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THE MECHANISMS OF BLOOD SUPPLY OF MUCOUS MEMBRANE OF ORAL CAVITY AND NOSE

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ABSTRACT
The effect of neurotransmitters and biologically active substances on upper respiratory tract vascular smooth muscles are due by the specific receptors in the blood vessels and by the peculiarities of their innervation. By the histochemical and physiological methods detected adrenergic, purinergic, peptidergic and other receptors. From these positions have been assessed the regulating mechanisms of the blood flow in the nasal and oral cavity mucosa. It is known that the nasal mucosa of the nose is observed with afferent C fibers that contain Calcitonin Gene-Related Peptide (CGRP). These nerve terminals are predominantly located in the mucous membrane (Alving.et al., 1991), and are thus quite likely to participate in the regulation of nasal mucosa membrane circulation. It is also known that in nasal cavity and addition sinuses accumulate nitric oxide, which has vasodilation affect. Absorption of this substance becomes in mucous membrane (DuBois et al., 1998). Because nitric oxides have vasodilator properties, it can (with Calcitonin gene-related peptide) plays an important role in regulation blood supply to the upper respiratory tract of mucous membranes. Both (CGRP) and (NO) vasodilator effect wears a regional character. In this regard, little is known about the relaxation mechanism of localized blood vessels in the nasal and oral cavity mucosa in which their participation is expressed at the cellular level. It is important the separation and accumulation of nitric oxide in the upper respiratory tract, and its ability of vasodilatation.

KEYWORDS: Calcitonin gene-related peptide (CGRP), nitric oxides (NO), N -Nitro-L-arginine methyl ester isomers (L-NAME), 7-nitroindazol (7-NI).

INTRODUCTION
Calcitonin gene-related peptide (CGRP) causes nasal mucous membrane's vascular relaxation, probable caused by CGRP receptors activation, which occurs as after peptide injection, as well after sensory C- fibers activation. The cause of depression of the bloodstream in mucous membrane of oral cavity, during systemic input of L-NAME, is a local vasoconstriction. That the neuronal nitric oxide inhibition caused by 7-nitroindazole does not change the intensity of blood flow in the pharyngeal mucosa, indicate that neuronal nitric oxide is not involving in the regulation process of blood flow. One of the main regulatory factors in blood flow in oral mucous membrane is endothelial nitric oxide. Calcitonin gene-related peptide does not affect the circulatory process of oral mucous membrane.

The goal of research
The goal is to study blood circulation regulation in the upper respiratory tract tissues (nasal and mucous membranes) from the perspective of improvement in blood circulation. Such research is recommended as for clinical otorhinolaryngology, as well it is important to keep the upper airway lumen within the optimum. As well as the improvement of blood circulation in the tissues of the same roads.

To achieve a set goal, the following specific tasks were needed

1. Registration the changing of local blood flow in nasal mucous membrane of rat
2. Registration the changing of local blood flow in pharyngeal mucosa
3. Registration the changing of local blood flow in pharyngeal mucosa after administration LNAME (N-nitro l-arginine methyl ester) non-selective inhibitor of nitric oxide synthesis, both independently and in combination with l- arginine, and also after administration 7-Nitroindazole, a selective inhibitor of nitric oxide synthase.

4. Registration the changing of local blood flow in nasal and pharyngeal mucosa after administration Calcitonin gene-related peptide receptor antagonist (CGRP8-37), both independently and in combination with Calcitonin gene-related peptide (CGRP).

2 series of experiments were conducted in 350-400G. White, outbred, adult male rats with chloral hydrate (0,4 mg/kg) anesthesia. Animals basked by electric blanket, temperature was automatically regulated within 36-37℃. Arterial blood pressure was monitoring from tail artery without blood. The dynamic of nasal (the first series of experiments) and pharyngeal (the second series of experiments) local blood flow was accounting by clearance method (Aukland.et al., 1964). For the injection of pharmacological substances, the right femoral vein was catheterized.

