Activity of the Adrenergic Nerve System in the Airways Permeability of Healthy Persons

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ABSTRACT

Objective: In this work, role of the adrenergic nerve system (α_{11} and β_{22}) in adjustment of the bronchomotor tonus in healthy people was researched. **Methods:** Parameters of the lung function are determined by Body plethysmography. Raw and ITGV were registered and SRaw was calculated as well. Aerosolization is done with standard aerosolizing machines – Asema. **Results:** Results gained

shows that following the blockade of β_{22} adrenergic receptor with Propranolol (20 mg-aerosol), stimulation of α_{11} adrenergic receptor with Oxedrine (120 mg-aerosol) and blockage of these receptors with Tolazoline (20 mg-aerosol), does not change significantly the bronchomotor tonus of the tracheobronchial tree ($p > 0.1$). Meanwhile, stimulation of the β_{22} adrenergic receptor with Hexoprenaline (2 inh x 0.2 mg) is associated with a significant increase of

the peripheral resistance of the airways ($p < 0.01$). **Conclusion:** This suggests that the activity of the α_{11} -adrenergic receptor, unlike the activity of the β_{22} -adrenergic receptor in the healthy people smooth musculature, is not significant and as such is insufficient to oppose to the tonic activities of the cholinergic system.

Key words: Propranolol, Oxedrine, Tolazoline, Hexoprenaline, and Histamine.

1. INTRODUCTION

In the normal regulation of the tonus of smooth muscles exists a slight, but constant, bronchoconstrictor tonus that is maintained through the intermediation of cholinergic impulses. Role of the adrenergic nervous system in the state of silence at normal persons was researched very less. They might affect through the beta or alpha - adrenergic receptors in the airways smooth musculature and to modify their permeability (1).

In adjusting of the airways caliber, predominant role has the cholinergic nerve system. Supposedly, in asthmatic patient it is manifested with a hyperactivity of the cholinergic system due to the fact that anticholinergic drugs may cause emphasized bronchodilator effect in these patients whilst this effect does not manifest in healthy persons. Although, mechanism of this hyperactivity of this system is not yet entirely

known (2, 3, 4). Tonus of the airways smooth musculature is under influence of some other **different neurotransmitters**, hormones, drugs and mediators that manifest their action through the connection with the specific receptors surface in the airways smooth musculature cells. All these factors related to the airways smooth musculature tonus manifest their action through excitatory effect (agonist) and inhibitor (antagonist) during the connection to respective receptors localized in the cells of airways musculature (5).

Activation of some of the aforementioned factors can be initiated by the factors of the **external environment** such are physical activity or exposure to the cold air. Actually, it is assumed that during the exposure to the cold air bronchoconstriction can be initiated through the increase in the activity of alpha-adrenergic receptor. Therefore, this fact has placed in the focus the role of the alpha-

adrenergic receptor in the asthma mechanism.

In the bronchial tree of the healthy person there is equilibrium of an activity of the alpha-adrenergic and β_{22} -adrenergic system in favor of dominating of the β_{22} -receptor activity. Due to this fact it was supposed that in the case of the hypoactivity of the β_{22} -adrenergic system dominates the alpha-adrenergic system, as a mechanism thought to play key role in the bronchoconstriction of the diseased with bronchial asthma (6).

"In vivo" researches in the experimental animals and in the isolated segments of the bronchi in humans have proved the presence of a small number of alpha-adrenergic receptors. Also, in these researches was proved that number of these receptors in pulmonary diseases has increased by suggesting the role of these receptors in the pathophysiological mechanism (7). Up to date,

some pathophysiological aspects, diagnosis, and therapeutic treatment and prophylaxis of asthma have remained unexplained (8).

In order to evaluate the role of the adrenergic system in the regulation of the bronchomotor tonus of healthy persons, effects of the stimulator (Oxedrine), blocker (Tolazoline) in the alpha adrenergic system, effects of the blocker (Propranolol), and stimulator (Hexoprenaline) to the beta₂-adrenergic system in this adjustment was researched in this work.

2. MATERIAL AND METHODS

Examinations are carried in 51 healthy persons. Basic features and the pulmonary function are provided in the Tables 1 and 2.

