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XESTOSPONGIN DIMINISHES OVERACTIVE CONTRACTIONS IN THE OBSTRUCTED GUINEA PIG BLADDER.

Hypothesis / aims of study

Unvoluntary detrusor contractions play an important role in the development of urge incontinence. Also in vitro, contractions which develop spontaneously can be seen; a parallel with the in vivo observations is likely. Our previous research showed that in vitro spontaneously developing contractions can be stopped using the IP3 (inositol-tri-phosfate) inhibitor Xestospongin. In order to study this in an animal model we used the model of the obstructed guinea pig.

Study design, materials and methods

We used a model of partial urethral obstruction in the guinea pig. We placed jeweler's jump rings (2mm) loosely around the proximal urethra of immature guinea pigs and allowed the obstruction to develop gradually as the animal grew. We used fourteen immature male albino guinea pigs (Hartley strain). After 3 and 5 weeks of obstruction we studied the filling and emptying characteristics of the bladder during three repetitive continuous fillings under Ketamine (43.3 mg/kg i.m.) en Xylazine (0.87 mg/kg s.c.) anesthesia. A 24 gauge 1.6 cm pediatric angiocatheter was used and inserted percutaneously into the bladder. This catheter was connected to a continuous infusion pump and filled the bladder with a continuous rate of 0.95 ml/min. We defined the term overactive' contractions in this protocol as repetitive low amplitude contractions which achieved at least one third of the normal voiding pressure. When overactivity was seen during the urodynamic investigation we used Xestospongin (4µM) bladder instillations in 2 filling cycles and before and after this intervention control filling cycles. For the last filling, saline was used to see if the bladders still had the capacity for a 'normal'voiding contraction. All raw data was stored digitally and analyzed in Matlab®. We calculated the 'area under the curve'and the number of contractions during 3 minutes after the overactivity started. The animals than were sacraficed using a high dose of barbiturate.

Results

Of the 14 animals, 4 animals developed 'overactive'contractions after 3 weeks and 3 after 5 weeks. Two animals, one of the 3 week group and one of the 5 week group, were used as controls. During the three fillings no significant changes were seen in overactivity in the control animals. In 4 animals that showed bladder overactivity, as defined, the instillations with Xestospongin led to a significant reduction in overactive contractions in all three parameters (table 1). Voiding was still achieved with a pressure of 36% compared to normal in this group. In the last filling phase with saline a voiding was achieved with a pressure of 68 % of normal. In one animal there was no response to Xestospongin.

Table 1.

Reduction in overactivity after Xestospongin instilations		
Area under the curve	86%	P= 0.016
Frequency of contractions	82%	P= 0.022
Amplitude of contractions	78%	P= 0.027

Concluding message

The IP3 inhibitor Xestospongin is capable of reducing bladder overactivity considerably in obstructed guinea pigs. Still significant bladder pressure amplitudes were achieved during a voiding contraction. This indicates a new approach to the treatment of detrusor overactivity.