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EFFECTS OF PROPIVERINE AND THREE OF ITS METABOLITES ON JUVENILE PIG DETRUSOR CONTRACTION

Hypothesis / aims of study

Propiverine as a standard spasmolytic drug used for the therapy of overactive bladder syndrome, appears to have other spasmolytic effects in addition to its antimuscarinic action. Propiverine is rapidly absorbed after oral administration and is subject to extensive first-pass metabolism giving rise to several active metabolites. In isolated detrusor strips, propiverine is known to decrease contractions elicited by electric field stimulation (EFS) to a larger extent than the antimuscarinic drug atropine. Here we investigated whether propiverine and three of its main metabolites (M-5: 2,2-diphenyl-2-propoxy-acetic acid [1-methyl-piperid-4-yl]-ester-N-oxide-trans; M-6: 2,2-diphenyl-2-hydroxy-acetic acid [1-methyl-piperid-4-yl]-ester-N-oxide-trans; M-14: 2,2-diphenyl-2-propoxy-acetic acid [piperid-4-yl]-ester) retain their pharmacodynamic properties also in juvenile organisms.

Study design, materials and methods

Urothelium-free detrusor strips from juvenile pig urinary bladders (8-12 weeks) obtained from a local abattoir were suspended in a perfusion organ bath. Muscles from 9 male and 3 female pigs of 12 to 35 kg body weight were used. Contractile responses were measured in response to EFS (pulse duration 1 ms, amplitude 90 mA, frequency 30 Hz, trains of stimuli for 5 s and 2 min between the trains of stimuli). Effects of propiverine and the three metabolites (M-5, M-6, M-14) were compared with those of atropine and tolterodine.

Results

Figures 1 and 2 summarize the concentration-response curves for M-6, M-14 and atropine as well as propiverine, its N-oxide M-5 and tolterodine, with time-matched control experiments (TMC) shown in both figures.

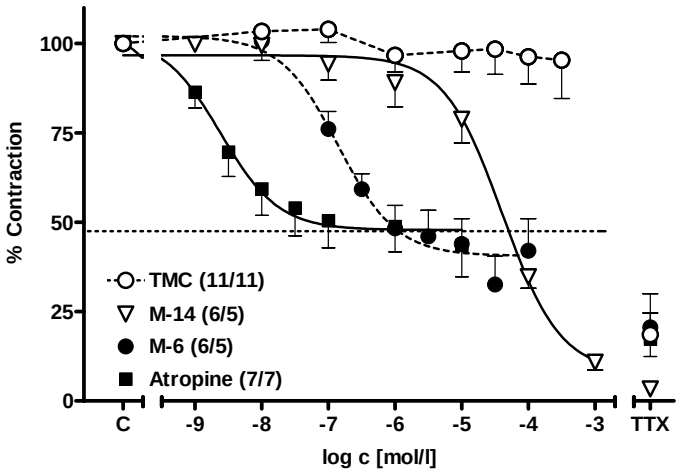

Figure 1: Concentration-dependent effects of M-6, M-14 and atropine on electrically stimulated force development in juvenile pig detrusor muscle strips in comparison to TMC recordings. Contractions in the presence of a given drug concentration are expressed in percent of the pre-drug control value (=100%). Data as mean ± SEM from n investigated detrusor strips from x animals.

EFS-evoked contractions remained constant over the time course of the experiment. After 4 hours tension was still 95±11% of control (n=11). In juvenile pig detrusor atropine (10 µM) reduced electrically evoked contractions to 44±9% of control (n=7/7). Former studies on mature pigs showed that the same concentration of atropine depressed EFS-contractions to

about 20% [1]. Also potency of atropine was significantly higher in juvenile compared to mature pigs (-log IC_{50} [M]: 8.49±0.14 versus 7.82±0.08, $p<0.001$). In juvenile pigs M-6 reduced detrusor contraction to the same amount as atropine but with slightly lower potency (-log IC_{50} [M]: 6.85±0.13), whereas M-5 and M-14 were similar potent and efficient as the parent compound propiverine (-log IC_{50} [M]: 4.14±0.21 for M-5; 4.23±0.08 for M-14; 4.76±0.24 for propiverine).
Adding 1µM of the neurotoxin tetrodotoxin (TTX) at the end of the TMC experiments contraction amplitudes were reduced to 21±7% of control (Figure 1). Additional exposure to TTX on top of the maximum atropine concentration further reduced EFS-induced contractions to 17±5% of control indicating a non-adrenergic, non-cholinergic (NANC) component of contraction of about 27% under our experimental conditions.

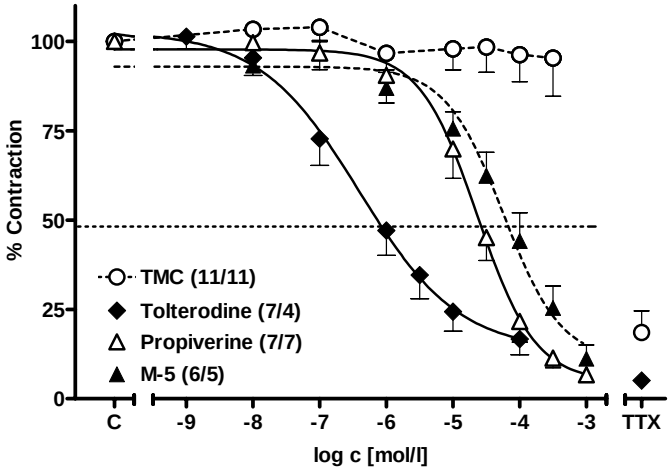

Figure 2: Effects of propiverine, M-5 and tolterodine on electrically stimulated force development also in comparison to TMC recordings. Layout like Figure 1.

Interpretation of results

EFS-induced contractions of detrusor strips from juvenile pigs are more sensitive to atropine than strips from mature pigs. Our data with TTX suggests that the atropine-resistant and therefore the NANC neurotransmitter mediated contribution to contractile responses after EFS is larger in juvenile pigs and probably decreases during functional maturation in pig urinary bladder. While signal transduction via muscarinic receptors is fully developed at birth and seems to be not changed during maturation, ATP and noradrenaline mediated contractile responses are thought to be developmentally regulated [2].The additional mode of action of propiverine is shared by its two metabolites M-5 and M-14, whereas the metabolite M-6 does not impair the atropine-resistant and therefore NANC component of contraction. Comparison of –log IC_{50} values gave the following order of potency: atropine > M-6 > propiverine ≈ M-5 ≈ M-14. We speculate that oxidation of the tertiary amine may have a negative influence on the drugs' potencies, change to a secondary amine structure has little effect, but loss of the aliphatic side chain results in pure antimuscarinic action.

Concluding message

Juvenile pig detrusor possess a higher NANC component of EFS-elicited contraction. Nevertheless the spasmolytic effects of propiverine and its metabolites M-5, M-6 and M-14 (order of potency and maximum inhibition of contractions) are similar in juvenile and mature pigs.

References

[1] Different responses to drugs against overactive bladder in detrusor muscle of pig, guinea pig and mouse. *Eur. J. Pharmacol.* 2002; 454: 59-69.
[2] Developmental aspects of bladder function. *Scan. J. Urol. Nephrol. Suppl.* 2004; 215: 11-19.