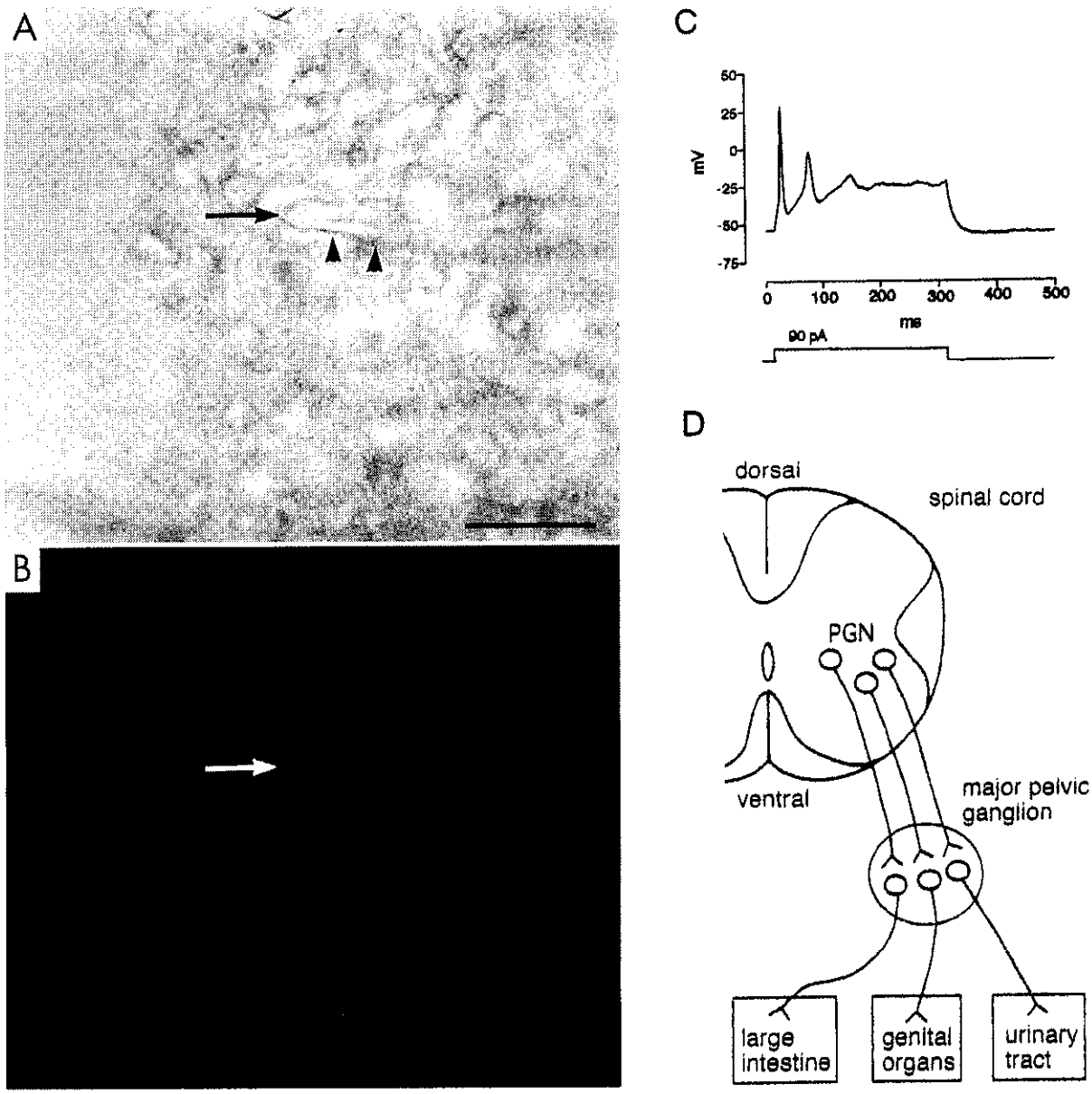

Fig. 1. Photographs of parasympathetic preganglionic neurons (PGN) in a thin slice of the lumbosacral spinal cord (7-day-old rat). (A) PGN viewed with Nomarski optics (black arrow). Two arrow-heads pointing to the tip of a patch electrode. Calibration bar, 50 μm (B) same neuron as in A, but viewed with fluorescence optics (white arrow). PGN had been retrogradely labelled with fast blue. (C) The firing evoked by 300 ms current pulse (90 pA) in same neuron as in A. (D) Schematic diagram showing various types of parasympathetic preganglionic neurons in lumbosacral spinal cord. PGN, parasympathetic and the peripheral pathways to the pelvic organs.

the neonatal rat [2–4], to examine the intrinsic properties of PGN and the firing evoked by depolarizing current pulses. A preliminary report of these observations has been presented in an abstract [16].

2. Materials and methods

Sprague–Dawley rats, 5–11 days old, were killed by decapitation and the spinal cord was rapidly removed. The L6-S1 segments of spinal cord were embedded in 2% agar (Sigma) in a physiological salt solution (see composition of external solution below) at 8°C. The spinal cord was sectioned into 150 μm transverse slices using a vibrating slicer (Vibratome, Technical Products International, St. Louis, MO). The slices were incubated at 37°C for 1 h in oxygenated external solution and then transferred to a recording chamber (0.5 ml) on an upright microscope equipped with fluorescent optics (Olympus BH-2, Tokyo, Japan). Slices were perfused continuously with the external solution at a rate of 1.5 ml/min. PGN in lumbosacral spinal cord slices were identified by retrograde axonal transport of a fluorescent dye (Fast Blue, EMS-Polyloy, GrossUmstadt, Germany) that was injected (5 μl of 4%

solution) into the peritoneal space 3–7 days before the experiment. This procedure has been shown to efficiently label autonomic PGN in the spinal cord [1].

The basic procedures for recording whole cell currents from individual neurons in slice preparations of the cord were identical to those reported previously [2–4,35]. Each slice of lumbosacral cord was surveyed for fast-blue-containing neurons along the intermediolateral border of the gray matter under an upright microscope equipped with fluorescence optics (Fig. 1A,B). Motoneurons in the ventral horn were often dye labeled, but it was easy to distinguish between PGN and motoneurons by their location. After identification of a fluorescent PGN, the neuron was viewed with Nomarski optics and its surface was cleaned by a stream of the external solution from a glass pipette positioned near the cell. Membrane potentials were recorded from the labeled neurons using an Axopatch 200A patch-clamp amplifier (Axon Instruments, Foster City, CA). The patch pipettes were made from borosillicate glass capillaries (1B150F-4, World Precision Instruments, Sarasota, FL) and had resistances of 2.5–3.5 MΩ when filled with pipette solution (see below) and after the tip had been heat polished. The measurement of cell sizes was made under Nomarski optics using a graticle in the eyepiece of the microscope. Cell diameter was measured along the cell's long axis. Then the cell's firing properties in response to prolonged depolarizing current pulses (300 ms) was examined. The duration and amplitude of the spike after-hyperpolarizations were measured from action potentials initiated by brief (5 ms) depolarizing current pulses. The electrode capacitance was compensated during cell-attached recording. All experiments were performed at room temperature (20–25°C). Voltage records were filtered at 1–5 kHz, digitized using the Digidata 1200 interface (10 kHz, Axon Instruments), and stored on a ZIP drive disk connected to an IBM-compatible personal computer for off-line analysis using pClamp6 software (Axon Instruments). Numerical data are presented as mean±standard error of the mean (S.E.M.). Statistical analysis was performed using a two-tailed t-test or the Mann–Whitney test with a significance limit of $P<0.05$.

The standard external solution contained 130 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid (HEPES), and 11 mM glucose. The pH was adjusted to 7.40 with NaOH. The pipette solution (pH 7.3) contained 140 mM KCl, 1 mM $CaCl_2$, 2 mM $MgCl_2$, 11 mM ethylene glycol-bis (β-aminoethyl ether) -N, N, N',N'-tetraacetic acid (EGTA), and 10 mM HEPES. 5 μM 6-Cyano-7-nitroquinoxaline-2, 3-dine (CNQX; Research Biochemicals International), 50 μM 2-amino-5-phosphonovalerate (APV; Sigma), 10 μM bicuculline methiodide (Sigma), and 1 μM strychnine sulfate (Sigma) were always applied in the external solution to block spontaneous excitatory (EPSCs) or inhibitory postsynaptic currents (IPSCs) [2,3].

3. Results

Recordings were obtained from 110 PGN labeled by retrograde axonal transport with a fluorescent dye (Fig. 1B). The mean resting membrane potential was −50.8±0.6 mV (n=110 cells), when measured just after achieving whole-cell recording. The cells were usually oval in shape and varied in size from 13.3 to 28.8 μm (long axis diameter) (Fig. 2). The mean input resistance estimated from the change in membrane potential in response to a −10 pA step pulse (300 ms duration) was 774.2±45 MΩ (n=110 cells). The threshold for action potential generation was −35±0.5 mV (n=110 cells).

