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Bladder filling inhibits somatic spinal motoneurones

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Abstract

Objectives: Despite evidence that the activation of visceral afferents modulates spinal motoneurone activity in humans the responsible circuits remain unclear. We investigated changes in spinal motoneurone excitability during bladder filling in 8 healthy subjects and in 8 patients with spinal cord lesions and 5 patients with multi-infarct encephalopathy.

Methods: Spinal motoneurone excitability was studied by analysing changes in H-reflex, F-wave and motor-evoked potential (MEP) size recorded from the calf muscles under different bladder filling conditions.

Results: In normal subjects, maximal bladder filling significantly suppressed the H-reflex, F-wave and MEPs; after bladder voiding these responses returned to normal. In patients with encephalopathy maximal bladder filling strongly reduced H-reflex size; similarly to normal subjects H-reflex returned to control value after bladder voiding. In patients with spinal cord lesions, activation of bladder afferents left the H-reflex unchanged.

Conclusions: These findings indicate that bladder distension induces post-synaptic inhibition of spinal motoneurones through a suprasegmental pathway, which is interrupted by rostral spinal cord lesions. This vesical-induced inhibition is probably mediated by the propriospinal system rather than by the diffuse noxious inhibitory control circuit. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Motoneurone excitability; Bladder proprioception; H-reflex; Motor-evoked potential

1. Introduction

The neuronal mechanisms activated during the filling and voiding phases of bladder function involve several structures: somatic and autonomic peripheral pathways from and to the bladder, segmental spinal circuits and the supraspinal control centres (de Groat et al., 1981; Mc Mahon, 1986; de Groat, 1998). Urinary bladder control involves a continuous interaction between the central and peripheral nervous systems. Distension of the bladder leads to a gradual increase in pelvic nerve afferent firing, but initially evokes no pelvic nerve efferent firing; subsequently, when the micturition threshold is reached, the efferent pathway is switched on (Habler et al., 1993) in an 'all-or-nothing' fashion. The micturition reflex is elicited by the activation of afferent unmyelinated C fibres and the finely myelinated A delta fibres of pelvic nerves connected to the slowly adapting mechano-receptors of the bladder wall (de Groat et al., 1982, 1998; Habler et al., 1993; Sengupta and Gebhart, 1994). Neurones that receive input from the urinary bladder (Fields et al., 1970; Milne et al., 1981) can be found in the dorsal horn cells connected to supraspinal structures controlling the micturition reflex (Mc Mahon and Morrison, 1982; de Groat et al., 1998; Blok and Holstege, 2000). The same neurones increase their firing rates as vesical pressure increases to a level that might be considered noxious. Urinary bladder distension in monkeys (Brennan et al., 1989), however, inhibits spino-thalamic tract cells (i.e. wide dynamic range, high threshold and high threshold inhibitory cells). It also depresses the activities of most convergent neurones in rats (Cadden and Morrison, 1991). Other studies have demonstrated that bladder distension or contraction in animals decreases respiratory activity, probably by acting on the brainstem (Schondorf and Polosa, 1980; Gdovin et al., 1994).

In this study we investigated the effects of urinary bladder filling on spinal motoneurone excitability in humans. In normal subjects, we assessed the soleus H-reflex changes under different bladder filling conditions. We recorded the muscle-evoked potentials after transcranial magnetic stimulation in normal subjects to see whether the effects are pre-

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Table 1
Clinical features of patients with spinal cord lesions[a]

Patient	Age (years)	Level of lesion	Clinical features	Aetiology
1	58	D1	P, A, H, B	Infarction
2	76	C5–C6	P, A, H, B	Spondilosys
3	57	C4–C5	T, A, H, B	Traumatic
4	33	C5–C6	P, A, H, B	Traumatic
5	43	C7	P, A, H, B	Traumatic
6	48	C5–C7	P, A, H, B	Traumatic
7	48	C5–C7	P, A, H, B	Traumatic
8	74	D3	P, A, H, B	Traumatic

[a] T, tetraplegia; P, paraplegia; A, anesthesia; H, lower limb hyperreflexia; B, Babinski sign.

or post-synaptic in origin. In order to demonstrate the importance of spinal loop integrity, in patients with multi-infarct encephalopathy (ME) and in patients with spinal lesions we studied the soleus H-reflex changes.

