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Endogenous Sensitizer of Beta-Adrenergic Receptors (ESBAR) and its Analogs

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Abstract

The results of the 20 years studies of the presence in blood serum and other body fluids of endogenous modulators of adrenergic and M-cholinergic impact as a component of humoral link of autonomic nervous system. The article is devoted to the Endogenous Sensitizer of Beta-Adrenergic Receptor (ESBAR)-water-soluble low molecular weight substances, analogs of which are histidine, tryptophan, tyrosine, mildronate and preductal. It is shown, that separate dilutions of human serum and animal (as a source of ESBAR) and analogs of ESBAR ways to enhance the effectiveness of activation of beta-Adrenoceptors (AR) of smooth muscle (uterus, coronary and renal arteries, trachea, stomach), myocardium, erythrocytes and platelets (respectively influenced of histidine and tryptophan). It is reported that content of ESBAR in human serum (according to the titers of its dilution) depends on the sex and the presence of somatic diseases and at women are also on the stage of reproduction and obstetric complications. It is discussed possible mechanisms of ESBAR action, its physiological role, including as a component of beta-adrenoceptor inhibitory mechanism for myometrium, as well as the prospect of the use of analogs of ESBAR, including for the prevention of preterm labor, and for the treatment of bronchial asthma, coronary heart disease, hypertension and heart failure.

Keywords: Catecholamines; Beta-adrenergic receptors; Endogenous modulators of adrenergic receptors; Smooth muscle; Myocardium; Erythrocytes; Platelets; Pregnancy; Labor; Beta-adrenoceptor inhibitory mechanism

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Abbreviations

ANS: Autonomic Nervous System; AR: Adrenoceptors; Beta-ARIM: Beta-Adrenoceptor Inhibitory Mechanism; CA: Contractile Activity (of strips); CAU: Contractile Activity of the Uterus; EBAAR: Endogenous Blocker of Alpha-Adrenoceptors; EBBAR: Endogenous Blocker of Beta-Adrenoceptors; EBMChR: Endogenous Blocker of M-Cholinergic Receptors; ESAAR: Endogenous Sensitizer of Alpha-Adrenoceptors; ESBAR: Endogenous Sensitizer of Beta-Adrenoceptors; ESMChR: Endogenous Sensitizer of M-Cholinergic Receptors; HRV: Heart Rate Variability; LPC: Lysophosphatidylcholine; LS NPRUH: Longitudinal Strips of Non-pregnant Rat Uterine Horn; M-ChR: M-Cholinergic Receptors; TPL: Threat of Premature Labor; WLA: The Weakness of Labor Activity.

Introduction

Studying chemoreactivity of isolated myometrium of pregnant women and animals (rat, rabbit, pig), we have identified, that there are a variety of uterostimulatory, i.e. substances, which increase of Contractile Activity of the Uterus (CAU), e.g., oxytocin, serotonin, histamine, but there is only one substance that able to inhibit spontaneous activity and/or induced (by utero stimulators) activity [1-5]. It is likely, adrenaline, which interacts with $beta_2$-Adrenoceptors (AR) of myometrium. Given the available by the time the data is relatively high effectiveness of $beta_2$-agonistin at pregnant

women with Threat of Premature Labor (TPL), we have proposed a hypothesis about the functioning the so-called beta-Adrenoceptor Inhibitory Mechanism (beta-ARIM) at pregnant women, the degree of influence on the CAU reduced only before labor [6-9]. According to this hypothesis at pregnancy in uterine myocytes increased expression of $beta_2$-AR gene that leads to the dominance of the $beta_2$-AR above alpha-AR. Therefore catecholamine of blood serum and amniotic fluid, activating the $beta_2$-AR of uterine muscle cells, inhibit the spontaneous CAU and induced CAU, for example, by oxytocin, serotonin and histamine (with appropriate receptors). But contrary to this hypothesis, a circumstance known by that time well enough-a phenomenon of desensitization, i.e., loss of effectiveness of the activation of membrane receptors during continuous exposure to the agonist. It was demonstrated in our experiments with isolated myometrium of human and animals, including in relation to the interaction catecholamine's with $beta_2$-AR [10]. But in that time the mechanism of desensitization does not have any detailed information about the process of phosphorylation of receptors associated with G-protein as the basis of desensitization and the existence of enzymes, it is now considered to be involved in this process, including kinases of alpha-AR or beta-AR, protein kinase A, and protein kinase C [11-13]. However, we have assumed that the effective functioning of the beta-ARIM addition to $beta_2$-AR agonist and it is necessary factor preventing desensitization of these receptors and thereby constantly maintain the effectiveness of their activation [7-9]. We hypothesized that this factor is contained in the blood of mother and possibly of the fetus. In this regard, we conducted an experiment with the Longitudinal Strips of Non-pregnant Rat Uterine Horn (LS NPRUH), in which assessed the efficacy of the effect of adrenaline on the CA of the strips three times- 1) initially, 2) against exposure to blood serum of pregnant women and 3) after its removal. It was assumed that the presence in the serum of the desired factor in certain dilutions of blood serum should rapidly and reversibly raise the efficiency of inhibition of spontaneous CA of these strips under the influence of adrenaline. Should take two fundamentally important in terms of methodological explanations: 1) LS NPRUH unlike the circular strips of non-pregnant rat uterine horn mainly reflect the activity of the longitudinal layer of the myometrium, which is characterized by high expression of $beta_2$-AR, in connection with which the adrenalin even in very low concentrations inhibits of spontaneous CA of these strips; but in the circular layer of the uterus of non-pregnant rats no dominance $beta_2$-AR, in this connection, the adrenaline does not inhibit spontaneous CA of these strips, even in very high concentrations [14]. Therefore, to detect the presence of serum hypothetical modulator of $beta_2$-AR best suits LS NPRUH. 2) The threshold concentration of adrenaline, which causes the inhibition of spontaneous CA of LS NPRUH depends on the phase of the estrous cycle (maximum-in metaestrus), and also depends on the season and other climatic factors [4,14,15]. Therefore, for the detection of the blood factors, that increases the effectiveness of $beta_2$-AR activation in experiments with LS NPRUH. Initially need to find the concentration of adrenaline, which is close to the threshold or slightly above it. All these factors taken into account when searching factor, which enhance the effectiveness of $beta_2$-AR activation. The result of this research was a series of your publications in 1997 year, which reported that the serum of pregnant women in a dilution of 1:100, 1:500 or even $1:10^3$ is able to increase the degree of inhibition of spontaneous CA of LS NPRUH under the influence of a threshold concentration of adrenaline [16-18]. Those, in the presence of blood serum of adrenaline in the concentration close to the threshold, he showed himself as adrenaline in a concentration close to the maximum [16-18]. In these articles, the first time a hypothetical factor that increases the effectiveness of the $beta_2$-AR activation was named endogenous sensitizer of beta-AR, or ESBAR. They have also been reported, that the content of ESBAR, according to the titers of blood serum dilution in which there is ESBAR-activity, depends on gender-men have content of ESBAR lower than that women, and women depends on the presence of pregnancy-at pregnancy content of ESBAR increases, which probably contributes to the formation of beta-ARIM [16-18]. It was noted, that ESBAR was found in urine, saliva, in the cerebrospinal fluid, and at pregnant women-in the amniotic fluid [16-18]. This meant that ESBAR can pass through various barriers-to the brain, kidneys, salivary glands, to the fetus, and from it-in the amniotic fluid. Thus, it has been proved the existence factor that enhances the efficiency of the $beta_2$-AR activation, i.e. ESBAR.

These publications preceded yet another of our paper, which was first reported that a 100-fold dilution of serum of umbilical cord blood of newborns improves beta-adrenoreactivity circular segments of the pig coronary arteries [19]. If the initially adrenaline, even in very high concentration (10^{-6} g/mL) did not reduce their tone, increased high potassium solution (25 mM KCl) Krebs, then the action of adrenaline along with 100-fold dilution of serums causes a very marked decrease in tone. This allowed concluding that serum indeed contains ESBAR which can improve efficiency of $beta_2$-AR activating not only myocyte of uterus but myocytes of coronary artery. We believed that these works are of interest to ESBAR [16-19]. However, it took almost 20 years, during which time there and our other articles on ESBAR, but so far we have not seen a single work of other laboratories, which would confirm or refute our findings. Perhaps this is due to the fact that to date nature ESBAR is not defined, it is not isolated in pure form and is not set location (s) of its synthesis.

During these years, efforts have been made to clarify the physiological role of ESBAR, in particular, the ability of ESBAR to improve the efficiency of activation of $beta_2$-AR of smooth muscle from pig coronary artery, the arteries and veins of human umbilical cord, renal artery pigs, cow trachea, rat stomach, and also myocardium of frog, rats and humans and human erythrocytes [20-46]. In addition, our efforts were made to find analogs of ESBAR, to study the mechanism of action of ESBAR and its analogs, on the role of ESBAR in the pathogenesis of systemic diseases-coronary heart disease, arterial hypertension, bronchial asthma, and gastric acid-related disease, as well as a number of obstetric complications as the Weakness of Labor Activity (WLA), Threat of Premature Labor (TPL), preeclampsia and placental insufficiency [15,21,25-31,33,35-43,45-67]. Preliminary analysis of these dates has been made in our two books [15,68].