The first series of experiments
Experiments were done on 6 groups of rats. Each group contained 6 rats. In each group was measuring local blood flow in the mucous membrane of the nose, accompanied by regulation systemic arterial pressure.

In the first group were studied changes of the background indicators of the local blood flow of the nasal mucosa observed after 5 minutes of administration of capsaicin (21µmol, SERVA). In the second group, instead of capsaicin, was used Calcitonin gene-related peptide (CGRP, 1µmol). In the third group, 20 minutes before the administration of capsaicin, the intravenously (IV) was administrated L-NAME (Nnitro l-arginine methyl ester) non-selective inhibitor of nitric oxide synthesis (NOS) 30 mg / kg, and then capsaicin in the same dose. On the background of L-NAME in the fourth group, instead of capsaicin, was used a Calcitonin gene-related peptide (CGRP) (in the same the dose what was above). In the fifth and sixth groups, was studied the effect of capsaicin and CGPR on blood flow in the nasal mucous membrane of the nasal mucosa on the background of CGRP8-37 (Calcitonin gene-related peptide receptor antagonist) (16 µmol).

After chlorarhydrate anesthesia, a head of rat was placed on the back of the experimental table, separate the vein of the thigh and placed the catheter in it. The blood flow measuring electrodes was placed (teflonated 60µm platinum) in the mucous membrane of the nose by selecting the vertical position of the electrodes, minimal damage to the tissue without any additional fixation. Very thin (15µm) output golden wire did not cause a change in the condition of the electrode. Reference electrode was tightly fixed on the surface of the shaved ear.

The second series of experiments
Experiments were done on 10 groups of rats. Each group contained 6 rats. in all groups with the measurement local blood pressure was accompanied with the measurement of systemic arterial blood pressure from the rat tail.

The sequence of experiments was the following
In the first group was studied background indicators of local blood flow and systemic arterial pressure of the pharyngeal mucosa.

In the second group before registration indicators local blood flow of pharyngeal mucosa IV injection LNAME was performed (30 mg/kg).

In the third group, unlike second group, 30 minutes earlier before l-name intravenously l- arginine (300mg/kg) was performed.

In the 4-th and 5-th groups of the rats, the tests were similarly, but the dose of l-name was different, it was used 5 mg / kg of l-name, and l-arginine dose remained unchanged (300 mg / kg).

In 6-th group intravenously was injected calcitonin gene-related peptide (CGRP) 10 µmol/kg and after every 15 minutes after injection the local blood flow was registered.

In the 7th group, 15 minutes earlier of the same procedure (like 6th group) calcitonin gene-related peptide receptor antagonist (cgrp8-37) 0,3 mg/kg was performed intravenously.

In the 8-th control group was performed intravenously 0.5 ml. saline solution and was registered local blood flow in the pharyngeal mucosa.

In the 9th group, the change in local blood flow was studied after beforehand Intraperitoneal injection (IP) of 7-nitroindazole (7-NI) (30 mg / kg, 1 ml solution). The 7 NI is a selective inhibitor of Neuronal Nitric Oxide Synthases (nNOS). Accordingly, instead of 7 NI in the 10th (control) group, 1 mL saline solution was injected.

Measurement of systemic arterial blood pressure
Systemic arterial blood pressure was measurement discretely in every 5-6 minutes. The small size of cuff was fixed on rats' tail, which continuously heated up to 37 degrees. The date was registered by the oscillator. The systolic and diastolic blood pressure was measured and then the average systemic blood pressure was counted.

Local blood flow measured
The Local blood flow was measured by hydrogen clearance method (Auckland et al. 1964).

Pharmacological preparations
- N -Nitro-L-arginine methyl ester isomers (L-NAME)
- L- arginin
- 7-nitroindazol (7-NI)
- Capsaicin

- Calcitonin gene-related peptide (CGRP)
- calcitonin gene-related peptide antagonist (CGRP8-37) – SERVA.
- IV and IP solution was made before the experiment.

Statistical analysis of the data
For statistical processing was used parametric statistical technique variable analysis (ANOVA).

