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Denervation Supersensitivity of the Urethra to α-Adrenergics in the Chronic Neurogenic Bladder

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Summary. The response of the urethral pressure profile to the administration of various autonomic drugs was compared between a group of eight patients with chronic neurogenic bladder as evidenced by denervation supersensitivity to besacholine^R and a group of 10 control subjects. A supersensitive response to the administration of an α-stimulant with a rise of maximum urethral pressure of 10 mmHg or more above the control urethral pressure was uniformly observed in the urethra of patients with chronically denervated bladders. Mechanisms of supersensitivity are postulated and the significance of α-adrenergic innervation of the urethra are stressed. These results appear to add pharmacological evidence of α-adrenergic predominance in the urethra which is now believed to be dually innervated.

Key words: Denervation supersensitivity - Urethra of chronic neurogenic bladder - α adrenergic stimulation.

Recent investigations (6, 12, 13) and clinical experience (14, 20) indicate the significance of α-adrenergic innervation of the sphincteric urethra. When a unit is destroyed in an efferent nerve pathway, an increased sensitivity to chemical agents develops in the isolated structure, the effect being maximal in the part denervated (5). If α-adrenergic innervation plays a primary role in the function of the sphincteric urethra, a supersensitive response to α-adrenergic stimulation should occur in the urethra after denervation. To investigate this possibility the response of the urethra to various autonomic stimulants was compared in a group of patients with chronic neurogenic bladder and in control subjects whose bladder did not show any evidence of chronic denervation (16).

MATERIALS AND METHODS

A modification of the urethral pressure profile (UPP) study described by Brown and Wickham (4) was used and the method has been reported previously (12). A maximum urethral pressure (UPmax) was measured in a preliminary UPP study and repeated following the administration of various autonomic stimulants to determine the difference in UPmax. The autonomic agents employed in the investigation were an α-stimulant (4 mg of intravenous ethylphenylephrine), β-stimulant (0.2 mg of isoproterenol in 100 cc of normal saline as i.v. drip) and a parasympathomimetic (2.5 mg of subcutaneous bethanechol chloride - Besacholine^R).[1]

Eighteen individuals were examined. Group 1 comprised eight patients with established autonomous neurogenic bladders due to various causes, which had in common the finding of denervation supersensitivity of the bladder (15, 16) to besacholine^R. Four of these patients were flaccid paraplegics who had suffered traumatic low lumbar and sacral cord injuries; three patients had undergone

[1] Besacholine^R - bethanechol chloride. Eisai pharmac. Co., Japan

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Table 1. Cases 1-4, paraplegics from spinal cord injury, Cases 5-7, patients with autonomous bladder from radical pelvic operations. Case 8, congenital myelodysplasia. Cases 9, L2 spinal shock. Cases 10-12, patients with simple stress incontinence. Cases 13-16, normal individuals. Cases 17, 18, patients after retroperitoneal lymphadenectomy with ejaculatory failure

	UPmax in mmHg							Blood pressure in mmHg		
Case	(a) control	(b) α-stimulant	b-a	(c) besacholine	c-a	(d) β-stimulant	d-a	(a) control	(b') α-stimulant	b'-a'
Group 1										
1	26	36	10	28	2	26	0	132/80	142/82	10/2
2	28	39	11	34	6	28	0	140/90	160/94	20/4
3	30	46	16	30	0	30	0	104/76	130/80	26/4
4	20	42	22					88/68	94/70	6/2
5	26	38	12					154/90	160/94	6/4
6	52	65	13	52	0	52	0	120/70	126/74	6/4
7	52	65	13	53	1	53	1	114/70	120/72	6/2
8	30	40	10	33	3	30	0	120/70	160/100	40/30
			mean 13.4		mean 2.0		mean 0			mean 15/7
Group 2										
9	46	50	4					120/80	140/90	20/10
10	36	42	6			36	0	140/88	160/92	20/4
11	44	48	6					116/80	140/84	24/4
12	37	40	3					110/70	130/76	20/6
13	58	58	0			58	0	120/70	150/86	30/16
14	60	60*	0					150/100	210/130*	60/30
15	56	57*	1			56	0	120/80	180/110*	60/30
16	60	62	2					110/70	132/104	22/34
17	60	62*	2			60	0	124/70	186/112*	62/32
18	56	57	1					114/72	136/100	22/28
			mean 2.5				mean 0			mean 22/14

*... I. V. drip of 0.1 per cent noradrenaline 1 ml in 500 ml normal saline as α-stimulant.

radical pelvic operations for malignancies, and one patient had congenital myelodysplasia.

Group 2 consisted of ten patients with negative besacholine^{R} tests and served as controls. One of these patients was a paraplegic in spinal shock, three had simple stress incontinence, two had undergone retroperitoneal lymphadenectomy with loss of ejaculation (10), and four were normal. In selected cases from the control group (marked * in the Table 1) an intravenous drip of 0.1% noradrenaline 1 ml in 500 ml normal saline was used to exaggerate the cardiovascular response to determine its effect on the urethral pressure. Throughout the examination, blood pressure, pulse rate, and cardiac status were carefully monitored.

