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J. Le Feber, E. Van Asselt and R. Van Mastrigt

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A comparative study of voiding in rat and guinea pig: simultaneous measurement of flow rate and pressure

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Van Asselt, E., J. Groen, and R. van Mastrigt. A comparative study of voiding in rat and guinea pig: simultaneous measurement of flow rate and pressure. *Am. J. Physiol.* 269 (Regulatory Integrative Comp. Physiol. 38): R98–R103, 1995.—In this study, the voiding phase of the micturition cycle in the anesthetized rat and guinea pig is analyzed. In both animals, voiding is characterized by an increase in intravesical pressure and then a decrease, which is accompanied by flow through the urethra and emission of urine. An ultrasonic flow probe was used in both species to measure the flow rate in relation to the intravesical pressure. In the (male) rat, so-called high-frequency oscillations are superimposed on the decreasing bladder pressure. These oscillations do not occur in the guinea pig. It is concluded that the high-frequency oscillations are caused by intermittent flow and not by variations in the bladder contraction. The intermittent flow most likely is caused by the relaxation and contraction of the external urethral sphincter and may have a function in territory marking. In our view, it is not likely that the oscillations enhance bladder emptying, as has been suggested in the literature.

micturition; bladder pressure; flowmeter; high-frequency oscillations

THE MICTURITION CYCLE of rat and guinea pig consists of a collecting or filling phase and a voiding phase. The filling phase is the same in both species and usually shows a slow increase in bladder pressure, which is followed by a sudden rise at the start of voiding. The voiding phases of the rat and the guinea pig are somewhat different. In the rat, three (sub)phases have been distinguished (15, 17): 1) a sudden rise in bladder pressure, during which there is no flow, 2) a decrease in pressure, on which usually a series of so-called high-frequency oscillations are superimposed (these are accompanied by flow through the urethra and emission of drops in a spurtlike fashion), and 3) another rise of pressure to approximately the same height as before and then a drop in pressure back to baseline values (Fig. 1). From the literature, data are available on rat bladder capacity, voided and residual volumes, and intravesical pressures (1, 13, 15, 17, 18, 21, 22, 31), but there is no detailed insight into the cause and function of the interrupted flow pattern. Less research has been done on the micturition cycle of the guinea pig. During guinea pig voiding, two (sub)phases have been distinguished (16, 26): 1) an initial rise in intravesical pressure followed by 2) a sustained pressure wave, during which fluid emission occurs in a streamlike fashion, and a decrease in pressure back to baseline values. In our recordings, another rise of pressure after the sustained pressure wave, before the decline to baseline values, could be distinguished, as in the rat (Fig. 2).

Although voiding has not been described in detail, it is known that the flow patterns of rat and guinea pig are very different. Most striking is the appearance of high-frequency oscillations in the intravesical pressure during voiding in the rat. Occasionally, rapid oscillations have been seen in the guinea pig as well, but to a much smaller extent (16).

Theories have been presented on the origin and the function of the high-frequency oscillations, suggesting that contraction of striated musculature causes the changes in bladder pressure and that this phenomenon somehow facilitates the emptying of the bladder. Which specific muscles (urethral, periurethral, and/or pelvic floor) are involved is still a question under debate. In this study, simultaneous measurements of flow rate and bladder pressure were performed to compare the voiding pattern of rat and guinea pig and to elucidate the origin and function of the high-frequency oscillations in the rat.

MATERIAL AND METHODS

Male Wistar rats (446 ± 32 g) and male Dunkin-Hartley guinea pigs (940 ± 29 g) were anesthetized with urethan (1.2 g/kg body wt ip). The animals were placed on a heated pad. The urinary bladder and the distal part of the urethra were exposed through an abdominal incision. A 24-gauge needle was inserted into the bladder dome and, via tubing and a T connector, was attached to an infusion pump (Harvard) and a pressure transducer (Statham Gould). The bladder was filled with room-temperature saline at an infusion rate of 0.1 ml/min (rat) or 0.5 ml/min (guinea pig). The distal (most superficial) part of the urethra was dissected from the underlying tissue. A 3-mm-diameter ultrasonic flow probe was placed around the distal urethra and connected to a flowmeter (Transonic Systems). Flow and pressure signals were recorded by computer at a sampling rate of 100 Hz (rat) or 10 Hz (guinea pig) with use of dedicated PC software. The bladder was filled until the initial fast pressure increase occurred. The filling time was used to calculate the filled volume (capacity). The voided volume was collected in a glass funnel and measured. After voiding, the residual volume was removed from the bladder with a syringe attached to the inserted needle. The procedure was repeated several times, including a rest period between fillings of 30 min. At the end of the experiments, the animals were killed by an intracardial injection with KCl.