2. Materials and methods

This study was conducted in 8 normal subjects (age: 57.8 ± 9.2 years – mean ± SD), 8 patients with spinal cord lesions (age: 54.6 ± 14.8 years) and 5 patients with ME (age: 68.2 ± 6.2 years). Of the patients with spinal cord lesions, one had a spinal cord infarction, one had spondilosys and 6 had spinal cord injuries. Magnetic resonance imaging (MRI) scans showed an area of increased T2 signal within the central portion of the spinal cord at D1 level in the patient with infarction, and a disc protrusion compressing the spinal cord in the patient with spondilosys. In the post-traumatic patients, who had had the injuries at least 6 months before examination, MRI scans showed various combinations of spinal bone fractures, spinal cord segmental atrophy or hyperintense T2 areas attributed to gliosis (Table 1 summarises the different level of lesion for each patient). All the patients with spinal cord lesions had tetraplegia- or paraplegia, sensory loss and lower limb hyperreflexia. In all the ME patients, who had paraparesis and tetrahyperreflexia neuroimaging confirmed a ME. All participants gave their written informed consent to the study and the local ethical committee approved the procedures. To exclude bladder outlet obstruction, all normal subjects underwent uroflowmetry, cystometry and a pressure/flow study. With the subjects lying in the gynecological position, a Nelaton 6 Ch catheter (Porges-La Boursidiére, France) was introduced into the bladder through the urethra (Fig.

