Реферати

ДИСБИОЗЫ РОТОВОЙ ПОЛОСТИ ПРИ ДЛИТЕЛЬНОМ ВЛИЯНИИ ОПИОИДНОГО АНАЛЬГЕТИКА В ЭКСПЕРИМЕНТЕ

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Эксперименты проводили на белых крысах-самцах (20), возраст 3,5-7,5 мес. Животные получали опиоидный анальгетик, производное морфина на протяжении 10 недель. Проводили микроскопическое исследование мазков и бактериологические посевы. Микробиологические исследования указывают, что при опиатной интоксикации развивается дисбактериоз ротовой полости, появляются патогенные и активизируются условнопатогенные виды бактерий. Результаты наших исследований совпадают с данными литературы, которые указывают на значение грамположительной микрофлоры в развитии гнойно-воспалительных процессов в ротовой полости, в частности, значение St. aureus, которому свойственный широкий диапазон адаптационных свойств и наличие токсинов с некротическим действием.

Ключевые слова: ротовая полость, опиоид, микробиологическое исследование.

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ORAL CAVITY DYSBIOSIS UNDER THE DURABLE OPIOID ANALGESIC INFLUENCE IN EXPERIMENT.

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Experiments were hold on white male rats (20) aged 3,5-7,5 months. Experimental animals had been receiving opioid analgesic, derivative of morphine, once a week during 10 weeks. Bacteriological investigation included taking a culture and microscopic investigation of the smear. Microbiological investigations show that changes of bacterial population of the oral cavity which develop under the opioid intoxication can be characterized as dysbiosis. Results of our investigation which indicate the importance of the gram-positive microflora in development of inflammatory process in the oral cavity, in particular, importance of the St. aureus, which has wide range of adaptability characteristics and toxins with necrotic influence.

Key words: oral cavity, opioid, microbiological investigation.

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MAJOR PATHWAYS OF ENDOTHELIAL DYSFUNCTION UNDER EXPERIMENTAL MILD HYPOTHYROSIS

Present research demonstrates metabolic correlation between mild hypothyrosis and endothelial dysfunction (ED). The subclinical hypothyrosis is associated with increased serum levels of LDL and reduced HDL, and finally, with increased atherogenic index (0,530 ± 0,035), that can be interpreted as atherogenic dyslipidemia, which largely contributes to ED. Parameters of nitric oxide system showed decrease in nitrite-ion concentration in rat blood. It can predict the tendency to endothelial dysfunction in SH. According to our research, thyroid function is significantly related to the changes of free-radical component of metabolism. We found the activation of lipoperoxidation (LPO) processes in blood, and, moreover, the antioxidant enzymes activity was to the contrary depressed under mild thyroid failure. Intermittent hypoxic training (IHT) was tested with a purpose to correct the biochemical abnormalities and showed positive effects, in fact, in regard to all investigated parameters.

Key words: subclinical hypothyrosis, nitrite - ion, intermittent hypoxic training.

The study is conducted as part of scientific research «Investigation of functional and metabolic stress-limiting body reserves in extreme conditions with a purpose to identify effective ways of correction» (№ state register. 0111U000121).

Subclinical hypothyrosis (SH) or mild thyroid failure reflects declined thyroid activity without clear symptoms, but with elevated thyroid stimulating hormone (TSH) and normal range off ree thyroxine (FT4) and triiodothyronine (FT3) as the diagnostic indicators [6,8]. The endothelial dysfunction, is one of the earliest signs for atherosclerosis, which frequently observed in experimental and clinical investigations, prior to any overt manifestations of SH [3]. The predisposition to ED under condition of SH may be partially explained by the factors including changes in lipid profile, oxidative stress, disturbances in NO synthesis [1, 3]. Therefore, endothelial dysfunction would be a favorable triger factor to investigate the correlation between SH and cardiovascular disease [7, 11]. The detailed mechanisms underlying the correlation remains unknown. The present study is trying to establish novel aspects linking SH and endothelial function.

