Functional Asymmetry in the Innervation of Smooth Muscle Organs

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We studied functional asymmetry in the innervation of smooth muscle organs (right and left ureter, and right and left fallopian tubes). Asymmetry in the innervation of the right and left ureter is provided by activation of the purinergic system. Asymmetry in the innervation of the fallopian tubes is determined by the purinergic and serotoninergic mechanisms.

Key Words: *innervation asymmetry; right and left ureter; right and left fallopian tubes; purinergic and serotoninergic systems*

Activation of the parasympathetic nerve is followed by muscle contraction in the urinary bladder. The contractile and relaxation effects of purines on smooth muscles are realized via activation of P_2 and P_1 receptors, respectively [9]. Administration of serotonin induces spasm of the ureter. This action is similar to the vasoconstrictor effect of serotonin [7] realized via activation of 5-HT_2 receptors [3].

The vagus nerve (VN) is responsible for cholinergic innervation of the uterine fundus [2,8]. Cholinergic neurons form a moderately dense plexus in the myometrium and microarterial system of the fallopian tubes. Published data suggest that acetylcholine stimulates uterine contraction [4,6].

Acetylcholine, norepinephrine, and serotonin dose-dependently regulate motor function of the uterus and hormonal status. β-Adrenoceptor blockade in longitudinal muscles prevents the decrease in contractile activity of the myometrium, while α-adrenoceptor blockade in circular muscle fibers prevents muscle tone drop produced by norepinephrine [1]. Experiments on rat uterus showed that acetylcholine, histamine, serotonin, phenylephrine, and oxytocin cause uterine contraction, which can be inhibited by ATPase blocker [5].

Here we studied functional asymmetry in the innervation of smooth muscle organs at rest and under conditions of the synergistic interaction between various parts of the autonomic nervous system (ANS).

MATERIALS AND METHODS

Experiments were performed on 24 Chinchilla rabbits weighing 3.5-4.0 kg. The animals were intraperitoneally narcotized with 40 mg/kg nembutal. Electromotor activity (EMA) of the right and left ureter, urinary bladder, right and left fallopian tubes, and corpus uterus was recorded with bipolar silver electrodes (contact area 1.5-2.0 mm^2, interelectrode distance 1.5 mm). The nerves were stimulated with electric pulses (2 msec, 1.5-15.0 V, 10 Hz) using Medicor-St-02 electrical stimulators. EMA was recorded on a Mingograf-82 device. We measured the amplitude (mV) and frequency of slow waves in EMA. Spike activity was expressed in the number of spikes per 100 slow waves in EMA.

Baseline EMA of organs and systems was recorded in series I. We compared EMA of the right and left ureter and right and left fallopian tubes. Control stimulation was applied to the peripheral cervical segment of the right VN. Optimum parameters of electrical stimulation (vagal optimum) were selected so that EMA exceeded baseline activity by not more than 3 times and long-term stimulation of VN (up to 1.0-1.5 min) was not accompanied by an increase in the frequency of slow waves and spike activity. Control

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stimulation was also applied to the peripheral cervical segment of the left sympathetic trunk. EMA of the right and left ureter and right and left fallopian tubes was compared upon simultaneous stimulation of VN and sympathetic trunk.

Possible role of purinergic structures in the asymmetry of EMA in the ureter and fallopian tubes was studied in series II. Experiments were performed with a purinoceptor antagonist theophylline in doses of 20-80 mg/kg.

The involvement of ganglionic serotonin receptors (5-$HT_{3,4}$) and pre- and postganglionic fibers in the mechanism for asymmetric innervation and synergistic effect of VN and sympathetic nerve on EMA of effector organs was studied in series III. Experiments were performed with droperidol in doses of 0.5-1.0 mg/kg.

The role of peripheral serotonin receptors (5-$HT_{1,2}$) in asymmetric innervation of paired organs (ureter and fallopian tubes) and synergistic interaction between various parts of ANS was studied in series IV. Experiments were performed with an antagonist sumatriptan in doses of 0.5-1.0 mg/kg.

RESULTS

Control series revealed differences in the baseline EMA recorded in the right and left ureter. However, the amplitude and frequency of EMA were similar in the left ureter and urinary bladder. Stimulation of the peripheral segment in the right VN was followed by activation of slow waves in EMA of the ureter and urinary bladder (Table 1).

Stimulation of the peripheral segment of the left sympathetic trunk produced no stimulatory or inhibitory effect. Simultaneous stimulation of the sympathetic nerve and VN increased motor activity of the urinary bladder and ureter (Table 1).

The sympathetic nerve potentiated vagal stimulation of EMA in urinary organs only upon stimulation of the right VN and left sympathetic nerve on the neck. This effect was observed under specific conditions of VN stimulation (vagal optimum).

No differences were found in the frequency of slow waves in EMA of the urinary bladder and left ureter. However, the frequency of slow waves in EMA of the right ureter was higher than in the urinary bladder and left ureter by 38-40%. We revealed a synergistic effect of stimulation applied to various parts of ANS: urinary bladder (77.1%), right ureter (70%), and left ureter (49.5%).

