Urol Res (1993) 21:239–244

Urological Research

Original articles

A rat model for investigation of spinal mechanisms in detrusor instability associated with infravesical outflow obstruction

Y. Igawa[1], K.-E. Andersson[2], C. Post[2], B. Uvelius[1], A. Mattiasson[1]

Departments of [1]Urology and [2]Clinical Pharmacology, Lund University Hospital, S-22185 Lund, Sweden

Received: 15 September 1992 / Accepted: 16 February 1993

Summary. A rat model of infravesical outflow obstruction was modified to allow cystometric investigation in conscious, free-moving animals after intrathecal drug administration. The catheter position and extent of drug distribution were controlled by injection of dye and dissection of the spinal canal. Continuous cystometries were performed in awake normal rats as well as rats with bladder hypertrophy and hyperactivity following infravesical outflow obstruction. In some animals of each group, cystometry was performed with simultaneous recording of intra-abdominal pressure. The possible effects of the presence of the intrathecal catheter were studied, as well as the effects of saline, local anesthetics, morphine and naloxone administered through the catheter. Neither the presence of the intrathecal catheter nor injection of saline affected the cystometric pattern. Bupivacaine (50 μg) produced paralysis of both lower extremities and a complete, though reversible, suppression of micturition in normal rats. In rats with hypertrophy, intrathecal bupivacaine in doses of 50 μg and 100 μg produced decreases in micturition pressure, increases in bladder capacity and dribbling incontinence. However, the amplitude of spontaneous contractile activity increased after the administration. The inhibitory effects of morphine (0.5–10 μg) on micturition in normal rats, which were rapidly reversed by naloxone, were in accordance with results obtained in previous studies in anesthetized animals. Rats with bladder hypertrophy showed a similar response to morphine and naloxone. However, the bladder hyperactivity was not inhibited by morphine. We conclude that the present model seems reliable for the study of spinal mechanisms in the development of detrusor instability associated with infravesical outflow obstruction.

Key words: Detrusor instability – Infravesical outflow obstruction – Rat urinary bladder – Spinal mechanism(s)

Correspondence to: Y. Igawa; FAX: 46(46)-112598

Rate subjected to infravesical outflow obstruction are known to develop detrusor hyperactivity [10]. In such rats, neuronal hypertrophy in both the pelvic and dorsal root ganglia has been found [21, 23], and also changes in the sacral reflexes, with the appearance of a short-latency reflex [22]. Such factors may be of importance for the development of detrusor hyperactivity, even if causal relationships are difficult to demonstrate. In addition, changes within the bladder may be contributory factors, such as changes in innervation pattern and transmitter contents [1, 15], changes in receptor populations [15] and changes in the smooth muscle cells [6, 11].

We wanted to investigate the possible importance and the nature of central nervous events at the spinal level in the development of detrusor hyperactivity in the rat. The first step was to establish a model of bladder hyperactivity in which it was possible to administer drugs at appropriate spinal cord levels and to study their effects on micturition by means of continuous cystometry. We therefore modified our previously described model for cystometrical investigation of rats with infravesical outflow obstruction [10], and adopted the procedure of Yaksh and Rudy [24] for intrathecal (i.t.) administration of drugs.

In this investigation we tested how the modifications of the model and the i.t. catheter influenced the cystometrogram in normal rats and rats with infravesical outflow obstruction. In addition, we tested in both types of animal the effects of i.t. administration of some drugs with known effects on micturition in normal rats, i.e., bupivacaine [25], morphine and naloxone [3, 20].

Materials and methods

Animals

Female Sprague-Dawley rats (weighing 200–260 g) with or without previous infravesical outflow obstruction were used.

Experimental procedures

The methods used for establishing an infravesical outflow obstruction [14] and the technique of cystometry in awake rats [10] have been described in detail previously. The animals were subjected to cystometric evaluation 6 weeks after a partial ligature of the urethra. Partial obstruction of the urethra induces a significant bladder hypertrophy [14] and hyperactivity [10]. Within 2 days after removal of the ligature, when the animals of this study were investigated, the bladder still exhibits a significant degree of hypertrophy and hyperactivity [12, 13]. For simplicity, these previously obstructed rats are referred to as "rats with bladder hypertrophy".