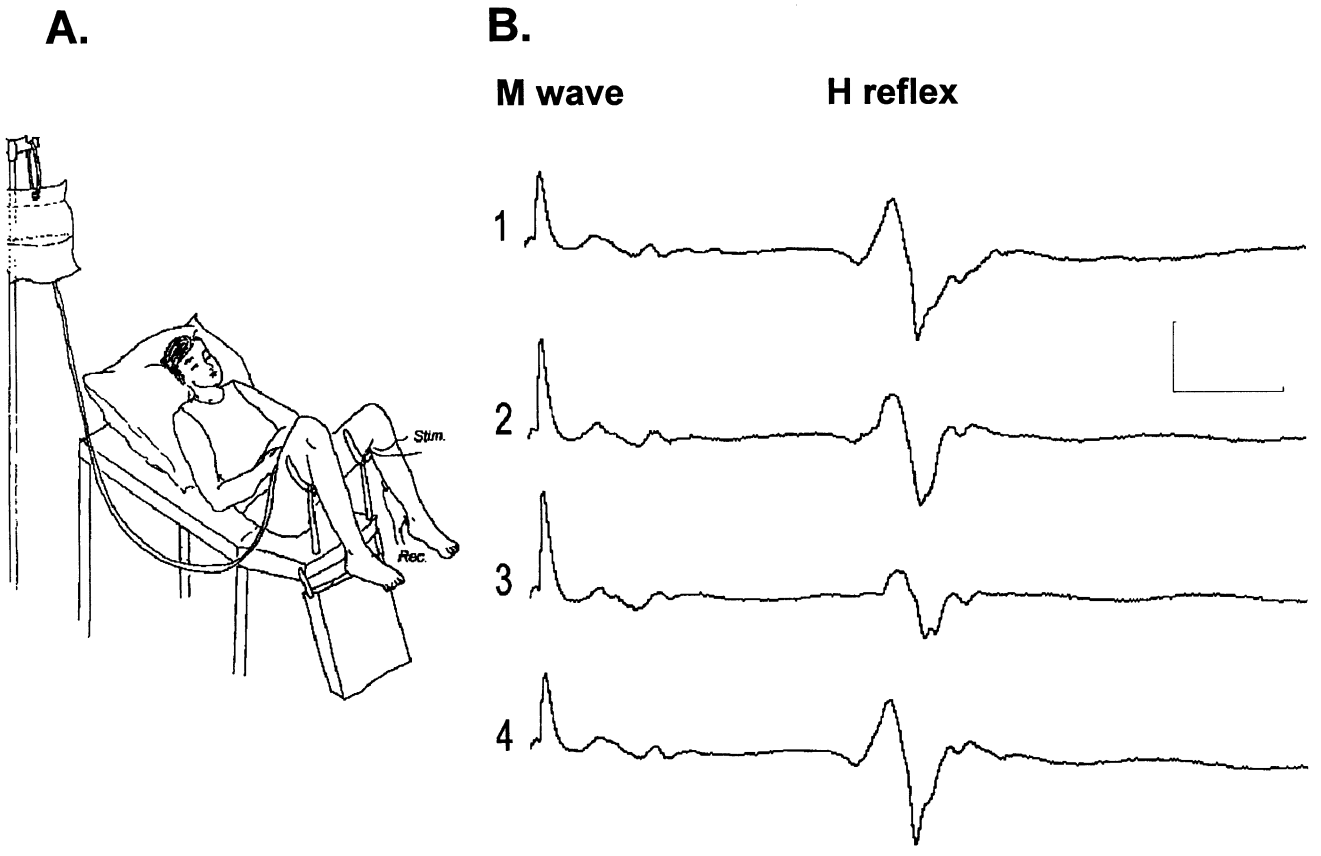

Fig. 1. (A) Drawing illustrating the subject's position and the stimulation and recording set. (B) H-reflex evoked by tibial nerve stimulation obtained in a normal subject. Each trace is the average of 10 trials. Calibration: *Y* axis 500 μ, *X* axis 15 ms. Trace 1, H-reflex obtained at empty bladder; Trace 2, at medium bladder filling; Trace 3, at maximum bladder filling; Trace 4, H-reflex after bladder voiding.

1A) and a balloon was introduced into the rectum to record simultaneously intravesical, rectal and detrusor pressures, with urodynamic equipment (Dantec Duet-Medtronic Inc., MN, USA). Filling velocity was kept constant at 20 ml/min. The 'threshold' was defined as the bladder volume at the first filling sensation felt by normal subjects and ME patients (sensory threshold); in patients with spinal cord lesions, owing to the sublesional sensory loss, the threshold was defined as the minimum bladder volume inducing the first overactive detrusor contraction (reflex threshold).

In normal subjects and ME patients, we measured the cystometric capacity, the corresponding bladder volume and intravesical pressures. Pressures and flows were then recorded using a PQ plot advanced computerised analysis of the data.

3. Stimulation

Electrical stimuli were delivered to the right tibial nerve (0.5–1.0 ms, 20–100 mA) with a Grass S88 electric stimulator through monopolar needle electrodes placed in the popliteal fossa. For the H-reflex study, stimulus intensity was set to evoke a constant M-wave of low amplitude. For the F-wave study, stimulus intensity was set at the maximum output of the stimulator.

Transcranial magnetic stimuli were delivered with a Novametrix Magstim D200 device (Novametrics, Whitland, Wales, UK) connected to a flat round coil placed over the vertex, with the current flowing anticlockwise. The intensity of stimulation used was 150% of the motor threshold (Mth). The Mth was defined as the minimum stimulus intensity that induced, in 8 consecutive trials, a clear motor-evoked potentials (MEP) with an amplitude of at least 100 μV, during a slight voluntary contraction of the target muscle.

4. Recording

Electromyogram (EMG) signals were recorded from the soleus-muscle using Ag–AgCl surface electrodes (bandwidth 20 Hz–10 kHz) and analysed by means of a Mystro Vickers apparatus (Vickers Medical, Woking, Surrey, England). Ten trials were collected and then averaged for each condition. Each trial was repeated at 30 s intervals. H-reflex, M-wave and MEP amplitudes were measured peak-to-peak; the F-wave area was calculated after full-wave rectification of the EMG trace. H-reflex and MEP amplitudes and F-wave area were expressed as a percentage of the unconditioned response. Stimulus intensity was adjusted to evoke an M-wave of low amplitude and an H-reflex of about 50% of the maximum. To control the efficacy and the stability of the nerve stimulation, the size of the M-wave was measured at the beginning of the experiment and monitored throughout.

In normal subjects, the H-reflex was tested under various conditions: empty bladder (control value); medium filling (about 200 ml); maximum bladder capacity (when subjects felt they could no longer delay micturition) and 10 min after voiding. In 6 of the 8 normal subjects, the F-wave and MEP were also tested under the two conditions: empty and full bladder. In patients with ME and spinal cord lesions, the H-reflex was tested with the bladder empty (control value), at medium filling and at maximum bladder capacity and 10 min after voiding. We tested the F-wave only in 3 of the 8 patients with spinal cord lesions under two conditions: empty and full bladder as high-intensity electrical stimulation evoked a flexion reflex altering cistomanometric recording. Medium filling and maximum bladder capacity were assessed according to the cystometric data previously obtained for each subject.

The Wilcoxon test, analysis of variance (ANOVA) and Student's t test ($P < 0.05$) were used for statistical analysis.

