ADRENERGIC REGULATION OF URETERIC CONTRACTILITY IN MAN AND THE DOG

I. S. Mudraya and V. I. Kirpatovskii

UDC 612.467.1.014.46:615.217.22].085

KEY WORDS: isolated fragments of human and canine ureters; isometric contractions, adrenomimetics, adrenoblockers.

Existing information on the role of α- and β-adrenoreceptors in ureteric function is quite contradictory. Judging from the results of studies on isolated fragments, most research indicates a stimulating action for α-adrenoreceptors and an inhibitory action for β-adrenoreceptors [4, 6, 8, 10, 11]. However, the presence of stimulating β-receptors has been described in the proximal parts of the human and rabbit urinary tract, similar to the myocardium [9]. Other workers did not find β-receptors in the ureters of man, rabbits, and guinea pigs [3, 4, 6]. Considering that models of urologic diseases are often created in dogs, the question of the particular features of adrenergic regulation of ureteric contractility in dogs compared with man is a task of some urgency.

The aim of this investigation was to compare contractility of isolated fragments of human and canine ureters and to study particular features of its adrenergic regulation.

METHODS

Experiments were carried out on 40 fragments of human ureter from the upper third, obtained immediately after nephrectomy for a tumor of the kidney, and on 92 fragments of canine ureters from the upper and lower thirds. Isometric contractions of circular fragments of the ureters were studied in oxygenated Locke's solution [7], containing (in g/liter): NaCl 9.0, $CaCl_2$ 0.24, KCl 0.42, Na_2CO_3 0.3, glucose 1.0, at 37°C by means of a mechanotron in an experimental system and recorded on an automatic writer. Fragments of the ureters were made to contract by electrical stimulation at above-threshold voltage, with a frequency of 6 pulses/min, and a duration of 5-500 msec. The fragments were stretched to a length at which the force of contraction was maximal. Contractility of the different fragments was compared by calculating the maximal isometric tension, for which purpose the force of contraction was normalized for the thickness of the fragments or the area of cross section [2, 5]. The maximal contractile response of the fragments to depolarization of the cell membrane was studied by determining the contracture developing after complete replacement of the Na^+ ions in the nutrient solution by K^+ ions; its value also was normalized for the thickness of the fragment. Adrenergic regulation of ureteric contractility was judged from the change in amplitude of their contractions after addition of one of the following adrenomimetics to the surrounding nutrient solution: noradrenalin, adrenalin, or isoproterenol. Dose-dependent effects of the adrenomimetics were studied by successive addition of increasing concentrations of agonist (10^{-7}, 10^{-6}, and 10^{-5} M) in the nutrient solution, and plotting cumulative curves. Adrenoblockers — propranolol or phentolamine — were added after the ureteric fragments had been rinsed, and when a constant level of contractile activity had been reached, in concentrations of 10^{-4} M.

Research Institute of Urology, Russian Ministry of Health. (Presented by Academician N. A. Lopatkin, Academy of Medical Sciences.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 113, No. 4, pp. 363-365, April, 1992. Original article submitted July 11, 1991.