Intrathecal catheter. A polyethylene catheter (Clay-Adams PE-10, USA) was used. The i.t. portion of the catheter was heated under warm water (approximately 50°C), and elongated to about twice its original length in order to make it slender and soft.

Insertion of the intrathecal catheter. The original procedure for insertion of an i.t. catheter described by Yaksh and Rudy [24] was followed. Rats were anesthetized with ketamine (75 mg/kg intramuscularly) and xylazine (15 mg/kg intramuscularly). The atlanto-occipital membrane was exposed through a dorsal incision, and a small hole made in the dura at this level. The saline-filled catheter was inserted into the subarachnoid space through the atlanto-occipital membrane and advanced caudally until the tip reached the level of the L6–S1 spinal cord segments. Preganglionic neurons of the sacral parasympathetic nucleus in the rat have been reported to be located almost exclusively at this level of the spinal cord segments [17]. The catheter was fixed by a suture in the superficial dorsal muscle layer. The free end of the catheter was sealed.

Position of the catheter. After dissections in several rats, the following i.t. lengths of catheter were chosen: 8.5 cm ($n = 14$), 9.0 cm ($n = 30$ and 9.5 cm ($n = 11$). Ten microliters of dye (1% methylene blue) were administered by i.t. injection. The rat was killed 15 min after the injection and the position of the catheter and extent of dye distribution were examined.

Bladder catheterization and continuous cystometry. Two days after the i.t. catheterization, a polyethylene catheter (Clay-Adams PE-50, USA) was inserted into the bladder through the dome. In some animals ($n = 6$) a separate catheter with a balloon tip was placed in the peritoneal cavity for recording of intra-abdominal pressure. In obstructed rats the urethral ligation was removed at the same time. Cystometry without any anesthesia was performed 1 and 3 days after bladder catheterization in animals with bladder hypertrophy and in normal animals, respectively. Saline was infused into the bladder at a constant rate of 10 ml/h and 20 ml/h in normal rats and in rats with bladder hypertrophy, respectively [12].

Intravesical pressure and micturition volume were recorded continuously on a Grass Polygraph (Quincy, Mass.). Three reproducible micturition cycles were recorded before drug administration. This corresponded to a 20-min period before drug administration. After each i.t. administration of drug the recording was continued for another 60 min. In a control group of animals ($n = 6$) only the bladder catheter was inserted, and the cystometric pattern was compared with that in animals subjected to i.t. catheterization.

The following urodynamic parameters were analysed [12]: basal pressure, threshold pressure, micturition pressure, micturition volume, bladder capacity, residual volume, and amplitude and frequency of spontaneous contractile activity. Analysis was performed for a 20-min period before drug administration. Drug effects on cystometrical parameters were assessed for 60 min, and the most effective two or three micturition cycles were subjected to analysis.

Drugs and administration protocols

Drugs were administered by i.t. injection in 10 µl saline followed by a flush of 15 µl saline for 10 s. An i.t. injection of 10 µl saline was given as control prior to drug administration. The injection sites in the spinal cord and the extent of dye distribution were confirmed by injection of dye in every animal at the end of the experiment. The following drugs were used: methylene blue, naloxone hydrochloride (Sigma, St. Louis, Mo.), bupivacaine hydrochloride (Astra, Södertälje, Sweden) and morphine sulphate (Gacell, Malmö, Sweden).

The dose of morphine giving complete suppression of the micturition reflex was defined as the lowest dose which produced dribbling incontinence. Increasing doses of the drug were administered at 60-min intervals.

Statistical analysis

The results are given as mean values ± SEM. Student's paired *t*-test was used for comparison between treatments within the normal or the hypertrophied group. Comparison between the groups was performed by factorial analysis of variance. A probability level of $< 5\%$ was accepted for significance.