5. Results

In normal subjects and patients, electrical stimuli delivered to the tibial nerve elicited a soleus-muscle H-reflex at a similar latency (31.2 ± 1.8 ms and 30.4 ± 2.2 ms). Conversely, under baseline conditions, i.e. with an empty bladder, the amplitude differed (5.4 ± 3.7% and 12.0 ± 4.5% of the maximum M-wave – $P < 0.01$). MEP-size, which could be checked only in normal subjects, was similar to the H-reflex amplitude (6.7 ± 1.5% of the maximum M-wave).

In normal subjects, EMG recordings at medium bladder filling indicated a slight but not significant reduction in H-reflex size (74.8 ± 30% of the control – n.s.). At maximum bladder filling, the size of the H-reflex decreased significantly (51 ± 30% of the control – $P < 0.001$). Ten minutes after voiding H-reflex size recovered to 96.4 ± 31% of control values obtained before bladder filling (Fig. 1B; Table 2). Maximum bladder filling decreased the F-wave size (63.3 ± 27% of the control – $P = 0.02$) and MEP-size (61 ± 21% of the control – $P = 0.025$).

In patients with ME the H-reflex at medium bladder filling remained similar to the control value, at maximum filling the H-reflex size decreased significantly (45 ± 14% of the control – $P = 0.02$). Ten minutes after voiding the H-reflex size recovered to 97.0 ± 11% of control (Table 3).

In patients with spinal cord lesions, the H-reflex increased slightly though not significantly in amplitude at maximum bladder filling and decreased again after voiding (120.4 ± 29% and 106 ± 7.3% of the control) (Table 4). In the 3 patients with spinal lesion in which we studied the F-wave, maximum bladder filling left the F-wave size unchanged (103, 110 and 108% of the control response).

6. Discussion

The effects of urinary bladder filling on spinal motoneurone excitability differed distinctly in healthy subjects, ME patients and spinal lesion patients. Whereas in normal

Table 2
Changes in spinal excitability during urinary bladder filling: controls[a]

Subjects	Proprioceptive threshold (ml)	Max bladder capacity (ml)	H-reflex amplitude (% control)		
			Med	Max	After voiding
1	153	430	11	2	32
2	110	420	77	31	95
3	130	360	100	27	78
4	100	320	97	76	118
5	190	530	100	77	118
6	110	300	68	44	135
7	120	340	58	80	90
8	216	400	89	73	106
Mean ± SD	128.6 ± 29	387.5 ± 74	74.8 ± 30 n.s.	51 ± 30 $P < 0.0001$	96.4 ± 31 n.s.

[a] Proprioceptive threshold, medium (med), maximum (max) bladder capacity and H-reflex amplitude (expressed as a percentage of control values) in normal subjects.

subjects and ME patients bladder filling suppressed the H-reflex, in patients with spinal lesions it did not. In normal subjects, at maximum bladder filling the size of the EMG responses (the H-reflex, F-wave and MEP) decreased.

Similar findings were described by Koley et al. (1984) who studied monosynaptic reflexes in animals. They showed that the viscero-somatic responses after bladder distension are inhibitory, inhibition being highest in decerebrated but lowest in spinal animals. Another set of visceral afferent fibres having regulatory effects on spinal somatic circuits is pulmonary C fibres which produce powerful inhibition of spinal motoneurones (Deshpande and Devanandan, 1970; Anand and Paintal, 1980).

The H-reflex depression observed in healthy subjects could originate from a pre-synaptic inhibition exerted by interneurones activated by the vesical afferent input. Yet in our experiments, maximum bladder filling in healthy subjects also reduced the size of the MEP. MEPs are evoked by descending corticospinal discharges impinging, directly or through interneurones, on the same motoneurones responsible for the H-reflex (Jankowska et al., 1975). As long as cortico-motoneuronal connections undergo no pre-synaptic inhibition (Nielsen and Petersen, 1994), this finding suggests that the activation of bladder afferents directly changes the level of spinal motoneurone excitability through a post-synaptic mechanism. A post-synaptic mechanism is further confirmed by our observation that bladder filling in normal subjects also reduced the size of the F-wave, a response that directly tests motoneuronal excitability.