Researched were informed regarding the aim of examination. At least 48 hours prior research commence, examined persons has not administered any of the drugs or substances which to affect the results of the examination. Lung function was determined in the silence condition. This determination is composed of the measurement of the slowed vital capacity (VC), forced expiratory volume (FEV₁) with Godardt Company pneumotest, and afterwards by metering of the resistance of the air flow in lung (Raw) and intratoracic volume of gases (ITGV) with the body plethysmography. From the gained Raw and ITGV results, specific resistance (SRaw) was calculated.

$$SRaw = Raw \times ITGV$$

a) Measurement of parameters of the gas volume in the sternum (ITGV); registration of curve flux-volume (inspiratory flux and expiratory flux-L/min);

b) Resistance of airways (Raw-L/sec.) expressed in kPa.

In the first group of the researched (n=15) propranolol (beta₂-adrenergic antagonist) was applied with inhalator route (20 mg-aerosol). After 5 minutes, Raw and ITGV were measured, and afterwards ox-

n	Age (v)	Height (cm)	Mass (kg)
51	22.19 ± 0.46	179.19 ± 1.17	70.81 ± 0.78

Table 1. Basic feature of the researched persons

n	VC (%)	FEV ₁ (%)	Raw (kPa L/s)	ITGV (L)
51	101.21±3.2	106.35±3.46	0.11±0.01	4.08±0.14

Table 2. Pulmonary function features of the researched persons

Figure 1. Measurement with Body plethysmography:

edrine as aerosol was applied to them (alpha₁-adrenergic agonist) in a dose of 120 mg, 5 min.; then hexoprenaline (beta₂-adrenergic agonist) was applied (2 inh. x 0.2 mg), Raw and ITGV were measured again and SRaw was also calculated.

In the second group of the researched (n=15) propranolol (beta₂-adrenergic antagonist) was applied with inhalator route (20 mg-aerosol). After 5 and 30 minutes, Raw and ITGV were measured, and afterwards hexoprenaline (beta₂-adrenergic agonist) was applied (2 inh. x 0.2 mg), Raw and ITGV were measured again and SRaw was also calculated.

In the third group of healthy persons (n=10) propranolol (beta₂-adrenergic antagonist) was applied with inhalator route (20 mg-aerosol). After 5 minutes, Raw and ITGV were measured, and afterwards tolazoline as aerosol (alpha₂-adrenergic blocker) was administered in a dose of 20 mg 5 min. After 5 minutes (of tolazoline administration) Raw and ITGV were measured, and in the end hexoprenaline (beta₂-adrenergic agonist) was applied (2 inh. x 0.2 mg), Raw and ITGV were measured again and SRaw was also cal-

culated.

In the last group (n=11) histamine as aerosol was administered and after 5 minutes Raw and ITGV were measured; 2 hour following the histamine, propranolol (beta₂-adrenergic antagonist) was applied with inhalator route (20 mg-aerosol). After 5 minutes, Raw and ITGV were measured. Afterwards, histamine applied again with inhalator route and after 5 minutes Raw and ITGV were measured. In the end, hexoprenaline (2 inh. x 0.2 mg) was applied, and Raw and ITGV were measured and SRaw was also calculated.

Results were processed in the computer statistical program GraphPad InStat III with the t-test of comparison of two working groups.

3. RESULTS

In researched healthy persons, following the blockage of beta₂-adrenergic receptor with propranolol (to eliminate the beta₂-adrenergic impact), stimulation of alpha adrenergic receptor with oxedrine or their blockage with tolazoline has not caused any significant change ($p > 0.1$) of the specific resistance (SRaw) of the airways (Figure 2 and 3). Whilst, hexoprenaline (beta₂-adrenergic agonist) is very effective in

Figure 2. Effect of the Propranolol (20 mg-aerosol), Oxedrine (120 mg-aerosol) and Hexoprenaline (2 inh x 0.2 mg); with calculated SRaw (Raw x ITGV) in healthy persons ($\bar{X} \pm \text{SEM}$).

Figure 3. Effect of the Propranolol (20 mg-aerosol) and Hexoprenaline (2 inh x 0.2 mg); with calculated SRaw (Raw x ITGV) in healthy persons ($\bar{X} \pm \text{SEM}$).