Results

Length of intrathecal catheter and extent of dye distribution

The level of the L6–S1 spinal cord segments, where the preganglionic neurons of the sacral parasympathetic nucleus in the rat are located almost exclusively [17], corresponds to the vertebral level L2–L3 [7]. The catheter-tip was located at this level in 5 of 14 animals with a catheter 8.5 cm long, 27 of 30 with a catheter 9.0 cm long and 3 of 11 animals with a catheter 9.5 cm long. At 15 min after injection of methylene blue through the 9.0 cm catheter the dye was distributed from the vertebral level of T5–10 to L2–S4 (median vertebral level T9–L4, which corresponds to the T9–S4 level of the spinal cord) [7]. With the 8.5 cm catheter the dye was distributed more rostrally. For further study, therefore, 9.0 cm was chosen as the i.t. length of the catheter.

Cystometric evaluation after intrathecal catheterization

In order to eliminate animals with possible injury of the spinal cord caused by the catheterization itself, paralysed animals were killed immediately and in the remaining animals 10 µl saline was injected before the bladder catheter was inserted. Some animals were paralyzed immediately after this injection, even though their appearance and behavior were normal before the injection. These animals were not used for further experiments; dissection revealed injuries to the spinal cord with penetration of the catheter into the spinal cord or subarachnoid hemorrhage. Finally, after the cystometric studies, every animal was given i.t. methylene blue (1% 10 µl), killed and then dissected to confirm the position of the catheter and to demonstrate diffuse spread of dye and absence of injury to the spinal cord. In the first consecutive 50 animals the success rate was 32%. In the following 50 animals this rate increased to 70%.

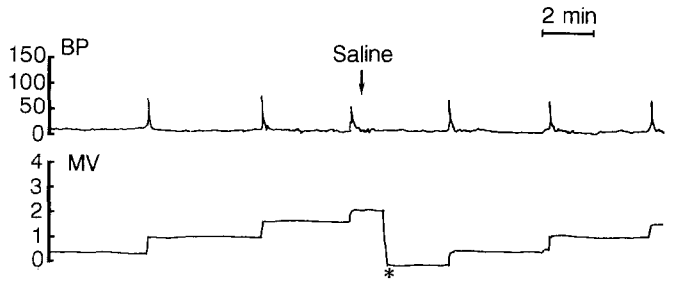

Fig. 1. Original recording of bladder pressure (*BP*, cmH_2O) and micturition volume (*MV*, ml) during cystometry before and after intrathecal administration of normal (= 0.9%) saline in a normal rat with an intrathecal catheter. *Asterisk* indicates adjustment to baseline position

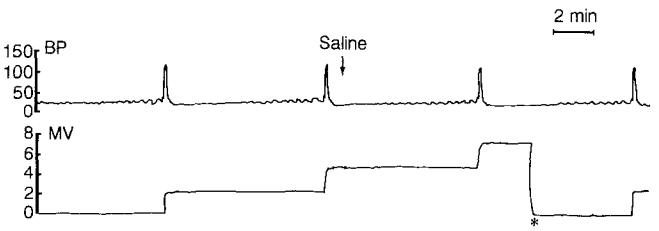

Fig. 2. Original recording of bladder pressure (*BP*, cmH_2O) and micturition volume (*MV*, ml) during cystometry in a rat with bladder hypertrophy. Compared with controls, an increase in the spontaneous activity is noted during filling. Intrathecal injection of normal (= 0.9%) saline did not affect the cystometric pattern. *Asterisk* indicates adjustment to baseline position

Table 1. Effects of intrathecal administration of morphine (0.1 μg) on cystometric parameters in normal rats and rats with bladder hypertrophy

	Normal ($n=6$)		Hypertrophied ($n=6$)	
	Control	Morphine	Control	Morphine
BP	4.8 ± 0.9	4.5 ± 0.8	7.6 ± 0.7[c]	8.2 ± 0.5
ThP	10.8 ± 2.5	19.9 ± 4.2[a]	13.2 ± 1.1	19.2 ± 1.8[a]
MP	62.0 ± 18.0	40.1 ± 6.3	83.0 ± 20.1	78.2 ± 18.4
MV	1.12 ± 0.07	1.47 ± 0.15[a]	2.52 ± 0.47[c]	3.50 ± 0.59[b,d]
RV	0.04 ± 0.03	0.04 ± 0.02	0.14 ± 0.05	0.17 ± 0.10
BC	1.16 ± 0.10	1.51 ± 0.15[a]	2.65 ± 0.51[c]	3.67 ± 0.70[b,c]