Nature of ESBAR, analogs of ESBAR and sources of ESBAR production

We have attempted to study the nature of ESBAR. But to get pure ESBAR, determine its structure and molecular weight failed, including the lack of expensive equipment. At the same time determined that ESBAR-activity of blood serum a is relatively stable to 60 minutes of boiling and also for long-term storage, including up to 24 hours at 37°C, or up to 14 days at 4°C or 90 days at -20°C. It is also obvious, that ESBAR is the water-soluble substation as all blood serum dilutions, including exhibiting ESBAR-activity, preparing with Krebs solution [15,18,68]. Pre concluded that ESBAR is a low molecular weight substances, as an ultra filtrate of blood serum of pregnant women,

as well as its low molecular fraction which obtained by gel filtration on Sephadex G10, retain ESBAR-activity in experiments with LS NPRUH [15,68]. In view of these data it has been searched substances capable exhibits ESBAR-activity. It was found, that among of the 37 different substances (of low molecular weight with a different physiological effect) including 20 amino acids, 30 substances did not have ESBAR-activity [68-70]. Among them-antihipocsants (meksidol and emoksipin), acids of Krebs cycle and its salts (α-ketoglutaric acid, oxaloacetic acid, fumarate, succinate sodium), nicotinic acid, blocker Na^+-K^+-pump (strophanthin K), hormones (thyroxine, hydrocortisone), protein synthesis blocker (adriablastin), a substance similar in structure to trimetazidine (piperazine) or histidine (imidazole), and 17 amino acids (β-alanine, L-arginine, L-asparagine, L-aspartic acid, L- glutamine, DL-glutamic acid, L-lysine, L-leucine, L-cysteine, DL-glycine, DL-valine, DL-isoleucine, DL-methionine, DL-proline, DL-serine, DL-threonine, DL-phenylalanine. At the same time it was established, that ESBAR-activity exhibited 3 amino acids-L-histidine (3×10^{-8} g/mL to 3×10^{-5} g/mL), L-tryptophan (10^{-5} g/mL) and DL-tyrosine (2×10^{-6} g/mL to 2×10^{-5} g/mL), as well as used in cardiology metabolic drugs-trimetazidine (preductal) and trimethyl hydrazine propionate (mildronat) [15,47-50,52,53,55,56,58,68,70]. Furthermore, ESBAR-activity showed nitroglycerin (10^{-5} g/mL) and ethanol in high concentrations (9.6×10^{-3} g/mL) [68,69]. Data on the ability of the histidine, tryptophan, tyrosine, mildronat and preductal improve efficiency activate of $beta_2$-AR were obtained in experiments with the LS NPRUH, including background spontaneous CA and under tone caused by high potassium (60 mM KCl) Krebs solution and against the background of an artificial reduction of the efficiency of the activation of $beta_2$-AR by ozonated (5×10^{-8} g/mL) Krebs solution, lysophosphatidylcholine or non-selective beta-blocker propranolol [51-53,56,58,59,71]. When this has been shown relative selectivity analogs ESBAR-in experiments with LS NPRUH they did not exhibit this effect against acetylcholine response [72]. Given that the histidine, tryptophan, and tyrosine are natural components of blood serum, it was suggested that ESBAR is at least one of these three amino acids. Taking into account the concepts of beta-ARIM, the degree of influence on the myometrium which should increase during pregnancy, as well as our data about increasing of ESBAR-activity of blood serum at pregnancy, was studied blood levels of 20 amino acids, including histidine, tryptophan and tyrosine at pregnant women and parturient [7-9,16-18]. These studies, however, have not confirmed our hypothesis [54,67]. Contrary to expectation levels of these three amino acids are not increased at pregnancy. Therefore, we hypothesized that ESBAR-activity of blood serum is determined not only by the content of the three amino acids, but also the presence in its other any substances [54,67].

Adrenergic synapses of the myometrium as a source of ESBAR

Given the fact that among the amino acids having ESBAR-activity was tyrosine, known as a precursor of the catecholamines, we hypothesized, that the adrenergic synapses fibers of myometrium can to be source of ESBAR. To prove this hypothesis a series of experiments held [15,18]. In this experiments part of the longitudinal strips of uterine horn of non-pregnant and pregnant rats, as well as strips of myometrium of non-pregnant or pregnant women served as a prospective source of ESBAR («donors» of ESBAR) and identification of ESBAR-activity of perfusate flowing from the strip-«donors», carried out on a test object, in which quality in all series used LS NPRUH. At the same time, the ability of the perfusate flowing from the «donor» strip, modify the test object response to adrenaline, which was used at concentrations close to the threshold (10^{-9} g/mL, 10^{-8} g/mL or 10^{-7} g/mL). In experiments in which strips-donors were strips of non-pregnant uterine horn of rats, it was found that the perfusate collected from donor strip after the beginning of perfusion prior to onset of spontaneous CA (about 20 minutes) had ESBAR-activity, i.e., enhanced the inhibitory effect of adrenaline (10^{-9} g/mL, 10^{-8} g/mL or 10^{-7} g/mL) in 38.6% of experiments. Against the background of spontaneous CA of strips-«donor» ESBAR-activity of perfusates was observed in 46.2% of experiments. Against the background of the 20-minute transmural electrical stimulation of the strips-«donor», which was held in a 30-second bursts of electrostimulation (inside-3 impulse/s, duration-0.5 ms, voltage-50 V), going every 30 seconds, i.e., just 10-11 packs, ESBAR-activity was noted in 33.3% of experiments, and after transmural electrostimulation-in 46.2% of experiments (respectively, P1-, P2-, P3- and P4- perfusates collected for 20 minutes each). If the "donor" is the longitudinal strips of uterine horn of pregnant rats, the values were, respectively, 21.4%, 42.8%, 57.3% and 36.4%. In similar experiments, in which «donors» were strips of myometrium non-pregnant women (obtained at hysterectomy about uterine fibroids), these values were, respectively, 42.9%, 28.6%, 0% and 14.3%, and in experiments in which the strips-«donor» were strips of myometrium of pregnant women (they are dissected with a planned caesarean section from the lower uterine segment)-respectively, 30.0%, 10.5%, 50.0% and 36.8% of experiments. These data allow us to conclude that: 1) the myometrium of rat and human can produce ESBAR; 2) in rats, when in strips generate of spontaneous CA it was increases of productions of ESBAR, and women (non-pregnant and pregnant women), by contrast, is reduced; 3) with transmural electrical products ESBAR at non-pregnant rats and (especially) at non-pregnant women is reduced, and in pregnant rats and pregnant women, on the contrary, increases. It is suggested that during pregnancy the so-called physiological sympathectomy of the uterus, which is described in the literature, is not a true denervation of the uterus, and it is the conversion of the mediator in the adrenergic terminals of the uterus- instead of noradrenaline, has a pronounced fluorescence, mediator becomes a precursor of catecholamine's - tyrosine having a less pronounced fluorescence, which creates the illusion of sympathectomy [73,74]. It is possible that this phenomenon is due to the suppression in the adrenergic synapses (under the influence of progesterone) of the expression of enzymes genes involved in the synthesis of Dihydroxyphenylalanine (DOPA), dopamine and noradrenaline from tyrosine. Therefore neurotransmitter in the synapse becomes tyrosine which has high ESBAR-activity. Thus, tyrosine enhances the effectiveness of beta-AR activation on postsynaptic and extra synaptic sites of the plasma membrane of muscle cells of the uterus under the influence of catecholamine's of blood and amniotic fluid that prevents desensitization of these receptors. This provides braking CAU, i.e., implementation beta-ARIM. On the eve of the labor is likely to be gradual restoration of synthesis of classical adrenergic mediator-in the beginning it becomes dopamine and then noradrenaline. This reduces the degree of the effect of beta-ARIM on the myometrium and promotes the induction of labor, especially in this period and increased expression of alpha-AP gene.

Physiological properties and mechanisms of action of ESBAR and its analogs

The study of this issue mainly conducted experiments on LS NPRUH showing, that the blood serum of pregnant women and

umbilical cord blood serum (as a source of ESBAR) and analogs of ESBAR-histidine and tyrosine, and in some cases tryptophan increase the inhibitory effect of above-threshold (but not maximum) concentrations of adrenaline, noradrenaline, and dopamine, but not enhance the inhibitory effects of synthetic $beta_2$-agonists (gynipral and partusisten) [61,68]. This suggested that ESBAR and its analogs bind to the so-called amino acid site of $beta_2$-AR and thus allosterically enhance its affinity to catecholamines, but not to synthetic agonists of adrenoceptor having different structure [61,68].

It has also been demonstrated, that the ability of ESBAR and its analogs (histidine, tryptophan, tyrosine) to improve the inhibitory effect of adrenaline is manifested not only on intact LS NPRUH having spontaneous CA, but also on LS NPRUH whose activity is enhanced artificially, e.g., high potassium depolarization (KCl 60 mM) Krebs solution or oxytocin (5×10^{-3} IU/mL) [61,68]. It speaks of the universality action of ESBAR and its analogs, capable in any environment to improve the efficiency of $beta_2$-AR activation. In experiments with LS NPRUH was found, that the effect of ESBAR and its analogs observed relatively quickly-within the first 1-3 minutes from the start of exposure [61,68]. After a 20-minute application of ESBAR its effect lasts 10 min (after exposure to 500-fold and 10^3-fold dilutions of serum) or 80 min (after exposure to 100-fold dilutions serum). ESBAR and its analogs exert their activity on the background of blockade of alpha-AP by nicergoline (10^{-6} g/mL) [68]. All this has allowed to argue, that ESBAR and its analogs are positive modulators of direct action, the effect of which is associated with increased affinity of receptor to agonist, to increase the efficiency of the transmission signal from the $beta_2$-AR inside the cell effectors and to counter the development of desensitization [61,68]. Indeed, in experiments with LS NPRUH it is shown that histidine (3×10^{-8} g/mL, 3×10^{-7} g/mL and 3×10^{-6} g/mL, but not 3×10^{-11} g/mL) inhibits the development of desensitization observed during the 30-minute continuous exposure at high concentration of adrenaline (10^{-6} g/mL), and histidine (10^{-6} g/mL) counteracts desensitization, developed at 5-fold the short-term (10 min) effects of adrenaline (10^{-7} g/mL) as an inhibitor of spontaneous contractions [58,68,75]. Accordingly, the histidine may have anti desensitization effect in different types of effects of adrenaline to the test object. We suggested, that the basis of histidine anti desensitization effect (histidine as analog ESBAR) is its ability to inhibit enzymes that cause phosphorylation of the $beta_2$-AR (kinase of $beta_2$-AR or protein kinase A or protein kinase C) and/or activate of phosphatase and thereby reduce the degree of phosphorylation of the $beta_2$-AR, which increases the efficiency of their activation [58,68,75]. Unfortunately, we have not studied the effect of serum (as a source of ESBAR), histidine and other analogs of ESBAR on activity of enzymes involved are known to desensitization and on phosphatase activity, which is known prevents desensitization [11-13,76]. However, regardless of the mechanism of histidine anti desensitization effect, we can talk about the possibility of using ESBAR and its analogs (tryptophan, tyrosine, mildronat, preductal) in clinical practice in order to improve the efficiency of activation of $beta_2$-AR of cells [58]. In this aspect is important data on the interaction of blood serum (as a source of ESBAR) with analog of ESBAR [59]. They were obtained in experiments with LS NPRUH, which evaluated the effect of a unique ESBAR (histidine, tryptophan, tyrosine, mildronat and preductal) on the inhibitory effect of adrenaline (10^{-8} g/mL), including the presence in the environment 100-fold dilution of serum of non-pregnant women study was conducted on the background tone, caused by high potassium (60 mM KCl) Krebs solution. Thus the inhibitory effect was evaluated adrenaline source (1) its effect when combined action with one of the analogues of ESBAR at concentration of 10^{-4} g/mL, (2) the effect of adrenaline together with 100-fold dilution of the serum of non-pregnant women, (3) and the effect of adrenaline together with the 100-fold dilution of serum and with one of the analogues ESBAR, (4) It was found that the 100-fold dilution of serum of non-pregnant women as a source ESBAR not prevent the expression of beta-adrenosensibilizatory activity of histidine and other analogues of ESBAR though potentiating effect analogues of ESBAR not observed. These data support our proposal about possibility of ESBAR analogs in clinical practice to increase the efficiency of activation of beta-AR of myometrium and other entities, for example, in the treatment of brachial asthma or for inhibiting preterm labor.

