Pathogenesis of Bronchial Obstruction under Conditions of Disturbed Adrenoception

D. V. Akimov and A. I. Shevchenko

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Experimental disturbances in β-adrenoception cause non-specific changes in the development of bronchial obstruction in response to humoral and neural bronchoconstrictor stimuli, which are manifested in bronchial smooth muscle hyperreactivity. The bronchospastic reaction develops more rapidly, persists for a longer time, and is always accompanied by early activation of non-smooth muscle pathogenetic mechanisms.

Key Words: *bronchospasm; bronchial obstruction; bronchial hyperreactivity; adrenoception*

Acute respiratory insufficiency induced by prolonged attack of bronchial asthma or status asthmaticus is a consequence of severe impairment of bronchial patency and airway muscle insufficiency due to muscle fatigue [7].

The bronchial obstruction (BO) syndrome is caused by bronchial hyperreactivity that results from significantly decreased threshold of bronchial smooth muscle to various bronchoconstrictor stimuli [4]. In particular, bronchial hyperreactivity can be caused by an adrenoception imbalance with decreased β-adrenoreactivity and enhanced α-adrenoreactivity of the target cells known as an α-dominant adrenergic imbalance [2,5, 11,12]. The adrenergic imbalance is a complex polyetiological and polypathogenetical phenomenon predominantly resulting from inflammation or treatment with β_2-agonists. This imbalance is a generalized phenomenon occurring not only in tracheobronchial effector cells, but also in peripheral blood cells [1,6,9,10].

We studied BO induced by various humoral and neural bronchoconstrictor stimuli under conditions of impaired β-adrenoception.

MATERIALS AND METHODS

The study was carried out on 100 outbred cats weighing 3-4.5 kg anesthetized with Nembutal (40 mg/kg) and curarized with pancuronium (0.2 mg/kg, Pavulon, Infar). Airway resistance (R_{aw}) was determined according to the method of H. Konzett *et al.* by changes in the intratracheal pressure under constant minute respiratory volume. Adrenergic imbalance was modeled by injection of propranolol (0.5 mg/kg, Obsidan, Schwarz Pharma) 5 min prior to bronchoconstriction. The bronchoconstrictor stimuli were intravenous histamine (10 μg/kg), serotonin (10 μg/kg), bradykinin (0.2 μg/kg), prostaglandin $F_{2\alpha}$ (0.1 μg/kg), and slowly reacting anaphylactic substance MPC-A (20 mg/kg).

The neural mechanisms of bronchospasm were studied using stimulation of the central and peripheral ends of the right vagus nerve with the help of bipolar copper electrodes and an ES-50-1 electric stimulator (1.5-2.0 V pulse amplitude, 1 msec pulse duration, 30 min^{-1} stimulation rate). Anaphylactic bronchospasm in the cats sensitized with normal serum was provoked by injecting a permissive dose of serum (0.5 ml/kg) [8].

R_{aw} was evaluated by the ratio (K) of maximum amplitude of piston shift in the piston-recorder after bronchoconstrictor intervention to its amplitude under the baseline conditions R_{aw} (K_{bgr}=1).

The rectal temperature was maintained at 38-39°C. The data were recorded and statistically analyzed using original software.

RESULTS

All bronchoconstrictor agents significantly increased R_{aw} (K_1, Table 1). The maximum increase in R_{aw} was observed after injections of MPC-A and serotonin and

Department of Pharmacology, State University, Petrozavodsk

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TABLE 1. Airway Resistance (R_{aw}) under the Effect of Bronchoconstrictor Stimulation ($M \pm m$)

Bronchoconstrictor stimulation	Initial data (K_1)	Against the background of propranolol (K_2)	K_1/K_2
Background values (n=10)	1	1.045±0.014	—
Prostaglandin (n=10)	1.478±0.065	2.211±0.245**	1.496
MPC-A (n=10)	1.605±0.026	1.98±0.04***	1.234
Anaphylaxis (n=20)	1.671±0.029	2.052±0.056***	1.228
Serotonin (n=10)	1.596±0.022	1.954±0.031***	1.224
Stimulation of peripheral end of *n. vagus* (n=10)	1.247±0.025	1.463±0.059*	1.173
Bradykinin (n=10)	1.466±0.028	1.687±0.031***	1.151
Stimulation of central end of *n. vagus* (n=10)	1.175±0.017	1.331±0.041*	1.133
Histamine (n=10)	1.424±0.018	1.583±0.027**	1.112

Note. *p<0.05, **p<0.01, ***p<0.001 compared to the initial value.

in anaphylactic bronchospasm and less pronounced after injection of histamine, prostaglandin, and bradykinin. The minimal changes in R_{aw} were caused by stimulation of the vagus nerve, especially its proximal end.

The development of BO under the effect of the examined bronchoconstrictor stimuli was also different. The vagal and serotonin-induced bronchospasm quickly developed during the first few seconds after stimulation, the serotonin-induced bronchospasm was short-lasting (2-3 min) and the vagal bronchospasm resolved immediately after the end of stimulation. Bronchospasm induced by prostaglandin, histamine, and bradykinin developed during the first 10-20 sec postinjection and lasted for 10-15 min. The disturbances in bronchial patency caused by MPC-A and anaphylactic reaction developed 40-60 sec postinjection and persisted for a long time (the baseline level of R_{aw} did not restore), probably due to successive contribution of other pathogenic elements of BO (edema and obstruction with bronchial secretion).

Propranolol caused an insignificant increase in R_{aw}, but considerably increased bronchial sensitivity (K_2/K_1) to all bronchoconstrictor stimuli, primarily to prostaglandin and to a lesser extent to serotonin, MPC-A, and anaphylactic reaction (Table 1), while the sensitivity to other bronchospastic agents was only insignificantly increased.

In this experimental series the dynamics of BO also changed. Reaction to MPC-A developed more rapidly (latency 20-25 sec). The disturbances in bronchial patency induced by all bronchoconstrictor factors were indefinitely long, and R_{aw} never returned to the baseline level, which indicated a more regular involvement of the non-bronchospastic processes in BO formation under conditions of β-adrenoception imbalance. It agrees with the evidence that large doses of theophylline (24-48 mg/kg) did not normalize R_{aw}.

Thus, experimental disturbances of β-adrenoception (pharmacological adrenergic imbalance) considerably modulate the development of BO induced by bronchoconstrictor stimuli: disturbances of the bronchial patency develop more rapidly, persist for a longer period, and are always accompanied by early activation of the non-smooth muscle mechanisms, while the increase in R_{aw} in the early (bronchospastic) phase is more pronounced (bronchial hypersensitivity).

The data suggest that the dynamics of BO under conditions of adrenergic imbalance little depends on the nature of bronchoconstrictor stimulus. It can be suggested that bronchial hypersensitivity under conditions of adrenergic imbalance is underlain by common subcellular mechanisms such as increase in intracellular Ca^{2+}. Circulating catecholamines are known to maintain a certain level of hyperpolarization of myocyte membrane via interaction with β_2-adrenoreceptors of bronchial myocytes. In our experiments, propranolol prevented the effect of catecholamines on β_2-adrenoreceptors and decreased hyperpolarization. Therefore, smaller depolarizing stimuli are needed to activate voltage-dependent Ca^{2+} channels and to increase the intracellular Ca^{2+} concentration to a critical level inducing muscular contraction. Probably, this mechanism underlies bronchial hypersensitivity to various bronchoconstrictor stimuli under conditions of disturbed β_2-adrenoception.

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