0007-4888/92/0004-0474$12.50

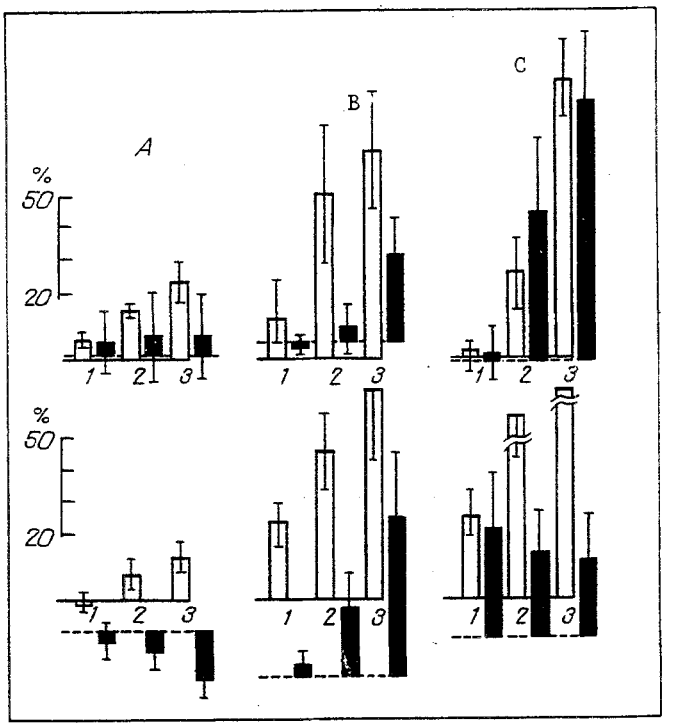

Fig. 1. Dose-dependent reactions of isolated fragments of human and canine ureters to action of adrenergic drugs, expressed in % of initial level of contractility before addition of test substance. Columns indicate effects of noradrenalin (top row) and adrenalin (bottom row) in concentrations of 10^{-7} (1), 10^{-6} (2), and 10^{-5} (3) M on fragments of upper parts of ureters contracting isometrically under the influence of electrical stimulation: a) human ureters; B) canine ureters, upper third; C) canine ureters, lower third. Broken line indicates altered background of contractile activity of ureteric fragments after addition of adrenoblockers to nutrient Locke's solution in concentrations of 10^{-4} M; black columns show schematically effects of noradrenalin against the background of β-adrenoreceptor blockade by propranolol (top row) and of adrenalin against the background of α-adrenoreceptor blockage by phentolamine (bottom row).

RESULTS

The mean statistical parameters of mass, size, tone, and initial contractility of the test fragments are given in Table 1. Differences were found with virtually all the parameters studied (except length). The mean mass of fragments studied from the upper ends of the ureters was 1.5 times greater in man than in the dog, but maximal isometric tension during repetitive electrical stimulation was 1.8 times greater in the dog ($p < 0.05$) than in man, and differed only a little in fragments of human ureters and the lower portions of canine ureters. Conversely, potassium contracture was twice as great in fragments of human ureters ($p < 0.02$) than in the upper region of the canine ureter, and three times greater ($p < 0.001$) than in the lower regions of the canine ureters. The resting tension of fragments of the canine ureters was 1.5-2.0 times lower ($p < 0.05$) than fragments of human ureters, both in absolute terms and calculated per unit area of cross section. The differences given above characterize differences in functional activity of human and canine ureters, due evidently to the different position of the body.

TABLE 1. Characteristics of Fragments of Human (I) and Canine Ureters (II — upper third, III — lower third) and Their Contractility (M ± m)

Parameters	I	II	III
Mass, mg	30±3 (38)	24±3 (39)*	23±1 (40)*
Length, mm	6.3±0.4 (40)	6.5±0.5 (37)	5.3±0.2 (40)
Resting tension, mN	±1.4 (38)	3.2±0.7 (35)*	2.6±0.3 (34)*
Resting tension, mN/mm²	1.2±0.2	0.9±0.2*	0.6±0.1*
Potassium contracture, mN/mm²	8.5±1.6 (27)	4.0±0.8 (33)*	2.6±0.7 (33)*
Maximal isometric tension, mN/mm²	1.7±0.4 (36)	3.1±0.5 (37)*	1.4±0.5 (39)

Note. Number of observations given in parentheses. Asterisk indicates values differing significantly ($p < 0.05$) from value for human ureter.

TABLE 2. Adrenergic Reactions of Ureteric Fragments (in % of initial levels) before Addition of Adrenergic Agents (during isometric contractions in Locke's solution at 37°C with electrical stimulation) (M ± m)

Adrenergic agent	Fragments of human ureters	Fragments of canine ureters	
		upper third	lower third
Noradrenalin (NA)	145±12 (19)	182±20 (19)	133±12 (22)
Propranolol (P)	100±3 (25)	102±9 (27)	96±6 (26)
NA preceded by P	118±7 (20)	148±13 (17)	144±18 (18)
Adrenalin (A)	133±11 (27)	151±15 (20)	206±21 (22)
A preceded by P	112±16 (8)	124±10 (6)	136±12 (7)
Isoproterenol (I)	130±11 (5)	50±14 (7)	116±13 (11)
Phentolamine (Ph)	94±5 (29)	73±5 (22)	74±5 (28)
I preceded by Ph	81±5 (5)	57±18 (7)	84±6 (9)
A preceded by Ph	87±4 (26)	148±18 (16)	153±25 (22)

Note. Adrenomimetics used in a concentration of 10^{-5} M, adrenoblockers 10^{-4} M. Number of observations given in parentheses.

Differences also were found in adrenoreactivity, affecting both the qualitative and the quantitative aspect of the reactions. Contractility of fragments of canine ureters could be increased by 1.5-2.1 times under the influence of adrenomimetics, whereas for the human ureter, the greatest increase was by 1.4 times (Table 2, Fig. 1).

The weaker reactions of the human ureters also were observed under the influence of the α-adrenoblocker phentolamine, which inhibited contractility of electrically stimulated ureteric fragments by 6 ± 5%, compared with 16 ± 5 and 17 ± 5% for the upper and lower thirds of the canine ureters, respectively. Data on inhibition of contractions of all the ureteric fragments studied after addition of phentolamine to the nutrient solution point to an important role of α-adrenoreceptors in the mechanism of the basic contractile function of the ureters.