RECEIVED RESULTS
Registration the changing of local blood flow in nasal mucous membrane.
In all groups of animals except of the 3rd and 4th groups where was used L-NAME injection, systemic blood pressure was ranged within 90 millimeters of mercury (mm Hg) and consisted 92,3 ± 7,8 mm. In any of the stages of the experiment a reliable substantive change of average systemic blood pressure was not recorded. In the 3rd and 4th groups of animals, here 20 minutes before the injection of capsaicin (3rd group) and calcitonin gene-related peptide (4th group) IV was injected L-NAME (N-nitro l-arginine methyl ester) 30 mg/kg, as a result the systemic arterial blood pressure increased 52 ± 7 mmHg.

The average statistical level of local blood flow in the mucous membrane of the nose was 37,1 ± 6,8 ml/100g. min. After 5 minute of capsaicin injection this indicator increased by 73,2 ± 9,2 ml/100g. min., and 78,2 ± 10,1 ml/100g. min. after calcitonin gene-related peptide injection.

On the background of the action of non-selective nitric oxide synthase (NOS) inhibitor L-NAME neither capsaicin nor CGRP didn't give any statistically significant difference compared to the results received without this inhibitor, in both cases, partial growth of the blood flow was noted (probably related to systemic blood pressure rises). The level of local blood flow in this case Amounted to 80,1 ± 8,2 and 84,4± 7,1 ml/100g. min. as already noted, it does not give statistically significant difference to the results obtained without L-NAME. In group where Calcitonin gene-related peptide receptor antagonist (CGRP837) was used he principal difference was noted: neither capsaicin nor the CGRP wasn't given statistically significant difference results from control. This indicates that in nasal mucosa the CGRP 8-37 blocking the rise of local blood flow caused by capsaicin and CGRP. it's should be noted that the date obtained in the I-IV groups on the increase in local blood flow statistically significantly different (P< 0,01) from the results as of control group results and from V and VI groups results. In addition, the results obtained in the I-IV groups do not give a relative difference between them. The same is true of the results of the control, V and VI groups, among them the difference is not reliable. That may conclude that statistically significant change in the intensity of blood flow received only using the Calcitonin gene-related peptide receptor antagonist, after the local blood flow increasing caused by capsaicin and CGRP.

Changing of local blood flow in pharyngeal mucosa
Under narcosis (Intraperitoneal Injection of chloral hydrate (IP) 0, 4 g/kg) in the pharyngeal mucosa of white rats it was fixed platinum electrodes for hydrogen clearance method (teflonated wire diameter, 60 - μm without isolation). Very thin (15km) golden wire is very thin electrode, which by the minimum weight can fixed on the mucous membrane only with their own weight, without any additional fixers. During this fixation the electrode moves freely with tissue, which significantly reduces the number of artifacts associated with accidental movement of the animal. The second auxiliary electrode chlorinated silver round plate (3mm) was fixed on rat's ear. The maximum duration of the test was 60-70 minutes, during which the cavity of the rat was fixed openly by the 1,5-2 cm. stainless steel stem, which by the acrylic fixed between the upper and lower jaws. This allows for all manipulation in the oral cavity.

The average statistical data of the results of measurement local blood flow, show that every day this date is maintained at a sufficiently high level and the difference is not statistically significant among the different days' results.

The same parameter was recorded after intravenous injection of 0,5 ml. saline in rats (the control group). Measurements were done every 15 minutes after injection within one hour and then at 10th and 14th day from injection. This data is proof of the high level of stability of the registered parameter.

After receiving control date, test was performed by the L-NAME non selective inhibitors of nitric oxide synthase (NOS), two different doses (5 and 30 mg / kg) in 0,5 saline solutions was done intravenously. The Administration of this Preparation caused a dose-dependent changes in the animal's systemic arterial blood pressure (**Table 1**). Also changes were recorded in the pharyngeal mucosa during the local blood flow registration (**Table 2**). It should be emphasized that the introduction of L-NAME on 30th minute of injection has caused a statistically reliable decrease of local blood flow of pharyngeal mucosa (as low and especially high doses), despite the increase of systemic arterial pressure. Before that (at the 15th minute of injection) the local blood flow partly increased in the pharyngeal mucosa, which should be directly associated with increased systemic arterial pressure.

in the mucous membrane the local blood flow's described changes completely blocking if before the LNAME IV injected L-arginine (300 mg / kg, once again in 0,5 ml physiological solution). Physiological data indicate that despite of dose of L-NAME, L-arginine injection slow down the increase of systemic arterial pressure as well as

reduction of local blood flow in pharyngeal mucosa, what were happened only after L-NAME injection.