Results are expressed as mean ± SEM
Control vs. Morphine: [a] $P<0.05$; [b] $P<0.01$
Normal vs. hypertrophied: [c] $P<0.05$; [d] $P<0.01$
BP, basal pressure (cmH_2O); *ThP*, threshold pressure (cmH_2O), *MP*, micturition pressure (cmH_2O); *MV*, micturition volume (ml); *RV*, residual volume (ml); *BC*, bladder capacity (ml)

The influence of the procedure of i.t. catheterization and i.t. injection itself upon cystometric evaluation was also investigated. Repeated cystometries in the animals subjected to i.t. catheterization gave reproducible results both in normal animals and in animals with bladder hypertrophy. In normal animals the bladder pressure was low and almost devoid of spontaneous fluctuations during the filling phase (Fig. 1). On the other hand, cystometry in animals with bladder hypertrophy showed bladder hyperactivity during filling (Fig. 2). The micturition volume and bladder capacity were larger ($P<0.05$) in animals with hypertrophy ($n=6$) than in normal animals ($n=6$). Also, the basal pressure was higher ($P<0.05$) in animals with bladder hypertrophy than in normal animals (Table 1). There were no significant differences between any urodynamic parameters in control animals ($n=6$) and i.t. catheterized animals ($n=6$). Neither did i.t. saline injection affect the cystometric pattern in any of the groups (Figs. 1, 2).

Recording of intra-abdominal pressure during continuous cystometry was performed in both normal animals ($n=4$) and animals with bladder hypertrophy ($n=2$). Minor fluctuations ($<2\,cmH_2O$) in intra-abdominal pressure were recorded only when the animals were moving during filling. A rise in intra-abdominal pressure (2–6 cmH_2O) was noted concomitantly with each micturition contraction (see Fig. 7).

Effects of bupivacaine

Normal rats. Bupivacaine (50 μg i.t., $n=7$) produced paralysis of the hindlimbs, and dribbling incontinence due to urinary retention (Fig. 3). These effects came on within 10 s and persisted for 8–15 min (mean 10.7 min) and 16–31 min (mean 25.0 min) as regards the hindlimbs and micturition, respectively. The effects were reversible, and the cystometric parameters were restored to the starting level within 40 min.

Rats with bladder hypertrophy. Bupivacaine, given by i.t. injection in doses of 50 μg ($n=5$) and 100 μg ($n=6$), produced paralysis of the hindlimbs and an inhibition of micturition (Fig. 4). Micturition pressure decreased from a mean of 103 ± 32 to 49 ± 17 cmH_2O ($P=0.127$) and from 116 ± 25 to 59 ± 21 cmH_2O ($P<0.05$), and bladder capacity increased from 1.92 ± 0.51 to 3.64 ± 0.56 ml ($P<0.001$) and 3.02 ± 0.62 to 4.95 ± 0.68 ml ($P<0.001$)

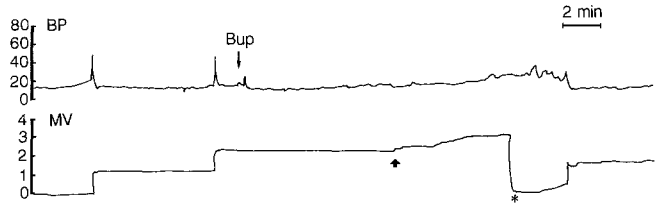

Fig. 3. Original recording of bladder pressure (*BP*, cmH_2O) and micturition volume (*MV*, ml) during cystometry before and after intrathecal administration of bupivacaine (*Bup*, 50 µg) in a normal rat. *Asterisk* and *arrow* indicate adjustment to baseline position and start of dribbling incontinence, respectively

after the injection of 50 and 100 µg, respectively. Dribbling incontinence was noted after injection of both 50 µg (4 of 5 animals) and 100 µg (6 of 6 animals). The duration of the dribbling incontinence ranged from 3 to 34 min (mean 12.6 min). The amplitude of the spontaneous contractile activity increased ($P < 0.001$) from a mean of 8.4 ± 0.9 to 16.3 ± 1.5 cmH_2O after the injection (50 or 100 µg, $n = 11$) (Figs. 4, 5).