Sixteen voiding contractions from three rats and fifteen voiding contractions from five guinea pigs were analyzed. The analysis was confined to the second phase of the voiding contraction, which is characterized by the sustained pressure wave, the high-frequency oscillations (rat), and urethral flow. Numerical results are expressed as means \pm SD.

Statistical significance was evaluated with Student's *t*-test and the Pearson correlation test (SPSS).

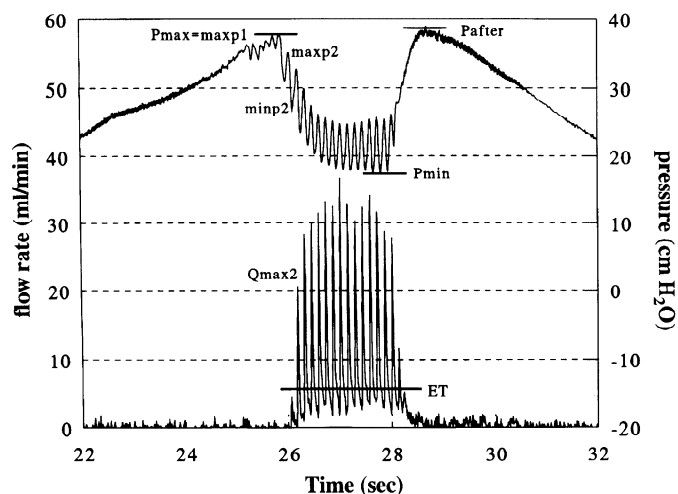


Fig. 1. Urinary bladder voiding in a rat. During voiding phase, a rise in intravesical pressure (*subphase 1*) is followed by a decrease in pressure and a series of high-frequency oscillations accompanied by flow (*subphase 2*), which in turn is followed by another rise in pressure (*subphase 3*). Flow rate and intravesical pressure data are plotted. Pressure curve can be described by maximum pressure just before voiding (P_{\max}), minimum pressure during voiding (P_{\min}), and rebound pressure after voiding (P_{after}). ET, expulsion time; $\max_{p2} - \min_{p2}$, pressure decrease during 2nd oscillation; $Q_{\max2}$, maximum of 2nd flow rate peak.

RESULTS

Flow. The filled volume (capacity) in the rat ranged from 0.3 to 1.3 ml (0.7 ± 0.3 ml). About 42% of this volume was voided, which left a mean residual volume of 0.4 ± 0.3 ml (58%). The expulsion time, defined by the time interval between the first and the last flow peak (Fig. 1), ranged from 0.5 to 3.0 s (1.7 ± 0.8 s; Table 1). There was a significant correlation between expulsion time and voided volume ($R = 0.79$, $P < 0.001$) and between expulsion time and residual volume ($R = -0.73$, $P < 0.001$).