Figure 4. Effect of the Propranolol (20 mg-aerosol), Tolazoline (20 mg-aerosol) and Hexoprenaline (2 inh x 0.2 mg); with calculated SRaw (Raw x ITGV) in healthy persons ($\bar{X} \pm \text{SEM}$).

Figure 5. Effect of the Histamine (1 mg-aerosol), Propranolol (20 mg-aerosol) and Hexoprenaline (2 inh x 0.2 mg); with calculated SRaw (Raw x ITGV) in healthy persons ($\bar{X} \pm \text{SEM}$).

elimination of increased bronchomotor tonus, by causing significant decrease of the resistance (Raw), respectively of the specific resistance (SRaw) ($p < 0.01$). See Figures 2, 3, 4 and 5.

4. DISCUSSION

Results of this work indicate that blockage of beta-adrenergic system with propranolol in healthy persons (by eliminating the opposing action of adrenergic system towards cholinergic one) has caused slight increase of the specific resistance, respectively decrease of the airways conductance, but the rate of the change is not significant ($p > 0.1$).

Five minutes after stimulating of the alpha-adrenergic receptors with oxedrine, changes cannot be seen in the airways permeability ($p > 0.1$). As it can be seen from the figure 1, hexoprenaline (by stimulating of the beta₂-adrenergic system) inhibits parasympathetic impulses and their bronchoconstrictor effects, manifested with the significant decrease of the specific resistance and with increase of the expiratory flow ($p < 0.01$) in healthy persons.

These results match with results of other researchers which following the application of alpha-ad-

cause that very rare sympathetic innervations lies on bronchial tree. Meanwhile, other published data does not prove that physiologic concentrations of catecholamines in circulation may affect in the human's airways diameter.

Our results indicate that the activity of alpha-adrenergic receptor in the smooth bronchial musculature of healthy persons is minimal, not significant.

In the favour of the facts for non-significant role of the phentolamine in airways are conclusions of the author Mue et al. which presents that phentolamine does not cause myorelaxant effect after inducing the bronchoconstriction from the inhalator therapy with methacholine and histamine in the experiment with apes. Isoprenaline has manifested direct myorelaxant effect after inducing the bronchoconstriction with aerosol therapy with methacholine and histamine. Meanwhile, atropine has manifested a partial bronchodilator effect only after inhaling of methacholine but not after the inhalator therapy with histamine (10).

Alpha adrenergic antagonists (e.g. indoramine) cause bronchodilation due to the blockage of alpha-adren-

ergic agonists have not found any increase of the resistance in the healthy persons airways. During the last years, researches with experimental animals provided contradictory results over the role of the alpha-adrenergic receptor in regulating of bronchomotor tonus. Data exists regarding presence of the alpha-adrenergic receptor in airways of healthy people, but in a small number. Thus, Daniel et al. (9) consider that alpha adrenergic receptors in the smooth bronchial musculature may be stimulated only with an direct action of catecholamines in circulation and only in physiologic doses be-

cause that very rare sympathetic innervations lies on bronchial tree. Meanwhile, other published data does not prove that physiologic concentrations of catecholamines in circulation may affect in the human's airways diameter.

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Alpha adrenergic antagonists (e.g. indoramine) cause bronchodilation due to the blockage of alpha-adren-

ergic receptor and may be useful therapeutics for a certain population (11). Remains unclear whether these results are caused by the blocking of stimulation alpha-adrenergic receptor of mastocytes or airways smooth musculature (12).

5. CONCLUSION

Slight bronchomotor tonus exists in the healthy people, which are formed with an intermediation of the cholinergic system. Adrenergic ac-

tivity of the airways in healthy people is not studied enough. Blockage of the β_2 -adrenergic receptors with propranolol (excluding opposing action of the adrenergic system to cholinergic impulses) has caused non-significant increase of the airways resistance – SRaw ($p > 0.1$). Stimulation of **β_2 -adrenergic** receptors and their bronchoconstrictor effect manifest with significant decrease of the airways resistance ($p < 0.01$) of healthy people.

Stimulation and blockage of alpha-adrenergic receptor has not caused significant changes in the permeability of airways ($p > 0.1$).

We hereby declare: that the manuscript is original and the work has not been published elsewhere.

The authors have no conflicts of interest that are directly relevant to the content of this article.

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