Effects of morphine and naloxone

Normal rats. Morphine (0.1–10 µg i.t., $n = 13$) produced a dose-dependent inhibition of micturition contraction and a delay in the onset of micturition, eventually causing dribbling incontinence (Fig. 6). The dose of morphine needed to produce this complete suppression of the micturition reflex ranged from 0.5 µg to 10 µg (median 0.5 µg, $n = 7$). The time to the start of dribbling incontinence varied between 10 and 55 min with a mean of 28 min. Dribbling incontinence persisted for at least 30 min.

A dose of morphine (0.1 µg i.t., $n = 6$) lower than those producing retention increased threshold pressure, bladder capacity and micturition volume significantly ($P < 0.05$), and tended to reduce micturition pressure (ns) (Table 1). The time of onset of these effects ranged between 20 and 30 min after morphine administration, and the maximum effect was seen 30–50 min after administration.

Naloxone, administered by i.t. injection in doses of 10 ($n = 7$) and 100 µg ($n = 6$) by itself had no effects on the micturition pattern. However, naloxone (10 µg i.t., $n = 7$) rapidly reversed the inhibitory effect of morphine on each occasion it was tested (Fig. 6).

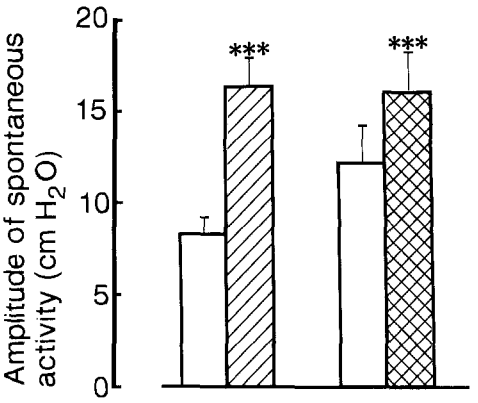

Fig. 5. Effects of intrathecal administration of bupivacaine (50 or 100 µg, $n = 11$) and morphine (0.1–10 µg, $n = 12$) on the amplitude of the spontaneous contractile activity in rats with bladder hypertrophy. *** $P < 0.001$; □ control; ▨ bupivacaine; ▩ morphine

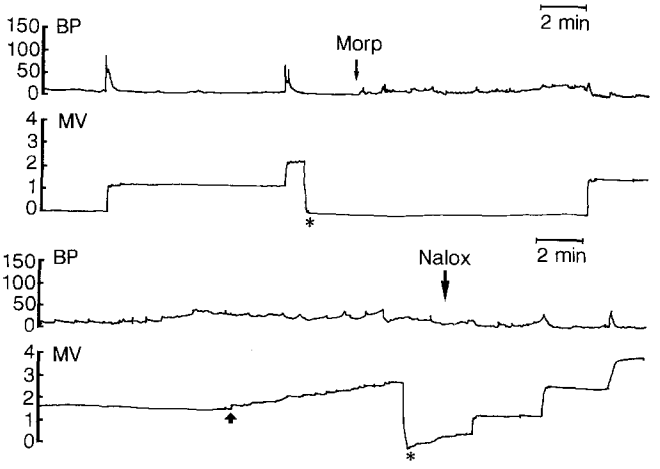

Fig. 6. Effects of morphine and naloxone in a normal rat. Morphine (*Morp*, 10 µg i.t.) produced urinary retention ending with dribbling incontinence. Naloxone (*Nalox*, 10 µg i.t.) reversed this inhibitory effect in the same animal. *Asterisk* and *arrow* indicate adjustment to baseline position and the start of dribbling incontinence, respectively. *BP*, Bladder pressure (cmH_2O); *MV*, micturation volume (ml)

Rats with bladder hypertrophy. Morphine (0.1–10µg i.t., $n = 12$) produced a dose-dependent inhibition of micturition, eventually causing retention (Fig. 7). Dribbling incontinence due to urinary retention persisted for at least 30 min. The amplitude of the spontaneous contractile