The aim of research was to determine and investigate mechanisms of early, potentially reversible pre-atherosclerotic changes in the endothelium under subclinical hypothyrosis, compare our results to the recent literature data, giving a new interpretation to all indexes mentioned above. With a purpose to correct thyroid failure has been proposed and tested a method of IHT (intermittent hypoxic training).

Material and methods of research. The experiments were carried out on the intact male rats (weight 180-220g, control and experimental group). The model of mild thyroid failure was induced by the oral administration of mercazolilum in doses of 3 mg/kg during 3 weeks (method, proposed by E.S.Detyuk et al.). Function of thyroid gland was assessed by the serum concentration of thyroid

hormones - thyroxine (FT4) and triiodothyronine (FT3), thyroid stimulating hormone (TSH) by radioimmunoassay analysis. Total cholesterol (TCh), high-density lipoprotein (HDL), low-density lipoprotein (LDL), atherogenic index, metabolites of lipid peroxidation system - diene conjugates (DC), TBA - active products, activity of antioxidant enzymes - superoxide dismutase, catalase, glutathione peroxidase, TAS (total antioxidant status) as well as metabolites of nitric oxide - nitrite-ion, under conditions of hypothyrosis were biochemically measured. Experimental group was exposed to 10-days of IHT. It was gradually decreased in oxygen content in inhaled air: the 1-st day – to 18,5 %, 2-d day – 16,4 %, 3-d day – 14,5 % all resting days.

Results of research. Due to the administration of a given dose of mercazolilum, the laboratory profile of an elevated serum thyroid stimulating hormone (TSH) and normal free thyroid hormone levels was found. Recent literature sources support correlation between overproduction of TSH and endothelial dysfunction indicating that the action of TSH on extrathyroidal-stimulating hormone receptor (TSHR) is a possible mechanism underlying this association [12, 17, 19]. Elevated TSH alone, independent of FT3 and FT4, has been shown to modulate all mechanisms connected with ED. It has been discovered that TSH is able to bind hepatocyte TSHR to promote cholesterol synthesis, bind adipocyte TSHR to induce IL-6 synthesis and bind bone marrow cell TSHR to increase TNF-α secretion [16]. These actions of TSH are closely connected with altered endothelial function, and therefore could be promising mechanisms underlying the correlation between SH and endothelial function [17]. The discovery by Balzan et al that TSHR is expressed by microvascular endothelial cells opens up a novel prospective for understanding the association. A correlation between serum TSH and oxidative stress indicators was also observed [7], a direct effect of TSH to promote oxidative stress is possible.

Hyperlipidemia is one of the most common causal factors of endothelial dysfunction. In endothelial cells, hyperlipidemia can disturb the NO synthesis pathway by increasing levels of asymmetric dimethylarginine (ADMA), the endogenous NO synthesis inhibitor, possibly by reducing enzyme dimethylarginine dimethylaminohydrolase (DDAH) activity [10]. High density lipoprotein (HDL) cholesterol has also been reported to improve the endothelial dysfunction by stimulating NO release and inducing vasodilation, and therefore is protective to endothelial function [11]. However, SH is also known for its correlation with dyslipidemia. Therefore, SH may induce endothelial dysfunction by increased lipid disorders.

Our data supports a correlation between SH and atherosclerosis lipid profile changes. It has been revealed increased serum levels of LDL, and reduced levels of HDL, in experimental rat blood compare to control values (Tabl.1). Among the parameters that directly point the ratio of pro- and antiatherogenic LP and, accordingly, may manifest as a marker of disturbed lipid profile, atherogenic index has been proposed by us under given condition. It can be calculated by the formula: AI = (LDL + VLDL cholesterol) / HDL cholesterol. We found this index to be significantly higher in hypothyroid rat blood (0,530 ± 0,035) compare to the control group (0,370 ± 0,024). The results correlate with the literature sources, according to which even mild form of SH significantly modifies the process of synthesis, secretion and metabolism of lipoproteins.