Functional asymmetry in EMA of the ureter slightly decreased during VN stimulation (from 26.7 to 20.8%), but returned to 30% under the synergistic interaction between various parts of ANS.

Series II showed that stimulation of the sympathetic trunk and VN before administration of theophylline increases EMA of the ureter and urinary bladder. This phenomenon was also observed during stimulation of the sympathetic trunk and VN after theophylline administration. After treatment with purinoceptor antagonist this effect slightly decreased in the right ureter (from 70 to 52%), but increased in the left ureter (from 49.5 to 54.1%).

After administration of theophylline the sympathetic nerve more significantly potentiated vagal sti-

TABLE 1. EMA of Ureters and Urinary Bladder during Stimulation of VN and Sympathetic Trunk before and After Administration of Serotonin Receptor Antagonists

Organ	Baseline EMA, per min		VN stimulation		Simultaneous stimulation of the sympathetic trunk and VN	
	frequency	%	frequency	%	frequency	%
Control						
right ureter	17.5±1.6	26.7	24.0±1.9*	20.8	40.5±3.8+	30.0
left ureter	12.8±1.3		19.0±1.8*		28.4±2.3+	
urinary bladder	12.5±4.8		17.5±1.3*		31.0±3.1+	
Droperidol						
urinary bladder	7.0±0.6	9.2	12.5±0.8*	26.2	12.5±0.8	23.5
right ureter	17.3±1.0		28.3±2.1*		25.5±1.5	
left ureter	15.8±1.8		20.9±1.5*		19.5±2.2	
Sumatriptan						
right ureter	21.0±1.1	52	31.0±2.6*	40	29.7±3.3	48
left ureter	9.9±1.6		18.6±1.2*		15.4±2.2	

Note. Here and in Tables 2 and 3: $p<0.05$: *compared to baseline EMA; +compared to VN stimulation.

mulation of EMA in the urinary bladder (108 *vs.* 77.1% before theophylline administration).

These data show that purinoceptor antagonist did not abolish the synergistic interaction between the sympathetic and parasympathetic systems. Therefore, this phenomenon is not realized via $P_{1,2}$ receptors.

Functional asymmetry in EMA of the right and left ureters decreased or disappeared after purinoceptor blockade. Thus, the purinergic system plays a role in functional asymmetry of the ureter.

Possible involvement of intramural ganglionic 5-$HT_{3,4}$ receptors in the synergistic interaction between the sympathetic and parasympathetic systems and functional asymmetry of EMA of the right and left ureters was studied in series III (Table 1).

Functional asymmetry in EMA of the right and left ureters was observed in animals not receiving droperidol. Before nerve stimulation, functional asymmetry in EMA of the ureters decreased to 9.2% in animals receiving 5-$HT_{3,4}$ receptor antagonist. Functional asymmetry in EMA of the right and left ureters in animals receiving 5-$HT_{3,4}$ receptor antagonist increased to 26.2% under conditions of VN stimulation. It remained practically unchanged during simultaneous stimulation of VN and sympathetic trunk (23.5%). These results indicate that functional asymmetry in EMA of the ureters does not depend on functional activity of 5-$HT_{3,4}$ receptors in ganglionic neurons. However, droperidol abolished the synergistic effect of the sympathetic and parasympathetic systems.

Series IV evaluated whether 5-$HT_{1,2}$ receptors in effector tissues play a role in the synergistic effect of ANS and functional asymmetry in EMA of the right and left ureters (Table 1).

Administration of 5-$HT_{1,2}$ receptor antagonist increased functional asymmetry in EMA of the ureter from 37 to 52%. The degree of asymmetry in EMA remained high during VN stimulation (40%). This parameter increased to 48% upon simultaneous stimulation of the sympathetic trunk and VN. However, the synergistic interaction between various parts of ANS

TABLE 2. EMA of the Uterus and Fallopian Tubes during Stimulation of VN and Sympathetic Trunk before and After Treatment with Antagonists of Purinoceptors and Serotonin Receptors

Organ	Baseline EMA, per min		VN stimulation		Simultaneous stimulation of the sympathetic trunk and VN	
	frequency	%	frequency	%	frequency	%
Control						
uterus	8.6±1.1		11.2±1.5*		16.1±2.4+	
right fallopian tube	31.4±4.2	36.3	45.6±4.4*	42.5	54.7±4.6+	42.4
left fallopian tube	20.0±2.8		26.2±2.3*		31.5±2.7+	
Theophylline						
uterus	8.8±0.8		15.0±2.6*		26.1±4.5+	
right fallopian tube	30.6±2.2	36.3	36.4±3.4*	42.5	48.5±6.6+	42.4
left fallopian tube	22.2±3.2		36.3±3.3*		44.0±3.8+	
Droperidol						
uterus	9.9±1.6		14.8±2.5*		12.0±1.4	
right fallopian tube	23.8±2.7	35.0	28.0±3.1*	1.5	27.0±3.2	5.2
left fallopian tube	15.5±3.2		28.4±3.9*		28.4±3.9	
Sumatriptan						
uterus	8.0±0.7		13.0±2.1*		10.0±1.2	
right fallopian tube	17.7±3.7	49.9	29.0±2.8*	56	26.0±3.0	54
left fallopian tube	8.9±0.8		12.8±1.0*		11.9±0.9	