Ability of ESBAR and its analogs to restore the effectiveness of the activation of beta-AR, which decline by the ozone, lysophosphatidylcholine or blocker of beta-AR

As part of the study of the mechanism of action of ESBAR and his counterparts in the experiments with LS NPRUH it was studied the role of these factors in the recovery efficiency of the activation of $beta_2$-AR artificially reduced ozonated Krebs solution, or lysophosphatidylcholine, or blocker of beta-AR propranolol [51,53,56,58,71,77].

In particular, it has been established, that perfusion with ozonized Krebs solution (at a concentration of ozone in the environment 5×10^{-8} g/mL) reduces beta-adrenoreactivity of strips, i.e. reduces of the ability of adrenaline to inhibit their spontaneous CA or tonus induced by high potassium (60 mM KCl) Krebs solution [51,53,77]. It was found that a 100-fold dilution of the serum of non-pregnant women as a source of ESBAR and L-histidine (3×10^{-6} g/mL), L-tryptophan (10^{-6} g/mL), DL-tyrosine (2×10^{-6} g/mL), preductal (10^{-6} g/mL) and mildronat (10^{-5} g/mL), even on the background of the ozonized Krebs reduced adrenoreactivity of the strips to the initial level, i.e., remove beta-adrenoblocking effect of ozone. It is set for strips having spontaneous CA, and strips, which initially increased the tone of high potassium (60 mM KCl) Krebs solution. Moreover, in these experiments we have shown that a 100-fold dilution of serum and L-histidine (3×10^{-6} g/mL) even increased adrenoreactivity of myometrium i.e., increased the inhibitory effect of adrenaline (10^{-8} g/mL). Although the nature of beta-adrenoceptor blocking action of ozone is unclear, it can be assumed that the ozone is due to the accumulation of reactive species of oxygen destroys the native structure of proteins involved in signal transduction from the $beta_2$-AR into the uterine muscle cells. Therefore, we identified the fact indicates the ability of ESBAR and its analogs (as original chaperones) to restore the native structure of proteins involved in signaling induced by activation of the $beta_2$-AR.

We have also been shown, that beta-adrenoreactivity of LS NPRUH reduces by lysophosphatidylcholine (LPC)-at a concentration 10^{-4} g/mL it reduces the ability of adrenaline (10^{-8} g/mL) to inhibit spontaneous CA of strips or lower tone of strips, which induce by high potassium (60 mM KCl) Krebs solution [58,71]. Thus histidine (10^{-4} g/mL) restores the effectiveness of $beta_2$-AR activation. Similar results were obtained using a chicken egg yolk as a source of well-known LPC [78]. It been shown, that a chicken egg yolk in dilution 1:50 reduces beta-adrenoreactivity of LS NPRUH but histidine (10^{-5} g/mL) even in the presence of egg yolk restore it [58]. We explain the effect of beta-adrenoceptor blocking of LPC his ability as shown by

several authors, to activate protein kinase C, which is known, together with the protein kinase A and kinase of $beta_2$-AR phosphorylation of $beta_2$-AR and thus speeds up the process of desensitization [11-13,78]. From this perspective, it is believed, that the ability of histidine to restore the effectiveness of $beta_2$-AR activation is probably due to his influence increased of $beta_2$-AR dephosphorylation, which is likely to occur due to activation of phosphatase and inhibition of protein kinase C.

In another series of our experiments with LS NPRUH nonselective blocker of $beta_1$- and $beta_2$-AR propranolol (obzidan) at concentrations of 10^{-9} to 10^{-6} g/mL dose-dependently partially or completely block the ability of adrenaline (10^{-7} g/mL) to lower the tone, increased high potassium (60 mM KCl) Krebs solution [56,58]. Unlike propranolol selective $beta_1$-AR blockers metoprolol and atenolol (10^{-9} g/mL to 10^{-6} g/mL) did not show this effect, indicating the absence of $beta_1$-AR in myocytes of longitudinal layer of the uterine horn of non-pregnant rats [56,58]. On the background of propranolol 100-fold dilution of the serum of non-pregnant women (as a source of ESBAR) and any of its analogs-histidine, tryptophan and tyrosine (all- 10^{-5} and 10^{-4} g/mL), and mildronat and preductal (both- 10^{-6} g/mL) restores the ability of adrenaline to show an inhibitory effect or hinder manifestation of the blocking action of propranolol. Thus, a series of control experiments indicated that partial blockade of inhibitory effect of adrenaline used in a concentration of 10^{-7} g/mL, propranolol should be applied at a concentration of 10^{-9} g/mL, and for full blockade-at a concentration of 10^{-7} g/mL. On a 100-fold dilution of the blood serum, these values for propranolol were respectively 10^{-8} g/mL (partial blockade) and 10^{-6} g/mL (complete block), i.e., in 10 times higher than in controls. On the background of histidine (10^{-5} and 10^{-4} g/mL), propranolol could partially or totally block the effect of adrenaline at a concentration of only 10^{-7} g/mL, against tryptophan-at a concentration of 10^{-6} g/mL, against tyrosine-in concentrations 10^{-7} g/mL, against mildronat-in concentrations of 10^{-7} and 10^{-6} g/mL, respectively, against preductal- 10^{-9} and 10^{-6} g/mL. Thus, blood serum as the source of ESBAR and all analogues of ESBAR increased concentration of propranolol necessary for blockade inhibitory effect of adrenaline. Given that the propranolol is blocker of competitive type, i.e., it competes with catecholamines for binding site to the active site of beta-AR, the results suggest that ESBAR joining away from the center binding allosterically increases the affinity of agonist to the receptor and thus prevents the action of the blocker [79]. A similar effect ESBAR and its analogs observed in experiments with rat myocardium, as detailed below [39,42,80].

Thus, in general, the results of our experiments with the LS NPRUH suggest that the basis for action of ESBAR and its analogs (histidine, tryptophan, tyrosine, preductal and mildronat) is their ability to increase the affinity of the active site relative to the catecholamines, the ability to counter the desensitization of beta-AR (by reducing the activity of enzymes involved in phosphorylation beta-AP? i.e., kinase of beta-AR, protein kinases A and C), by increasing the activity of phosphatase, and the ability to restore the native structure of proteins involved in beta-AR-signaling. Results of experiments with other objects, listed below, support this idea about the mechanism of action of ESBAR and its analogues.

Influence of ESBAR and its analogs on efficiency of activation of beta-AP of other smooth muscle, myocardium and blood cells

To study the mechanism of action of ESBAR and its analogs and physiological role of ESBAR we examined the ability of blood serum as a source of ESBAR and analogues ESBAR (histidine, tryptophan, tyrosine, preductal, mildronat) for the manifestation of the effects of adrenaline on smooth muscle of the uterus of women, cow trachea, pig coronary artery, rat stomach, and myocardium of frog, rats and humans and also human blood cells-erythrocytes and platelets.

Myometrium of pregnant women: We have previously found that physiological properties of isolated myometrium of non-pregnant and pregnant women differ significantly from the myometrium non-pregnant and pregnant rats rabbits and pigs [1-3,5,14,15]. It has been shown, that adrenaline increases the Contractile Activity (CA) of isolated myometrium non-pregnant women, due to the activation of alpha-AR, but inhibits CA of myometrium of pregnant women (due to activation of $beta_2$-AR) and again increases CA of myometrium from parturient (due to activation of alpha-AR). In the clinical setting we have identified that the 10-minute intravenous infusion of adrenaline (0.6 micrograms/min) to women before the onset of labor significantly reduces the numbers of uterine contractions (3.2 and 2.5 for 10 minutes, or up to 76% of baseline), and its introduction into an active phase I of stage of labor is the reduction in the contraction frequency (c 3.3 to 2.9 for 10 minutes, i.e., up to 86%) was not statistically significant [1,7,15]. Consequently, in labor's ability of adrenaline reduced of Contractile Activity of Uterus (CAU) decreases. At the same time, in both cases adrenaline caused a statistically significant increase in maternal heart rate (corresponding up to 124% and 113% of baseline), systolic pressure (up to 110% and 108%) and diastolic pressure (up to 110% and 112%), i.e., reaction of the cardiovascular system to the introduction of adrenaline during labor has not changed. In another study, when using outdoor hysterography set, that 5-minute intravenous infusion of $beta_2$-adrenormimetic partusisten (0.00125 mg per minute) in pregnant women at 28-36 weeks gestation (in the absence of symptoms of Threat of Premature Labor (TPL) significantly reducing amplitude of large waves (on 52% of the original level), frequency of contractions generation (on 47%) and the total activity (on 74%) [8,15]. In women in late pregnancy i.e., at time of 38-42 weeks, the same dose of partusisten causes less decrease CAU-including amplitude (on 27%) and the total activity (on 42%), while women in the active phase of the first stage of labor, the introduction of this dose is much less pronounced reduction of large amplitude waves (only on 16%) and the total activity (only on 25%). These observations suggest that before labor and during labor agonist's beta-AR partusisten even in a small dose can inhibit of the CAU. However, this ability in labor is clearly reduced, that indicating a decrease of beta-adrenoreactivity of myometrium of women *in vivo*. In similar studies, we have shown that in pregnant women (28-36 weeks) with no signs of Threat of Premature Labor (TPL) partusisten test, which performed as described previously, inhibits background of CAU, while in pregnant women with signs of Threat of Premature Labor (TPL) this test in some cases was negative, i.e., not accompanied with inhibition of CAU [8,15]. This is evidenced about the decreasing of beta-adrenoreactivity of myometrium at TPL. All these data support the notion that activation of the myometrium $beta_2$-AR in pregnant women results in inhibition of CAU before labor and this inhibitory effect before labor is significantly reduced.

Investigation isolated myometrium of pregnant women showed, that the blood serum of pregnant women (in dilutions 1:50, 1:100, 1:500, $1:10^3$) and amniotic fluid (at dilutions 1:10, 1:100, 1:500, $1:10^3$) did not affect the expression of the stimulating effect of adrenaline (10^{-7} and 10^{-6} g/mL), but reduce it after removal of serum or after

prolonged (up to 90 min) exposure to amniotic fluid [15-18,68]. Thus, these experiments no clearly demonstrate the ability of ESBAR to enhance of beta-adrenoreactivity of pregnant women myometrium of failed. At the same time histidine (3×10^{-7} g/mL and 3×10^{-6} g/mL) prevented the manifestation of the stimulating effect of adrenaline, used at a concentration of 10^{-8} g/mL and 10^{-7} g/mL, as well as reversal uterostimulatory effect of adrenaline in inhibitory effect. In other words, histidine showed beta-adrenosensibilizatory activity. Unfortunately, such studies have not been conducted using other analogs of ESBAR-tryptophan, tyrosine, mildronat and preductal. Thus, experiments with isolated myometrium of pregnant women are not given conclusive evidence of the applicability of the hypothesis of beta-ARIM against the CAU and the participation of ESBAR in its implementation at women.