Table 1

Lipid profile in rat blood and IHT correction under mild thyroid failure (M±m)

Parameters	Control (n=6)	Control+IHT (n=6)	Hypothyrosis (n=6)	Hypothyrosis +IHT (n=6)
Total cholesterol, mmol/l	1,480± 0,144	1,325± 0,070*	1,855± 0,156*	1,520± 0,194
Triglycerides, mmol/l	1,140± 0,156	0,760± 0,080*	1,080± 0,084	1,200± 0,106
VLDL, mmol/l	0,228± 0,031	0,152± 0,020*	0,216± 0,040	0,240± 0,022
LDL, mmol/l	0,270± 0,019	0,125± 0,004*	0,330± 0,028*	0,270± 0,020▪
HDL, mmol/l	1,350± 0,090	1,050± 0,042*	1,030± 0,041*	1,300± 0,012▪
Atherogenic index	0,370± 0,024	0,263± 0,020*	0,530± 0,035*	0,392± 0,029▪

* significance (p<0,05) in respect to control, ▪ significance (p<0,05) in respect to hypothyrosis

It was well established positive effects in response to IHT in experimental group of rats. All parameters of cholesterol providing system had a tendency to become close to almost normal values (Tabl.1). Atherogenic index in experimental group has decreased by 37,3%. An important effect of

training is to restore the content of HDL cholesterol as a factor that prevents the accumulation of cholesterol in the tissues of the vascular wall atherosclerotic changes and providing antioxidant properties of LP.

In conclusion, according to the recent data, the mechanism between SH and hyperlipidemia has been interpreted to a certain extent. New research demonstrates that TSH, acting on the TSHR in liver cells, upregulated the expression of hepatic 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCR), a rate-limiting enzyme in cholesterol synthesis in the liver [16]. The results revealed the direct effect of TSH on cholesterol levels in the liver form a novel perspective and possibly partially explained hypercholesterolemia in SH.

Declined NO activity caused by various factors impairs vasodilation in response to various stimuli. Besides vasodilation, NO also regulates a number of diverse biological processes, such as vascular permeability, neurotransmission, and mitochondrial respiration [14]. It is experimentally widely used, to detect the changes in NO production in plasma by measurement of NO metabolites. We have measured in rat blood a concentration of nitrite-ion under given condition. According to the results of present research, the blood of animals with hypothyroidism had a tendency to decrease in the nitrite - ion content, compared to control values (Tabl.2). It corresponds to the recent literature data, according to which ED is commonly associated with reduced nitric oxide (NO) bioavailability, and hence an inability of the endothelium to initiate vasodilation in response to vasodilatory stimuli [4, 11]. It represents an initial reversible step in the development of atherogenesis, and for this reason, early clinical identification of ED may become an important tool in the prevention of atherosclerosis.

It has been observed positive response of experimental animals to periodic hypoxic exposures. IHT significantly restored the contents of nitrite - ions to the limits of control values (Tabl.2). Our results correlate with the literature, which also shows that adaptation to hypoxia and hypoxia periodic in organs and tissues changes the expression of genes responsible for NO-synthase coding and vascular NO-dependent reactions [2, 14].

Table 2

Products of lipid peroxidation, concentration of nitrite-ion in rat blood under SH, corrected by IHT method (M±m; n=8)

Parameters	Control	Control + IHT	Hypothyrosis	Hypothyrosis + IHT
TBARS (mcmol/ml)	92,57±7,53	102,63± 12,09	117,53± 8,16*	99,31± 12,10
DC (un E/ml)	1,35± 0,11	1,40± 0,08	1,97± 0,18*	1,44± 0,12
NO2 –(nmol/ml)	12,50±1,68	18,04±2,57*	10,96±1,11	12,30±1,65

* significance ($p<0,05$) in respect to control, significance ($p<0,05$) in respect to hypothyrosis.