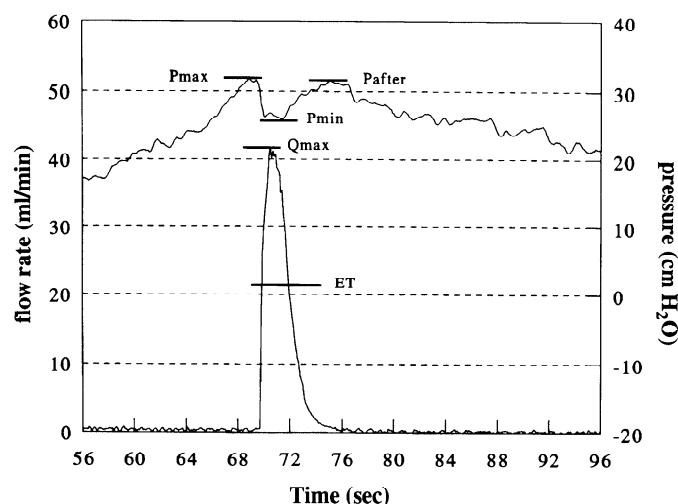


Fig. 2. Urinary bladder voiding in a guinea pig. During voiding phase, a rise in intravesical pressure (*subphase 1*) is followed by a small decrease in pressure accompanied by flow (*subphase 2*), which is followed by another rise in pressure. Flow rate and intravesical pressure data are plotted. Pressure curve can be described as in legend to Fig. 1. Q_{\max} , maximum flow rate. Note absence of high-frequency oscillations.

The time course of the flow rate in the rat showed a very characteristic pattern, which consisted of several peaks (Fig. 1). Because the frequency of the flow rate peaks was very constant (7.8 ± 0.5 Hz), the number of flow rate peaks depended on the expulsion time; the longer the flow lasted, the more flow rate peaks occurred. Although there was no strict pattern, the peaks tended to be low at the onset of flow, higher toward the middle of the second phase, and low at the end (Fig. 1). When the voided volume was calculated by integrating the flow rate (adding all recorded flow rate samples during the expulsion time and dividing the sum by the sampling frequency), it was lower than the voided volume collected in the glass funnel. To correct for the discrepancy, all flow rate values were multiplied by an individual correction factor (collected voided volume/calculated voided volume).

The mean flow rate of the rat voidings was 9.2 ± 1.5 ml/min (range 7.3–12.3 ml/min). The maximum flow rate was 46.3 ± 11.7 ml/min (range 28.7–68.4 ml/min; Table 1).

The capacity of the guinea pig bladder was significantly larger than that of the rat bladder, with a range of 1.7–6.2 ml (4.0 ± 1.3 ml; Table 1). As in the rat, ~40% of this volume was voided, which left a mean residual volume of 2.3 ± 1.0 ml (60%). The expulsion time, also significantly larger than in the rat, ranged from 2.6 to 11.5 s (6.6 ± 2.3 s; Table 1). There was a significant correlation between capacity and voided volume ($R = 0.65$, $P < 0.01$) and between residual and voided volume ($R = -0.80$, $P < 0.001$).

The flow rate pattern of the guinea pig did not show obvious discontinuities (Fig. 2). The voided volume was significantly larger than in the rat (1.7 ± 1.1 vs. 0.3 ± 0.1 ml, $P = 0.002$; Table 1). The mean flow rate was somewhat higher than in the rat: 16.1 ± 9.5 ml/min (range 4.0–30.5 ml/min, $P = 0.044$; Table 1). The maximum flow rate was significantly lower: 26.6 ± 14.3 ml/min (range 7.1–46.3 ml/min, $P = 0.004$; Table 1).

Pressure. The pressure recordings in all rat voidings appeared similar, despite the differences in voided volumes and expulsion times. The curves could be described by the maximum pressure just before voiding (P_{\max} , 41 ± 5 cmH₂O), the minimum pressure during voiding (P_{\min} , 19 ± 3 cmH₂O), and the maximum pressure after voiding (P_{after} , 38 ± 5 cmH₂O; Fig. 1, Table 2). ($P_{\max} - P_{\min}$) was 22 ± 4 cmH₂O, and the increase thereafter, ($P_{\text{after}} - P_{\min}$) was 19 ± 3 cmH₂O and ($P_{\max} - P_{\text{after}}$) was 3 ± 5 cmH₂O. The mean of the pressure decreases during all oscillations was calculated from the recordings and amounted to 8 ± 4 cmH₂O. The mean decrease in pressure compared with P_{\max} of all oscillations ($P_{\max} - \min_{p2}$; Fig. 1) was 20 ± 6 cmH₂O.