Earlier we reported on the studies, which demonstrated the ability of an isolated myometrium of non-pregnant and pregnant women produce ESBAR in the environment [15,18]. In these experiments, it was shown that a 20-minute transmural electrical stimulation of non-pregnant uterine biopsies reduces the production of ESBAR, while similar electrical stimulation of biopsies from pregnant women uterus, on the contrary, increases the production of ESBAR. This suggests that 1) the women myometrium capable of producing of ESBAR, including in adrenergic synapses, in which probably during pregnancy there is a conversion of the mediator (instead of catecholamines released tyrosine, which increases the efficiency of the activation of beta-AR myometrium) and 2) ESBAR ensure effective functioning of the beta-ARIM.

Smooth muscle of cow trachea: The smooth muscle of the airways is known to contain the $beta_2$-AR and $beta_1$-AR, 70% of which falls on the $beta_2$-AR and whose activation causes relaxation of muscle cells [81]. This is shown in our experiments with strips of cow trachea [15,18,21,29-31,68]. In their experiments the basal tone of the strips increased either with acetylcholine (ACh, 10^{-6} g/mL) or with high potassium (60 mM KCl) Krebs solution. Against this background, adrenaline (10^{-8} g/mL to 10^{-6} g/mL) produced a dose-dependent relaxation of the strips, which was blocked by propranolol (10^{-6} g/mL), but not prazosin (10^{-6} g/mL). Cord blood serum of newborns (1:100), itself caused by reduced of stripe tone, due to the presence in serum of so-called Endogenous Blocker of M-Cholinergic Receptors (EBMChR), but it did not affect on the KCl-induced tone. At the same time serum enhanced the relaxing effect of adrenaline, observed on the background of ACh-induced tone and, most importantly, as in this case, EBMChR not manifest itself against KCl-induced tone. Such ESBAR-activity of blood serum of healthy non-pregnant women showed at dilutions 1:50, 1:100 and 1:500, and also histidine (3×10^{-6} g/mL), tryptophan (10^{-6} g/mL), tyrosine (2×10^{-6} g/mL), mildronat (10^{-5} g/mL) and preductal (10^{-6} g/mL), and even if initially $beta_2$-adrenoreactivity of tracheal myocytes were reduced by ozonated (5×10^{-8} g/mL) Krebs solution [15,21,29,48,51,68]. Thus, the experiments with strips of cow trachea support the notion about content of ESBAR in blood serum which is capable, like its analogs (histidine, tryptophan, tyrosine, mildronat and preductal) enhance efficiency of activation of $beta_2$-AR. This indicates promising application analogs of ESBAR for treatment Bronchial Asthma (BA), in which, as will be indicate below, revealed reduction of ESBAR content at patient with bronchial asthma [30,31]. The important fact is revealed by the ability ESBAR and its analogs to restore the effectiveness of the activation of trachea myocytes $beta_2$-AR, which initially reduced by ozonated Krebs solution.

Smooth muscle of pig coronary artery: It is known that myocytes and endothelial cells of coronary artery contain the $beta_2$-AR, which is activated relaxes muscle cells, including by improving the product no [82-84]. It has already been mentioned that the first journal publication about identifying of ESBAR in blood serum touches the ring segments of the pig coronary artery with intact endothelium [19]. In these experiments a tone of the ring segments increased potassium (25 mM KCl) Krebs solution slightly decreased by the action of adrenaline (10^{-6} g/mL), but the relaxing effect of adrenaline influenced significantly increased by 100-fold dilution of umbilical cord blood serum. Subsequently, this fact was confirmed, and it is shown that addition of serum in conditions of 25 mM KCl-induced tonus of the pig coronary arteries ESBAR-activity exhibit histidine (3×10^{-6} g/mL), tryptophan (10^{-6} g/mL), tyrosine (3×10^{-6} g/mL) and mildronat (10^{-5} g/mL) and preductal (10^{-5} g/mL) at the action of adrenaline (10^{-7} g/mL) [15,48,68,85]. We have found that the ozonized (5×10^{-7} g/mL) Krebs solution reduces $beta_2$-adrenoreactivity of strips, i.e., ability of adrenaline (10^{-6} g/mL) to relax tone of the smooth muscle of pig coronary artery, increased 30 mM KCl, and it restores by histidine [20,21,68]. In analogy to the experiments with the LS NPRUH and tracheal smooth muscle we suggest that under these conditions, histidine, tryptophan, tyrosine, mildronat and Preductal will also restore the lowered by ozone $beta_2$-adrenoreactivity of myocytes and possibly endothelial cell of pig coronary arteries [68]. However, direct evidence of this provision has yet been received. Thus, data on the impact of ESBAR and his counterparts on the beta-adrenoreactivity of myocytes and endothelial cells of pig coronary artery are unfortunately not as many as for LS NPRUH. Nevertheless, these data indicate that the relaxing effect of adrenaline against pig smooth muscle of coronary arteries can be enhanced by ESBAR and its analogues. This indicates a promising application of exogenous sensitizers of beta-AP for the treatment and prevention of Coronary Heart Disease (CHD) and explains the effectiveness of mildronat in this disease, not only as a metabolic product (as is commonly believed), namely as exogenous sensitizer of beta-AP that probably the majority of physicians is not considered.

The smooth muscle of the rat stomach: Smooth muscle of the rat stomach is known to contain beta-AP and alpha-AR, where its activation decreases tone of the smooth muscle [86,87]. Our experiments with circular strips from fund us of rat stomach, which are pre-tone increased high potassium (60 mM KCl) Krebs solution and confirm the presence of beta-AR in myocytes of rat stomach fund us activation which adrenaline (10^{-6} g/mL) for background blockade of alpha-AR nicergoline (10^{-6} g/mL) reduced the tone of the strips; with 50- and 100-fold dilutions of blood serum neonatal cord blocked this reduction [32]. This is due to the presence in blood serum of an Endogenous Blocker of Beta-AP (EBBAR), or Endogenous Sensitizer of Alpha-AP (ESAAR) which restores the effectiveness activation of alpha-AR reduced blockade of the alpha-AR by nicergoline. The latter assumption is based on the fact that according to our data [32], activation of the alpha-AR by adrenaline (10^{-6} g/mL) against the background of the blockade beta-AR by propranolol (10^{-6} g/mL), including background tone, increased high potassium (60 mM KCl) Krebs solution further increases the tone of the strips, although according to the, the tone should be reduced [86,87]. Under these conditions, serum of the umbilical cord blood of newborns at dilutions 1:50, 1:500 and $1:10^3$ further enhances the tonotropic effect of adrenaline. This is explained by the presence in the blood serum of Endogenous Sensitizer of Alpha-AR (ESAAR). Obviously, the

presence ESBAR in serum of umbilical cord blood could manifest itself in reducing of the tonotropic effect of serum blood as ESBAR could overcome the blocking effect of propranolol. In experiments with intact rat stomach strips we have shown, that the activation of alpha-AR by adrenaline (10^{-6} g/mL) against blockade of beta-AR with propranolol (10^{-6} g/mL) also increases their tone [33]. Under these conditions the blood serum of patients suffering with acid dependent gastrointestinal disease, in dilutions of 1:100, 1:500 and $1:10^3$ reduces this effect of adrenaline. In our article, this phenomenon is explained by the presence in the blood serum of endogenous blocker of alpha-AR (EBAAR) [33]. Today, however, it can be explained by the presence in the blood serum ESBAR, as in our other studies demonstrated the ability of blood serum as a source of ESBAR remove the blocking effect of propranolol in experiments with LS NPRUH and with right ventricular of rat heart [39,56,58]. Thus, the smooth muscle of the rat stomach contain alpha-AR activation which increased their tone, and AR-beta, which upon activation, in contrast, tone decreases. The presence in the blood serum of Endogenous Sensitizer of Alpha-AR (ESAAR) increases the likelihood of tonotropic effect of adrenaline, and the presence of ESBAR contributes to the manifestation of its relaxing effect. Consequently, the final physiological activation effect of sympathetic fibers or circulating catecholamine production *in vivo* against the smooth muscles of the stomach, on the one hand, is determined by the ratio between populations of alpha-AR and beta-AP in myocytes of the stomach, and on the other hand-the ratio of the content of ESAAR and ESBAR in serum blood.

Myocardium of frog heart ventricle: Cardiomyocytes of frog heart ventricle, as shown, contain beta-AR, activation of which increases the strength of cardiac contractions [88,89]. In our experiments with isolated frog heart ventricle adrenaline in concentration 5×10^{-8} g/mL reduced the force of contraction caused by electrostimulation (1 Hz, 5 ms, 5 V to 10 V), that probably due to activation of alpha1-AR and 100-fold dilution of serum umbilical cord blood of newborn translates this effect is positive due to the presence of serum ESBAR [90,91]. At higher concentrations (5×10^{-7} g/mL and 5×10^{-6} g/mL) the adrenaline initially increased of contration force, and a 100-fold dilution of umbilical cord blood serum enhance this effect, particularly in experiments with adrenaline at a concentration of 5×10^{-7} g/mL, which also explains the presence of ESBAR in serum [90,91]. However, in some experiments, 100-fold dilution of serum reduced the ability of adrenaline to increase the contaction force due to the presence of Endogenous Blocker of Beta-AR (EBBAR) whose level is at delivery is supposed elevated [90,91]. In another series of similar experiments confirmed, that in low concentrations (10^{-10} g/mL) adrenalin decreased of contaction force, and this effect is blocked by nicergoline (10^{-6} g/mL), that is, indeed, due to activation of alpha-AR [37]. Adrenaline in concentrations 10^{-9} g/mL to 10^{-7} g/mL did not influence on the the contaction force, and at concentrations of 10^{-6} and 10^{-5}g/mL to raise it. In these conditions the blood serum of non-pregnant women in dilution 1:500 increased the positive inotropic effect of adrenaline (10^{-6} g/mL), which indicates the presence of ESBAR in blood serum, and 10- and 50-fold dilutions of serum reduces this effect of adrenaline, as indicated the presence of Endogenous Blocker of Beta-AR (EBBAR) in the serum [37].

In another series of similar experiments we investigated the relationship ESBAR-activity of blood serum of men and women from a number of factors, including the availability of Essential Hypertension (EH) [25,26,66,92]. It was found that the ability of blood serum show beta-adrenosensitizer activity, i.e., increase the positive inotropic effect of adrenaline (10^{-7} g/mL) depending on the sex, the presence of EH) and its stages. Thus, serum of healthy 40-55 year old men exhibited ESBAR-activity at a dilution of 1:100, and at women with stage II EH-at a dilution 1:50, but from women with stage III EH serum did not show it, regardless of the multiplicity of dilution. This indicates a significant reduction in content of ESBAR at stage III EH. In healthy men and also in men with stage II EH or stage III EH serum showed no ESBAR-activity, which indicating a low level of ESBAR in men ncluding man with stage II EH or stage III EH.

