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Originals

Comparison of Long-Term and Short-Term Stretch on Rat Urinary Bladder in Vitro

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Summary. Distension of the human urinary bladder often causes prolonged impairment of its function. To investigate the effects of the duration of stretch on bladder smooth muscle the active length-tension relation, electrically evoked, was described in rat detrusor strips during a short-term and a long-term stretch. The amplitude of active tension increased at first and then decreased abruptly at greater stretch lengths, the maximum being at muscle lengths 230–250% (100% = resting length) in both types of stretches. When the strips had been at maximum length (300%) for three hours the amplitude was significantly decreased during release as compared to the amplitude found during stretch to the maximum length at comparable lengths. If the strips were released immediately from the maximum length the amplitude responded in an opposite manner. Therefore we conclude that the duration of stretching of bladder smooth muscle significantly affects its mechanical activity.

Key words: Electrical stimulation – Stretching – Time factor – Bladder strip – Rat

Introduction

Prolonged bladder distension may affect a patient as an acute urinary retention or it may be used as a method in the treatment of a bladder disease [7, 9]. After large volume retention of urine patients may have prolonged difficulties in voiding [20]. The duration of overstretching may also be of importance [16]. It has previously been suggested that the reason for this impairment in function may be due to a decrease in bladder elasticity [17] or to injuries of nerves in its wall [18]. Excessive deformation of the bladder wall may irreversibly damage motor nerves, postjunctional membranes or contractile elements [6].

Muscle fiber length is a linear function of bladder radius, and muscle fibers increase in length nearly two-fold when the bladder is filled to its physiological limits [5]. The bladder reacts to external stimulation with larger contractions when it is full and the fibers are at their optimum length [2], but the force of contraction decreases when the muscle fibers are stretched beyond the optimum length [5, 8].

The aim of the present study was to compare the effects of long-term and short-term stretch on electrically evoked mechanical responses of the rat bladder strip.

Material and Methods

Nineteen Sprague-Dawley male rats weighing 360–420 g were used. They were bred at 22–24 °C in two separate cages. The light cycle was 12L/12D. There was an adequate supply of tap water and commercially-made pellets available in the cages. The experimental animal was decapitated, the bladder dissected and quickly removed into an oxygenized (100% O_2) physiological buffer solution (PBS) (8.6 g NaCl, 0.42 g KCl, 1.2 g HEPES, 0.24 g $CaCl_2$, 0.025 g $MgCl_2$, and 0.5 g glucose added in 1,000 ml distilled water, pH 7.4). The dome and the base of the bladder were transversally cut on a microscope (Nikon 8X). The ring consisting of about 70% of the whole bladder and being about 5–6 mm wide was cut open. At both ends of the strip a small hook and a teflon coated copper wire (diameter of 0.03 mm) were attached. The strip was then transferred into a 40 ml chamber with continuously oxygenized PBS at 30 °C. A water jacket kept the temperature constant. One of the wires was connected to a force transducer and the other to the drive carriage of a perfusion pump (Model 352 Sage Instruments). The resting length (L_0 = 100%) chosen was 10 mm. Two additional metal wires coming from an electrical stimulator (GRASS S48) were connected directly to the hooks. The strip was allowed to adapt for 30 min before the experiments commenced. The signal coming from the isometric transducer passed through a low-level DC preamplifier and through an oscilloscope (TEKTRONIX model 5103N with 5A2ON differential amplifier and 5B1ON time base/amplifier) running into an one-channel inkwriter (BBC GOERTZ Servogor S RE 541) running at the speed of 30 mm/min. With the help of the perfusion pump the strip was stepwise stretched at 3 mm/min, first to a length at which the amplitude of the active tension was almost undetectable (300%) and was then released at the same speed to a length of 10 mm. The strip was supramaximally stimulated about ten times at each step (myogenic stimulation; 1/min, 500 ms, 30 V, 250 Ohms) after an adaptation period of 5 min and the responses were recorded. Two different types of experimental protocols were used, eight rats in