Table 1: The changes of average arterial pressure of rat every 15 minutes after injection of L-NAME. The result shows significant changes of systemic arterial blood pressure.

L-NAME (mg/kg)	The initial value (mm Hg)	15'	30'	45'	60'
5	100 ± 12	139 ± 10	134 ± 10	135 ± 13	130 ± 10
30	100 ± 7	165 ± 11,8	162 ± 13,4	166 ± 13	136 ± 10

Table 2: In the pharyngeal mucosa the change of intensity of local blood flow after injection of L-NAME.

L-NAME (mg/kg)	The local blood flow (ml/100g/min) every 15 minutes after L-NAME injection				
	The initial value	15'	30'	45'	60'
5	52 ± 8	58 ± 10	34 ± 6	34 ± 6	32 ± 5
30	55 ± 6	60 ± 9	40 ± 6	30 ± 5	30 ± 5

In the next series of experiments, it used the Selective Neuronal Nitric Oxide Synthase Inhibitor 7Nitroindazole (7-NI)- 1 ml of 30 mg / kg intraperitoneal (IP) injection. The data provided in **Table 3** indicate that the parameters we have recorded within an hour after the injection of this preparation did not have any statistically significant changes.

Table 3: The changes of local blood flow and systemic blood pressure in the pharyngeal mucosa caused by 7Nitroindazole (7-NI) intraperitoneal (IP) injection.

Parameters	The initial value	30 mg/kg 7-NI IP			
		15'	30'	45'	60'
Average systemic arterial pressure (mm Hg)	98 ± 7,7	101 ± 6,2	100 ± 5,8	98 ± 4,4	99 ± 6,0
Blood flow in the pharyngeal mucosa	53 ± 8,1	56 ± 5,1	54 ± 7,0	55 ± 6,8	52 ± 7,7

Table 4: The changes of intensity of local blood flow in the pharyngeal mucosa caused by CGRP and CGRP8-37 + CGRP successive intravenous injections.

CGRP 8-37 [mg/kg]	CGRP [nmol/kg]	The local blood flow (ml/100g/min) every 15 minutes after CGRP injection				
		The initial value	15'	30'	45'	60'
-	10	61 ± 11	60 ± 10	64 ± 9	62 ± 10	59 ± 9
0.3	10	57 ± 8	61 ± 9	60 ± 7	59 ± 9	62 ± 10

Different results were obtained where was used Calcitonin gene-related peptide (CGRP) and Calcitonin gene-related peptide receptor antagonist CGRP-(8-37) (**table 4**). Intravenous injection of CGRP in one group of animals did not cause any change in the intensity of local blood flow in the pharyngeal mucosa. the same happened in the second group of animals whom had been injected (15 minutes earlier), the Calcitonin gene-related peptide receptor antagonist CGRP-(8-37). The injection of this peptide with the same dose did not cause statistically significant change of local blood flow.

RESULTS REVIEW

Based on the research we had set out, the principal importance had the accurate measurement of local blood flow in the mucous membrane of tissue. That is why was used hydrogen clearance method for registration of local blood flow, which allows quantitative measurement of blood flow, is high accuracy, and is highly successful in measuring local blood flow in the brain tissue (Aukland,1965; Demchenko1985), oral cavity and gut mucosa (Hirose et al., 1992;) Liver, kidneys, etc.