P_{\max} was significantly lower in the guinea pig than in the rat and reached a value of 27 ± 4 cmH₂O (range 23–37 cmH₂O). P_{\min} during the plateau phase was the same as in the rat: 21 ± 3 cmH₂O. The mean fall in pressure was thus only 6 ± 2 cmH₂O compared with 22 ± 4 cmH₂O in the rat. P_{after} was also significantly lower than in the rat and, as in the rat, somewhat smaller than P_{\max} : 25 ± 5 cmH₂O (range 15–35 cmH₂O;

Table 1. Cystometric parameters

Animal	Capacity, ml	Voided Volume, ml	Expulsion Time, s	Residual Volume, %	Mean Flow Rate, ml/min	Maximum Flow Rate, ml/min
Rat	0.7 ± 0.3 (16,3)	0.3 ± 0.1 (10,2)	1.7 ± 0.8 (16,3)	58 ± 23 (16,3)	9.2 ± 1.5 (10,2)	46.3 ± 11.7 (10,2)
Guinea pig	4.0 ± 1.3 (15,5)	1.7 ± 1.1 (10,4)	6.6 ± 2.3 (15,5)	60 ± 20 (15,5)	16.1 ± 9.5 (11,4)	26.6 ± 14.3 (11,4)
P*	0.001	0.002	< 0.001	0.773	0.044	0.004

Values are means ± SD; nos. in parentheses are no. of contractions and no. of animals. *Values for rat and guinea pig were compared with Student's *t*-test.

Table 2). The mean increase ($P_{\text{after}} - P_{\text{min}}$) amounted to only 4 ± 4 cmH₂O, whereas ($P_{\text{max}} - P_{\text{after}}$) was 2 ± 4 cmH₂O. High-frequency oscillations did not occur in the guinea pig.

Pressure-flow relation. Analogous to the description of the second phase of the voiding contraction by P_{max} and P_{min} , each oscillation was also described by its maximum pressure (max_p) and its minimum pressure (min_p ; Fig. 1). In the rat recordings, the maxima of the flow rate peaks coincided with oscillation pressure maxima. Correlating max_p values of the separate oscillations with the maximum value of the coinciding flow rate peaks resulted in $R = 0.03$. This low value of R suggests that it is unlikely that the coincidence of both peaks represents a causal relationship. Correlating min_p values of separate oscillations with coinciding flow rate peaks resulted in $R = -0.28$ ($P < 0.01$). After these calculations, the amplitudes of the flow rate peaks of a particular contraction were plotted as a function of the pressure decreases during the oscillations (Fig. 3). Correlating the flow rate peaks with the immediately preceding pressure decreases in this voiding resulted in $R = 0.97$. Correlating the flow rate peaks with the immediately following pressure decreases resulted in $R = 0.45$. Correlating the flow rate peaks with the pressure decreases before the immediately preceding one resulted in $R = 0.55$ (Fig. 3). The high value of 0.97 found in the contraction shown in Fig. 3 was reason to correlate the pressure decreases with the heights of the immediately following flow rate peaks in all 111 oscillations from 10 voidings. This resulted in $R = 0.52$ ($P < 0.001$; Fig. 4). When ($P_{\text{max}} - \text{min}_p$) values were correlated with the immediately following flow rate peaks for all 111 oscillations, $R = 0.27$ ($P < 0.01$). Thus the pressure decrease

just before a flow rate peak ($\text{max}_p - \text{min}_p$) showed the highest correlation with the height of that peak.

The delay between the pressure minimum and the following flow rate maximum is related to the position of the flow probe with regard to the pressure transducer. The recorded delay of 0.08 s, together with the length of the urethra (± 5.5 cm) and the position of the flow probe

Table 2. Pressure parameters during voiding contractions

Animal	P_{max} , cmH ₂ O	P_{min} , cmH ₂ O	P_{after} , cmH ₂ O
Rat	41 ± 5 (16,3)	19 ± 3 (16,3)	38 ± 5 (16,3)
Guinea pig	27 ± 4 (15,5)	21 ± 3 (15,5)	25 ± 5 (15,5)
P*	< 0.001	0.073	< 0.001

Values are means ± SD; nos. in parentheses represent no. of contractions and no. of animals. P_{max} , maximum pressure just before voiding; P_{min} , minimum pressure during voiding; P_{after} , maximum (rebound) pressure after voiding (see Figs. 1 and 2). *Values for rat and guinea pig were compared with Student's *t*-test.