RESULTS (Table 1.)

Group 1: The urethras of the patients with chronically denervated bladders showed supersensitive responses to α-stimulation with a mean elevation of UPmax of 13.3 mmHg (10-22 mmHg) (Fig. 1a). The administration of an α-stimulant after α-blockade (phentolamine 10 mg. I. V.) failed to evoke these supersensitive responses even with α-stimulant dosage strong enough to cause systemic hypertension (Fig. 1b). Parasympathomimetic drugs did not affect the urethras of neurogenic bladder patients but their bladders responded to this drug in a supersensitive manner (Fig. 1c). The difference of UPmax

after 2.5 mg of subcutaneous besacholine^{R} averaged 2 mmHg (0-6 mmHg).

Group 2: In the patient with acute spinal shock from traumatic transverse myelitis at the L2 level, UPmax rose by only 4 mmHg after α-stimulation. In three patients with simple stress incontinence, the difference in UPmax averaged 5 mmHg (3-6 mmHg). There was an average rise of 0.7 mmHg (0-2 mmHg) in the four normal individuals, and 1.5 mmHg in both patients with retroperitoneal lymphadenectomy and ejaculatory failure. Thus in the 10 patients who served as controls, the average rise in UPmax was only 2.5 mmHg after administration of a α-stimulant (Fig. 2).

There was no supersensitive response of the urethra to β-stimulation in either group (Fig. 1 d).

The mean hypertensive (systolic/diastolic) response in the patients with neurogenic bladders was 15/7 mmHg with α-stimulation and 13.7/4 mmHg with β-stimulation, whereas it was 22/14mmHg and 15/9.5 mmHg respectively in the control group. The supersensitive response of the urethra of α-stimulation lasted longer than its systemic effect (Fig. 1 a). In the selected control cases in whom an intravenous drip of noradrenaline was used instead of ethylphenylephrine, urethral pressure remained unchanged despite a disproportionate rise (60/34 mmHg) in blood pressure.

DISCUSSION

Sympathetic contributions from the hypogastric plexus form the bulk of the pelvic plexus in addition to the sacral ganglion of the sympathetic trunk and the sacral parasympathetic nerves (pelvic nerves). Extensions from the pelvic plexus, carrying both sympathetic and parasympathetic elements, are distributed to the lower urinary tract (3). The traditional concept of innervation of the lower urinary tract has been challenged by a modern, histochemically documented description of dual sympathetic-parasympathetic innervation, a widespread intrinsic short adrenergic neuronal system, free communications of nerve networks of adjacent organs and the existence of parasympathetic postganglionic synapse in the sympathetic ganglia of the short neuron system (7, 19). The vesicourethral junction and urethra conform to this general pattern of urinary tract innervation.

When a unit of these intricate neurons is destroyed by either spinal cord injury or radical operation for pelvic malignancy both parasympathetic and sympathetic neurones are affected. Cannon's law of denervation states

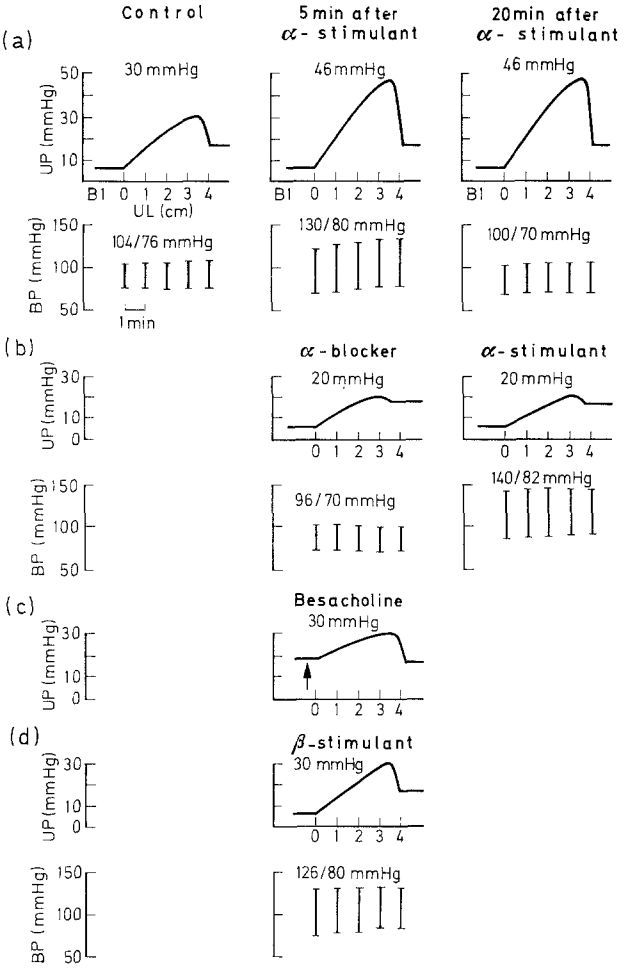

Fig. 1. Urethral pressure profile of a patient with chronic neurogenic bladder (Case 3, Table 1). UP = Urethral pressure, UL = urethral length. (a) Supersensitive response of UPmax (30-46 mmHg) to α-stimulant, lasting even after the latter's systemic effect was abated. (b) The profile was lowered after α-blocker. α-stimulant following the administration of α-blocker failed to induce this supersensitive response of the urethra. (c) Effect of Besacholine^{R}. Note its effect on the bladder (indicated with an arrow ↑) and the absence of effect on the urethral pressure. (d) Effect of β-stimulant "when in a series