3.1. Classification of neurons on the basis of firing pattern

Application of a series of depolarizing current pulses (300 ms duration) that were incremented in steps of 10 pA between 10 and 120 pA elicited action potentials that were initiated at threshold depolarizations ranging between −23 and −45 mV. In some neurons (n=67), increases in the strength of the current pulse produced a graded increase in the number (average maximum 5.6 spikes) of action potentials that occurred throughout the duration of the current pulse (Fig. 3A), while in others (n=43), suprathreshold depolarizing current pulses elicited only a single or a few action potentials (average maximum 1.4 spikes) at the beginning of the depolarizing current (Fig. 4A). In these neurons stronger depolarizing current pulses did not increase the number of action potentials (Fig. 4D). In the former neurons that represented about 60% of the population, rhythmic firings during the depolarizing current pulse and firing frequency increased in proportion to the magnitude of depolarizing current pulses (Fig. 3C). These two firing patterns, which have been described in other autonomic neurons [7], have been termed 'tonic' and 'phasic'. These terms will also be used in this paper.

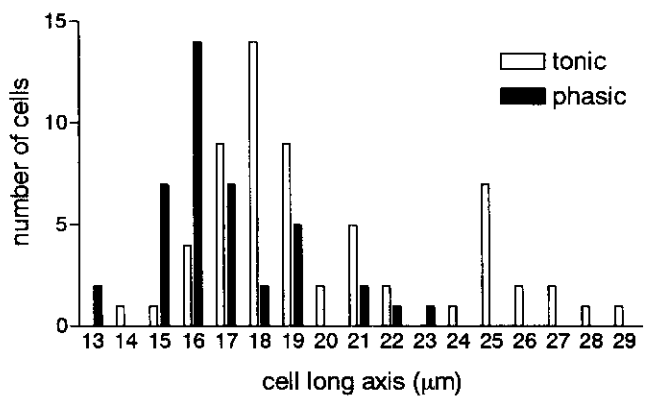

Fig. 2. Cell size distributions showing length (μm) of the long axis of tonic (n=67) and phasic PGN (n=43) measured in spinal slice preparations. Ordinate, number of cells. Abscissa, long axis of the cells.

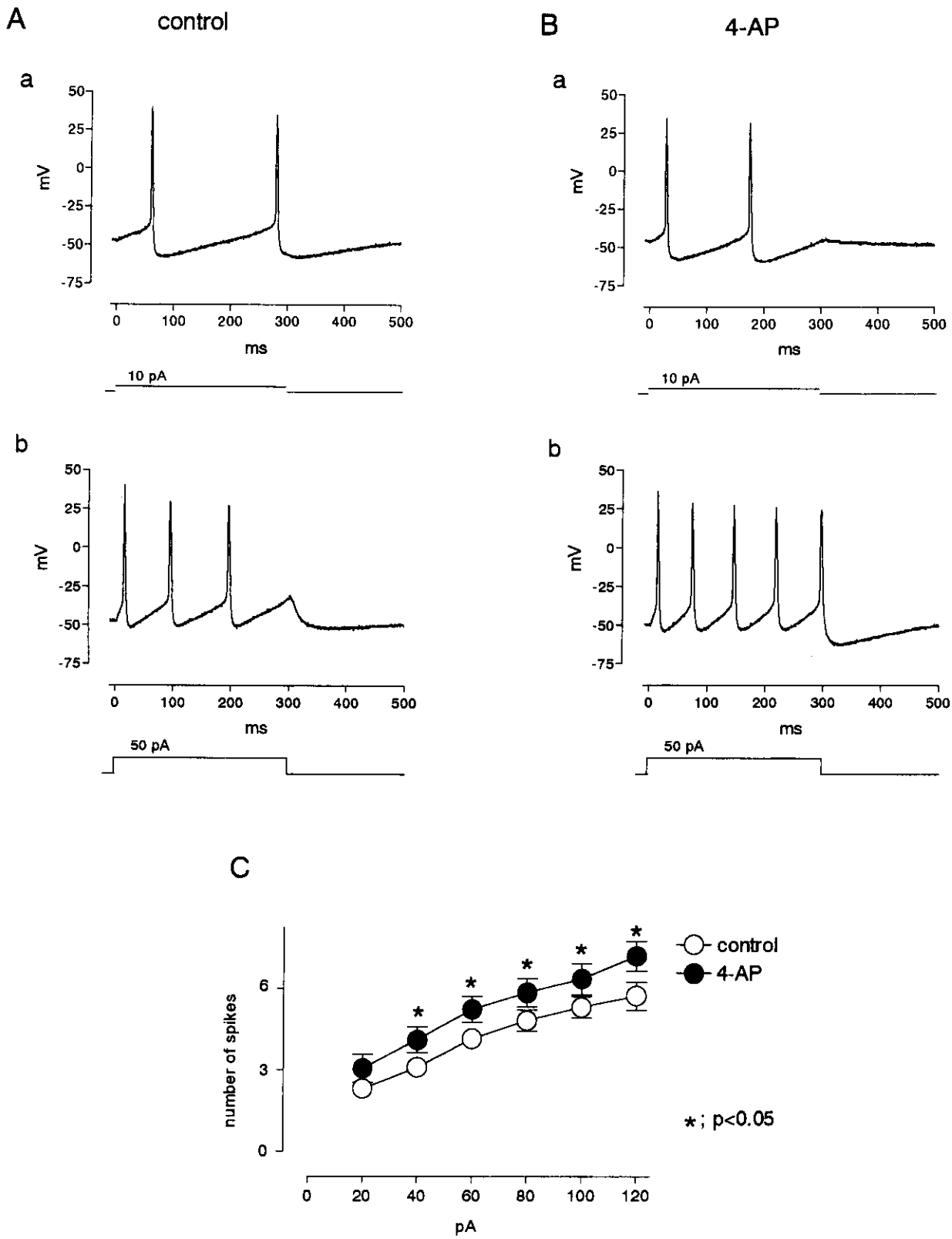

Fig. 3. Effect of 4-AP on the firing properties of tonic PGN. (A) The firing before 4-AP evoked by 300 ms current pulses (10 and 50 pA, shown at the bottom of each trace). Note that the number of action potentials increased with increasing magnitude of injected current pulses. (B) In the presence of 4-AP (0.5 mM) the number of action potentials evoked by the depolarizing current pulses increased and the latency of the first spike evoked by low intensities of stimulation was reduced in the same cell as in A. (C) The relationship between the number of action potentials and injected current in tonic PGN ($n=7$) before (○) and after application of 4-AP (0.5 mM) (●) Ordinate, number of spikes elicited during the current pulse; abscissa, stimulus intensity in pA.

