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A SPECIES COMPARISON OF THE URETHRAL PROPERTIES IN THE FEMALE GUINEA-PIG AND RAT.

Hypothesis / aims of study:

The mammalian urethra is a complex organ constructed of smooth and striated muscle and vascular urothelium, however, the role of the two muscle layers are relatively unknown. In human, the urethra is in part responsible for urinary continence by generating sustained tone during bladder filling, with external urethral sphincter electromyographic activity (EMG) low during the early filling phase, rising with increases in bladder volume cumulating in complete inhibition immediately prior to bladder emptying when the urethra relaxes. The main aim of this study was to profile the urethra of both species and perform urodynamic characterisation of the distinctive patterns of the micturition cycle. This will enable us to determine the regional contributions to urethral function during micturition, and to provide some insight into the possible species-related differences when determining a suitable animal model for the human urethra.

Study design, materials and methods:

Female Dunkin-Hartley guinea-pigs, weighing 400-500g, and Sprague-Dawley rats, weighing 200-300g were used throughout. Urodynamic studies were performed under urethane anaesthesia (intraperitoneal injection of 0.5ml/100g body weight), in accordance with the protocol described within project and personal licences issued by the UK Home Office. Arterial and venous lines for blood pressure recording and drug administration were inserted respectively. Following a small incision in the abdomen a 2F cannula was inserted into the bladder for bladder filling (saline at 150$\mu l min^{-1}$guinea-pig and 45$\mu l min^{-1}$rat) and secured with silk thread at the dome. Bladder and arterial pressures were recorded using in-house pressure transducers and amplifier. A tension probe was introduced to the urethra through the external urethral opening and secured at the required position or fixed to an electronic pump for urethral pull throughs. Finally EMG electrodes were implanted on either side of the urethra under the pubic symphosis to measure external urethral sphincter activity. For organ bath experiments the animals were sacrificed by cervical dislocation. Opening the abdomen and dividing the pubic symphysis enabled access to the underlying urethra, which was carefully dissected. Urethral rings of 3mm (guinea-pig) and 4mm (rat) in thickness were obtained in an axial orientation from the bladder neck through to the external urethral opening. Muscle rings were immediately suspended vertically for tension recording in 5ml perfusion organ baths using silk ligatures; drugs were added to the bathing solution.

Results

Species and urethra functional length (mm)	Min pressure (mmHg)	Min pressure zone (mm)	Max pressure (mmHg)	Max pressure zone (mm)
Guinea-pig (18mm)	4.69	7-11	23.68	1-7
Rat (16mm)	7.08	12-16	46.14	1-8

Figure 1 – in vivo pull through pressures and regions measured at 80% bladder capacity.

Species and urethra functional length (mm)	Min tension (mg)	Min tension zone (mm)	Max tension (mg)	Max tension zone (mm)
Guinea-pig (18mm)	15	7-11	501	14-18
Rat (16mm)	0	12-16	417	1-4

Figure 2 – Responses to phenylephrine (10^{-4}M) in vitro and regions measured.