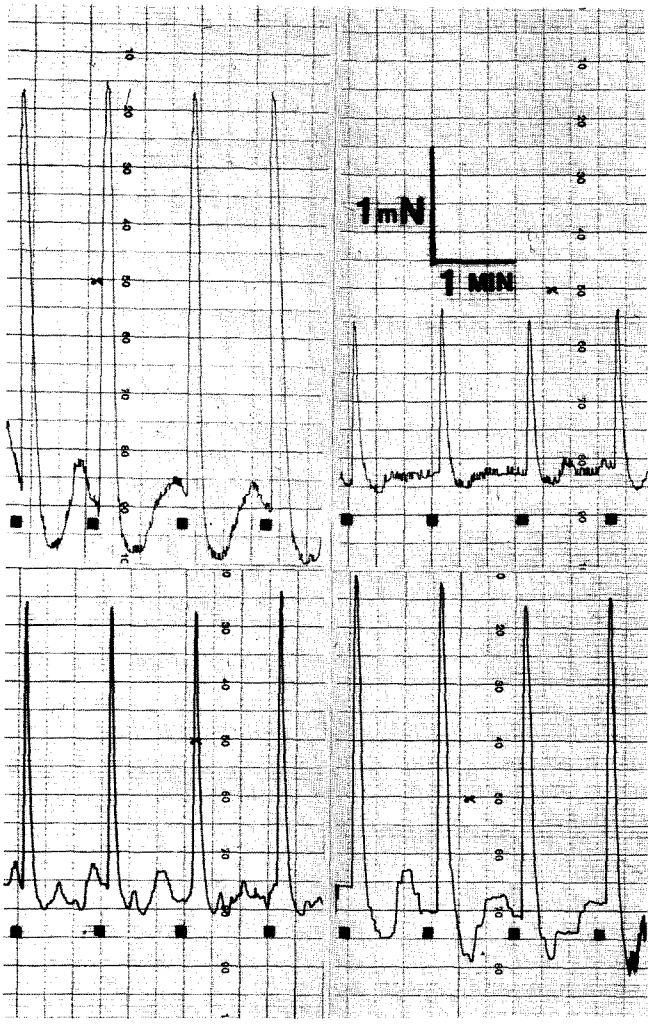

Fig. 1. Parts of a stretch-release cycle in two rat bladder strips at a length of 20 mm. Peaks on the left have been recorded during stretch and peaks on the right during release. The black dots indicate the point of time of myogenic stimulation. The upper strip remained at its maximum length for 3 h (= long-term stretch) before releasing but the lower strip was released immediately after maximum length had been reached (= short-term stretch). Note the changes of active tension in the strips at comparable lengths

each. In the first experiment, when the strip had been stretched to the maximum length it was immediately released (= short-term stretch). In the second experiment, the strip was allowed to remain at maximum length for 3 h before the release phase was started (= long-term stretch). Three control experiments were made. Strips at a length of 150% were allowed to remain in the bath for 5 h and were electrically stimulated several times every hour.

A paired Student's *t*-test was used for statistical analysis of the results.

Results

When the strip was stretched from one length to another a sharp rise in the tension which then fell to a new constant level in five minutes was noticed. All strips responded to a myogenic electrical stimulation with contractions. A typical part of the recordings is presented in Fig. 1. It can be

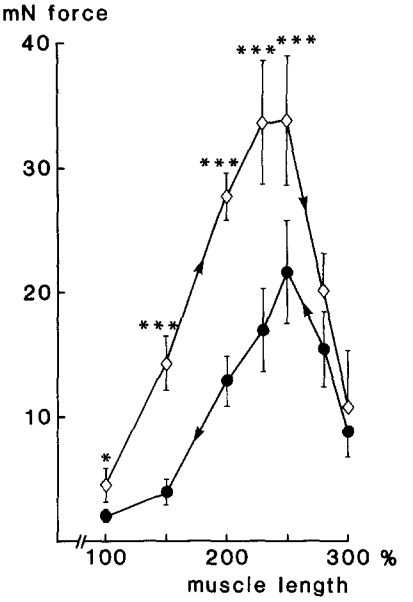

Fig. 2. Changes in active tension of rat bladder strips ($n = 8$) during stretch (◇) and during release (●) in the case of long-term stretch (3 h). Vertical bars indicate mean ± SEM, and the asterisks the statistical significance of a difference (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). The paired Student's *t*-test was used

seen that during both stretch and release the active tension consists of equal amplitudes at a certain length of the strip. There also occur spontaneous contractions in the strips, which are shown in Fig. 1 as a fluctuation of the baseline between peaks. The duration of each peak was almost invariable in all experiments. Both in the case of long-term stretch and in the case of short-term stretch, the changes in amplitude per tissue length were larger near the maximum length than near the resting length (Figs. 2 and 3). Amplitudes were significantly larger during stretch than during release at lengths from 100% to 250% when the strips had been stretched for 3 h at the length 300% before releasing, as shown in Fig. 2. When the release was started immediately after achieving maximum length the amplitudes of active tension were similar compared with the amplitudes during stretch, as shown in Fig. 3. Some changes did occur, however, in amplitudes close to the maximum amplitudes found at the lengths of 230–250% during both stretch and release. The amplitudes were significantly larger during release than during stretch at three different lengths (Fig. 3).

The strips in the control experiments reacted to the electrical stimulus with amplitudes of equal length during the whole period of the experiment (not shown).