The statistically significant results obtained by multiple measurements show that the vasodilation caused by capsaicin and CGRP in the nasal mucous membrane do not change the synthesis of Nitric Oxide after the injection of non-selective NOS inhibition - L-NAME. It should be noted that in this case Nitric Oxide does not play any role in vasodilatation caused by capsaicin and CGRP. That the nitric oxide does not play any role in the vasodilation caused by capsaicin and CGRP, it is logical if we consider that the nitric oxide is produced in large quantities in the nasal cavity where it is absorbed (DuBois et al., 1998) and more part of it goes to the lungs where it plays an important role in vascular dilation. It is therefore not surprising that the nasal cavity mucous membrane blood vessels functioned by other

mechanisms, otherwise they would be in a vasodilator condition.

Calcitonin gene-related peptide (CGRP) is a 37-amino acid peptide, it is a potent vasodilator. It is known that the CGRP infusion in the mucous membrane of nose causes the concentration-dependent vasodilation (Stjarne.et al., 1989). This experiment shown mediator role of CGRP in lingual artery vasodilation. It is also established that within a few seconds of intravenous infusion the CGRP reaches target tissue (Wimalawansa,1996). CGRP8-37 was initially considered as a possible antagonist of the CGRP - receptor (Chiba.et al., 1989). It suppressed in Guinea pigs' contractile reactions induced by CGRP (Dennis et al.,1990) and relax the a. mesenterica (Han et al.,1990). This work also shows that there may be two types of CGRP receptors: CGRP1 and CGRP2. CGRP1 is sensitive to CGRP8-37 and CGRP2 is not.

Analysis of the data obtained in the results and literature shows that the Peptide-like CGP (CGRP) of the calcitonin gene causes the relaxation of vascular vein of the nasal mucosa and is conditioned by the activation of CGRP receptors, which occurs when injecting the peptide itself, as well as by capsaicin caused sensory c-fibers Activation. It should be noted once, even though the important role of nitric oxide and related components in the regulation of vascular tone (Toda, Okamura, 1990) we do not confirm this outcome in the case of the mucous membrane of the nose and, as already said, the main mechanism of relaxation in this case we should consider the CGRP-receptors activation located in smooth muscle's membrane.

There is a certain dependence between blood flow and epithelial thickness. Using radioactive microspheres and histological analysis has shown that blood flow in oral cavity is much higher than in skin. According to the thickness of epithelium these tissues are divided into 4 groups: 1. pharyngeal 2. lingual dorsal surface, dorsal surface of gingiva 3. Jaws and lips, 4. All areas of skin. Positive correlation is determined between blood flow and epithelium thickness. The thick epithelium associated with high levels of blood flow, that why, the thick epithelium has a higher metabolic demand (Johnson et a., 1987).

It is also shown that the cause of the necrosis of the epithelial cells in the initial stage, with inflammatory processes, is micro circular disorders in the mucous membrane, and later in the process involves the dysregulation of nitric oxide that causes accelerate apoptosis of epithelialocytes (Crouser.et al., 2000). The excess of nitric oxide is associated with barrier disruption and the development of hyper conductive during chemotherapy.

The presence of nitric oxide synthesis (NOS) in the oral cavity tissue of different species is determined by using histochemical and immune histochemical methods. NOS was found in the oral mucosa of rats in the gum (Handa.et al., 1996; kerezoudis.et al., 1993), tongue (Crozdanovic.et al., 1992; Funk et al., 1994) - lingual artery branches were found to be innervated NOS - containing fibers (Lohinai.et al., 1997). The same work shows that endothelial cells also contain NOS.

In 1980, Furhgott and Zawadski showed the necessity of endothelium for acetylcholine-induced vasodilation. Since then, a number of vasoactive substances have been identified, which carry out their vasodilator effect from the vascular endothelium - Endothelium - dependent factor (Furhgott, Vanhoutte, 1989). In about the same period it was established that the nitric oxide synthesized from L-arginine responsible for endothelium -depend factor action (Palmer et al., 1987). Moreover, NO-'s strong inhibitors in different diameter blood vessels inhibit vascular relaxation, induced by action endothelium demand factors (Moncada.et al., 1991).