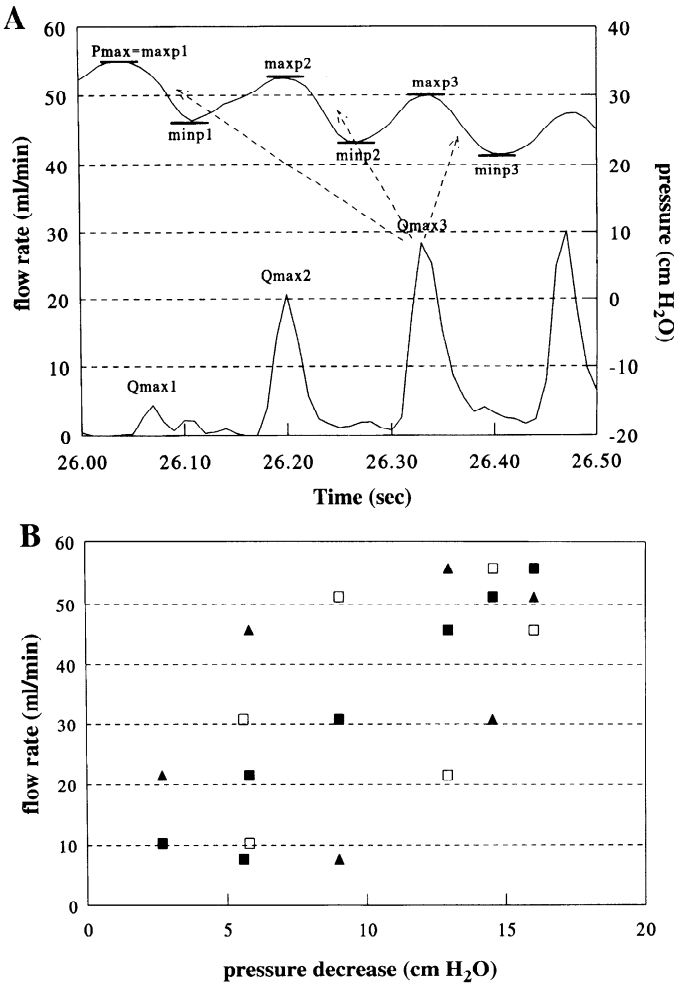


Fig. 3. A: detail of subphase 2 of 1 particular rat contraction; 4 of 7 oscillations are shown. Amplitudes of flow rate peaks were correlated with following and preceding pressure decreases. B: flow rate peaks ($Q_{\text{max}1} - Q_{\text{max}7}$) during subphase 2 of a rat contraction plotted as a function of 1) immediately preceding pressure decreases [■; Pearson correlation coefficient (R) = 0.97], 2) immediately following pressure decreases (▲; $R = 0.45$), and 3) pressure decreases before immediately preceding pressure decreases (□; $R = 0.55$).

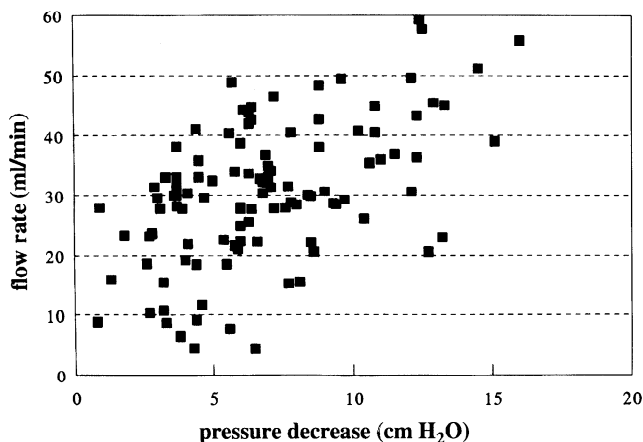


Fig. 4. Pressure decreases during all measured oscillations in rats ($\max_{pi} - \min_{pi}$, see Fig. 1) plotted as a function of maximum flow rates of immediately following flow rate peaks; 111 oscillations from 10 contractions are shown (2 rats). $R = 0.52$.