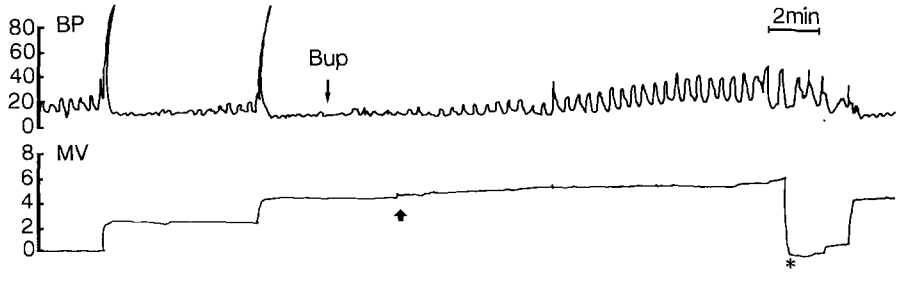

Fig. 4. Original recording of bladder pressure (*BP*, cmH_2O) and micturition volume (*MV*, ml) during cystometry before and after intrathecal administration of bupivacaine (*Bup*, 100 µg) in a rat with bladder hypertrophy. *Asterisk* and *arrow* indicate adjustment to baseline position and start of dribbling incontinence, respectively

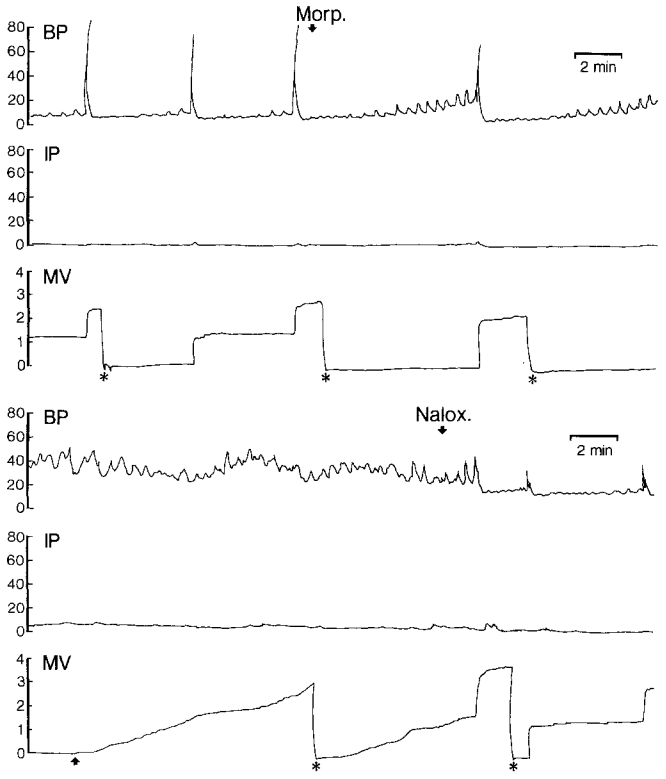

Fig. 7. Effects of morphine (*Morp*, 10 μg i.t.) and naloxone (*Nalox*, 100 μg i.t.) in a rat with bladder hypertrophy. *Asterisk* and *arrow* indicate adjustment to baseline position and start of dribbling incontinence, respectively. *BP*, Bladder pressure (cmH_2O); *IP*, intra-abdominal pressure (cmH_2O); *MV*, micturition volume (ml)

activity increased ($P < 0.001$) from a mean of 12.9 ± 1.7 to 16.0 ± 2.1 cmH_2O after morphine administration (Fig. 5).

A dose of morphine (0.1 μg i.t., $n = 6$) lower than those producing retention increased threshold pressure ($P < 0.05$), bladder capacity ($P < 0.01$) and micturition volume ($P < 0.01$) (Table 1). The effects of this dose of morphine on bladder capacity and micturition volume were more pronounced ($P < 0.05$ and $P < 0.01$, respectively) in animals with bladder hypertrophy than in normal animals (Table 1).