Oxidative stress appears to be the common underlying cellular mechanism for the development of ED in all the risk factors discussed above. Since ROS reacts with NO extremely readily, producing even more harmful reactive nitric intermediates, minimum oxidative stress in endothelial cells can uncouple NO synthesis and overwhelms the defensive mechanisms of the vascular endothelium ultimately initiating endothelial dysfunction [13, 18]. The content of some products of free radical metabolism was biochemically measured. Activation of lipoperoxidation (LPO) processes has been established in rat blood (Tabl.3). The concentration of TBA-active products in the blood significantly exceeds parameters of control values (due to the content of MDA – 27 %, DC – 46 %.). Correspondively, the activity of antioxidant protection system was depressed (SOD – by 30.5%, GPO - by 37.1% and TAS - by 9% compared to normal values). Our data suggest the impairment of the antiradical protective link and correspond to the literature sources according to which even mild hypothyroid disorders are associated with disturbances of oxygendependent metabolism [6, 15]. Oxidative stress comprises increased rates of oxidant production and decreased levels of antioxidant activity (superoxide dismutase (SOD), vitamin C and E, etc.) [13].Under physiological conditions, the enzyme SOD regulates the levels of O2–. However, increased generation of O2– overwhelms the defensive mechanisms of SOD, leaving O2– free to react with other molecules, particularly NO, for which it has a greater affinity [13, 18]. O2– is implicated in the direct induction of ED by the scavenging of NO, leading to the production of the highly reactive and harmful reactive nitrogen species (RNS), peroxynitrite.

Table 3

Antioxidant enzymes activity under condition of mild hypothyrosis and correction by IHT (M ± m; n = 8)

Parameters	Control	Control+ IHT	Hypothyrosis	Hypothyrosis + IHT
SOD(act.un./ml·min	559,63±46,44	638,26±49,12	389,05±44,02*	635,53±54,38▪

GPO (mcmol GSH/ g·min	1,22±0,08	1,38±0,11	0,88±0,06*	1,67±0,003*▪
Catalase (mcmol H2O2/ ml·hour) serum blod	 0,137±0,020 66,65±5,01	 0,135±0,018 57,87±4,46	 0,103±0,021* 52,71±8,34*	 0,112±0,013 61,33±5,34
TAS	1,45±0,09	1,46±0,20	1,32±0,15	1,59±0,20

* significance (p<0,05) in respect to control, significance (p<0,05) in respect to hypothyrosis.

Adaptation to periodic hypoxia showed increase in activity of AOS enzymes, and to the contrary decrease in parameters of LPO in hypothyroid group of rats, similarly as in the control series [2].

However, more research aiming at improving our understanding of ED is necessary in order to establish its detection and propose novel metabolic aspects linking benefits of IHT in SH.

Conclusions

1. Several cellular mechanisms and markers of ED that could potentially lead to the development of early detection and therapeutic interventions under condition of mild thyroid failure have been determined.
2. The subclinical hypothyrosis is associated with increased serum levels of LDL and with reduced HDL, and finally, with increased atherogenic index (0,530 ± 0,035). It can be interpreted as dyslipidemia, which is a structural and functional background for atherogenesis.
3. Mobilization of LPO processes under condition of impaired antioxidant protective link were well identified in experimental SH.
4. NO –derivatives as good indicators of ED have been reported to be decreased in rat blood (hypothyroid group) compare to control value.
5. All the markers of cholesterol providing system, metabolites of NO system, and oxygen dependent parameters were decreased under correction by IHT. Obtained results allowed us to recommend IHT as preventive and correcting factor under experimental hypothyrosis.
6.However, more research aiming at improving our understanding of ED is necessary in order to establish its detection and propose novel metabolic aspects linking benefits of IHT in SH.