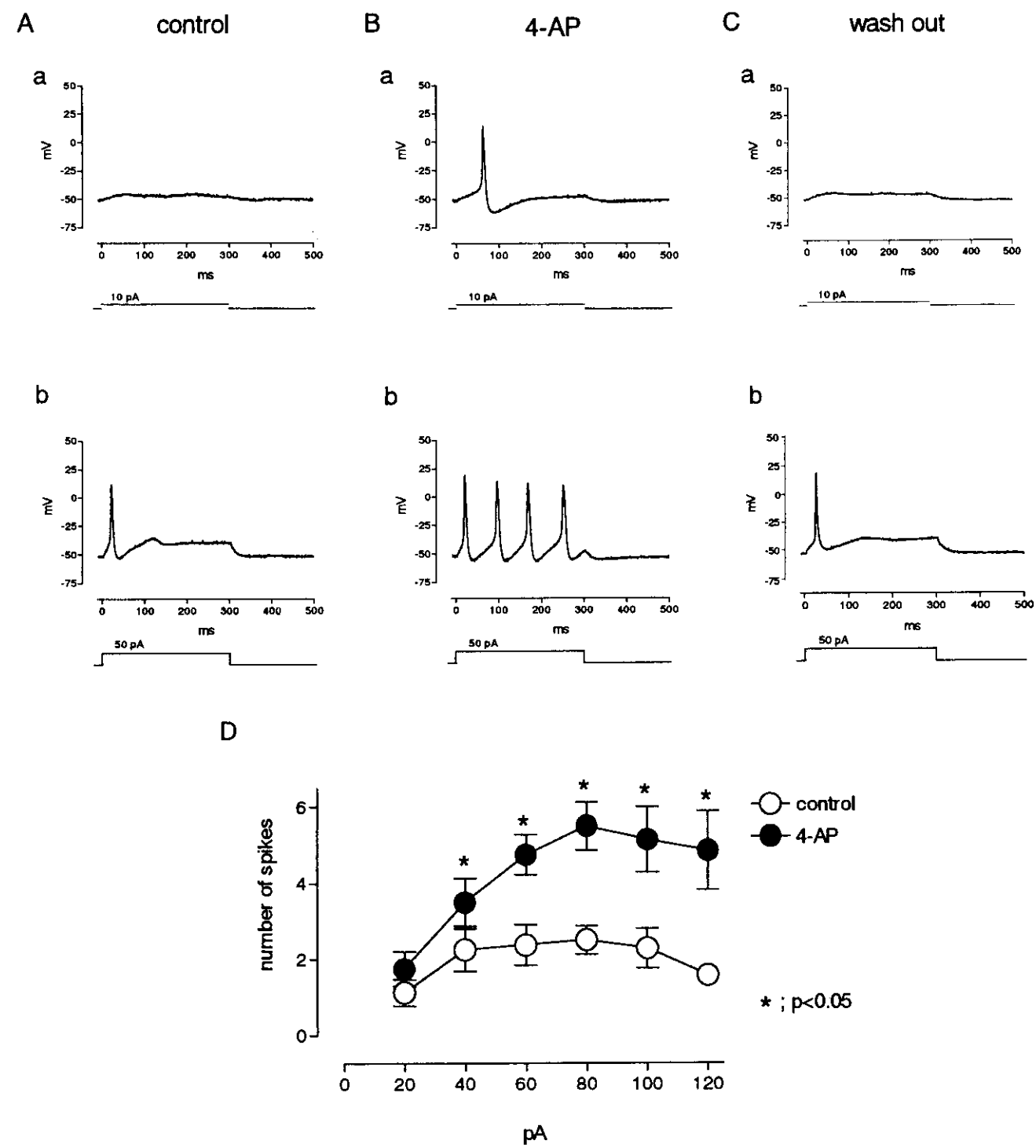

Fig. 4. Effect of 4-AP on the firing properties of phasic PGN. (A) The firing before 4-AP evoked by 300 ms current pulses (10 and 50 pA). Note stimulation generates only a single action potential in this neuron even during a high intensity current pulse. (B) In the presence of 4-AP (0.5 mM) phasic firing was converted to tonic firing in the same cell as in A. (C) Wash out. (D) The relationship between the mean number of action potentials and injected current in phasic PGN ($n=8$) before (○), and after application of 4-AP. The number of action potentials did not increase significantly as the intensity of current pulses was increased from 20 to 120 pA prior to 4-AP, but increased significantly ($P<0.05$) in the presence of 4-AP.

3.2. Properties of tonic and phasic PGN

PGN that were divided into two populations (tonic and phasic) on the basis of their firing properties evoked by depolarizing current pulses had similar mean resting membrane potentials, input capacitances (tonic PGN, 26.8±0.7 pF, $n=67$ and phasic PGN, 26.5±1.5 pF, $n=43$) and input resistances (776.3±58.9 MΩ and 771.3±70.7

Table 1
Comparison of the properties of tonic (n=67) and phasic PGN (n=43)*

	Tonic (n=67)	Phasic (n=43)
RMP (mV)	−51.0±0.7	−51.0±1.1
Spike threshold (mV)	−35.0±0.7	−35.0±0.8
Spike duration (ms)	2.4±0.3	2.7±0.3
AHP duration (ms)	200.5±11.9	137.6±9.8*
AHP amplitude (mV)	7.5±0.6	6.0±0.8
Cell diameter (μm)	20.7±0.5	16.7±0.3*
Input capacitance (pF)	26.8±0.7	26.5±1.5
Input resistance (MΩ)	776.3±58.9	771.3±70.7
Threshold current (pA)	12.1±1.0	29.0±4.0*
Latency of 1st AP (ms)	99.4±9.4	49.6±2*

* Data are mean±S.E.M. *P<0.05 indicates differences between tonic and phasic neurons. RMP, resting membrane potential; AHP, after-hyperpolarization; AP, action potential.

MΩ) (Table 1). Action potentials evoked by short duration (5 ms) depolarizing pulses (50–150 pA) occurred at similar thresholds in both populations of neurons (Table 1) and were blocked by TTX (1 μM). However, the duration of the after-hyperpolarization (AHP) was significantly different (P<0.05, unpaired t-test) in the two populations (Fig. 3A and 4A); tonic PGN had long duration AHPs (mean 200.5±11.9 ms, n=25), and phasic PGN had shorter duration AHPs (mean 137.6±9.8 ms, n=23) (Fig. 3A and 4A; Table 1), but the mean peak amplitude of the AHPs was not significantly different in the two populations (7.5±0.6 mV in tonic PGN; 6±0.8 mV in phasic PGN). Although there was considerable overlap in the sizes of tonic and phasic neurons (Fig. 2) the tonic PGN were on average larger (mean long axis diameter: 20.7±0.5 μm, n=62; P<0.0001, Mann–Whitney test) (Table 1), than phasic PGN (mean: 16.7±0.3 μm, n=43). All large cells (24–29 μm) were tonic neurons (Fig. 2).

When depolarizing current pulses were increased from 10 to 120 pA in 10 pA increments, action potentials were generated in tonic PGN (Fig. 3) at a mean intensity of 12.1±1.0 pA with a narrow range between 10 and 20 pA (Table 1). The latency (termed 'peak latency') of the first action potential, measured between the start of a suprathreshold current pulse and the peak of the first action potential was 99.4±9.4 ms (Table 1) in tonic PGN. On the other hand, in phasic PGN, the threshold current was significantly higher (P<0.005, unpaired t-test) (29±4 pA, with a broad range between 10 and 80 pA). However, the peak latency of the first action potential evoked by a suprathreshold current pulse was significantly shorter (49.6±3.2 ms, P<0.005) than in tonic PGN. Increasing the magnitude of the depolarizing current pulse markedly decreased the peak latency in both types of PGN (Fig. 3A and 4A).

Current-voltage relationships were examined in PGN (n=17 tonic; n=13 phasic neurons) by applying 300 ms duration current pulses (ranging from −60 to 110 pA) in the presence of 1 μM TTX (Fig. 5). In tonic PGN, inward rectification was evident at potential levels greater than −86.6±3.7 mV (Fig. 5); but in phasic PGN, inward rectification was not observed (Fig. 5). In tonic PGN, membrane potential changes induced by hyperpolarizing current pulses (ranging from −30 to −60 pA) were significantly smaller (by 76.8–90%; P<0.05, Mann–Whitney test) than in phasic PGN. Outward rectification was observed in both types of neurons.

3.3. Effect of 4-AP on electrophysiological properties of tonic and phasic PGN

In phasic PGN under control conditions, only a single or a few action potentials occurred at the beginning of depolarizing current pulses, ranging in amplitude up to 120 pA (Fig. 4A, C). Bath application of 4-AP (0.5 mM) for 1 min converted phasic discharges into tonic discharges (n=8) (Fig. 4B, D). 4-AP significantly increased the number of spikes by 155–309% for depolarizing current pulses ranging from 20 to 120 pA (P<0.05, unpaired t-test, N=8) (Fig. 4D). 4-AP did not affect the latency for firing in phasic PGN. After washing out of 4-AP, the phasic discharge reappeared (Fig. 4C).

Prior to treatment, tonic PGN discharged rhythmically (Fig. 3A) in response to depolarizing current pulses. The number of action potentials increased with increments in the current pulses; the mean number increasing from 2.5 to 5.6 at 20 pA and 120 pA, respectively (Fig. 3A, C). Application of 4-AP (0.5 mM) significantly (P<0.05, unpaired t-test, n=7) increased by 11–19% the mean number of action potentials evoked by a range of depolarizing current pulses (10 pA to 120 pA) (Fig. 3C). In tonic PGN, 4-AP also reduced the latency for firing induced by low intensity current pulses (P<0.05, paired t-test) but did not alter the latencies of firing evoked by high intensities of stimulation.

When 4-AP (0.5 mM) was added to external solution containing CNQX (5 μM), APV (50 μM), bicuculline (10 μM) and strychnine (1 μM) to block EPSCs or IPSCs [3], it produced a negative shift in the mean threshold for generating an action potential from −33.9±1.6 mV to −39.2±1.4 mV in tonic PGN (P<0.05, paired t-test) and from −30.7±1.8 mV to −36.1±1.9 mV in phasic PGN (P<0.0005) (Table 2). 4-AP also prolonged (P<0.05) the mean duration of the action potentials (measured at half amplitude width) from 2.2±0.3 ms to 2.7±0.4 ms in phasic PGN, but did not significantly change the duration of the action potentials in tonic PGN (Table 2). 4-AP did not significantly change the mean duration and amplitude