A study of the effects of α-adrenoreceptor stimulation showed that both adrenalin and noradrenalin have a positive inotropic effect on electrically stimulated fragments of human and canine ureters. It will be clear from Fig. 1 that noradrenalin had a dose-dependent positive inotropic action on fragments of human ureters (a, top row of columns), and this effect was reduced after addition of the β-blocker propranolol to the nutrient solution. A similar picture was observed for the upper thirds of canine ureters — the β-blocker propranolol inhibited the positive inotropic effect of noradrenalin by 34%, but potentiated the positive inotropic action of noradrenalin in the lower thirds by 11%.

Adrenalin also had a concentration-dependent positive inotropic effect on human and canine ureters (Fig. 1, bottom row of columns). After α-adrenoreceptor blockage by phentolamine, a switch from positive inotropic to negative inotropic effect was observed in human ureters, also proportional to the concentration of the agonist. In the upper parts of the canine ureters the positive inotropic action of β_2-adrenoreceptor stimulation (adrenalin preceded by phentolamine) remained positive inotropic and dose-dependent only at a lower level of original contractility. In the lower parts of the canine ureters, the positive inotropic effect of adrenalin, directly proportional to concentration, remained so after treatment of the fragments with phentolamine, but the effect of the agonist was not increased by an increase in its concentration in the solution.

Stimulation of β-adrenoreceptors by isoproterenol increased the force of contractions of fragments of the upper parts of the human ureters (+30 ± 11%), but after α-adrenoreceptor blockade by phentolamine the positive inotropic action of isoproterenol disappeared and a definitely negative inotropic effect appeared (−19 ± 5%). The possible explanation of this fact may be stimulation of β_1-receptors, which cause noradrenalin release [1], and thereby increase the force of contractions of human and canine (lower parts) ureteric fragments. During α-adrenoreceptor blockade by phentolamine the positive inotropic effect or noradrenalin is blocked and the effect of β-adrenoreceptor stimulation is observed; as our investigations showed, this effect consists of inhibition of contractions of fragments of the human

ureter. As already pointed out, stimulation of β_2-adrenoreceptors in human ureters also reduced the force of contractions. These results are in agreement with information in the literature on the existence of recessive [8] or uninnervated [10] β-adrenoreceptors in the human ureter, which exhibit their activity only after α-adrenoreceptor blockade.

Unlike in man, in the upper parts of the canine ureters isoproterenol had a negative inotropic effect, but a positive effect in the lower parts. After treatment of fragments of the ureters with phentolamine, isoproterenol inhibited the force of contractions in all parts. Thus we can speak of a negative inotropic effect of β_1-adrenergic stimulation in the upper parts of the canine ureters, and of the existence of recessive β-receptors in the lower parts of canine ureters, inhibiting the force of contractions, in a similar manner to what was found in human ureters. Data indicating that adrenalin, preceded by phentolamine, increased the force of contractions of fragments of the canine, but not the human, ureter suggest the existence of β_2-adrenoreceptors, stimulating the force of contractions, over the whole length of the ureter in dogs.

The results demonstrated differences in the contractile function and adrenergic reactivity of different parts of the ureters in dogs and man, which must be taken into account when the mechanisms of regulation of contractions of upper urinary tract in man and animals are discussed.

LITERATURE CITED

1. O. M. Avakyan, *Pharmacologic Regulation of Adrenoreceptor Function* [in Russian], Moscow (1988).
2. V. I. Kapel'ko, *Byull. Éksp. Biol. Med.*, No. 12, 6 (1970).
3. R. Bloch, N. Decker, and A. Kostakopoulos, *Urol. Int.*, **39**, No. 5, 308 (1984).
4. J. A. Gosling and A. N. C. Waas, *Eur. J. Pharmacol.*, **16**, No. 1, 100 (1971).
5. K. W. Hong, P. Biancani, and R. M. Weiss, *Invest. Urol.*, **17**, 459 (1980).
6. N. Longrigg, *J. Urol. (Baltimore)*, **114**, No. 3, 325 (1975).
7. J. M. Malin, S. Bojarsky, P. Labay, et al., *J. Urol. (Baltimore)*, **99**, No. 4, 396 (1968).
8. J. M. Malin, D. Fletcher, and R. S. Bojarsky, *Br. J. Urol.*, **42**, No. 2, 171 (1970).
9. T. Morita, *J. Urol. (Baltimore)*, **135**, No. 3, 604 (1986).
10. R. M. Weiss, *The Ureter*, H. Bergman (ed.), New York (1981), pp. 137-162.
11. S. Yano, S. Ueda, K. Ikegami, et al., *Urol. Int.*, **39**, No. 2, 100 (1984).