(1 cm from the meatus), allows an estimation of a mean fluid velocity of 0.6 m/s in the rat urethra.

DISCUSSION

As stated in the introduction, the micturition cycles of rat and guinea pig have been fairly well described in terms of capacity, intravesical pressure changes, and oscillation frequencies. The course of the pressure changes during the voiding contractions measured in our study is comparable to that shown in the literature (15–18, 26). Comparison of our data in rats and guinea pigs showed that the bladder capacity of the guinea pig was six times that of the rat (4.0 vs. 0.7 ml; Table 1); this difference is larger than that expected on the basis of body weight; the guinea pigs were only twice as heavy as the rats.

In our data, there was a discrepancy between collected and calculated voided volumes. The apposition of urethra and flow probe determines the accuracy of the measurement and depends on the placement of the probe and the diameter of the urethra. These may differ among measurements. Flowmeter readings thus needed to be calibrated by comparing collected and calculated voided volumes.

Although the maximum flow rate was lower in the guinea pig than in the rat, the mean flow rate was somewhat higher in the guinea pig than in the rat. As a result of the larger capacity, the expulsion time of the guinea pig was four times as long as that of the rat (Table 1).

All animals had residual volumes. Other investigators found residual volumes as well. While using urethan, Mostwin et al. (23) found residual volumes up to 12% of capacity in male guinea pigs. In awake female guinea pigs, Peterson et al. (26) reported residual volumes of <0.1 ml. In the rat, high residual volumes have been found in male (46 and 64%) and female (47%) urethan-anesthetized animals (13, 18). In awake male rats, Carpenter (1) showed residual volumes of <10% of capacity with a mean of 0.05 ± 0.01 ml. Yaksh et al. (31) stated that residual volumes in awake male and female

animals are too small to measure (2–4% of voided volume). Morikawa et al. (21, 22) found no residual volumes in awake restrained rats and residual volumes of 14–20% in urethan- α -chloralose-anesthetized animals. The general impression is therefore that awake animals do not have large residual volumes; high residual volumes apparently are caused by anesthetics.

The pressures just before and immediately after voiding (P_{\max} and P_{after}) were higher in the rat than in the guinea pig, but the pressure during voiding (P_{\min}) was the same (Table 2). In both species, P_{after} was equal to or lower and only occasionally higher than P_{\max} . The drop in pressure at the onset of voiding and the rise in pressure again at the end of voiding can be explained by the force-velocity relation as shown by van Mastrigt and Griffiths (29). The shortening of the bladder wall muscle causes flow and is related to a decrease in active muscle tension. When shortening and flow stop, the tension or pressure rises again to the isometric value. Although this second rise of pressure is explained by the force-velocity relation, it is possible that the presence of (residual) fluid in the bladder also contributes to further emptying by stimulating afferent nerve endings. Recording afferent nerve activity during the rebound phase will clarify whether the increase in pressure is functional and meant to further empty the bladder. Some authors described the expulsion of one to three drops during the rebound phase (15, 17); whether this also occurs in unanesthetized animals is not known.

The major difference between rat and guinea pig voiding resides in the occurrence of high-frequency oscillations in the rat. In the rat recordings, flow rate peaks coincided with pressure peaks. Therefore it might be hypothesized that the flow rate peaks are caused by variations in the contraction of the bladder. However, because smooth muscle is not able to contract and relax at such a pace (8 Hz) (20), this possibility is unlikely. In the literature, it is generally accepted that the high-frequency oscillations are caused by contraction and relaxation of striated musculature (15–18). Evidence stems from various experiments: when the bladder is disconnected from the urethra and contraction is induced by filling, high-frequency oscillations occur at the urethral site but not in the bladder (3). The application of neuromuscular blocking agents known to paralyze striated musculature (e.g., pancuronium bromide) eliminates high-frequency oscillations (18). In the present study, the magnitude of the flow rate peaks correlated significantly with the bladder pressure changes just before the flow rate peaks and not with the pressure maxima. This supports the idea that urethral (striated) muscle and not bladder muscle is responsible for the high-frequency oscillations. Most likely, the intermittent flow caused the bladder pressure oscillations and not vice versa. Striated muscle cells around the proximal urethra have been described in the rat (30) and the guinea pig (4, 5). The absence of high-frequency oscillations in the guinea pig thus cannot be explained by a lack of striated cells associated with the urethra.

