Silodosin reduces pressure in vivo of the obstructed rat ureter and inhibits nerve-mediated contractions of the human ureter


Aim of the work
α1-adrenoceptor(AR) antagonists show inhibitory effects on isolated ureter from different species and appear to facilitate stone passage in humans. Silodosin is distinctively selective for the α1A-AR, with a 593- and 57-fold selectivity for the α1A-AR versus the α1b- and α1D-AR. The aim of this study was to evaluate the effect by silodosin on ureter and blood pressures in a rat in vivo model for ureter obstruction, and on nerve-mediated contractions of the human isolated ureter. Comparisons were made to tamsulosin.

Materials and methods
After Ethics Committee approval, the left ureter of male Sprague-Dawley rats (250-300 gr) under isoflurane anesthesia, was cannulated beneath the kidney pelvis with a polyethylene(PE)-10 catheter. Saline was infused at a speed (0.4 ml/hour) corresponding to the normal urine-production of a rat. The psoas muscle was sutured around the distal ¼ of the ureter to cause a partial distal obstruction. A PE-50 catheter was positioned in the carotid artery and a PE-10 catheter was positioned in the femoral vein. Autonomous peristaltic pressure-waves and MAP of the rat ureter were recorded via a Grass polygraph and a Biopac system. Silodosin (0.1 or 0.3 mg/kg; n=12) or tamsulosin (0.01 or 0.03 mg/kg; n=12) were given intravenously. Effects by silodosin or tamsulosin on perioperatively obtained human proximal ureter preparations (n=4) were evaluated in organbaths. Values are given as mean plus standard error of the mean.

Results
At baseline before obstruction, spontaneous peristaltic pressure waves were recorded with a minimum and maximum pressure of 18.9±4.2 and 33.9±7.7 cmH2O. Obstruction increased minimum and maximum pressures to 38.1±7.0 and 51.1±9.4 cmH2O but had no effect on MAP. Silodosin 0.1 and 0.3 mg/kg reduced the minimum pressure after obstruction by 18.4±6.6% and 22.0±2.7%. Corresponding effects by tamsulosin 0.01 and 0.03 mg/kg were 11.3±3.9% and 13.7±5.3%. Maximum pressure was reduced by 20.7±4.5% and 39.0±3.8% by silodosin (0.1 and 0.3 mg/kg) and 15.3±7.5% and 19.5±7.6% by tamsulosin (0.01 and 0.03 mg/kg). Silodosin reduced MAP by 9.1-10.9%, whereas tamsulosin reduced MAP by 16.5-22.3%. Maximal inhibitory effects of 74±3 % (silodosin) and 24±15% (tamsulosin) on nerve-induced contractions of the human ureter were recorded at 100µM.

Discussion
At amounts approximately corresponding to human therapeutic doses, silodosin reduced pressure in vivo of the obstructed rat ureter with less effect on blood pressure than tamsulosin. Silodosin had better efficacy than tamsulosin to inhibit endogenous nerve-mediated contractions of isolated human ureter.

Conclusions
Silodosin exhibits large effect on ureter pressure but small effect on blood pressure in a rat model for the study of ureter obstruction. In addition, high selectivity for the α1A-AR seems to be of relevance to counteract nerve-mediated contractions of the human isolated ureter.