Collected data indicates that nitric oxide is not just vasodilator it's also an intercellular messenger, for example, it is believed that odorant induced NO may play an important role in olfactory adaptation (Breer, Shepherd, 1993).

Dose-dependent change of systemic blood pressure described in my dissertation after L-NAME systemic input. Once again confirms the importance of nitric oxide in the regulation of systemic blood circulation. systemic vasoconstriction increases blood pressure, which is probably the result of reduced nitrogen oxide production. Such assumption is also expressed in other works (Fazekas.et al., 1994; Kerezoudis.et al., 1993; Izumi et al., 1997). It should also be noted, that the blood flow in the mucous membrane has decreased, despite of parallel developed hypertension. This indicates that, the local depression of blood flow in the mucous membrane of pharynx, causes local vasoconstriction, that's confirmed by that, at the same time the blood flow in the nasal mucosa has not changed, not counting the initial growth, which has been caused by a systemic blood pressure. it's shouldn't be doubtful that the vasoconstriction in the mucous membrane of oral cavity was induced by L-NAME, whose mechanism of action is determined by the synthesis of nitrogen oxide (NOS). The additional proof of this is that the introduction of L-arginin neutralize the effect of L-NAME and reduction of blood flow in the mucous membrane of the pharynx has not been pronounced.

A number of researches were conducted to explain the origin of nitrogen oxide regulating blood flow in the mucous membrane of the oral cavity (pharynx) in basal conditions. For this purpose, an intraperitoneal injection of 7-nitroindazole, which is known as the neuronal NOS inhibitor and which also possible has an inhibitor effect on inducible nitric oxide (i NOS). It is shown that in the cats 7nitroindazole (40 mg / kg) significantly reduces the

activity of neuronal NOS (Kovach et al., 1994)). In our research, 7-nitroindazol did not change the intensity of blood flow in the mucous membrane of pharynx. In spite of selective inhibition of NOS by 7-nitrindazol the variation of intensity of basal blood circulation confirms that blood flow regulation in the oral mucous membrane should be caused by endothelial nitrogen oxide. A similar result was previously described by Nielson (Nielson, 2000), which showed that in the cats, 7-nitroindazole (30 mg / kg) also does not cause any effect on the vasodilation in eye's blood circulation. If we summarize the results of the test conducted in basal conditions we may find out that in one area of oral cavity: one of the main regulatory factors of local blood flow in the mucous membrane of pharynx is nitric oxide, and inhibition of its production, despite the rapid increase of systemic blood pressure, in this tissue reduce blood flow. The main role in this mechanism play endothelial and non-neuronal or inducible nitric oxide. It should also be noted that the inability of L-arginin to increase the local blood flow in basal conditions indicates that the mucous membrane in the oral cavity is an enough number of this substratum, which is perfectly satisfying the function of NO forming enzyme (Rees et al., 1989).

CONCLUSIONS

Different factors effect on blood vessels diameter of upper respiratory tract mucous membrane, vasoconstriction and vasodilatation can effect breathing, nose and oral bleeding and development of inflammatory processes. the study requires more experiments.

The studies have shown that vasodilation of blood vessels of mucous membrane of the nasal cavity, is effected by Calcitonin Gene-Related Peptide (CGRP). The same effect causes activation by capsaicin the sensory c-fibers.

To the background of hypertension induced by L-NAME, the decrease of blood flow in the mucous membrane of pharynx caused by local vasoconstriction, which is induced by non-selective nitric oxide synthase inhibition.

The constriction of blood vessels in the mucous membrane of pharynx is caused by non-selective NOS inhibition, which excludes involve in this reaction other non-specific mechanisms.

The main role in regulation of blood flow in oral mucosa membrane, play endothelial and non-neuronal or inducible nitric oxide synthase activation.

Calcitonin Gene-Related Peptide (CGRP) does not have an effect on vessels of mucous membrane of pharynx.

It is recommended that in Artificial ventilation be provided the concentrations of nitrogen oxide, which has during nasal breathing. This would require the creation of a special meter.

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