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Реферати

МЕХАНИЗМЫ ФОРМИРОВАНИЯ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ ПРИ ЭКСПЕРИМЕНТАЛЬНОМ СУБКЛИНИЧЕСКОМ ГИПОТИРЕОЗЕ

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Исследованы параметры холестеринового обмена, активность процессов перекисного окисления липидов и антиоксидантной защиты, концентрация метаболита системы монооксида азота в крови в условиях экспериментального донозологического гипотиреоза (моделированного путем 3-х недельного введения тиреостатического препарата мерказолила белым крысам). Результаты показали, что при данной форме гипофункции щитовидной железы инициируются механизмы свободнорадикальных реакций, активируются процессы липопероксидации. В крови экспериментальных животных обнаружено снижение одного из метаболитов цикла монооксида азота – нитрит-иона, что, вероятно, может быть одной из причин нарушения вазодилятационных эффектов при гипотиреозе. Исходя из полученных результатов, следует полагать, что при данных условиях, формируются структурно-функциональные предпосылки к развитию эндотелиальной дисфункции. Показан положительный эффект от использования ИГТ как неспецифического корректирующего метода.

Ключевые слова: субклинический гипотиреоз, нитрит-ион, индекс атерогенности.

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ОСНОВНІ ШЛЯХИ ФОРМУВАННЯ ЕНДОТЕЛІАЛЬНОЇ ДИСФУНКЦІЇ ПРИ СУБКЛІНІЧНОМУ ЕКСПЕРИМЕНТАЛЬНОМУ ГІПОТИРЕОЗІ

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Досліджено параметри обміну холестерину, активність процесів перекисного окислення ліпідів та антиоксидантного захисту, концентрація метаболіту системи монооксиду азоту в крові в умовах експериментального донозологічеського гіпотиреозу (модельованого шляхом 3-х тижневого введення тиреостатичного препарату мерказоліла білим щурам). Результати показали, що при даній формі гіпофункції щитовидної залози ініціюються механізми вільнорадикальних реакцій, активуються процеси ліпопероксидації. У крові експериментальних тварин виявлено зниження одного з метаболітів циклу монооксиду азоту - нітрит-іона, що, ймовірно, може бути однією з причин порушення вазоділятаційних ефектів при гіпотиреозі. Виходячи з отриманих результатів, слід вважати, що за даних умов, формуються структурно-функціональні передумови до розвитку ендотеліальної дисфункції. Показаний позитивний ефект від використання ІГТ як неспецифічного коригуючого методу.

Ключові слова: субклінічний гіпотиреоз, нітрит-іон, індекс атерогенності.

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ПОРІВНЯЛЬНЕ ДОСЛІДЖЕННЯ ЕФЕКТИВНОСТІ ДІЇ ДЕЯКИХ ПРЕПАРАТІВ У ФОРМІ МАЗЕЙ І РОЗЧИНІВ НА СТАНДАРТНІ ТА ГОСПІТАЛЬНІ ШТАМИ БАКТЕРІЙ

Методом дифузії в агар досліджено антибактеріальну дію деяких препаратів у формі мазей та розчинів по відношенню до стандартних штамів S. aureus, E. coli та P. aeruginosa, а також клінічних штамів цих бактерій з полірезистентністю до антибіотиків. Препарати з діоксидином виявили високоефективну антимікробну дію щодо резистентних до антибіотиків клінічних штамів бактерій і мали у цьому перевагу перед іншими дослідженими препаратами, зокрема, перед мазями з офлоксацином та левоміцетином. Показано, що для виявлення високоефективної антибактеріальної дії відносно госпітальних штамів бактерій діоксидин слід включати у склад препаратів для місцевого лікування ран у концентраціях від 1,0 % до 1,5 %.

Ключові слова: антибактеріальна дія, бактерії, діоксидин, клінічні штами, мазь, розчин.

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Лікування інфікованих ран залишається однією з актуальних проблем медицини, рішення якої має велике соціально-економічне значення [1, 11, 15]. Останнім часом відбулися значні зміни в етіологічній структурі збудників гнійних хірургічних інфекцій. Провідними серед них стали стафілококи і грамнегативні бактерії, головним чином, синьогнійна паличка та кишкова паличка. При цьому прогресує розвиток антибіотикостійкості гноєтворних мікроорганізмів; різко зросла частота гнійних ускладнень, що викликаються госпітальними штамами з полірезистентністю до