Naloxone (10–100 μg i.t., $n = 6$) by itself had no effects on the micturition pattern, but reversed the inhibitory effect of morphine (Fig. 7).

Discussion

To investigate the central mechanisms involved in detrusor instability in our rat model of infravesical outflow obstruction, we wanted to be able to influence the spinal mechanisms involved in micturition. Therefore, an i.t. catheter for injection of drugs was desirable. Theoretically, the presence of a spinal catheter may influence the micturition pattern (as reflected by cystometry) differently in normal rats and rats with bladder hyperactivity. However, isertion of a spinal catheter 9.0 cm long according to the procedure described by Yaksh and Rudy [24], which produced a distribution of methylene blue with a maximum around the L6–S1 level of the spinal cord, caused no changes in the micturition pattern, either in normal animals or in rats with outflow obstruction. Thus, continuous cystometry in the intrathecally catheterized rat gave reproducible results in both groups of animals. This confirms the findings of Yaksh et al. [25], who described a cystometric model with an intrathecally implanted catheter in normal rats, and shows that such a model can be used also for studying rats with infravesical outflow obstruction and hyperactivity. We also showed by means of simultaneous measurements of intravesical and intra-abdominal pressure that the bladder pressure recordings reflected changes in detrusor pressure in both normal rats and animals with infravesical outflow obstruction. Particularly in the latter, it was important to show that the spontaneous contractions preceding the micturition contraction [10] were true changes in detrusor pressure.

Intrathecal administration of saline had no effect on the cystometrogram, either in normals rats or in animals with infravesical outflow obstruction. In contrast, i.t. injection of bupivacaine produced dribbling voiding (overflow incontinence) and complete paralysis in both lower extremities for several minutes; the changes were fully reversible. These findings are in good agreement with those of Yaksh et al. [25].

Previous studies in the rat [3, 4, 9, 20] and several other species, including man [5, 8, 18], have shown that morphine has an inhibitory action at spinal and supraspinal sites in the micturition reflex pathways, and that this inhibitory action can be antagonized by the opiate antagonist, naloxone. In the present study, this was confirmed. The dose of i.t. morphine needed to produce complete suppression of the micturition reflex in normal rats ranged from 0.5 to 10 μg. A dose not producing retention (0.1 μg) increased the threshold pressure, bladder capacity and micturition volume in both groups. All effects of morphine were rapidly reversed by intrathecal naloxone.

As in previous investigations [10, 12, 13], the cystometrogram in rats with infravesical obstruction showed spontaneous bladder contractions (hyperactivity) preceding the micturition contractions. In these animals bupivacaine (50–100 μ i.t.) caused an inhibition of the micturition contractions as in normal animals, though the bladder hyperactivity was not inhibited but rather increased by bupivacaine. In addition, morphine, in the same dose range as in normal rats (0.1–10 μg i.t.), caused an inhibition of the micturition contractions, eventually causing retention. However, the bladder hyperactivity in these animals was not inhibited by morphine. Naloxone (10–100 μg i.t.) by itself had no effects on the cystometric pattern in any of the groups. These findings were surprising, because studies with naloxone in cats [2, 19] and man [16] have suggested that opioid mechanisms may be one of the factors involved in bladder hyperactivity. Whether this means that bladder hyperactivity in rats with infravesical outflow obstruction is unrelated to central mechanisms (opioid or other) will be investigated further.

Acknowledgements. The authors thank Mrs. Magdalena Dawiskiba for skilful technical assistance. This study was supported by funds from the Sasakawa Health Science Foundation and by grants from the Swedish Medical Research Council (grants no. 6837 and 9479) and the Medical Faculty, University of Lund.