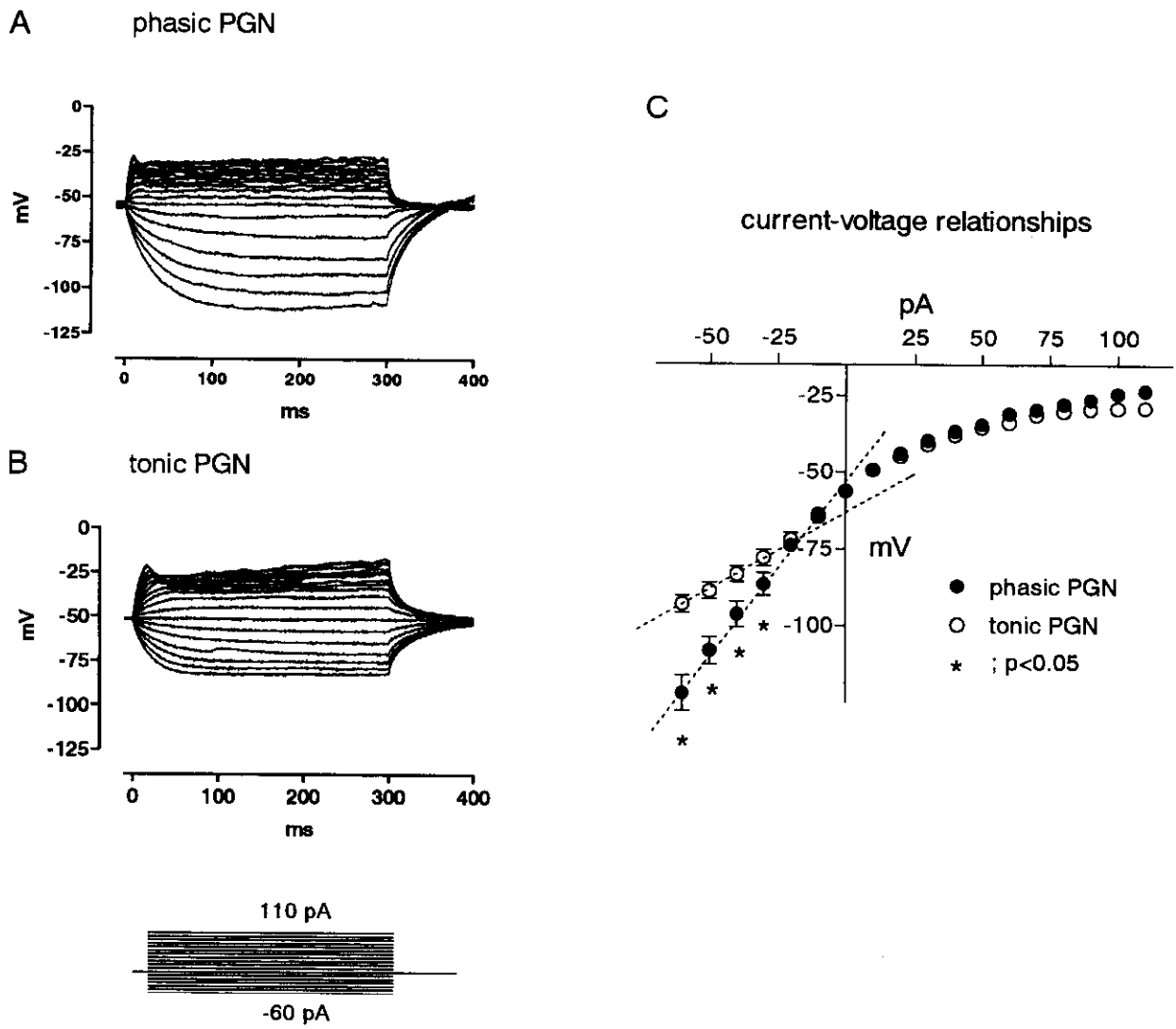

Fig. 5. Current-voltage relationships in PGN obtained in the presence of TTX (1 μM) to block voltage gated Na^+ channels. (A and B) Superimposed traces of membrane potential recordings in phasic and tonic PGN during depolarizing and hyperpolarizing current pulses (300 ms duration). The amplitude of the pulses was changed from −60 pA to 110 pA in 10 pA steps which are shown under each record. Note inward rectification in tonic but not phasic PGN, at membrane potentials more negative than −86 mV (B, C). Outward rectification occurred in both types of cells. Steady-state voltage values at the end of the negative current injection are plotted in C. Data were obtained from 17 tonic and 13 phasic PGN.

Table 2
Effect of 4-AP (0.5 mM) on action potentials in tonic and phasic PGN[a]

	Tonic (n=7)		Phasic (n=8)	
	Control	4-AP	Control	4-AP
Spike threshold (mV)	−33.9±0.8	−39.2±1.4*	−30.7±1.8	−36.1±1.9*
Spike duration (ms)	2.7±0.3	2.9±0.3	2.2±0.3	2.7±0.4*
AHP duration (ms)	185.5±22.4	221.1±17.2*	140.3±24.4	127.7±23.5
AHP amplitude (mV)	7.6±1.3	7.6±1.5	6.8±2.0	5.8±2.4
Threshold current (pA)	10.0±1.7	15.6±1.8	31.3±8.1	18.8±4.8*
Latency of 1st AP (ms)	111.0±22.1	56.7±11.0*	43.4±9.3	44.6±9.0

[a] Data are mean±S.E.M. *P<0.05 indicates differences compared with control.

of the spike AHP in PGN (Table 2), or the inward rectification ($n=8$) observed in tonic PGN.

4. Discussion

The present study revealed that parasympathetic PGN in the lumbosacral spinal cord of the neonatal rat can be divided into two groups on the basis of their firing patterns in response to depolarizing current pulses. A large proportion (61%) of PGN exhibited a tonic discharge pattern, whereas a small proportion exhibited phasic firing consisting of a short burst of spikes (mean 1.4, range 1–5) in the initial period of depolarizing current pulses even during high intensity stimulation. Because these two populations of neurons exhibited other electrophysiological and pharmacological differences it is possible that they have different functions and innervate different organs.

It has been reported previously that tonic and phasic firing patterns exist in varying proportions of neurons in the peripheral as well as the central nervous system. In the peripheral autonomic nervous system, the proportion of tonic neurons ranged from 93% in cat pelvic ganglia [19], 60% in coeliac ganglia [25], 35% in superior mesenteric ganglia [9], 40–100% in inferior mesenteric ganglia [7,22,38], 28% in cat renal ganglia [8], to 3% in lumbar sympathetic chain ganglia [7]. It has been suggested [20] that tonic and phasic peripheral autonomic neurons innervate different organs. On the other hand, at certain sites in the central nervous system, a more complicated pattern has been identified. For example in the nucleus tractus solitarius (NTS) of the rat four cell types have been identified on the basis of the responses to depolarizing current pulses: single action potential type (S1 neurons), tonic firing type (S2 neurons), initial burst type (S3 neurons), and delayed excitation type (S4 neurons) [29]. In the lumbosacral parasympathetic nucleus, we also identified phasic and tonic firing neurons similar to S1 or S3 and S2 neurons in the NTS. In addition a few cells also had properties similar to those of S4 neurons.

The two major groups of PGN in the rat lumbosacral parasympathetic nucleus also exhibited other differences. Although there was considerable overlap in the distribution of cell sizes of tonic and phasic PGN, the tonic PGN measured on their long axis were on average larger (20.7±0.5 μm) than phasic PGN (16.7±0.3 μm), but slightly smaller than sympathetic PGN in neonatal rat spinal cord (25.2 – 26.5 μm) [31,27]. In addition the larger parasympathetic PGN (greater than 23 μm) were all tonic neurons. However mean input resistance and capacitance were not significantly different for tonic and phasic PGN indicating that the surface area of the two types of cells is similar and that only the shape is different (i.e., tonic cells are on average more elongated).

The spike AHP was also longer in tonic PGN (200.5±11.9 ms) than in phasic PGN (137.6±9.8 ms). Cassell et al. [7] reported a similar difference in the mean duration of spike AHP of tonic and phasic neurons in guinea-pig sympathetic ganglia [7]. The spike AHP could contribute to the differences in firing properties of the two types of PGN as noted in other neurons. For example, Yarom et al. [39] reported that the firing patterns of frog vagal motoneurons can be affected by the slow AHP mediated by Ca^{2+}-activated K^+ channels [39]. They reported that the slow AHP prevented the membrane potential from reaching the threshold for spike generation and gradually slowed the frequency of discharge during long depolarizing current pulses. Although Ca^{2+} activated K^+ currents and AHP may modulate firing frequency it is not likely that the AHP is the critical factor in producing phasic firing in PGN because 4-AP treatment which unmasked tonic firing in phasic neurons did not suppress the AHP.

It has been reported that sympathetic PGN in the neonatal rat exhibited inward rectification without a depolarizing sag during current injection [27,31]. We also found that tonic parasympathetic PGN had inward rectification without a depolarizing sag but phasic PGN did not. Uchimura et al. [37] proposed that in nucleus accumbens neurons inward rectifying current may contribute to an enhancement of the resting membrane potential since activation occurred at potentials near the resting level [37]. However, inward rectification in the tonic PGN activated at about −87 mV which is considerably higher than the resting membrane potential. Inward rectification could also contribute to maintenance of tonic firing during prolonged synaptic input; because Travagli and Gillis [36] reported that vagal neurons which exhibited inward rectification had increased firing frequencies in response to excitatory postsynaptic potentials [36]. However inward rectification in tonic PGN was resistant to low concentrations of 4-AP, as reported by other investigators [17,27]. Therefore inward rectification can not be important in the facilitatory effects of 4-AP on tonic PGN firing.

The most prominent effect of 4-AP on PGN firing was the unmasking of tonic activity in phasic PGN. Zhang and Trussell [42] also reported that 4-AP converts single discharges into multiple discharges during prolonged depolarizing current injection in the avian nucleus magnocellularis (NMC) [42]. A similar unmasking of multiple action potentials by 4-AP was also observed in the chick NMC neurons [24] and in principal neurons of rat medial nucleus of the trapezoid body [5,18]. Thus a 4-AP sensitive current could contribute to the suppression of multiple action potentials in phasic PGN. In addition we also observed that 4-AP slightly increased firing frequency in tonic PGN during prolonged depolarizing current injection.