Already in the first experiments with isolated frog heart ventricle was found, that the histidine (3×10^{-5} g/mL), as well as blood serum, increases the ability of adrenaline (7×10^{-8} g/mL, 3×10^{-7} g/mL and 4×10^{-6} g/mL) exhibit a positive inotropic effect [35]. This is particularly pronounced in respect of the concentration of adrenaline in 7×10^{-8} g/mL at which he originally did not affect on the force of contraction, and histidine raised against it. Consequently, histidine is able to increase the effectiveness of beta-AR- activation of frog ventricle. However, repeated studies have not given such a clear result [37]. Indeed, in experiments with an isolated frog heart ventricle was confirmed that the positive inotropic effect of adrenaline (10^{-6} g/mL) increases by histidine at a concentration of 10^{-8} g/mL, but not at concentrations of 10^{-7} g/mL to 10^{-4} g/mL. Simultaneously, it was found that tryptophan exerts a similar effect (10^{-9} g/mL, but not at concentrations of 10^{-8} g/mL to 10^{-5} g/mL) and preductal (10^{-7} g/mL, but not at concentrations of 10^{-6} g/mL and 10^{-5} g/mL). However, tyrosine (10^{-6} g/mL, but not at a concentration of 10^{-8} g/mL, 10^{-7} g/mL, 10^{-5} g/mL and 10^{-4} g/mL) and mildronat (10^{-9} g/mL, but not at a concentration of 10^{-8} g/mL to 10^{-5} g/mL), on the contrary, reduces the effect of adrenaline.

Thus, only a portion analogs of ESBAR (and thus a certain concentration range) exhibit ESBAR-activity relative to intact myocardium frog. In these experiments it was established, that Lysophosphatidylcholine (LPC) at concentrations of 10^{-9} g/mL to 10^{-5} g/mL blocked the ability of adrenaline (10^{-6} g/mL) exhibit a positive inotropic effect, but this ability, even though the presence of LPC (10^{-7} g/mL) in the medium restores by histidine (10^{-4} and 10^{-3} g/mL, but not 10^{-5} g/mL) [36,37]. It is possible that a similar effect is to provide blood serum as a source of ESBAR, as well as other analogs of ESBAR, including tryptophan, tyrosine, mildronat and preductal. However, such experiments are not carried out frog heart, but they were performed on rat heart.

The results of our studies of isolated frog heart ventricle suggest that ESBAR can affect the Heart Rate Variability (HRV) [34]. In particular, we have been confirmed well-known in the literature fact, according to which at pregnant women HRV much lower than in non-pregnant women [34]. Previously, this was due to an increase in tone of the sympathetic nervous system. In our opinion, this is also due to an increase of content of ESBAR in the blood at pregnancy that enhances the effectiveness of adrenergic effects on the heart. Indeed, we have found that pregnant women have high levels of ESBAR and EBMChR in the blood and low level of ESMChR (subject to detection of these modulators in experiments with isolated frog heart ventricle) corresponds to a low HRV. Thus, in this work was first formulated the hypothesis that the HRV does not depend only on the state of the higher centers of ANS as this is considered to be, but is likely to depend on other factors, in particular on the presence of ESBAR and other modulators of chemoreactivity (EBBAR, EBMChR, etc.) in the blood [34]. Thus, the results of experiments with the isolated myocardium of frog heart ventricle showed that ESBAR and its analogs (in particular

histidine) capable to increase the efficiency of activation $beta_1$-AR and/or $beta_2$-AR, and their presence in the blood can change HRV. This means that a change in HRV parameters in humans, including pregnant women and women in labor can indirectly judge the level of ESBAR. It is also shown that the histidine is capable of restoring beta-adrenoreactivity of frog myocardium, reduced LPC.

The myocardium of rat right ventricle: Cardiomyocytes of rat right ventricle, is known contain $beta_1$-AR and $beta_2$-AR, the activation of which increases the strength of cardiac contractions [93,94]. According to our data adrenaline caused dose-dependent increases of contraction strength, induced electro-stimulation (1 Hz, 5 ms, 15 V or 20 V) of the strips of intact right ventricle of non-pregnant rats i.e., shows the positive inotropic effect [37-39,42]. Thus, serum of non-pregnant women (as a source of ESBAR and of other modulators) in diluted 1:500 increases inotropic effect of adrenaline, i.e., exhibits beta-adrenosensibilizatory activity, and dilution 1:10 on the contrary, it decreases, i.e., exhibits beta-adrenoblocking activity [37]. This indicates the presence of ESBAR and EBBAR in the blood serum of non-pregnant women and the ability of these factors to change the response of the myocardium to adrenaline. Surprisingly, analogs of ESBAR, including histidine (10^{-5} g/mL to 10^{-3} g/mL), tryptophan (10^{-5} g/mL to 10^{-3} g/mL), tyrosine (10^{-5} g/mL to 10^{-3} g/mL) and mildronat (10^{-8} g/mL to 10^{-4} g/mL) did not increase the positive effect of adrenaline (10^{-7} g/mL) when exposed to the intact myocardium, and histidine (10^{-3} g/mL) even reduced it [37]. Thus, in experiments with intact rat myocardium ESBAR-analogs do not exhibit beta-adrenosensibilizatory activity [37]. This phenomenon was confirmed in a similar experiment, but using these amino acids in a wide concentration range from 10^{-10} g/mL to 10^{-4} g/mL [40]. All three amino acids are generally not increase the ability of adrenaline (used in a concentration close to the threshold-10^{-9} g/mL) exhibit of positive inotropic effect, and in some concentrations histidine (10^{-9} g/mL) and tryptophan (10^{-7} g/mL) showed a weak beta-adrenergic blocker effect. An exception is the tyrosine that is at a concentration of 10^{-4} g/mL showed ESBAR-activity [40]. The lack ESBAR-activity of histidine and tryptophan in experiments with intact myocardium of rats, we explain the fact that these amino acids, increasing the efficiency of activation of $beta_1$-AR and $beta_2$-AR, enhance the effectiveness of activating $beta_3$-AR [40]. But, as is well known, the activation of $beta_3$-AR, which content in the myocardium of right and left ventricles of rat, causes a negative inotropic effect [95]. At the same time, it appears that under artificial decrease of the effectiveness of beta-AR-activation in myocardium by Lysophosphatidylcholine (LPC) or adrenoblockers-propranolol and atenolol all three analogs ESBAR, i.e., histidine, tryptophan and tyrosine, and also mildronat and blood serum (as a source of ESBAR) exhibit ESBAR-activity [36,37,39,40,42,80,96]. Indeed, in experiments with strips from rats right ventricle determined, that LPC (10^{-8} g/mL, 10^{-5} g/mL, 10^{-4} g/mL) reversibly reduces of the expression of the positive inotropic effect of adrenaline (10^{-7} g/mL) [36,37,96]. This beta-adrenoceptor blocking effect of LPC (it used in a concentration of 10^{-5} g/mL), was shot in the presence of LPC in experiments with adrenaline (10^{-7} g/mL) under the influence of 10^3- and 500-fold dilutions of blood serum of non-pregnant women, as well as histidine (10^{-5} g/mL to 10^{-3} g/mL), tryptophan (10^{-5} g/mL to 10^{-3} g/mL), tyrosine (10^{-5} g/mL to 10^{-4} g/mL) and mildronat (10^{-5} g/mL to 10^{-3} g/mL). This meant that the serum (as a source of ESBAR) and analogs of ESBAR capable restore of effectiveness of activation of beta-AP, which was reduce by LPC. In another series of experiments with strips of right ventricle of non-pregnant rats demonstrated, that at blockade of $beta_1$-AR and $beta_2$-AR by propranolol (10^{-8} g/mL), or at blockade of $beta_1$-AR by atenolol (10^{-8} g/mL) adrenaline (10^{-6} g/mL or 10^{-5} g/mL) instead of the positive inotropic effect has a negative inotropic effect [39,40,42,80]. We explain this surprising effect of the activation of existing in the rat myocardium $alpha_1$-AP, $alpha_2$-AP and may $beta_3$-AR [39,40,42,80]. It was found that under these conditions, a 100-fold dilutions of the blood serum of pregnant women or the serum of pregnant rats and also histidine (10^{-4} g/mL), tryptophan (10^{-4} g/mL), tyrosine (10^{-4} g/mL) and mildronat (10^{-5} g/mL) blocked the expression of negative inotropic effect of adrenaline, and tryptophan (10^{-4} g/mL) even restores the ability of adrenaline (10^{-6} and 10^{-5} g/mL) in the presence of a blocker propranolol (10^{-8} g/mL) to show a positive inotropic effect. All of this we explain the fact that ESBAR and its analogs partially or completely (as tryptophan) is restore efficiency of activation of $beta_1$-AR and $beta_2$-AR, reduced under the influence of competitive blockade of these receptors, i.e., atenolol and propranolol [39,40,42,80]. The laws revealed in experiments with right ventricle of non-pregnant rats on the effect ESBAR and its analogs on the effectiveness of activation of $beta_1$-AR and $beta_2$-AR, to a certain extent, confirmed in experiments with right ventricle of pregnant rats [42]. In these experiments serum blood (as a source of ESBAR) and analogs of ESBAR did not affect the efficacy of beta-AR activation of intact myocardium pregnant rat, but significantly increased it in situations where it was reduced by adrenoblockers. In experiments with pregnant rat myocardium first shown, that histidine itself at concentrations 10^{-10} g/mL to 10^{-4} g/mL exhibits a positive inotropic effect, although in the non-pregnant rat myocardium, as well as other analoges of ESBAR (tryptophan, tyrosine, mildronat) it does not affect on the strength of the contractions at all concentrations tested (10^{-10} g/mL to 10^{-4} g/mL) [42]. The mechanism of this phenomenon remains unclear, although the need and the prospects of its further study are obvious.

Thus, studies in the rat myocardium complemented the idea of participation of ESBAR in the regulation of adrenergic effects on the heart, which was first shown in experiments on the frog heart. In this regard it can be argued that, indeed, the presence of blood ESBAR can affect the Heart Rate Variability (HRV). According to our latest dates, HRV at women is substantially reduced during pregnancy, but for 10-15 days before labor it is partially restored, i.e., HRV increases, but decreases again in the labor [97-99]. If the reduction of HRV during pregnancy, in our opinion, mainly due to the increase in the content of ESBAR in the blood and cerebrospinal fluid, but the pre parturient partial recovery HRV, we tend to be regarded as a reflection of the change in expression of adrenergic receptors in the myocardium at this period. It is possible that this may be due to increase expression of $alpha_1$-AR gene required according to, for the induction of ventricle hypertrophy and heart to improve the survival of cardiomyocytes [100].

