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EFFECTS OF THE MUSCARINIC ANTAGONIST, SOLIFENACIN, ON BLADDER AFFERENT ACTIVITY OF THE RAT PELVIC NERVE

Hypothesis / aims of study

Recent findings have suggested that during the storage phase, there is an ongoing release of acetylcholine from nerves and/or urothelium acting on muscarinic receptors. Acetylcholine may act directly on afferent nerves to initiate the micturition reflex and contribute to the symptoms of OAB. Previous studies have revealed that intravesical administration of oxybutynin has a temporary anesthetic effect on pelvic afferent C fibers without any effect on Aδ fibers (1), whereas parenteral administration of oxybutynin decreases activity in both C and Aδ fibers (2). However oxybutynin is an anticholinergic agent with mixed actions, so theoretically the observed effects can be due to the anticholinergic, direct muscle relaxant or local anesthetic actions. To evaluate the effect of muscarinic receptor blocking during the storage phase, a pure antimuscarinic drug has to be studied. This study aims to evaluate the efficacy of solifenacin, on bladder afferent activity.

Study design, materials and methods

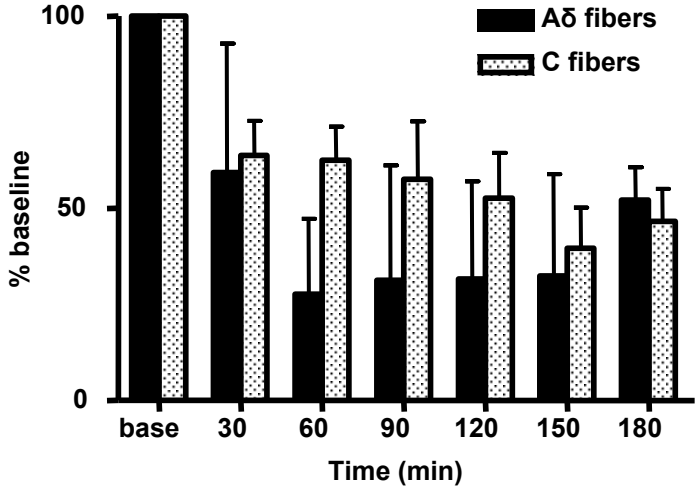
Eight female Sprague-Dawley rats were used for the experiments. After urethane anesthesia, the left pelvic nerve was identified and put on an electrode for electrical stimulation. A catheter was inserted into the bladder dome for filling and emptying. The lumbosacral spinal cord was exposed by laminectomy and the both L6 dorsal roots were cut. The dorsal skin was tied up to make a pool and the spinal cord was covered with body warm paraffin oil. Fine filaments were dissected from the left L6 dorsal root and placed on recording electrodes. Afferent fibers originating from the bladder were identified by electrical stimulation of the pelvic nerve and by bladder filling. Those with a conduction velocity <2.5 m/sec were considered to correspond with C fibers and those with a CV >2.5 m/sec with Aδ fibers (3).

Afferent activity was studied during constant flow cystometry at 0.08 ml/min until an intravesical pressure of 35 cm water was reached. The effect of intravenous solifenacin (1mg/kg) on bladder afferent fibers was evaluated. After a baseline bladder filling, solifenacin was administered and the afferent activity was again assessed during cystometry every 30 minutes up to 180 minutes after administration. Afferent activity after solifenacin is expressed as a percentage of baseline activity, integrated for the whole filling phase.

Results

Twelve single unit afferent fibers were isolated in 8 rats. Eight units corresponded to criteria for C fibers (CV: 1.327 ±0.1268 m/sec), and four for Aδ fibers (CV: 4.005 ±0.9722 m/sec). Six fibers out of eight C fibers and three out of four Aδ fibers showed a decrease in activity after solifenacin administration, with the remainder showing either inconsistent and small effect or no change. Only the 10 fibers that exhibited a response after drug administration were included for further analysis.

For the Aδ fibers, afferent sensitivity 30 min after solifenacin was 59 % ($P>0.05$) of the baseline sensitivity, 28 % after 60 min ($P<0.001$), 31 % after 90 min ($P<0.01$), 31 % after 120 min ($P<0.01$), 32 % after 150 min ($P<0.01$), and 52 % after 180 min ($P < 0.05$). For the C fibers, afferent sensitivity respectively was 64 % (30min, $P < 0.05$), 63 % (60min, $P < 0.05$), 58 % (90min, $P<0.01$), 53 % (120min, $P<0.01$), 40 % (150min, $P<0.001$), and 47 % (180min, $P<0.001$) compared with baseline activity. No difference was found between effect on Aδ and C fibers after solifenacin.



Interpretation of results

The results of this study show that solifenacin reduces afferent activity in the majority of both Aδ and C fibers. Because solifenacin is a pure antimuscarinic agent, the observed effects can be attributed to muscarinic receptor blocking. These data directly show that acetylcholine has an important role in afferent transduction.

It should be noted that not all fibers responded to solifenacin administration. The reason for this is not clear, but this finding may suggest that other new classification criteria are needed to evaluate the effect of antimuscarinics instead of conduction velocity. Further investigations will be needed to conclude this point.

Concluding message

The pure muscarinic antagonist solifenacin reduces a major part of both Aδ and C afferent activity of the rat urinary bladder. These results may explain that the efficacy of solifenacin in OAB symptoms is partly due to a decrease in bladder afferent activity.

References
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