The present results also indicated that the characteristics of the action potentials in parasympathetic PGN are regulated by 4-AP sensitive channels. 4-AP significantly increased the duration of the action potential in phasic PGN. This is similar to the effect of 4-AP on other neurons

in the superior cervical ganglia [6], rat pelvic ganglia [41] and NMC [24,32] where block of K^+ channels by 4-AP prolonged action potential duration. This indicates that 4-AP sensitive currents contribute to spike repolarization. In addition, 4-AP reduced the threshold for triggering an action potential in parasympathetic PGN. This been noted in other neurons including pedunculopontine neurons [23], relay neurons in the thalamus [30], small diameter dorsal root ganglion neurons [40] and NMC neurons [24].

4-AP also shortened the latency for firing in response to small depolarizing currents in tonic PGN. Other studies [33] have revealed that transient outward currents such as I_A and I_D, which are sensitive to 4-AP, can contribute to the delay between the start of depolarizing current injection and the occurrence of the first action potential. For example, in the rat NTS, I_A currents play an important role in the generation of this delay, whereas I_D currents regulate the steady-state firing rate in the neuron. Thus the delay of the first action potential and the high threshold for generating action potentials in the parasympathetic PGN might be due to I_A currents. It will be important in future experiments to perform a detailed analysis of the kinetics of 4-AP sensitive currents in PGN, and how these kinetics differ in tonic and phasic neurons.

The identification of lumbosacral PGN with different firing patterns raises the question as to whether these patterns reflect different physiological functions of the neurons. The lumbosacral parasympathetic pathways regulate the functions of various organs including the urinary bladder, urethra, distal bowel and the reproductive organs [10–15]. Previous studies in cats revealed that during micturition, bladder PGN exhibit an intermittent discharge characterized by burst-type firing for a short period separated by a long silent period. On the other hand, during defecation, colon PGN exhibit a tonic discharge. A relationship between function and firing pattern has also been detected in peripheral autonomic ganglia. For example, in the guinea-pig sympathetic ganglia, phasic neurons exhibiting an initial transient burst of activity during prolonged depolarizing current pulses innervate blood vessels; whereas tonic (continuous firing) neurons regulate the motility of visceral organs [7,21,26,34]. Thus tonic and phasic PGN might regulate different pelvic organs. This could be explored in future experiments by studying the electrical properties of functionally identified PGN by labeling the neurons with transneuronal tracers injected into different organs.

In summary, two types of neurons in the lumbosacral parasympathetic nucleus of the neonatal rat were identified on the basis of electrophysiological as well as pharmacological properties. One type of neuron (phasic) exhibited short latency and brief periods of firing in response to prolonged depolarizing current pulses. The other type (tonic) exhibited longer latency and more prolonged discharges. 4-AP increased the duration of firing in phasic neurons, shortened the latency of firing in tonic neurons and reduced the threshold for action potentials in both types of neurons. It is concluded that 4-AP sensitive K^+ currents play significant but different roles in regulating the firing properties of tonic and phasic PGN.

Acknowledgements

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原　著

脊髄過活動性膀胱に対するカプサイシン膀胱内注入療法の検討

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Intravesical capsaicin instillation for detrusor hyperreflexia in patients with spinal cord injury.

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We evaluated the instillation of intravesical capsaicin for in 4 patients with spinal cord injury. These patients with reflex urinary incontinence had been on self catheterization. Cystometry was performed before instillations of 2 mmol./l capsaicin in 30 % ethanol, then repeated 1 day, 1 week and 4 weeks after. In three of four patients, the mean maximal bladder capacity increased from 70 ml to 150 ml. In two of three patients, maximal urethral pressure decreased from 118 cm H_2O to 65 cm H_2O. After treatment, no satisfactory clinical improvement was noted since the bladder capacity for all patients remained less than 250 ml.
Key words: Capsaicin, reflex incontinence, spinal cord injury

要旨：脊髄過活動性膀胱に対するカプサイシン膀胱内注入療法の有用性を検討した．自己導尿で排尿管理をしている過活動性膀胱を示す尿失禁患者4例を対象とし，脊椎麻酔下または無麻酔下で，カプサイシン膀胱内注入療法（2mM, 100ml, 30分間）を行った．最大膀胱容量，最高尿道内圧を注入前，注入1日後，1週間後，1ケ月後で測定し評価した．カプサイシン投与により4例中3例で最大膀胱容量が増大し，3例中2例で最高尿道内圧が低下した．最大膀胱容量は増加したが，尿失禁は消失しなかった．また自律神経過緊張症状も消失しなかった．適応，方法，評価に関して更に症例を増やして検討する必要がある．
キーワード：カプサイシン膀胱内注入，反射性尿失禁，脊髄損傷

緒　　言

脊髄損傷患者の反射性尿失禁は自己導尿管理が普及した現在では，排尿筋過反射を抑えれば治せる時代となった．その方法として無菌間歇導尿膀胱過伸展療法の他，抗コリン剤内服治療，馬尾神経ブロック法などがある．抗コリン剤は口渇，便秘，視調節障害を起こしたり，保険で認められた

処方量では効果がないことが多く，馬尾神経ブロックは直腸・性機能障害を誘発しうる．

最近，排尿筋過反射に対する新しい治療法として，カプサイシン膀胱内注入療法が試みられている．カプサイシンは膀胱の知覚神経 C-fiber を選択的に刺激し，その後脱感作する[1]とされている．本療法はその脱感作作用を利用し膀胱の過活動を抑制する治療である．ヒトに対する治療として，Maggi ら[2]によって初めて報告され，国内では井川ら[3]により有効性が報告されている．

今回，自己導尿管理下の難治性尿失禁患者に対しカプサイシン膀胱内注入療法を施行し，その有用性を検討した．

対象と方法

院内倫理委員会の治験規則に従い，十分なインフォームド・コンセントのもとに文書で同意を得た4症例に限って治験が許可された．1998年9月から1998年10月までの間，抗コリン剤内服では尿失禁が改善しない脊髄過活動性膀胱の自己導尿患者4例を対象とした．

神経因性膀胱の基礎疾患は頚髄損傷2例，胸髄損傷1例，胸髄腫瘍1例，性別は男性3例，女性1例，年齢は28－52歳（平均42.3歳），全例において膀胱変形，膀胱尿管逆流症は認められなかった．

カプサイシン膀胱内注入は，以下の方針に従った．

（1）カプサイシンの注入方法は，2mM カプサイシンを10%エタノール溶液 100ml に溶かし，膀胱内に速度 50ml/min. で注入し（膀胱反射が生じた場合は 20ml/min. に速度を落とし全量注入した）30分後回収した．自律神経過緊張反射を有する症例には腰椎麻酔下で，過緊張反射の無い症例には無麻酔下で注入を行った．

（2）膀胱内圧の測定方法は，測定機器に TAKEI cystometer（TU-1065C）を用い，（尿道内圧測定用に作成した）先端より3cm の同部位両側に2孔ある 10Fr. サフィードネラトンカテーテルを用い，速度 50ml/min. にて生理的食塩水を注入した．尿道内圧は速度 10ml/min. で生理的食塩水を注入し，手動でカテーテルを引き抜き interrupted 法にて最高尿道内圧を測定した．注入前（注入前1ケ月以内），注入翌日，1週間後，1ケ月後に膀胱内圧測定を行い，最大膀胱容量は反射が生じる直前の膀胱容量とし，最高尿道内圧は膀胱を空にした状態で測定を行った．

（3）採血（特に腎機能），検尿，膀胱鏡を注入直前，注入1日後で行い変化を観察した．

（4）尿失禁の程度の評価は，排尿方法，導尿回数，一回の導尿量，尿失禁の有無（失禁尿量の定量はしていない）で行い，自律神経過緊張反射の評価は自覚症状の有無で行った．

経過観察期間は1ケ月から1年，中央値9ケ月であった．

結　　果

（1）カプサイシン注入直後の自他覚所見

全例に顔面や胸部の熱感など灼熱感が認められた．血圧，脈拍に変化はなかった．

（2）最大膀胱容量と最高尿道内圧（表2）

最大膀胱容量は3症例で増加し，平均は注入前 80ml 程度，注入1ケ月後 150ml 程度であった．

最高尿道内圧は2症例で低下し，最大膀胱容量が変化しなかった症例は最高尿道内圧も同様に変化がなかった．なお，症例1は測定を行っていなかった．3症例の平均は注入前 120cmH_2O 程度，注入1ケ月後 65cmH_2O 程度であった．

表1．対象患者の背景

症　例	性／年齢	基礎疾患	罹病期間	麻痺レベル	自己導尿期間[注1]
1	男性／42	胸髄損傷	12年	T10 完全麻痺	7日
2	男性／28	頚髄損傷	9年	C6 不全 T2 完全麻痺	7日
3	男性／47	頚髄損傷	3年	C8 不全 T7 完全麻痺	7日
4	女性／52	胸髄腫瘍	4年	L1 不全麻痺	4年

注1. 自己導尿期間とは自己導尿開始してからカプサイシン膀胱内注入するまでの期間を示す．

表2．膀胱内圧測定上の変化

症例	最大膀胱容量（ml）		最高排尿筋圧（cmH_2O）注意1.		最高尿道内圧（cmH_2O）	
	前	後注意2.	前	後	前	後
1	50	200	87	49	−	−
2	65	100	92	109	147	75
3	40	140	136	95	143	68
4	160	150	109	109	65	52