One attempt to study the effect of histidine as an analog of ESBAR on HRV was carried out by us in the study of the effect of a single oral dose of 2.0 g histidine on HRV and the electrical activity of the brain (EEG) of students (volunteers) [43,101]. It was found that under the influence of histidine instead of the expected decrease of HRV, on the contrary, HRV increased. Thus, at 30 min after administration of histidine decreased heart rate, increased the expected value of the interval RR and increased mode and decreased systolic blood pressure, which, in general, show a decrease in the activity of the sympathetic part of ANS or increase activity of parasympathetic part

of ANS. On the EEG activity decreased theta-rhythm (based on the index and amplitude of this rhythm) and increases the amplitude of all five components of the auditory evoked potentials. In another group of test it has been shown, that the young women (volunteers) receive simultaneously 50 g of cheese brand "Russian" (Vozhgaly, Kirov) as a product, which rich in histidine, tryptophan and tyrosine, after 3 and 5 hours post administration increases the activity of the parasympathetic part of the ANS, according to the direction of changing of the values of HRV as mode, expected value of the interval RR, variation range, pRR_{50}, power of long-term waves (LF), stress index and others indicators [101].

Thus, contrary to the expectation activated sympathetic part of ANS when taking 50 grams of cheese, as well as when taking 2 grams of pure histidine, there is activation of the parasympathetic part of ANS. This phenomenon we explained the body's response to activation of the sympathetic part of ANS [43]. We believe that the basis of this reaction is the activation of pressoreceptor reflex, as well as inhibition of the sympathetic centers, which regulate of activity of heart and blood vessels that occurs under the influence of the bulbar vasomotor center due to increased efficiency of the activation of presynaptic $alpha_2$-AP of its neurons under the influence of histidine. Thus, it is clear that increased levels of histidine in the blood no remains traceless-it changes the activity of the heart, blood vessels and cerebral cortex.

The myocardium of eyelet of human right atrium: During the aorto-coronary bypass is possible to fence of biopsies from eyelet of human right atrium. In the literature it noted, that this part of the human heart contains the $beta_1$-AR and $beta_2$-AR, and is the dominant population of $beta_2$-AR [102]. We had the opportunity to examine these tissue samples in the laboratory [44,45,60,101]. It was found, that the such strips are able to generate of contraction caused by electrostimulation (1 Hz, 5 ms, 25 V to 30 V) [44,45,60]. The strength of their contractions correlated with the magnitude of ejection fraction of left ventricular, estimated by Teyholts-the stronger the manifestation of heart failure, the lower was the contractility of the strips. Recently, it was noted by other authors [103]. According to our data, adrenaline at concentrations 10^{-9} g/mL to 10^{-8} g/mL had no effect on the strength of contractions of biopsies, and at concentration of 10^{-7} g/mL and 10^{-6} g/mL showed a dose-dependent positive inotropic effect [44,45]. A similar effect has also been provided histidine (10^{-5} g/mL), tryptophan (10^{-4} g/mL) and tyrosine (10^{-5} g/mL and 10^{-4} g/mL), while mildronat (10^{-8} g/mL) does not affect on the strength of contractions of biopsies. Thus, histidine increases contractility of myocardium of pregnant rats (but does not affect the myocardium of non-pregnant rats, and it also improve contractility of eyelet of human right atrium of patients with heart failure [42]. These data show promising use of histidine, tryptophan and tyrosine in clinical practice to improve cardiac contractility in patients with heart failure [60]. We have also shown that the blood serum of non-pregnant women at dilutions of 1:100, 1:500 or even $1:10^3$ enhances the ability of adrenaline at concentration 10^{-8} g/mL (i.e. in the sub-threshold or close to the threshold concentration) [45], have a positive inotropic effect, whereas the dilutions 1:10, 1:50 and $1:10^4$ did not affect it. This dilution of 1:10 and 1:50 on their like histidine has a positive inotropic effect. Thus, it was demonstrated that the serum as a source of ESBAR in certain dilutions can exercise beta-adrenosensibilizatory activity. At the same time, non-pregnant serum at dilutions of $1:10^4$, $1:10^3$, 1:100 and 1:50 does not affect on the positive inotropic effect of adrenaline used at a concentration of 10^{-6} g/mL, i.e., in near maximal, but dilution 1:500, even its lowered, i.e., exhibit beta-adrenergic blocking effect.

Thus, in experiments with human myocardium was first shown that blood serum, contained ESBAR and EBBAR, able to modify its responses to adrenaline-increase the effect of low concentrations of adrenaline (due ESBAR) or reduce the effect of high concentrations of adrenaline (due EBBAR), m. e. limit the effects of high concentration.

Much to our surprise, histidine (10^{-5} g/mL to 10^{-4} g/mL), tryptophan (10^{-5} g/mL to 10^{-4} g/mL), tyrosine (10^{-5} g/mL to 10^{-4} g/mL) and mildronat (10^{-6} g/mL) did not enhance the ability of low concentrations of adrenaline (10^{-8} g/mL) to a positive inotropic effect, as did the blood serum [45]. Wherein, as mentioned above, by themselves, these substances (except mildronat) exhibit positive inotropic effects. The question arises-why we failed to identify ESBAR-activity of histidine, tryptophan, tyrosine and mildronat that at other sites, including strips of rat myocardium provided it? The first explanation-after perfusion of myocardial strips by adrenaline (first test) in the chamber, in spite of her 5-minute perfusion with Krebs solution without adrenaline its concentration becomes very low (clearly sub-threshold), whose effect on the beta-AR of cardiomyocytes amplified followed by exposure to histidine, tryptophan, tyrosine and mildronat. In this regard, there is a pronounced positive inotropic effect of these substances as if in the absence of adrenaline. Subsequent perfusion of strips with the adrenaline does not lead to an additional increase in the force of contraction. However, contrary to this assumption result of experiments with blood serum-its 10^3-, 500- and 100-fold dilutions by themselves did not show positive inotropic effect, but it showed ESBAR-activity [45]. The second explanation-heart failure is so changed the properties of beta-AP myocardium and signal transmission system of this receptor into cardiomyocytes, therefore analogs of ESBAR (histidine, tryptophan, tyrosine, mildronat) are not able to show ESBAR-activity [45]. Thus, the question of why the blood serum as a source of ESBAR improves beta-AR-activation in cardiomyocytes of eyelet of human right atrium, but analogs of ESBAR (histidine, tryptophan, tyrosine, and mildronat) do not show such activity remains open and requires further research.

Human erythrocytes: It is known that human erythrocytes contain $alpha_1$-AR, $alpha_2$-AR, $beta_1$-AR, $beta_2$-AR and $beta_3$-AR [104-107]. We investigated the effects of catecholamines on the speed of erythrocytes agglutination, which induced by human isohemagglutinins serum (I blood group at system ABO) [108,109]. In experiments with erythrocytes of men it was shown that activation of $alpha_1$-AR increases speed of erythrocyte agglutination, if appears to reduce the time of the beginning of agglutination (TBA), while activation of $beta_2$-AR, it decreases. Wherein activation of $alpha_2$-AP, $beta_1$-AR and $beta_3$-AR it is not likely to affect this process. Therefore, it was concluded, that the change of the erythrocytes agglutination speed under the influence of adrenaline depends on the ratio of the population of $alpha_1$-AR and $beta_2$-AR in the erythrocyte [108,109]. In these experiments with erythrocytes of men it was established, that adrenaline (10^{-10} g/mL to 10^{-6} g/mL) dose-dependently increases speed of erythrocytes agglutination [46]. This confirms the idea that the dominant population of adrenoceptors in erythrocytes of men is $alpha_1$-AR [108,109]. It was found that propranolol (10^{-6} g/mL), which block $beta_2$-AR, increases the ability of adrenaline (10^{-10} g/mL to 10^{-6} g/mL) enhance of the erythrocyte agglutination speed, and histidine (10^{-4} g/mL) and mildronat (10^{-5} g/mL), on the contrary,

decrease its [46]. Effect of histidine proved reversible-triple washing of erythrocyte from the histidine regained their initial reaction to the adrenaline. Thus, histidine and mildronat as analogs of ESBAR increase efficiency activate $beta_2$-AR not only in the uterine myocytes and cardiomyocytes, as mentioned above, but also in the erythrocytes. This indicates that adrenoreactivity of erythrocytes is determined not only by the presence in their respective adrenoceptor and the presence in the medium of endogenous adrenergic modulators, including ESBAR.

Human platelets: It is known that platelets contain $alpha_2$-AP, activation of which increases their aggregation, and the $beta_2$-AR, activation of which, according to some authors, reduces it [110,111]. In experiments with platelets non-pregnant and pregnant women validated, that adrenaline (10^{-6} g/mL) increases the ability of platelet to aggregation, which is caused by activation of alpha-AP, as nicergoline (10^{-7} g/mL) removes this/the effect of adrenaline [112,113]. It is also evident that the activation of the $beta_2$-AR counteracts this process so as propranolol (10^{-9} g/mL), but not atenolol (10^{-6} g/mL) increases the adrenaline-induced aggregation of platelets.

We have shown that at pregnancy adrenaline-induced aggregation of platelets becomes lower than that at non-pregnant women, due to the higher content of $beta_2$-AR in platelets or increasing the efficiency of activation of $beta_2$-AR [113]. At parturient adrenaline-induced aggregation is reduced to the level which observes at non-pregnant women. It is probably due to a decrease in gene expression of $beta_2$-AR in platelets or decrease of the efficiency of their activation. In addition, we have shown, that tryptophan (10^{-7} g/mL) reduces adrenaline-induced aggregation of platelets at pregnant (III trimester) women [113]. This is because as a tryptophan as analog of ESBAR, improves the effectiveness of the activation of $beta_2$-AR, which reduces adrenaline-induced aggregation of platelets.

Thus, in the experiments with human platelets showed that analog of ESBAR (in this case, tryptophan), exerts beta- adrenosensibilizatory activity previously identified in respect of myocytes of uterus, trachea, coronary artery, cardiomyocytes of frog, rat, and human, and human erythrocytes.

Content of ESBAR in blood serum

Since ESBAR (as EBBAR) has not been isolated in pure form, i.e., its nature is unknown, evaluation of the content of ESBAR and EBBAR in serum were determined by titers of serum dilution in which there is a corresponding beta-adrenosensibilizatory effect or beta-adrenoblocking effect. As the test object is usually used LS NPRUH. This was taken as a basis for this figure as a percentage of experiments, in which there is a corresponding effect, or the presence of a statistically significant change in the inhibitory effect of adrenaline under the influence of the tested dilution [15,17,18]. It has been estimated ESBAR-content in the blood serum of men and women, including pregnant women and parturients, some of which had a certain obstetric complications, as well as in patients with coronary heart disease, arterial hypertension or with bronchial asthma [15,17,18,25,26,62-68].