Discussion

When a strip of rat detrusor muscle was stretched, the electrically evoked motor response first increased and then decreased abruptly at greater lengths. Similar observations were also made by Anderson et al. [2] and by Finkbeiner and Bissada [8], while in other studies the response to stimulation decreased more slowly [5, 21]. Our results agree

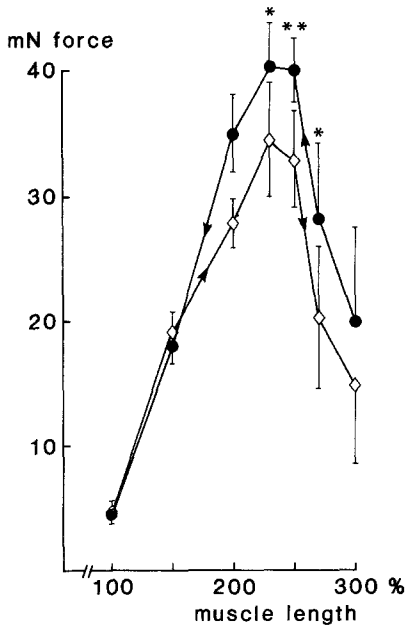

Fig. 3. Changes in active tension of rat bladder strips ($n = 8$) during stretch (◇) and during release (●) in the case of short-term stretch. Vertical bars indicate mean ± SEM, and the asterisks the statistical significance of a difference (* $p < 0.05$; ** $p < 0.01$). The paired Student's t-test was used

with the observations concerning the asymmetry of the active length-tension relation in other smooth muscles, e.g. vascular smooth muscle (for review see Arjamaa) [3]. The decrease was not due to cellular damage, but rather to changes in the properties of smooth muscle cells since activity was also found during release. According to Meiss [14] and to Mulvany and Warshaw [15] it is not possible to explain the active length-tension relation of smooth muscle in structural terms. One can only speculate that stretching somehow changes the physical properties of the smooth muscle membrane and thus facilitates the movements of trigger calcium through or from the membrane [11]. Another explanation would be that stretch changes the properties of the contractile apparatus; Hibberd and Jewell [10] found that the sensitivity of the contractile system to calcium increased with length in the rat heart muscle. Maximum contractility was achieved at muscle lengths 230–250% which agreed closely with other reports [2, 8]. Clinically this means that if the circumference of the bladder is 2.5 times larger than at its resting size it is near its upper functional limits [5]. Further stretching of muscle fibers can occur only in patients during anaesthesia or strong pain medication which impairs the sensitivity of micturition [1] as well as in those who are unable to micturate because of an infravesical obstruction [16].

After long-term stretching, the amplitude of active tension failed to respond during release to an electrical stimulus as strongly as it did during the stretch to the maximum length. Carpenter [5] found similar changes even after a distension of shorter duration. In our study, the short-term stretch stimulated the contractility of the bladder smooth muscle (Fig. 3), which is in agreement with previous findings concerning the cat ureter [23], the dog ureter [22] and the quail oviduct [4]. On the other hand the long-term stretch appeared to inhibit contractility (Fig. 3). There is no clear explanation for the major finding of this paper (compare Figs. 2 and 3). There is, however, always some amount of contractile capacity left in the contractile apparatus even though the muscle seems to have produced its maximum tension when stretched [12]. Therefore, the duration and perhaps also the velocity of stretch become important factors in the evaluation of the mechanical activity of the bladder. The decreased amplitude of active tension during release in the case of long-term stretch (Fig. 2) was not a result of any irreversible changes in the connective framework, as at each length tonicity was restored before any recordings were made.

When resting smooth muscles are rapidly stretched they exhibit a sharp rise in tension that then falls to a new constant level (stress relexation) within a few minutes [1, 19]. In our experiments it happened within five minutes. This type of muscular activity is described in terms of a contractile element in series with a viscoelastic element [1] that is thought to reside mainly in the crossbridges [13, 19]. With slow filling, there is a large-volume increment in the bladder without any appreciable elevation of bladder pressure. This plasto-elasticity is explained with a parallel elastic element [1].

The steeply rising pressure that is seen at the end of the cystometrogram may be associated with the irreversible creep phenomenon observed by Alexander [1] to be manifested at large bladder volumes. Alexander [1] concluded that it was due to a viscous element parallel with the contractile system. Ordinary stretches of the tissue will be acting on the series and parallel elastic elements working within the slack range of the parallel viscous element, so that there would not normally be any displacement of the viscous element itself. With stretches acting long enough, however, and with sufficient intensity to pull the slack element taut, the parallel element would exhibit a deformation for which there is no restoring force. Alexander [1] found this phenomenon to occur after a stretch of short duration at high pressures. It was not noticed in our experiments, however, except after three hours of stretching, giving support to the theory that the intensity of stretching is not the only factor in impairing detrusor contractility but that its duration is also of importance. This agrees with the observation that the tension-time coefficient, which is the product of detrusor tension and the duration of retention in hours, was an important factor for impaired bladder function after urinary retention [16]. In our experiment, the force of stretching was probably not as high as in Alexander's experiments [1] and – perhaps – was not unphysiological since stimulated contractility was still observed at the maximum length of the strip.

Our results show the importance of the time factor to the impaired contractility of the detrusor muscle during stretching. If the force of the stretching is high functional

changes will occur rather rapidly in the smooth muscle, which impairs its ability to contract effectively. This leads to a prolongation of micturition difficulties due to continued overdistension. The functional changes may be long-lasting or even irreversible. Especially prone to overdistension are patients whose micturition sensitivity has been depressed by anaesthetics. The patients should be carefully followed to diagnose urinary retention and to drain the bladder as rapidly as possible to prevent prolonged difficulties with micturition.

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