There are several indications that the muscle responsible for the high-frequency oscillations is the external

urethral sphincter. The occurrence of micturition, marked by the release of several drops of urine, takes place during a burst discharge in the external urethral sphincter [electromyogram (EMG) 6–8 Hz] and a concomitant oscillation in the bladder pressure recording with exactly the same frequency (14). Periods of complete inactivity during voiding probably correspond with a relaxation of the external urethral sphincter, which allows urine to pass. After neuromuscular blockade (pancuronium bromide, *d*-tubocurarine), external urethral sphincter activity disappears and no urine is released (3, 14, 18) or the flow rate is decreased by 38% (15). Electrical field stimulation of the external urethral sphincter produced slow tonic contractions on which a series of phasic twitchlike contractions was superimposed. Phentolamine (α -blocker) inhibited the slow component; *d*-tubocurarine and succinylcholine reduced the twitch (25). Transection of the pudendal nerve, which is known to innervate the external urethral sphincter (2, 8, 19, 20, 27), resulted in the absence of rhythmic urethral activity (3).

These findings stem from rat experiments, but similar results have been found in the dog (24). In the cat, intravesical pressure high-frequency oscillations seem to be caused by contraction of the bulbocavernosus muscle associated with contractions of all pelvic floor muscles (12).

Although male rats and male guinea pigs have a bulbocavernosus muscle, it seems unlikely that this muscle is responsible for the high-frequency oscillations, because it is absent (11) or very thin (19) in female rats, which, however, sometimes show high-frequency oscillations (13, 17).

McKenna and Nadelhaft (19) and Hart and Melese-d'Hospital (10) propose that the bulbo- and ischiocavernosus muscles in the rat (both close to the urethra and also innervated by the pudendal nerve) are involved in erection and ejaculation and that both muscles may be related to the expulsion of fluids in the marking of territory.

In conclusion, the simultaneous measurements of flow rate and bladder pressure presented here support the hypothesis that the high-frequency oscillations during voiding in the rat are caused by intermittent contraction and relaxation of urethral musculature. In the literature, the terms "urethral muscle" and "pelvic floor muscle" are often used without further specification. This lack of detail leads to confusion; it is not always clear exactly which muscles were investigated (3, 5–7, 9, 20, 30, 31). However, on the basis of neuromuscular blocking/denervation studies, EMG recordings, and our own results, we believe that it is most likely that the external urethral sphincter is the anatomic structure responsible for oscillating behavior.

As to the function of the high-frequency oscillations, it has been speculated that voiding is promoted by 1) an increase in bladder afferent firing caused by the closure of the urethral outlet by contraction of the external urethral sphincter (13, 14) and/or 2) the oscillating external urethral sphincter, which produces peristalsis, pumping urine out of the urethra (13). The guinea pigs

in this study, however, voided just as well (same voided volume percentage-wise) or just as poorly (same residual volume percentage-wise) without the oscillations. Therefore perhaps it is more likely that the function of the oscillations is to cause a high fluid emission velocity, which is necessary for territory marking. In support of this hypothesis is the fact that other animals that mark their territory, such as dogs and cats, show similar oscillations. A complicating factor (not in line) is that although rats void in spurts, in contradiction to dogs, they empty their bladders at once, not in several portions (28). Whether the high fluid velocity (0.6 m/s) of the emitted urine in the rat is caused only by the intermittent relaxation of the sphincter or is supported by an additional propulsing mechanism of fast-traveling waves through the urethral wall remains unclear. The exact and relative functional contribution to voiding of smooth and striated urethral muscle cells in the guinea pig urethra is to our knowledge not yet known. EMG recording and denervation/blocking experiments are needed in the guinea pig as well to sort out these questions.

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