注意1．最高排尿筋圧とはカテーテル周囲より初めて漏れる時点での膀胱内圧を示す．漏れがない場合は最大注入時の膀胱内圧を示す．

注意2．後は注入1ケ月後の測定値を示す，ただし症例3のみ1週間後の測定値

表3．自覚症状の変化

症例	導尿回数		一回導尿量（ml）		尿失禁		自律神経過緊張反射		最終排尿管理法
	前	後	前	後	前	後	前	後	
1	10	10	50	200	著明注意1.	有	無	無	自己導尿
2	5	7−8	50	250	著明	有	有	有	自己導尿
3	5	6	50	100	著明	著明	有	有	膀胱瘻
4	5−6	10	150	250	有	有	有	有	自己導尿

注意1．著明とは導尿量より失禁量が多い状態を示す．

（3）血液生化学所見，検尿所見，膀胱鏡所見注入前後で変化は認められなかった．

（4）臨床効果　尿失禁と自律神経過緊張反射（表3）

膀胱瘻抜去後に自己導尿を開始した症例1，2，3では，注入前は40−60ml しか蓄尿出来ず大部分失禁してしまう状態，症例4は以前より自己導尿管理の症例で導尿回数5−6回，150ml 程度蓄尿可能であった．注入後，症例3は著しい尿失禁のため患者が自己導尿管理を放棄し注入3週間後再び膀胱瘻管理に戻った．症例1，2，4では導尿回数8−10回，1回の導尿量200−250ml となった．最大膀胱容量の増加に従い，尿失禁はある程度は改善したものの患者の満足が得られる程度まで改善しなかった．また自律神経過緊張反射も消失しなかった．

考　　察

赤唐辛子の辛みの成分であるカプサイシンはバニロイドと呼ばれている．膀胱壁にはバニロイド受容体が存在し，無髄知覚神経 C-繊維を選択的にブロックすることで脊髄膀胱の排尿筋反射を抑える作用のあることが実験動物で知られており，臨床でもその有用性が諸家により報告されている．De Ridder ら[4]は排尿筋過反射による尿失禁79例に行い，完全な尿禁制は44%，ある程度の改善が36%，改善なしが20%であったとし，3−6ケ月効果が持続したと報告している．井川ら[3]は慢性期の脊髄損傷患者における排尿筋過反射および自律神経過反射を有する5例にカプサイシン膀胱内注入を行ったところ，全例で3−4時間ごとの自己導尿で尿失禁のコントロールが可能となり，自律神経過反射も消失したと報告している．de Seze M.[5]らは脊髄過活動性膀胱に対しカプサイシン膀胱内注入二重盲検法を行い，カプサイシン注入群は最大膀胱容量が300ml 程度まで増加し，コントロール群は膀胱容量に変化がなかったとしており，またカプサイシンによる副作用（頻尿，恥骨部痛など）は2週間以内で治まったと報告している．

今回，われわれの症例では，膀胱内圧測定上は膀胱容量増加が示唆されたが，尿失禁のコントロールが可能となる程の膀胱容量は得られなかった．膀胱容量が250−300ml 以上あって初めて自己導尿に有用であると思われる．

効果不十分の原因として，以下のことが考えら

れた．

（1）最大膀胱容量が 50ml 程度と著しい過活動性膀胱に施行したこと

本注入療法は，諸家により不安定膀胱や低コンプライアンス膀胱に対して少数例に試みられているが，十分効果が得られなかったと報告されている[6)7)]．本症例は不安定膀胱や低コンプライアンス膀胱ではないが，著しい過活動性膀胱であったため効果不十分であった可能性がある．諸家の報告では最大膀胱容量 50ml 程度の症例に施行した例は少ないようである．

（2）全身麻酔下ではなく脊椎麻酔下で施行したこと

カプサイシンはC繊維をまず刺激することで効果をあらわすとされている．したがって本症例では腰椎麻酔をおこない脊髄後根神経節をブロックしたため，C繊維を十分に刺激できなかった可能性がある．しかし Fowler ら[6)] は律動性排尿筋収縮を抑制するために局所麻酔薬の膀胱内注入をあらかじめ行い，局所麻酔は排尿筋過反射に対する慢性抑制効果には影響を与えなかったと報告している．麻酔による影響は現在のところ明らかになっていない．

（3）最高尿道内圧が低下したこと

最高尿道内圧が低下するか検討した報告は見当たらないが，我々の症例では低下を認めた．

カテーテル周囲から初めて漏れる時点での膀胱内圧（Leak Point Pressure 以下 L.L.P.）と最高尿道内圧が一致するとは限らず，実際に最高尿道内圧と L.L.P. は一致しなかった．脊髄過活動性膀胱の L.L.P. と空虚時の最高尿道内圧は必ずしも一致せず，排尿筋括約筋協調例と協調不全例とでは値に違いが生じると考えられる．

さらに，最高尿道内圧は極端には低下しておらずこの程度の尿道内圧が残っている場合は尿失禁の原因とならない可能性がある．

しかし，最高尿道内圧の低下が尿失禁のコントロールに無効であった可能性も完全には否定はできない．

（4）尿量が多量であった可能性がある

自己導尿患者は尿混濁に対し飲水量を増やして対応している場合が多い．飲水量と尿量が厳密に相関するとは限らないが，飲水量も評価する必要があったと思われる．

適応，方法，評価に関して更に検討する必要があると思われた．

結　　語

自己導尿管理下の難治性尿失禁患者4名にカプサイシン膀胱内注入療法を行った．膀胱内圧測定では膀胱容量が増加したが，最高尿道内圧が低下したこと，また著しい過活動性膀胱患者が対象となったためか，尿失禁に対する十分な効果は得られなかった．

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Bladder-Pumping Therapy for the Treatment of Low-Capacity or Low-Compliance Bladders

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The walls of low-capacity or low-compliance bladders are thought to be less elastic than normal. Pumping of the bladder was found to disrupt collagen-fiber bundles in the rat bladder wall, offering the promise of potential clinical application. This result prompted us to use bladder-pumping therapy to soften the bladder wall in patients with low-capacity or low-compliance bladders to restore bladder elasticity. CO_2 gas or air, at a volume below the maximum bladder capacity (≤200 mL), was repeatedly pumped in and out of the bladder through a catheter under caudal anesthesia in 26 patients with low-capacity or low-compliance bladders and without uninhibited bladder contractions, who presented with urinary frequency or incontinence. A respirator was used to control the pumping at 0.5 cycles/s for a duration of 15 minutes. No serious adverse effects were encountered during or after the procedure. Overall subjective improvement was noted 4 weeks after the procedure in 11 of 18 patients with a low capacity bladder (<300 mL) and in five of eight patients with a low-compliance bladder (<20 mL/cm H_2O). The procedure significantly increased the maximum bladder capacity, single voided volume, and average urinary flow rate after 4 weeks. In the responding patients, subjective improvement lasted from 3 months to over 6 years. Bladder-pumping therapy is an easy and safe procedure and exerts a beneficial effect for a long period, in patients with low-capacity or low-compliance bladders and without uninhibited bladder contractions. *Neurourol. Urodynam. 19:19–28, 2000.*

Key words: collagen fiber; elasticity; capacity; compliance; urinary frequency; urinary incontinence

INTRODUCTION

Anticholinergic agents relieve urinary symptoms, including frequency and incontinence, in patients with uninhibited bladder contraction (overactive bladder) [Tapp et al., 1989; Yarker et al., 1995; Kaplinsky et al., 1996]. However, patients with

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low-capacity or low-compliance bladders that are not overactive respond poorly to these agents. While cholinomimetic agents often reduce urinary frequency and obstructive symptoms, including hesitancy and intermittency, by decreasing residual urine in some patients with an underactive bladder [Finkbeiner, 1985], these agents often worsen urinary frequency in those with low-capacity or low-compliance bladders. Severely symptomatic patients with low-capacity or low-compliance bladders who are unresponsive to medical therapy may require surgical intervention or bladder augmentation [Stothers et al., 1994; Kajbafzadeh et al., 1995]. Although the causes have not all been clarified [McGuire, 1994], the bladder wall in patients with low-capacity or low-compliance bladders appears to be less elastic than normal. This led us to hypothesize that pumping of the bladder might soften the bladder wall. Therefore, we first tested bladder pumping on halothane-anesthetized rats [Sugaya et al., 1997]. The procedure involved pumping air (0.5–0.8 mL) in and out of the bladder through a transurethral catheter at 0.5 cycles/s for 5 minutes, using a 1-mL syringe. This procedure significantly increased the bladder capacity but did not change the post-voiding residual volume. Electron microscopy after the procedure revealed deranged and disrupted collagen-fiber bundles in the bladder wall [Sugaya et al., 1997]. The results of our animal experiment suggested the potential for clinical application, so we attempted bladder-pumping therapy on patients with various urinary disorders who complained of frequency or incontinence. Preliminary trials of bladder-pumping therapy under caudal anesthesia were effective in patients with low-capacity or low-compliance bladders, but this therapy could not be performed in patients with an overactive bladder because it induced uninhibited contractions even under caudal anesthesia plus local injection of 1% lidocaine chloride [Sugaya et al., 1997]. Therefore, we have used bladder-pumping therapy for patients with low-capacity or low-compliance bladders, and here report the method of this therapy and the results.

