Selective Pharmacological Blockade of Synaptic Transmission in Parasympathetic Pathways to the Heart in Rats

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INTRODUCTION

Parasympathetic hypertone is commonly thought to cause some widespread diseases, e.g., gastric or duodenal ulcers or even sudden cardiac arrest. Usually the former two diseases are treated by surgical vagotomy or pharmacological blockade of synaptic transmission in the parasympathetic pathways, mainly with administration of muscarinic antagonists. It was shown earlier [1] that the best healing of ulcers was observed when either sympathomimetics together with parasympatholytics, or “pure” parasympatholytics were used. Because of their low selectivity, the ganglionic blockers, commonly used in the past for treatment of various disorders of the autonomic nervous system [2], later were almost completely abandoned. They were replaced by more selective blockers of neuro-effector synaptic transmission.

However, interest in ganglionic blockers now is increasing again. This is due to recent findings of great diversity among the neurons of autonomic ganglia and plexus in their pharmacology, which provides a possibility for their highly selective pharmacological blockade [3-5].

Some selective blockers of synaptic transmission in parasympathetic versus sympathetic nerve pathways were recently developed [6, 7]. This work studied the effects produced by one of these newly synthesized compounds, IEM-1556 (Fig. 1), on the parasympathetic and sympathetic nerve pathways. In particular, transmission from the vagal nerve to the rat heart muscle was used as a model of parasympathetic efferent pathway.

In our recent study [5], we found that nicotinic acetylcholine receptors (NACHRs) of rat intracardiac ganglion neurons are unique in their very low sensitivity to the classical ganglionic blocker hexamethonium. We suggested that these NACHRs are closer to muscle-type receptors rather than to those of the ganglionic type. It therefore seemed interesting to compare the blocking effect of IEM-1556, observed in our model, with those of...
of hexamethonium and of one more ganglionic blocker, trimetaphane, on the one hand, and with the effects of classical muscle relaxants, pancuronium and decamethonium, on the other hand. In order to know what compartment of the IEM-1556 molecule determines its blocking potency and selectivity, we studied the blocking activity of two IEM-1556 derivatives, possessing a shorter aliphatic radical (N-hexyltropine iodide, IEM-1848), or only a methyl group instead of the decyl aliphatic radical (N-methyltropine iodide, IEM-1893, Fig. 1).

METHODS

Acute experiments were performed on rats anesthetized with urethane (1.0 g/kg, i.p.). Blocking effect of i.v. injected IEM-1556 on synaptic transmission through the cardiac ganglia was estimated from the change in the negative chronotropic effect produced by vagal stimulation. The left vagal nerve was cut at the neck region, and its distal segment was stimulated with 30-sec-long series of 1.0-msec-long stimuli at a frequency of 20/sec. During vagal stimulation, the ECG R-R interval was measured using an ink recorder. The blood pressure was measured in the femoral artery with a mercurial manometer.

For comparison, the blocking effect of IEM-1556 on synaptic transmission through the superior cervical ganglion (SCG) was estimated from the decrease in the amplitude of post-ganglionic action potentials evoked by single pre-ganglionic stimuli. For this purpose, 0.4-msec-long suprathreshold stimuli were applied at a 0.5/sec frequency to the proximal segment of the cut cervical sympathetic nerve through a sucking electrode. Similar sucking electrode was used to record action potentials from the internal carotid nerve containing postganglionic nerve fibers of the SCG. The blood supply of the ganglion remained intact. All drugs were tested by methods described above. Statistical data were processed using standard approaches and expressed as means ± s.e.m.

The following drugs were used: hexamethonium dibromide, trimetaphan (Roche, France), pancuronium bromide (Pavulon, India), decamethonium dibromide, N-decyltropine bromide (IEM-1556), N-methyltropine iodide (IEM-1893), and N-hexyltropine iodide (IEM-1848). The structure of the latter is shown in Fig. 1. Hexamethonium, decamethonium, IEM-1556, IEM-1893, and IEM-1848 were synthesized at the Institute of Experimental Medicine of the Russian Academy of Medical Sciences.

RESULTS

Stimulation of the peripheral end of the transected left vagus nerve increased the ECG R-R interval. The effect began at the first second of the stimulation, approached a stationary level at 3-4 sec, and disappeared after the stimulation termination (Fig. 2).

The blockers used (IEM-1556, IEM-1893, or IEM-1848) strongly reduced the vagus-induced bradycardia. IEM-1556, if used at the dose of 3.0 µg/kg, markedly reduced the negative chronotropic response of the heart muscle (Fig. 2). The effect was significant (P < 0.001), as found using Student’s paired test, and dose-dependent. Being used at a dose of 1.0-1.5 µg/kg, IEM-1556 decreased bradycardia by 25%, whereas at a dose of 5.0 µg/kg bradycardia was reduced by more than 50% of its control value. The IEM-1556-induced effect began 15-20 sec after an i.v. injection of the drug, reached its maximum within about 2 min, and ceased at the 30th-35th min (Fig. 3A). The mean value of ED estimated from four experiments was equal to 4.2 ± 0.5 µg/kg (-ranging from 3.2 to 5.3 µg/kg in various experiments).

IEM-1893 and IEM-1848 likewise reduced a