeyer (Fort Wayne, IN, USA), my teacher and pupil for more than 10 years, for numerous instructive discussions in and about our languages.

Conflict of interest

The authors have no conflict of interest to declare.

References

[1] Yarker YE, Goa KL, Fitton A. Oxybutynin. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. *Drugs Aging* 1995;**6**:243–62.

[2] Abrams P, Swift S. Solifenacin is effective for the treatment of OAB dry patients: a pooled analysis. *Eur Urol* 2005;**48**:483–7.

[3] Hu T. Costs of urinary incontinence and overactive bladder in the United States: a comparative study. *Urology* 2004;**63**:461–5.

[4] Badawi JK, Li H, Langbein S, Kwon ST, Kamp S, Bross S. Inhibitory effects of various l-type and T-type calcium antagonists on electrically generated, potassium-induced and carbachol-induced contractions of porcine detrusor muscle. *J Comp Physiol [B]* 2006;**176**:429–39.

[5] Masuda N, Uchida W, Shirai Y, Shibasaki K, Goto K, Takenaka T. Effect of the potassium channel opener YM934 on the contractile response to electrical field stimulation in pig detrusor smooth muscle. *J Urol* 1995;**154**:1914–20.

[6] Foster CD, Speakman MJ, Fujii K, Brading AF. The effects of cromakalim on the detrusor muscle of human and pig urinary bladder. *Br J Urol* 1989;**63**:284–94.
[7] Andersson KE. Clinical pharmacology of potassium channel openers. *Pharmacol Toxicol* 1992;**70**:244–54.
[8] Criddle DN, de Moura RS. Vasorelaxant effects of the potassium channel opener SR 47063 on the isolated human saphenous vein and rat aorta. *Braz J Med Biol Res* 2000;**33**:961–6.
[9] Goepel M, Wittmann A, Rubben H, Michel MC. Comparison of adrenoceptor subtype expression in porcine and human bladder and prostate. *Urol Res* 1997;**25**:199–206.
[10] Badawi JK, Ding A, Bross S. Inhibitory effects of different ATP-sensitive potassium channel openers on electrically generated and carbachol-induced contractions of porcine and human detrusor muscle. *Fundam Clin Pharmacol* 2008;**22**:75–86.
[11] Rizk DE, Arafat K, El-Sharkawy TY. Comparison of the inhibitory effects of cromakalim and pinacidil (potassium channel openers) with those of oxybutynin on stimulated guinea pig and rabbit detrusor muscle strips. *Arch Gynecol Obstet* 2001;**265**: 141–7.
[12] Vijayakumar C, Kathirvel K, Sardar KK, Parija SC. Effect of KATP channel openers on myogenic and neurogenic responses in goat urinary bladder. *Indian J Exp Biol* 2007;**45**:185–93.
[13] Moussa S, Kashiwabara T, Bialecki R, et al. Comparative study of the effects of ZD0947 and tolterodine on bladder function in a paraplegic rat model. Abstract (#221) presented at the annual meeting of the international continence society, Paris, 23–27 August 2004.
[14] Pinna C, Sanvito P, Bolego C, Cignarella A, Puglisi L. Effect of the ATP-sensitive potassium channel opener ZM 226600 on cystometric parameters in rats with ligature-intact, partial urethral obstruction. *Eur J Pharmacol* 2005;**516**:71–7.
[15] Malmgren A, Andersson KE, Andersson PO, Fovaeus M, Sjögren C. Effects of cromakalim (BRL 34915) and pinacidil on normal and hypertrophied rat detrusor in vitro. *J Urol* 1990;**143**:828–34.
[16] Martin SW, Radley SC, Chess-Williams R, Korstanje C, Chapple CR. Relaxant effects of potassium-channel openers on normal and hyper-reflexic detrusor muscle. *Br J Urol* 1997;**80**:405–13.
[17] Oger S, Behr-Roussel D, Gorny D, Bernabé J, Comperat E, Chartier-Kastler E, et al. Effects of potassium channel modulators on myogenic spontaneous phasic contractile activity in human detrusor from neurogenic patients. *BJU Int* 2011;**108**: 604–11.
[18] Hedlund H, Mattiasson A, Andersson KE. Effects of pinacidil on detrusor instability in men with bladder outlet obstruction. *J Urol* 1991;**146**:1345–7.
[19] Elzayat E, Khaled S, Kashiwabara T, Elhilali M, Corcos J. Effect of the potassium channel opener WAY-133537 on the overactive bladder of spinalized rats. *Neurourol Urodyn* 2006;**25**:808–14.
[20] Abdel-Karim AM, Bialecki RA, Elhilali MM. Effects of ZD6169 and ZD0947, 2 potassium adenosine triphosphate channel openers, on bladder function of spinalized rats. *J Urol* 2002;**168**: 837–42.