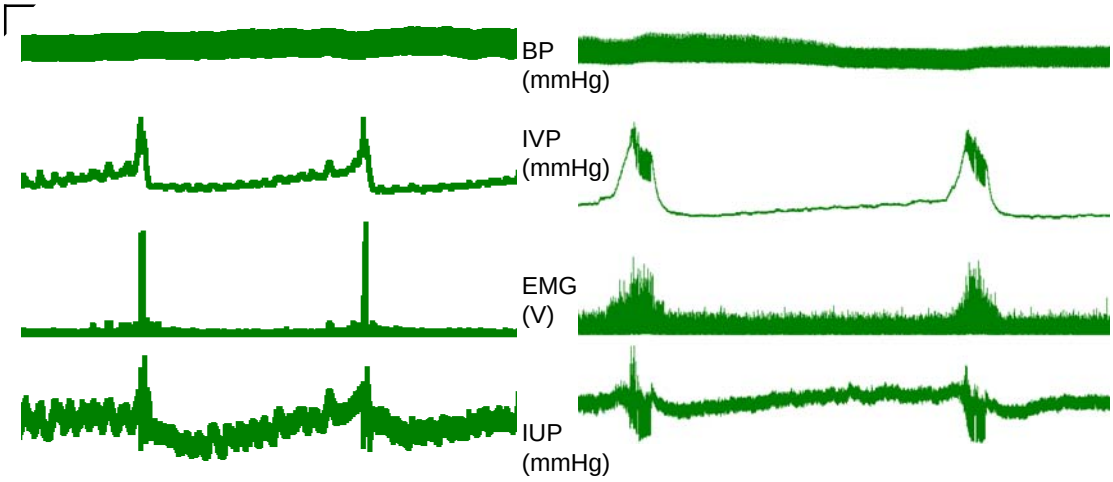

Figure 3 – Simultaneous recordings from top to bottom of blood pressure (mmHg), bladder pressure (mmHg), EMG activity (V) and proximal urethral pressure (mmHg) in (a) guinea-pig and (b) rat. Horizontal bar represents 30sec; vertical bar represents 20mmHg and 0.02V.

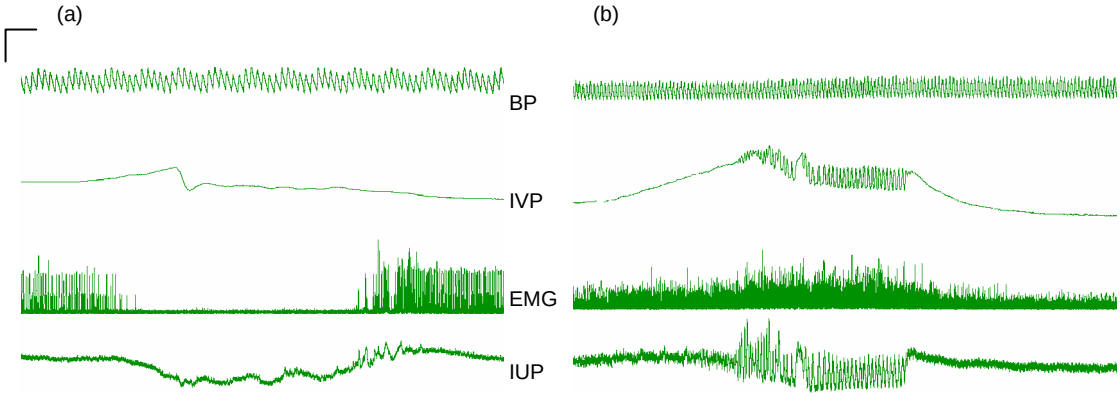

Figure 4 – Single recording of parameters (as above) during micturition in (a) guinea-pig and (b) rat. Horizontal bar represents 2sec; vertical bar represents 20mmHg and 0.02V.

Interpretation of results

Organ bath studies yielded maximum responses to phenylephrine in the proximal urethra with very little or no response in the distal region in the rat. The guinea-pig urethra contracted following application of phenylephrine along its entire length with greatest responses in the distal region (Fig 2). *In vivo* pull through studies yielded peak urethral pressures in the proximal region of the guinea-pig and rat urethra (Fig 1), therefore urodynamic studies were performed with the urethral probe fixed in the high pressure zones of the proximal urethra. During bladder filling in both species there was a build up in urethral tone when EMG activity was at its lowest, suggesting that the increase in urethral pressure was the result of the smooth and not striated muscle (Fig 3). However, during micturition the two species act quite differently. In the rat model the EMG exhibited high frequency bursts during urethral relaxation, which produced oscillations in urethral and bladder pressure. This was in contrast to the guinea-pig, which showed complete inhibition of sphincteric activity, a characteristic common to human (Fig 4).

Concluding message

The contractile response of the proximal urethra to phenylephrine demonstrates the presence of smooth muscle in both species, and the increase in urethral tone when EMG activity is at its lowest suggests the smooth muscle is responsible for the maintenance of continence at this phase of the cycle. However, in contrast to guinea-pig the EMG activity seen in the rat during micturition is presumably necessary for efficient voiding. Thus making the guinea-pig a more suitable comparative model for human in relation to urethral property during micturition.