PATIENTS AND METHODS

Bladder-pumping therapy was performed in 26 adult patients (12 men and 14 women) who presented with urinary frequency or incontinence at the outpatient clinics of Akita University Hospital and Ryukyu University Hospital from August 1991 to December 1998. Their ages ranged from 19 to 76 years, with a mean age of 57 years. All patients underwent urodynamic studies, including cystometry with electromyography of the external urethral sphincter, measurement of the single voided volume and residual urine volume, and/or uroflowmetry. They were confirmed not to have uninhibited bladder contractions on cystometry. They consisted of 16 patients with neurogenic bladder, seven with a low-capacity bladder (<300 mL) of unknown etiology, two with benign prostatic hypertrophy (BPH), and one with a mild cystocele (Tables I and II). None of them had bacterial urinary tract infection.

According to the results of the urodynamic studies, the patients were divided into two groups, i.e., 18 patients who had a low-capacity bladder (<300 mL, 130–290 mL) with or without underactivity and eight who had a low-compliance bladder (<20 mL/cm H_2O, 3.3–13 mL/cm H_2O) with or without underactivity. Four patients with a low-capacity bladder and four with a low-compliance bladder had an incompetent urethra with urinary incontinence. One patient with a low-compliance bladder had mild urethral obstruction due to BPH. Consent to undergo bladder-pumping therapy was obtained from all patients after they did not respond to anti-cholinergic or cho-

TABLE I. Characteristics of 18 Patients With a Low-Capacity Bladder*

Pt. No.-age-sex	Urological diagnosis	Underlying disease	Urodynamic study before BPT	4 weeks after BPT	Effective period of BPT (months)
1-38-F	Neurogenic bladder	Cervical Ca. post-op.	Low-capacity, underactive bladder Incompetent urethra	Good	3
2-40-F	Neurogenic bladder	Cervical Ca. post-op.	Low-capacity, underactive bladder Incompetent urethra	Unchanged	
3-43-M	Neurogenic bladder	Lumbar disc hernia	Low-capacity, underactive bladder	Good	5
4-46-M	Neurogenic bladder	Lumbar disc hernia	Low-capacity, underactive bladder	Unchanged	
5-63-M	Neurogenic bladder	Cerebral infarction	Low-capacity, underactive bladder Incompetent urethra	Fair	
6-64-M	Neurogenic bladder	Crow-Fukase's syndrome	Low-capacity, underactive bladder	Excellent	>36
7-65-M	Neurogenic bladder	OPLL	Low-capacity bladder	Fair	
8-65-M	Neurogenic bladder	Parkinson's disease	Low-capacity, underactive bladder	Good	12
9-67-M	Neurogenic bladder	Cerebral infarction	Low-capacity bladder	Unchanged	
10-71-F	Neurogenic bladder	Cerebral infarction	Low-capacity, underactive bladder Incompetent urethra	Fair	
11-75-M	Neurogenic bladder	Cerebral infarction	Low-capacity bladder	Good	>38
12-19-F	Low-capacity bladder	Unknown	Low-capacity bladder	Good	>50
13-46-F	Low-capacity bladder	Unknown	Low-capacity bladder	Excellent	>72
14-50-F	Low-capacity bladder	Unknown	Low-capacity bladder	Excellent	>48
15-53-F	Low-capacity bladder	Unknown	Low-capacity bladder	Excellent	>24
16-57-F	Low-capacity bladder	Unknown	Low-capacity bladder	Fair	
17-60-F	Low-capacity bladder	Unknown	Low-capacity bladder	Good	>30
18-62-F	Low-capacity bladder	Unknown	Low-capacity bladder	Good	10

*BPT, Bladder-pumping therapy; Cervical Ca. post-op., Cervical cancer post-operation; OPLL, ossification of the posterior longitudinal ligament.

linomimetic agents, or to other drugs. None of the patients had abnormalities of the upper urinary tract or bladder diverticulum on ultrasonography. The patients kept a diary of the frequency of micturition and incontinence from 1 week before to 4 weeks after bladder-pumping therapy.

The procedure consisted of the following. Air or CO_2 gas at a volume less than the maximum bladder capacity ($\leq$200 mL) was pumped in and out of the bladder through the channel of a 12-French transurethral two-way catheter with multiple holes near the tip. Another 6-French pigtail catheter (also with multiple holes near the tip) was placed in the bladder to allow the leakage of residual gas or air and thus to avoid an excessive increase of intravesical pressure, which was controlled by periodic manual opening or clamping as necessary. In the first two patients, bladder-pumping therapy was performed manually using a 200-mL syringe. In the next six patients, the procedure was performed using a motor-driven syringe. The remaining 18 patients

TABLE II. Characteristics of Eight Patients With a Low-Compliance Bladder*

Pt.No.-age-sex	Urological diagnosis	Underlying diseases	Urodynamic study before BPT	4 weeks after BPT	Effective period of BPT (months)
1-49-F	Mild cystocele		Low-compliance, underactive bladder	Excellent	>12
2-50-M	Neurogenic bladder	OPCA	Low-compliance, underactive bladder	Good	>36
3-52-F	Neurogenic bladder	Cervical Ca. post-op.	Low-compliance bladder	Good	3
4-55-F	Neurogenic bladder	Cervical Ca. post-op.	Low-compliance, underactive bladder Incompetent urethra	Good	3
5-65-F	Neurogenic bladder	Recta Ca. post-op.	Low-compliance, underactive bladder Incompetent urethra	Unchanged	
6-67-M	Neurogenic bladder	Rectal Ca. post-op.	Low-compliance, underactive bladder Incompetent urethra	Unchanged	
7-75-M	BPH		Low-compliance, underactive bladder Obstructive urethra	Fair	
8-76-M	BPH	Post-TUR-P	Low-compliance bladder Incompetent urethra	Excellent	>36

*BPT, Bladder-pumping therapy; OPCA, Olivo-ponto-cerebellar atrophy; Cervical Ca. post-op., Cervical cancer post-operation; Rectal Ca. post-op., Rectal cancer post-operation; BPH, Benign prostatic hypertrophy; TUR-P, Transurethral resection of the prostate.

underwent bladder-pumping therapy using a respirator (Shinano, SN-480-5, Tokyo, Japan) connected to a CO_2 gas outlet that allowed gas leakage at high intravesical pressures (i.e., >60–80 cm H_2O). The intravesical pressure was monitored via the other channel of the two-way catheter. Pumping in and out was repeated at 0.5 cycles/s, with pumping being initiated very slowly and increased gradually. All patients underwent bladder-pumping therapy for 10–15 minutes under caudal anesthesia with 20 mL of 1% lidocaine chloride. Oral prophylactic antibiotic therapy was administered for 2–3 days after the procedure to prevent urinary tract infection. The patients continued to take any medications that were being administered before bladder-pumping therapy, but no additional medications (except for the antibiotics) were given for at least 4 weeks after the procedure. Two weeks after bladder-pumping therapy, urine specimens from all patients were sent for urinalysis. Four weeks after the procedure, the patients underwent urodynamic studies and made a subjective assessment of the effect of bladder-pumping therapy (excellent, good, fair, unchanged, or worse for each symptom and for the overall impression of this therapy) based on the impressions of the patients themselves. The subjective assessment indicated the degree of patient satisfaction with the results of this therapy. Excellent and good meant that the patient was satisfied, corresponding to 0 or 1 points on the quality-of-life score. The patients were followed up for from 3 months to more than 6 years and were questioned the duration of effect of this therapy at our outpatient clinics.

Results are reported as the mean ± standard deviation. Student's *t*-test was used for statistical analysis of paired data. A P value of <0.05 was considered to be statistically significant.

RESULTS

During bladder-pumping therapy, nearly all of the patients reported a desire to void even under caudal anesthesia. The intravesical pressure increased to 5–70 cm H_2O (amplitude) when gas was injected into the bladder, while the baseline intravesical pressure (when gas was pumped out at the beginning of the procedure) was 20–40 cm H_2O at the time when the pigtail catheter was clamped (Fig. 1). Both the maximum intravesical pressure and the baseline intravesical pressure gradually decreased within 5–15 minutes at a gradient of 10–30 cm H_2O. In patients reporting a strong desire to void when gas was pumped in (because of insufficient anesthesia), the volume of gas could not be increased to 200 mL or near the maximum bladder capacity, and the baseline intravesical pressure did not decrease toward the end of bladder-pumping therapy. No difference between pumping air ($n = 8$) and CO_2 gas ($n = 18$) was recognized during or after the procedure, although CO_2 gas was used to avoid the risk of air embolism. No serious adverse effects were encountered during or after the procedure. At 2 weeks, urinalysis data remained normal.