Gender and age: It was found that in non-pregnant women ESBAR-content is higher than in men [15-18,67,68]. Thus, at non-pregnant women dilutions of serum 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$ showed ESBAR-activity respectively in 18%, 87%, 45%, 24% and 11% of the experiments; wherein a statistically significant showed ESBAR-activity dilution 1:100 and 1:500, but EBBAR-activity showed dilution 1:10 and 1:50 [67,68]. In younger men ESBAR-activity manifested respectively in 50%, 50%, 20%, 33% and 24% of the experiments, while none of the dilutions did not show statistically significant ESBAR-activity [67,68]. For 40-55-year-old men and women were no differences that we explain the decrease in the content of ESBAR at women with this age. The investigation of dilutions 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$ ESBAR-activity could be observed respectively in 8%, 17%, 14%, 36% and 50% of the experiments [68]. Thus, it appears that estrogen and progesterone are related to the regulation of ESBAR-production.

Pregnancy and labor: It was shown, that at pregnancy ESBAR-content in blood serum increases, in particular, according to the multiplicity of dilution in I-st trimester it rises in 2 times and in II-nd trimester-it is rises in 20 times [67,68]. However, on the eve of labor level of ESBAR returns to the level characteristic for the I-st trimester of pregnancy. In the labor and in the postpartum period remains high ESBAR-content. Indeed, ESBAR-activity in I-st trimester exhibit significantly dilutions 1:50, 1:100, 1:500 and $1:10^3$, in II-nd trimester-dilutions 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$, and in the III-rd trimester-dilutions 1:50, 1:100, 1:500 and $1:10^3$, and in the I-st stage of labor-respectively dilutions 1:100, 1:500, $1:10^3$ and $1:10^4$, in the next day after labor dilutions 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$.

Obstetric complications: It was shown, that the content of ESBAR in maternal blood serum and in serum of umbilical cord blood the increased at the Weakness of Labor Activity (WLA), and at preeclampsia, but reduced at Placental Insufficiency (PI) [67]. At the same time, it is not changed by the Threat of Premature Labor (TPL), as well as in pregnant women with hypertension or vegito-vascular dystonia. Thus, at WLA content of ESBAR was 2-fold higher than in women with normal labor activity and which correlated with higher levels of histidine (exceeding in 1.3 times), tryptophan (exceeding in 2.0 times), and tyrosine (exceeding in 1.4 times) [67]. This is consistent with the notion that the WLA is a consequence of inadequate preterm reducing of power of beta-ARIM, including the reduction of inadequate ESBAR-content in blood serum [15,67]. It was found, that women with mild preeclampsia have ESBAR-activity increased as significantly exhibit it's in dilution 1:10, 1:50, 1:100, 1:500 and $1:10^3$ (in the control group exhibit its dilutions in 1:50, 1:100, 1:500 and $1:10^3$). If this 1.5 times increased levels of tryptophan, indicating a reduction of kynurenine metabolism pathway of tryptophan, whereby, as is known, increases the activity of neutrophils and monocytes, which are major "blame" of the development of preeclampsia [67,114,115]. At placental insufficiency ESBAR-activity reduced in serum of cord blood-it only exhibit significantly dilution in 1:50 (control- 1:50, 1:100, 1:500 and $1:10^3$), although the levels of histidine and tyrosine are not changed, and content of tryptophan increased in 1.4 times [67]. At TPL ESBAR-activity was significantly exhibit dilutions 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$, i.e., as well as in pregnant women without TPL. Wherein level of histidine is not modified, level of tyrosine reduced in 1.4 times, and tryptophan level increased in 1.8 times [67]. The latter indicates a decrease formation of kynurenines that are known, reduces the maternal immune tolerance towards the fetus, since it increases the activity of T- and B-lymphocytes as well as monocytes and neutrophils [114].

Myocardial Ischemia (MI) or coronary heart disease: In experiments with LS NPRUH set that in the acute phase, i.e., on the first day of infarction (as a consequence of MI), the contents of ESBAR was lower than in healthy man and women-dilution

1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$ showed ESBAR-activity at MI respectively in 20%, 40%, 60%, 20% and 0.0% of experiments while in healthy man and women respectively in 30%, 70%, 90%, 80% and 50% of the experiments [62-64]. After 1.5 to 2 months post infarction (subacute stage) content of ESBAR remained low-ESBAR-activity marked by respectively in 10%, 20%, 50%, 60% and 40% of the experiments. After 6 months post infarction (scar stage) tended to increase the content of ESBAR as ESBAR-activity was detected respectively in 40%, 50%, 70%, 40% and 10% of the experiments. However, if the rehabilitation took place using systematic physical training, the more pronounced recovery observed content of ESBAR-in these patients ESBAR-activity observed respectively in 50%, 40%, 70%, 90% and 70% of the experiments. We believe that the low levels of ESBAR may be one of the causes of coronary heart disease, as in this case a reduced of ESBAR content decreases ability of ESBAR increase relaxing influence of adrenergic impact on coronary vessels. The gradual recovery of ESBAR-content probably helps to improve coronary blood flow, which is especially pronounced in the use of physical training, which is currently being considered as a way to distant post conditioning myocardium [116,117]. Note that some authors indicate the effectiveness of preductal as the metabolic drug (and in our opinion on how the analog of ESBAR) during physical training at the stages of rehabilitation [117]. We also believe that the increase of ESBAR-content at patients with MI will reduce the risk of heart failure, as in this case should be increase the effectiveness activation of myocardium beta-AR.

Essential hypertension (EH): In experiments with LS NPRUH as well as with isolated frog heart ventricle established, that at stage II EH content of ESBAR at 40-55 year old men and women is low (like their peers without EH) [25,26,65,66]. Indeed, in experiments with LS NPRUH it was showed that a serum of these patients statistically significant ESBAR-activity only at dilutions in 1:50 and 1:100, when serum of patients with stage III showed mostly EBBAR-activity, i.e., reduced the effectiveness of activation of beta-AP, that was significantly observed for dilutions of 1:50, 1:100, 1:500 and $1:10^3$. These data support the notion that EH develops if the effectiveness of activation of myocardium beta-AR reduced, therefore the compensatory increases the level of catecholamine in the blood, which gives rise to increased of blood pressure [118,119]. Moreover, in experiments with circular segments of cows renal artery we have shown, that at stage II of EH serum exhibits also alpha-adrenosensibilizatory activity (dilution 1:50), but as the disease progresses (stage III of EH) the is replaced by increasing of alpha-adrenoblockatory activity, i.e., increase content of EBAAR, which is typical for the dilutions 1:50, 1:100, 1:500 and $1:10^3$ [65]. This we regard as a poor prognostic sign, as in this case, lost the ability to $alpha_1$-AR increase the stability of cardiomyocytes to damage [100].

Bronchial asthma (BA): In experiments with LS NPRUH was demonstrate, that content of ESBAR in blood serum at 7-9 year old children with BA is the same as that of their peers without BA [30,31]. Indeed, in children with BA ESBAR-activity of dilutions 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$ exhibit respectively in 30%, 30%, 30%, 40% and 30% of the experiments, and at healthy children-respectively in 56%, 56%, 56%, 44% and 56% of the experiments. At the same time, evaluation beta-adrenosensibilizatory activity of urine of children in experiments with LS NPRUH showed, that it is lower than in healthy children-beta-adrenosensibilizatory activity of urine of children with BA statistically significant showed only for dilutions $1:10^3$ and $1:10^5$, while the urine of healthy children showed it in a dilution of 1:100, 1:500, $1:10^3$ and $1:10^5$ [30,31]. In adults (40-55 year old) patients with BA ESBAR-activity of serum blood determined in experiments with the LS NPRUH showed dilutions 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$ respectively in 20%, 40%, 60%, 20% and 0% of the experiments and their peers without BA-respectively in 60%, 60%, 67%, 53% and 53% of the experiments. It suggests reducing the content of ESBAR at asthma in adult patients. Overall, the deficit of ESBAR in children and adults with asthma, we regard as one of the reasons for the low efficiency of the activation of $beta_2$-AR myocytes of the respiratory tract, and as a key link in the pathogenesis of BA. It is no coincidence that a number of studies show the effectiveness of the treatment of BA with mildronat, which we regard as an analog of ESBAR [120]. Note that the reference literature indicated that one of the bases for use of mildronat is the presence of BA, although the feasibility of its reception is explained by the presence of immunosuppressive activity for mildronat [79].

Thus, the data of this section indicate that the content of ESBAR in blood serum changes, including the number of obstetric complications and somatic pathology. It is obvious that after will be isolated in pure form ESBAR, EBBAR and other endogenous modulators of adrenoreactivity; it will be possible to assess the true contribution of deficit or surplus of these modulators in the genesis of obstetric complications and somatic diseases.

ESBAR-activity of other human liquid media and blood serum of animals

From the study place of ESBAR- production and the ability of ESBAR passage through different histo-hematic barriers it was interest to study ESBAR-activity of blood plasma, serum of retroplacentary blood, capillary blood, umbilical cord blood, amniotic fluids, urine, cerebrospinal fluid and serum of venous blood of animals. Although the above has repeatedly reported about ESBAR-activity of urine and amniotic fluid, we consider it expedient to organize the data in this section. Typically, studies were conducted with LS NPRUH.

The blood plasma: Heparinized blood plasma of pregnant women (26-37 weeks) exhibits the same ESBAR-activity as blood serum-in experiments with LS NPRUH it showed that a statistically significant her show dilution 1:10, 1:50, 1:100, 1:500 and $1:10^3$ and wherein it is checked respectively in 80%, 80%, 70%, 90% and 70% of the experiments [15,18,68].

Serum of retroplacental blood: It shows the same ESBAR-activity as maternal venous blood serum-dilution 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$ showed ESBAR activity respectively in 74%, 79%, 79%, 68% and 53% of the experiments, while the maternal serum (II period of partus), respectively-in 71%, 86%, 71%, 71% and 28% of the experiments [15,18,68].

Capillary blood: ESBAR-activity of 10^3- and 10^4-fold dilutions of the capillary blood of pregnant women (26-32 weeks) was lower than that of the corresponding dilutions in venous blood of this women-it is checked, respectively in 50% and 25% of the experiments against 90% and 60% of the experiments with venous blood [15,18,68].

Serum of cord blood of newborns: The dilutions 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$ exhibits ESBAR-activity, respectively, in 85%, 85% and 46% of the experiments (statistically significant-for dilutions 1:50, 1:100, 1:500 and $1:10^3$), i.e., like serum of blood of mothers (II stage of labor), whose show ESBAR-activity, respectively in 71%, 86%, 71%, 71% and 28% of the experiments [22,23,67,68,121]. It is shown [67], that content of ESBAR increased in cord blood of fetuses,

which born from mater with the Weakness of Labor Activity (WLA) and decreased in fetuses, which born from matter with have placenta insufficiency (PN). Indeed, ESBAR-activity at WLA observed respectively in 70%, 70%, 90%, 100% and 70% of the experiments, while at PN it found respectively in 40%, 70%, 60%, 50% and 40% of experiments (in the control as mentioned above, ESBAR-activity found in 54%, 85%, 92% and 85% of experiments).