References

1. Andersson PO, Andersson K-E, Fahrenkrug J, Mattiasson A, Sjögren C, Uvelius B (1988) Contents and effects of substance *P* and vasoactive intestinal polypeptide in the bladder of rats with and without infravesical outflow obstruction. J Urol 140:168
2. Booth AM, Hisamitsu T, Kawatani M, deGroat WC (1985) Regulation of urinary bladder capacity by endogeneous opioid peptides. J Urol 133:339
3. Dray A, Metsch R (1984) Inhibition of urinary bladder contraction by a spinal action of morphine and other opioids. J Pharmacol Exp Ther 231:254
4. Dray A, Nunan L (1987) Supraspinal and spinal mechanisms in morphine-induced inhibition of reflex urinary bladder contraction in the rat. Neuroscience 22:281
5. Drenger B, Magora S, Evron S, Caine M (1986) The action of intrathecal morphine and methadone on the lower urinary tract in the dog. J Urol 135:852
6. Fovaeus M, Andersson K-E, Andersson PO, Malmgren A, Sjögren C (1988) Tetrodotoxin-resistant contractions induced by electrical stimulation of bladder muscle from man, rabbit and rat. Acta Physiol Scand 132:233
7. Greene EC (1955) Anatomy of the rat. Hafner, New York, pp 130–131, 149–152, 162
8. Hisamitsu T, deGroat WC (1984) The inhibitory effect of opioid peptides and morphine applied intrathecally and intracerebroventricularly on the micturition reflex in the cat. Brain Res 298:51
9. Kontani H, Nakagawa M, Sakai T (1989) Effects of central nervous system-acting drugs on urinary bladder contraction in unanesthetized rats. Jpn J Pharmacol 50:327
10. Malmgren A, Sjögren C, Uvelius B, Mattiasson A, Andersson K-E, Andersson PO (1987) Cystometrical evaluation of bladder instability in rats with infravesical outflow obstruction. J Urol 137:1291
11. Malmgren A, Andersson K-E, Andersson PO, Fovaeus M, Sjögren C (1988) Effects of nifedipine and Bay K8644 on normal and hypertrophied rat detrusor. Neurorourol Urodyn 7:27
12. Malmgren A, Andersson K-E, Sjögren C, Andersson PO (1989) Effects of pinacidil and cromakalim (BRL 34915) on bladder function in rats with detrusor instability. J Urol 142:1134
13. Malmgren A, Uvelius B, Andersson K-E, Andersson PO (1990) On the reversibility of functional bladder changes induced by infravesical outflow obstruction in the rat. J Urol 143:1026
14. Mattiasson A, Uvelius B (1982) Changes in contractile properties in hypertrophic rat urinary bladder. J Urol 128:1340
15. Mattiasson A, Ekström J, Larsson B, Uvelius B (1987) Changes in the nervous control of the urinary bladder induced by outflow obstruction. Neurourol Urodyn 6:37
16. Murray KHA, Feneley RCL (1982) Endorphine: a role in lower urinary tract function? The effect of opioid blockade on the detrusor and urethral sphincter mechanisms. Br J Urol 54:638
17. Nadelhaft I, Booth AM (1984) The location and morphology of preganglionic neurons and the distribution of visceral afferents from the rats pelvic nerve: a horseradish peroxodase study. J Comp Neurol 226:238
18. Rawal N, Möllefors K, Axelsson K, Lingårdh G, Widman B (1983) An experimental study of urodynamic effects of epidural morphine and of naloxone reversal. Anesth Analg 62:641
19. Roppolo JR, Booth AM, deGroat WC (1983) The effects of naloxone on the neural control of the urinary bladder of the cat. Brain Res 264:355
20. Sillén U, Rubenson A (1986) Central and peripheral motor effects of morphine on the rat urinary bladder. Acta Physiol Scand 126:181
21. Steers WD (1990) Neuroplasticity secondary to infravesical obstruction. Neurourol Urodyn 9:559
22. Steers WD, deGroat WC (1988) Effect of bladder outlet obstruction on micturition reflex pathways in the rat. J Urol 140:864
23. Steers WD, Ciambotti S, Erdman S, deGroat WC (1990) Morphological plasticity in efferent pathways to the urinary bladder of the rat following urethral obstruction. J Neurosci 10:1943
24. Yaksh TL, Rudy TA (1976) Chronic catheterization of the spinal subarachnoid space. Physiol Behav 17:1031
25. Yaksh TL, Durant PAC, Brent CR (1986) Micturition in rats: a chronic model for study of bladder function and effect of anesthetics. Am J Physiol 251:R1177