At 4 weeks, 11 of 18 patients (61%) with a low-capacity bladder and five of eight patients (63%) with a low-compliance bladder reported that the overall effect of bladder-pumping therapy was excellent or good (Tables I and II). From 50 to 75% of patients with a low-capacity or low-compliance bladder reported some improvement of storage symptoms (including urinary frequency and incontinence), as well as voiding symptoms (such as hesitancy, intermittency, and sensation of residual urine) immediately after the procedure (Table III). Seventy-five percent of patients who had lower abdominal discomfort including heaviness of the lower abdomen also reported a relaxed lower abdomen. There were no patients whose symptoms became worse. According to the diary notes made on 3 consecutive days before and 4 weeks after bladder-pumping therapy, the micturition frequency decreased significantly ($P < 0.0001$) from 12.2 ± 3.1 to 8.3 ± 1.5 times/day in 26 patients. Urinary incontinence also decreased significantly ($P = 0.0039$) from 2.1 ± 1.2 to 1.0 ± 0.7 times/day in eight patients having this symptom. These patients had stress incontinence with or without urge incontinence, although cystometry did not reveal uninhibited bladder contractions.

In patients with a low-capacity bladder, bladder pumping significantly increased the intravesical volume at the first desire to void (mean 57% increase), the maximum bladder capacity (52%), the single voided volume (89%), and the maximum (22%) and average urinary flow rates (41%) (Table IV). In patients with a low-compliance bladder, bladder-pumping therapy significantly increased the maximum bladder capacity (mean 20% increase), the bladder compliance (67%), the single voided volume (101%), and the average flow rate (93%) (Table IV). Residual urine volume was significantly decreased (mean 32% decrease) in patients with a low-compliance bladder (Table V). Cystoscopy 4 weeks after bladder-pumping therapy in the initial three patients with a low-capacity bladder and 3 months after the procedure in two patients with a low-compliance bladder, who exhibited a good response for only 3 months, revealed no remarkable changes of the bladder wall.

A single session of bladder-pumping therapy lasting for 10–15 minutes resulted in subjective improvement in patients with low-capacity or low-compliance bladders, and the improvement lasted from 3 months to over 6 years. In two patients with a low-compliance bladder who exhibited a good response, urinary frequency and in-

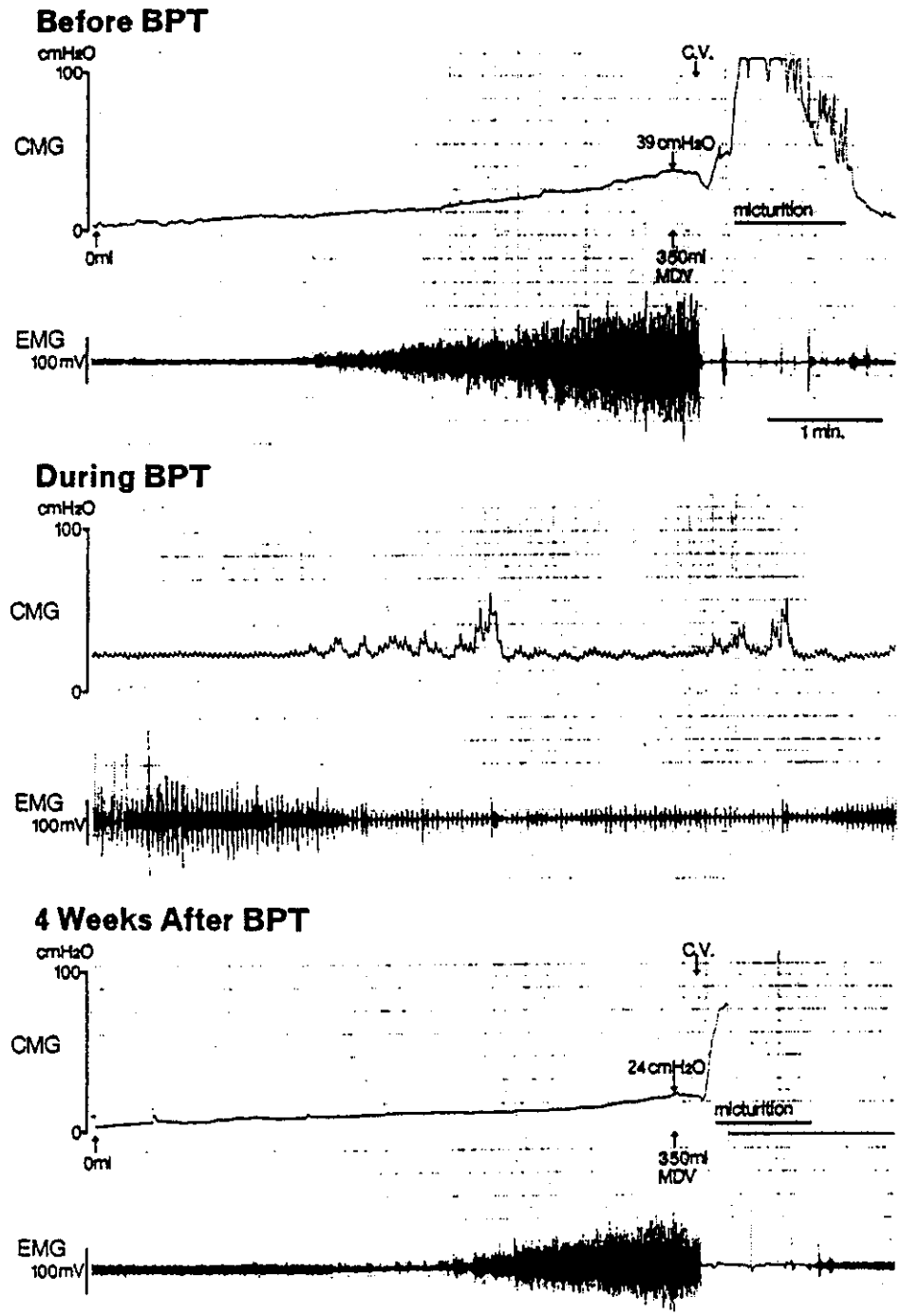

Fig. 1. Cystometrograms (CMG) and electromyograms (EMG) of the external urethral sphincter muscle obtained in a 76-year-old man with a low-compliance bladder before, during, and 4 weeks after bladder-pumping therapy (BPT). Cystometric capacity was 350 mL before BPT. Intravesical pressure at the maximum desire to void (MDV) was 39 cm H_2O and bladder compliance was 9.0 mL/cm H_2O. Micturition occurred on the command to void (C.V.). During BPT, the intravesical pressure and EMG activity changed rhythmically according to the rhythm (0.5 cycles/s) of bladder pumping with 200 mL of CO_2 gas. Four weeks after BPT, the intravesical pressure was 24 cm H_2O and bladder compliance was 14.6 mL/cm H2O when 350 mL of physiological saline was injected into the bladder, although this volume did not reach the maximum bladder capacity.

TABLE III. Subjective Assessment of the Effects of Bladder-Pumping Therapy on Each Symptom in Patients with Low-Capacity or Low-Compliance Bladders

Symptom	Excellent	Good	Fair	Unchanged	Worse	Total
Urinary frequency	6	9	5	4	0	24
		(63%)				
Urinary incontinence	2	3	2	1	0	8
		(63%)				
Hesitancy/intermittency	3	6	2	4	0	15
		(67%)				
Sense of residual urine	4	2	2	4	0	12
		(50%)				
Lower abdominal discomfort	5	4	3	0	0	12
		(75%)				

*Impression of patients (n = 26) 4 weeks after bladder-pumping therapy.

continence developed again 3 months after the procedure and an additional session of bladder-pumping therapy resulted in symptomatic relief that lasted for more than 2 years. Bladder-pumping therapy did not achieve symptomatic improvement in the remaining 10 patients (38%) with low-capacity or low-compliance bladders, probably because the volume of gas pumped in was not sufficient to increase the bladder volume due to insufficient anesthesia, since these patients reported a strong desire to void when the volume of gas was increased.

DISCUSSION

Bladder-pumping therapy was effective not only for urine storage symptoms but also for voiding symptoms in patients with low-capacity or low-compliance bladders, although the gas volume pumped in did not exceed the maximum bladder capacity during the procedure. Urodynamic parameters related to urine storage and voiding also improved 4 weeks after bladder-pumping therapy as well as the subjective assessments. Bladder-pumping therapy could be a treatment of choice for urinary symptoms in patients with low-capacity or low-compliance bladders, even in the presence of underactive bladder function.

Previous electron microscopic studies on rats subjected to bladder pumping have shown that this procedure deranges and disrupts collagen-fiber bundles in the bladder wall [Sugaya et al., 1997]. These alterations of the bladder wall may also

TABLE IV. Urodynamic Parameters Before and 4 Weeks After Bladder-Pumping Therapy (BPM) in Patients With a Low-Capacity Bladder*

Urodynamic parameter	No. Pts.	Pre-BPT	Post-BPT	*P* value
Volume at first desire to void (mL)	17	138 ± 31	216 ± 543	<0.0001
Maximum bladder capacity (mL)	18	244 ± 30	370 ± 90	<0.0001
Bladder compliance (mL/cm H_2O)	18	32.9 ± 9.3	28.0 ± 9.4	0.0078
Single voided volume (mL)	18	168 ± 43	318 ± 105	<0.0001
Maximum flow rate (mL/s)	15	13.9 ± 7.5	16.9 ± 4.8	0.0139
Average flow rate (mL/s)	15	6.6 ± 4.2	9.3 ± 3.3	<0.0001
Residual volume (mL)	18	30 ± 33	23 ± 34	0.1891

*Data are shown as the mean ± standard deviation.