TABLE 3. EMA of Ureters and Fallopian Tubes during VN Stimulation and Stimulation of VN and Sympathetic Trunk

Organ	Baseline EMA, per min		VN stimulation		Simultaneous stimulation of the sympathetic trunk and VN	
	frequency	%	frequency	%	frequency	%
Right ureter	17.5±1.6	36.6	24.0±1.9*	20.8	40.5±3.8+	30.0
Left ureter	12.8±1.3		19.0±1.8*		28.4±2.3+	
Right fallopian tube	31.4±4.2	57.0	45.6±4.4*	42.5	54.7±4.6+	42.4
Left fallopian tube	20.0±2.8		26.2±2.3*		31.5±2.7+	

was not observed after administration of a 5-$HT_{1,2}$ receptor antagonist (Table 1).

Our findings show that the serotoninergic system (preganglionic serotoninergic fiber, ganglionic serotoninergic neuron, and serotonin receptors in the effector tissue) is not involved in the realization of functional asymmetry in EMA of the ureters.

Functional asymmetry in baseline EMA of the right and left fallopian tubes was 36.3%. The degree of asymmetry increased during VN stimulation (42.5%) and remained practically unchanged during simultaneous stimulation of the sympathetic trunk and VN (42.4%, Table 2). The synergistic interaction between various parts of ANS in the right fallopian tube, left fallopian tube, and uterus was 60, 20, and 42.2%, respectively (Table 2). The frequency of slow waves in baseline EMA of the right fallopian tube was high and exceeded that in the left fallopian tube and fundus of the uterus by 1.6 and 3.7 times, respectively. Excitability of the uterine pacemaker localized in the site of contact between these structures is probably determined by high baseline activity of the right fallopian tube.

Functional asymmetry in EMA of the right and left fallopian tubes in animals receiving theophylline decreased from 22 to 9% during stimulation of VN (Table 2). Purinoceptor blockade did not abolish, but even potentiated the synergistic interaction between the sympathetic and parasympathetic systems in the uterus and right fallopian tube. However, this treatment slightly decreased the synergistic effect in the left fallopian tube (Table 2). These data show that the purinergic system plays a role in functional asymmetry of EMA in the fallopian tubes, but does not abolish the synergistic interaction between various parts of ANS.

The involvement of serotoninergic structures in asymmetric innervation of the fallopian tubes and synergistic interaction between various parts of ANS regulating motor activity of the uterus and fallopian tubes was studied in series III.

Droperidol decreased functional asymmetry in EMA of the fallopian tubes from 45 to 35% (Table 2). Simultaneous stimulation of the sympathetic trunk and VN before droperidol administration potentiated the vagal stimulatory effect. This phenomenon was not observed after administration of droperidol. Our results indicate that 5-$HT_{3,4}$ receptors in ganglionic neurons are involved in the synergistic interaction between various parts of ANS and mediate functional asymmetry in innervation of the fallopian tubes.

The role of 5-$HT_{1,2}$ receptors in functional asymmetry of EMA in the fallopian tubes and synergistic interaction between various parts of ANS in EMA of female smooth muscle sex organs was studied in series IV (Table 2).

Functional asymmetry in EMA of the right and left fallopian tubes was revealed in animals receiving sumatriptan (despite blockade of 5-$HT_{1,2}$ receptors in effector tissues, Table 2). Functional asymmetry in EMA of the fallopian tubes slightly increased after VN stimulation and remained unchanged after simultaneous stimulation of the sympathetic trunk and VN. These results indicate that 5-$HT_{1,2}$ receptors are not involved in the phenomenon of functional asymmetry in EMA of the fallopian tubes. However, 5-$HT_{1,2}$ receptor antagonist completely blocked the synergistic interaction between various parts of ANS.

EMA in right-side smooth muscle organs was higher than in the left ureter and left fallopian tube by 36.6 and 57%, respectively (Table 3). The degree of asymmetry in EMA of the ureter was less pronounced than in the fallopian tubes. These differences are probably associated with greater contribution of the right fallopian tube to pacemaking activity in the uterus (compared to the right ureter). Purinoceptor antagonist

theophylline abolished asymmetry in innervation of the right and left ureter. Hence, purine bases that serve as energy substrate initiate baseline bioelectric activity in the ureter. This is particularly pronounced in the right ureter.

Asymmetry in innervation of the fallopian tubes is provided by the purinergic and serotoninergic mechanisms. It contributes to a constant level of high baseline bioelectric activity in the right fallopian tube, which determines EMA frequency in the uterus. The serotoninergic constituent is provided by intramural chromaffin-like cells carrying 5-$HT_{3,4}$ receptors on the surface membrane.

The serotoninergic system determines the synergistic interaction between the sympathetic and parasympathetic systems in smooth muscle organs of the urinary tract and female smooth muscle sex organs.

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