Amniotic fluid (AF): In experiments with LS NPRUH shown, that AF in dilutions 1:10, 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$ exhibit ESBAR-activity respectively in 81%, 86%, 70%, 74%, 48% and 48% of the experiments, i.e., almost as well as the maternal serum and serum of newborn umbilical cord blood Installations, that AF, which obtained prior to delivery, ESBAR-exhibit activity statistically exhibit at dilutions 1:10, 1:50, 1:100 and 1:500; but AF, which obtained in the latent phase of I-st period of labor-at dilutions 1:10, 1:50 and 1:100, and AF, which obtained in the active phase of I-st period of labor-at dilutions 1:50, 1:100 and 1:500. Therefore, in delivery ESBAR-content in AF decreases [15,16,18,67,68].

Urine: In experiments with LS NPRUH shows, that urine has ESBAR-activity [15-18,30,31,68,122,123]. Thus, the urine of pregnant women at dilutions 1:10, 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$ it exhibits respectively in 40%, 50%, 70%, 90%, 90% and 60% of the experiments [68]. Urine of healthy 6-8 aged old children ESBAR-activity exhibit at dilutions of 1:100, 1:500, $1:10^3$, $1:10^4$, $1:10^5$ and $1:10^6$ respectively in 78%, 89%, 78%, 89%, 78% and 67% of the experiments, while the serum of these children showed ESBAR-activity at dilutions 1:50, 1:100, 1:500 and $1:10^3$ respectively in 56%, 56%, 56% and 44% of the experiments [122,123]. Content of ESBAR in the urine of 6-8 year old children is dependent on several factors [123]. At girls it is higher than at boys-dilutions of urine 1:100, 1:500, $1:10^3$, $1:10^4$, $1:10^5$ and $1:10^6$ marked ESBAR-activity in girls respectively in 80%, 94%, 78%, 83%, 58% and 65% of the experiments, and in boys-respectively in 51%, 59%, 64%, 56%, 38% and 25% of the experiments [123]. Content of ESBAR in the urine is higher in children from the II group of health, than at children with I group health, judging by the difference in dilution of 1:100, for which ESBAR-activity observed respectively in 80% and 40% of the experiments [123]. Content of ESBAR was higher in children with disharmonious physical development than at children with harmonious development so ESBAR-activity for the dilution of 1:100 observed respectively in 82% and 38% of experiments; for dilution of 1:500 to 88% and 6% of the experiments; for dilution of $1:10^4$ to 39% and 7% of the experiments) [123]. Content of ESBAR in the urine is higher at children with a high level of adaptation to the school, which was evaluated by the method of N. Luskanova, than children with symptoms of maladjustment to school so for dilution of 1:100 ESBAR-activity observed, respectively in 74% and 41% of experiments [123]. Content of ESBAR in the urine is higher at children with a higher success of educational activities in the three core subjects of the first class (14-15 points), than children with low success (6-10 points) so for a dilution of 1:100, respectively, marked ESBAR-activity in 93% and 54% of experiments [123]. At the same time ESBAR-activity of urine was independent of the somatotype of the child, the level of development of speech and thinking [123]. Overall, these data suggest a possible role of ESBAR in the activity of the neocortex. We have shown, that ESBAR-activity of urine at 6-8-year-olds have received the same children in the 7-9, 12-14 and 20-24 hours, it was maximal in the morning and evening hours and minimal in daylight hours-the difference found to dilutions of $1:10^4$, for which ESBAR-activity observed respectively in 70%, 50% and 90% of the experiments, as well as for the dilution of $1:10^6$ (respectively-in 38%, 0% and 38% of the experiments) [124]. Note that the content of Endogenous Blocker of M-Cholinergic Receptors (EBMChR) in the urine of children, on the contrary, it was the maximum in the daytime-the percentage of trials in which manifested EBMChR-activity at a dilution of urine 1:5 was respectively 40%, 100% and 50% [124]. Thus, it is obvious that ESBAR enters from blood in urine, therefore the content of ESBAR in urine indirectly reflects production of ESBAR, for which, as shown, and there is a circadian rhythm.

Cerebrospinal fluid or liquor: In experiments with LS NPRUH established, that the liquor produced from non-pregnant women (for suspected head injury) shows ESBAR-activity in dilutions of 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$, it was observed respectively in 60%, 70%, 50% 40% and 60% of the experiments, while for the blood serum of non-pregnant women ESBAR-activity observed respectively in 18%, 87%, 45 %, 24% and 11% of the experiments [15,16,18,68,125]. This means that level of ESBAR in the liquor not lower than in serum blood.

Saliva: In experiments with LS NPRUH it was found, that the saliva of pregnant women contains ESBAR, but its level lower than in serum [15,16,18,68]. In particular, saliva of pregnant women (38-40 weeks) at dilutions 1:10, 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$ exhibits ESBAR-activity, respectively, in 20%, 30%, 40%, 20%, 50% and 60% of the experiments, while the serum of pregnant women showing it in a 29%, 80%, 91%, 91%, 100% and 27% of the experiments, respectively.

Serum venous blood of animals (cows, mice, rats): In experiments with LS NPRUH shown, that cow blood serum has ESBAR-activity, but its expression in females does not depend on the presence of pregnancy [15,18,68]. Thus, dilution 1:10, 1:50, 1:100, 1:500, $1:10^3$ and $1:10^4$ of blood serum of non-pregnant cows showed ESBAR-activity respectively in 30%, 50%, 50%, 60%, 10% and 10% of the experiments, and the blood serum of pregnant cows-respectively in 30%, 10%, 40%, 40%, 22% and 33% of the experiments [15,18,68].

The blood serum of non-pregnant mice exhibits ESBAR activity at dilutions 1:50, 1:100, 1:500 and 1:1000 [15].

Blood serum of rat shows adrenomodulatory activity; the nature of which depends on the frequency of its multiplicity dilution and hormonal levels [126]. Thus ESBAR-activity exhibit dilutions 1:100 and 1:500 of blood serum of non-pregnant rats (phase metaestrus) and 1:100 of blood serum of pregnant (3-14 days) rats, while dilution 1:50 of blood serum of non-pregnant rats (phase proestrus) exhibit EBBAR-activity, judging by the experience with high potassium Krebs solution, and in pregnant rats dilution 1:50 of blood serum did not affect on the adrenoreactivity of test-object. It was found that 100-fold dilution of serum of pregnant rat's shows ESBAR-activity in experiments with myocardium of right ventricular of pregnant rat's adrenoreactivity which has been artificially lowered with propranolol or atenolol [127].

Thus, human blood serum and animal (cow, rat, and mouse) blood serum have ESBAR-activity. It is also inherent in the human body fluids as blood plasma, serum of retroplacental blood, serum of cord blood, urine, cerebrospinal fluid, saliva, and amniotic fluid. This suggests that the molecule of ESBAR is capable to passing through various blood-tissue barriers.

Conclusion

So, summarizing of the results of 20 year studies about presence

in the blood (as well as urine, cerebrospinal fluid, saliva, and amniotic fluid) of endogenous modulators of adrenergic and M-cholinergic reactivity, allow us to consider them as humoral components of the Autonomic Nervous System (ANS). The focus of this article is given to the Endogenous Sensitizer of Beta-Adrenergic Receptor (ESBAR). Most likely, that ESBAR is a water-soluble low molecular weight compound, and its analogs are histidine, tryptophan, tyrosine, mildronat and preductal. Several dilutions of human blood serum and the above analogs of ESBAR capable to increase the efficacy of activation of beta-AP of smooth muscle of the rat uterus, women uterus, pig coronary artery, cow renal artery, cow trachea, rat stomach and also beta-AP of myocardium from frog, rat and human, as well as beta-AP human erythrocytes (the action of histidine) and human platelets (under the action of tryptophan). Judging by the effective titer of blood serum dilution, content of ESBAR at human depends on gender (women, especially in pregnant women is higher than men), at pregnant women-from the presence of obstetric complications (increased in preeclampsia and the weakness of labor activity, or WLA, while reducing at placental insufficiency, or PI , but not changed at threat of premature labor, or TPL) and somatic pathology-reduced at Myocardial Ischemia (MI) or coronary heart disease, Essential Hypertension (EH) and Bronchial Asthma (BA). Although the nature of ESBAR hitherto unknown and ESBAR not isolated in pure form, that it is an obstacle to recognition of its existence, but the physiological effects of ESBAR and its analogs indicate, that ESBAR playing an important role in the regulation of the activities of internal organs and probably brain structures. In general, ESBAR and its analogs are considered to be direct modulators (urgent action) of $beta_1$-AR and $beta_2$-AR. In the various operating conditions of cells ESBAR and its analogs with short latency increase initial effectiveness of the activation of beta-AP or restore it if it was lowered during prolonged agonist interaction with beta-AP (i.e., at desensitization of beta-AP), or exposure adrenoblockers or when exposed to damaging factors such as ozone or LPC. It is assumed that the basis of this action of ESBAR is the ability of ESBAR or its analogs bind with amino acid site of beta-AR and thus allosterically enhance the affinity of the beta-AR to catecholamines. Simultaneously ESBAR and its analogs are likely to inhibit the phosphorylation of beta-AP (possibly due to inhibition of kinase of beta-AP, protein kinase A and protein kinase C) and accelerate the dephosphorylation of beta-AP by activating phosphatase, and (like chaperones) restore the native protein structure involved in the beta-AP-induced signaling. This is obvious evidence of the need for a more thorough study of these provisions and the selectivity with respect to different populations of beta-AR ($beta_1$-AR, $beta_2$-AR and $beta_3$-AR). Substantiates the notion that prevents of desensitization of beta-AR, ESBAR promotes the functioning of the beta-Adrenergic Inhibitory Mechanism (beta-ARIM) in pregnant women, necessary for inhibition of Contractile Activity of Uterus (CAU). This function of ESBAR is realized by involving adrenergic terminals which are supposed to occur conversion mediator at during pregnancy, i.e., instead of adrenaline or noradrenaline tyrosine temporarily becomes of mediator. Therefore ESBAR and its analogs can play an important role in the prevention of preterm labor. ESBAR involved in the regulation of activity of the heart, circulatory system and respiratory tracts. Therefore deficiency of ESBAR-content may be a cause of myocardial ischemia (coronary heart disease), essential hypertension or bronchial asthma, and the use of ESBAR and its analogs may be a promising method for the prevention and treatment of these pathologies, as well as such a formidable status as heart failure. It is alleged that the Heart Rate Variability (HRV) reflects not only the state of the ANS, as is commonly believed, but also reflects of the blood levels of endogenous modulators, including ESBAR. We believe that the selection ESBAR in its pure form, the development of reliable and affordable method for determining the content of ESBAR, creating unique arsenal analogs of ESBAR and study of the possibility and feasibility of clinical application-all this is an important tasks for future research.

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