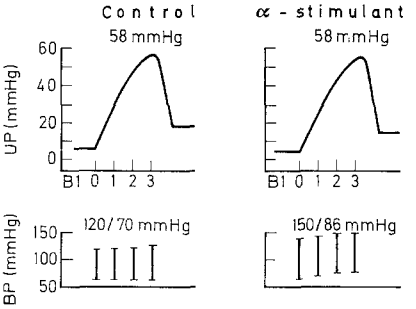

Fig. 2. Urethral pressure profile of a normal control (Case 13, Table 1)

of efferent neurons a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure, the effect being maximal in the part denervated" (5). Lapides contributed greatly to the diagnosis of neurogenic bladder by confirming Cannon's observations in relation to the detrusor muscle. He found that bladder becomes supersensitive to the parasympathomimetic bethanechol chloride when it is chronically and neurologically defunctioned (16). The urethra of the defunctioned bladder was found to respond in a supersensitive manner to α-stimulation in the present investigation. This appears to afford pharmacological confirmation of the recent data suggesting significant sympathetic activity in the sphincteric urethra (7, 13-20, 21).

After the denervation of motor fibres, the acetylcholine sensitive area, which normally is restricted to the end plate region, extends until it covers the entire postsynaptic muscle membrane (23). The mechanism of supersensitivity of the urethra may be much more complex. Cutting the sympathetic nerves to an organ destroys its capacity to take up catecholamine from the blood. This process, referred to as reuptake, normally serves as a rapid and economical mechanism for terminating the action of catecholamines. The effective concentration of unbound active catecholamines in the vicinity of the receptors in the denervated tissue would therefore be expected to persist for longer periods, resulting in a supersensitive response (1, 9, 25). Other factors that determine the magnitude of an organ response to injected catecholamines are the proportion of the injected material delivered to the organ by the circulation, and the sensitivity of the receptor site in the organ (26). A general increase in sensitivity of the receptors, as appears to be the case in skeletal muscle, could account for the uniform postsynaptic supersensitivity recently in smooth muscle as well, an increase in α-receptor activity in the urethral muscle after chronic parasympathetic denervation has been nicely shown by Sundin and Dahlström (21). This has recently been demonstrated in smooth muscle as well and cellular mechanism may be involved in this post synaptic supersensitivity (8, 24). Regardless of the mechanisms involved, the urethra becomes supersensitive to α-stimulation when its innervating pathway is chronically interrupted. In this regard it was interesting to observe the chronological changes in the urethral response of case 9 in group 2 who sustained an acute traumatic transverse myelitis at L2. His urethra eventually became supersensitive to α-stimulation two months after the injury when his bladder entered the chronic phase and was responding similarly to the administration of bethanechol chloride.

Although sympathetic nerve fibres are intimately related to the perivascular plexus, they merely use the vessel as a path along which they may run to their field of ultimate distribution (3). Similarly, concerning the mode of sympathetic involvement in the urethral wall, most of the evidence (6, 7, 12, 18), appears to indicate direct innervation through α-receptors in the urethral musculature rather than indirect through the intrinsic vascular system (22). Our results confirm these findings in that there was no correlation between the urethral and cardiovascular responses.

The results of β-stimulation indicate that the β-receptor component is not a prominant one (18), as suggested by the use of muscle strips (17).

The absence of a denervation response in the urethra of two patients who obviously sustained lumbar sympathectomy with retroperitoneal lymphadenectomy may be puzzling, because they were the patients with pure sympathetic denervation who should have shown maximum supersensitivity to α-stimulation. This might be explained either by the integrity of the "intermediate ganglia" (2) or the majority of the pelvic plexus including the second and third sacral ganglia (3), or most likely by the sparing of the intrinsic ganglion cells located close to the urethra (7, 19). Discussion of the differences of the sympathetic innervation patterns in the posterior urethra depending on its genital or urinary function, is beyond the scope of this paper. It seems likely, however, that the sympathetic system concerned with the latter is distinguished by its duality with the parasympathetic and short adrenergic system (11, 19). It is suggested that the urethra of these two patients failed to demonstrate the supersensitive response to α-stimulation because this intrinsic short adrenergic system was not affected by the lumbar sympathectomy. This also suggests that until there is proper understanding of the peculiar pattern of autonomic innervation, conflicting results will continue to be obtained in studies of the role of the sympathetic system in the urinary tract (19).

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