Barbiturates depress vagal motor pathway to ferret trachea at ganglia

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SKOOGH, B.-E., M. J. HOLTZMAN, J. R. SHELLER, AND J. A. NADEL. *Barbiturates depress vagal motor pathway to ferret trachea at ganglia*. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 53(1): 253-257, 1982.—To determine which site in the vagal motor pathway to airway smooth muscle is most sensitive to depression by barbiturates, we recorded isometric muscle tension in vitro and stimulated the vagal motor pathway at four different sites before and after exposure to barbiturates. In isolated tracheal rings from ferrets, we stimulated muscarinic receptors in the neuromuscular junction by exogenous acetylcholine, postganglionic nerve fibers by electrical field stimulation, and the postsynaptic membrane in ganglia by 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP). We also developed a tracheal nerve-muscle preparation to stimulate preganglionic fibers in the vagus nerve electrically. Activation of ganglia by DMPP or by vagus nerve stimulation was depressed by barbiturates at 10-fold lower concentrations than those depressing the activation of postganglionic nerves or the neuromuscular junction. These findings suggest that the postsynaptic membrane in parasympathetic ganglia is the site in the vagal motor pathway most sensitive to depression by barbiturates.

airway smooth muscle; vagus nerve; smooth muscle contraction; parasympathetic; nerve stimulation; acetylcholine

ALTHOUGH IT IS KNOWN that several general anesthetics, including barbiturates, depress the bronchomotor response to vagus nerve stimulation (1, 7-9), the site of this depression has not been determined. To determine which site in the vagal motor pathway to the airways is most sensitive to depression by barbiturates, we recorded isometric muscle tension in vitro and induced muscle contractions by stimulation of this pathway at four different sites before and after exposure to barbiturates (pentobarbital, amobarbital, and thiopental). We used isolated rings of ferret trachea to stimulate *1*) muscarinic receptors in the neuromuscular junction, *2*) postganglionic nerve fibers, and *3*) the postsynaptic membrane in ganglia. We developed a separate tracheal nerve-muscle preparation to activate *4*) the presynaptic membrane in ganglia by electrical stimulation of preganglionic nerve fibers.

METHODS

Tracheal ring experiments. Four ferrets were anesthetized with chloralose (100 mg/kg) and urethan (500 mg/kg), and the trachea was removed. Transverse rings (8 mm long) were cut from the trachea and mounted in glass chambers filled with 18 ml of Krebs-Ringer bicarbonate solution of the following composition (in mM): NaCl 118, KCl 5.9, $CaCl_2$ 2.5, $MgSO_4$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 25.5, and glucose 5.6. The solution was maintained at 38°C and was continuously aerated by bubbling a mixture of 94% O_2-6% CO_2, which produced a pH ≈ 7.4. Drugs added to the chambers were dissolved in 0.25 ml distilled water except for DMPP, which was dissolved in Krebs solution.

The tracheal rings were connected to strain gauges (Grass FT03) for continuous recording of isometric tension and placed between two rectangular platinum electrodes (6 × 40 mm) for electrical field stimulation. The rings were initially stretched to a tension of 20 g for 30 s and were then allowed to equilibrate for 1 h while the resting tension was adjusted to 6 g. Separate studies of the resting tension-active tension (electrical field stimulation, 12 Hz for 20 s) relationship showed a curve with a broad flat maximum between 4 and 8 g of resting tension for rings 8 mm long. Addition of both atropine (10^{-6} M) and terbutaline (10^{-5} M) to the rings showed them to be free of active contraction in the resting state.

In this ring preparation, the vagal motor pathway was stimulated at three of the four sites studied (Fig. 1) as described below. The contractile response at the muscle level was assessed as the developed active tension (peak tension-resting tension).

The muscarinic receptors at the neuromuscular junction were stimulated by acetylcholine added to the glass chambers. Blockade of postganglionic nerve fibers by tetrodotoxin (4×10^{-7} M) did not change the response to acetylcholine, implying that a possible stimulation of nicotinic receptors in ganglia did not substantially contribute to the induced contraction.

The postganglionic nerve fibers were stimulated by electrical field stimulation. Biphasic pulses (duration, 0.5 ms; supramaximal current) were delivered for 20 s from a laboratory-built direct-current supply with a built-in triggering stimulator. Blockade of ganglia by hexamethonium (10^{-5} M) for 20 min did not change the response to field stimulation, implying that a possible transmitter release in ganglia did not contribute to the induced contraction. Nerve fiber blockade by tetrodotoxin (4×10^{-7} M) abolished the response to field stimulation.

The postsynaptic membrane in ganglia was stimulated by adding to the glass chambers DMPP (1,1-dimethyl-4-phenylpiperazinium iodide), a known nicotinic ganglion