Because the H-reflex depression coincided with maximum filling, when subjects felt pain and could no longer delay micturition, the responsible vesical afferent fibres presumably conveyed a nociceptive input classically relayed by unmyelinated and thinly myelinated fibres. In humans, the visceral nociceptive inputs appear to act on at least two systems, the diffuse noxious inhibitory controls (DNIC) (Cadden and Morrison, 1991) and the propriospinal system (Schondorf et al., 1983; Weaver, 1985). The DNICs, postulated in animals and humans (Le Bars et al., 1979a,b, 1981; Villanueva et al., 1986a,b; Cadden and Morrison, 1991; De Broucker et al., 1990; Bouhassira et al., 1993), are mediated by a loop involving supraspinal structures and modulate the activity of spinal cord neurones that receive widespread noxious visceral and somatic stimuli. The propriospinal heterosegmental system is formed by neurones originating from circumscribed areas of the cervi-

Table 3
Changes in spinal excitability during urinary bladder filling: patients with ME[a]

Subjects	Proprioceptive threshold (ml)	Max bladder capacity (ml)	H-reflex amplitude (% control)		
			Med	Max	After voiding
1	137	300	100	60	110
2	122	350	98	30	80
3	110	380	n.e.	50	100
4	141	400	96	30	98
5	100	310	n.e.	57	97
Mean ± SD	122 ± 17	348 ± 43	98 ± 2	45 ± 14 $P < 0.022$	97 ± 11

[a] Proprioceptive threshold, medium and maximum bladder capacity and H-reflex amplitude (expressed as a percentage of control values) in patients with ME. n.e. indicates not evaluated.

Table 4
Changes in spinal excitability during urinary bladder filling: patients with spinal cord lesions[a]

Subjects	Proprioceptive threshold (ml)	Max bladder capacity (ml)	H-reflex amplitude (% control)		
			Med	Max	After voiding
1	150	460	n.e.	105	113
2	121	388	91	104	94
3	100	348	n.e.	178	105
4	80	165	n.e.	105	99
5	110	420	92	95	104
6	90	131	138	100	117
7	130	320	n.e.	152	105
8	170	220	107	123	109
Mean ± SD	118.8 ± 30	306.5 ± 121	107.4 ± 21 n.s.	120.4 ± 29 n.s.	106.0 ± 7 n.s.

[a] Proprioceptive threshold, medium and maximum bladder capacity and H-reflex amplitude (expressed as a percentage of control values) in patients with spinal cord lesions. n.e. indicates not evaluated.

cal, thoracic, upper lumbar or sacral cord that independently modulate background activity and noxious responses of multi-receptive lumbar dorsal horn neurones. At lumbar level, the propriospinal system is constituted by interneurones which relay di- or polysynaptically to lumbosacral motor nuclei and are modulated by descending reticulospinal pathways (Jankowska et al., 1974).

In our opinion, motoneurone inhibition secondary to bladder distension represents a viscero-somatic reflex activated by nociceptive afferent input and mediated by the propriospinal system. A propriospinal system-mediated reflex accords with previous studies suggesting that in cats, the propriospinal system is involved in the intersegmental transmission of input from bladder afferents to upper thoracic sympathetic pre-ganglionic neurones (Schondorf et al., 1983; Weaver, 1985). In addition, the activation of the DNIC by painful somatic stimuli leaves the H-reflex unchanged (Willer et al., 1989).

In patients with spinal cord lesions, we found that maximal vesical distension produced, instead of inhibition, a slight (though not significant) facilitation of the H-reflex. Similar results have been reported by Porter and Krell (1976), who found that urinary bladder distension increased the size of the H-reflex in paraplegic patients. Because in patients with spinal lesions the high-intensity stimuli necessary to produce the F-wave evoked flexion reflexes that could interfere with cistomanometric recordings, we studied the F-wave only in the first 3 patients. In these patients, however, the F-wave was completely unchanged by maximum bladder filling, consistently with the lack of H-reflex inhibition. The disappearance of the inhibitory viscero-somatic reflex can be attributed to removal of descending modulation relayed by reticulospinal pathways and acting on propriospinal interneurones and not by corticospinal tract because patients with ME and normal subjects had similar H-reflex inhibition.

Our findings are apparently in contrast with those by Dyro and Yalla (1986). These authors found that bladder filling potentiated reflex responses in the periurethral muscle in normal subjects though it did not in patients with upper motoneuron lesions. Probably slow bladder filling produces a complex response characterised not only by an increase in sphincteric muscle activity necessary to ensure the bladder continence, but also an inhibition of detrusor muscle activity (Shefchyk, 2001) and a weaker, diffuse inhibition of somatic, heteronimous muscles. In patients with spinal lesion, the control exerted by the pontine reticular formation is lost, resulting in sphincteric dyssynergia and absence of somatic muscle inhibition.

In conclusion, urinary bladder filling makes the spinal motoneurones hypoexcitable. This inhibitory effect arises through activation of a complex viscero-somatic circuit, possibly the propriospinal system, modulated by supraspinal influences and abolished by spinal cord damage.

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