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ISCHEMIC HEART DISEASE AND FAMILIAL HYPERCHOLESTEROLEMIA: ABOUT THE VIOLATION OF BIOGENIC AMINES METABOLISM

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Abstract:
The effectiveness of the fight against IHD depends primarily on preventive measures at the early stages, on the elimination or reduction of known factors of IHD.

Keywords: Sympathetic-Adrenal System, Hypercholesterolemia, Fluorimetric Method

INTRODUCTION: The main part of IHD is a multifactorial pathology, characterized by the formation of the disease in the process of complex interaction of genetic and environmental factors, for the manifestation of a hereditary predisposition, an adverse effect of environmental factors is necessary. Recent studies suggest that further study of circulatory regulation systems, in particular the sympathetic-adrenal system (SAS), is necessary to understand the pathogenesis of IHD.

THE AIM OF THE STUDY: To study the state of SAS in familial hypercholesterolemia (FH).

MATERIALS AND METHODS: A total of 124 people with FH were examined: 86 men, 38 women aged 18 to 65 years, and 15 healthy individuals aged 20 to 50 years. The study included patients over 18 years of age with a certain and probable IHD, according to the criteria of the Dutch Lipid Clinic Network (DLCN), depending on the manifestations of clinical signs of IHD, the subjects were randomized into 3 groups: I - control, healthy, n=15; II – IHD without signs of IHD, n=48 (38.7%); III - IHD with signs of IHD, n=76 (61.3%). The determination of total cholesterol, high-density lipoproteins (HDL), and triglycerides (TG) was carried out with biochemical express analyzers "Reflotron Plus" ("Roche" Germany). The content of LDL and VLDL was calculated according to the formula of A. N. Klimov. The daily urinary excretion of free and conjugated forms of catecholamines (CA) was studied by the fluorimetric method.
The determination of POL products in blood serum was performed according to the method of B. V. Gavrilov. Determination of MAO in blood serum was carried out by the method of A. I. Balakleevsky. Statistical processing of the obtained results was carried out using the Student's criteria.

RESULTS AND DISCUSSIONS: The comparative characteristics of the parameters of the blood lipid spectrum of the studied groups are given in Table 1.

Table 1.

Some clinical and biochemical parameters of lipids and POL products in the blood serum of patients with FH and in healthy subjects (P<0.001).

Indicators	Healthy ones (n=15)	FH without IHD (n=48)	FH without I (n=76)
Tendon xanthomas, abs (%)	-	34(71)	68(91)
Common cholesterol, mmol/l	4,5±0,3	7,5±1,2*	8,13±1,3^
TG, mmol/l	1,3±0,1	1,6±0,1*	1,8±0,1^
LDL cholesterol, mmol/L	3,1±0,3	6,3±0,4*	6,9±0,4^
HDL cholesterol, mmol/L	1,3±0,1	1,0±0,1*	1,1±0,1^
VLDL cholesterol, mmol/L	0,28±0,02	0,34±0,02*	0,36±0,02^
IA, ed	3.1±0,1	6.4±0,2*	6.7±0,2^
MDA, nmol/l	3,6±0,5	6,2±0,8*	7,8±0,7^

Note: IA - index of atherogenicity; MDA-malondialdehyde;*, ^ - differences in relation to the control group are significant (P<0.001).

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When studying the daily excretion of KA, DOPA, the following changes are observed (Table 2). In group II, there is a statistically significant (p<0.001) increase in the daily excretion of epinephrine (A) free by 24.4%, conjugated by 28.9% and total by 26.5% compared to the control group. The excretion of free norepinephrine (NA) increased by 12.1%, conjugated - by 16.8% and total - by 14.4% in relation to the control group (p<0.001). Dopamine (DA) free, conjugated, total increased by 8.5%; 10,%; 9.3%, respectively, in relation to the control (p<0.05). DOPA was increased by 4.5% in relation to the control group (p<0.001). In group III, there was a decrease in the daily excretion of catecholamines, in particular; A free by 31.1%, conjugated by 23.7%, total by 27.7% compared to the control group (p<0.001). For free, conjugated, total decreased by 31.3%, 25.3%, 29.3%, respectively, compared with healthy (p<0.001). There is a decrease in the excretion of DA: free - by 51.1%, conjugated - by 46.6%, total-by 48.8% in relation to the control (p<0.001). DOPA was reduced by 22.0% in relation to group I (p<0.001). When studying the activity of MAO in FH, a significant decrease in the activity of the enzyme was revealed in all the examined groups in relation to the control group (Table 2). In the control group, the MAO activity was 0.07-0.001 u / ex. In group II, the MAO activity was 0.05-0.003 u/ex, which is 28.6% lower than the control (p<0.001). In group III, there was a significant decrease in the activity of the enzyme by 42.9% compared to the control group and amounted to 0.04 0.004 u/ex. (p<0.001). The gender indicators in all the study groups were significantly different from those in the control group. In the control group, the level of malondialdehyde (MDA), a secondary product of LPO, ranged from 2.1 - 4.4 nmol/ml, with an average of 3.6±0.5 nmol/ml. In group II, there was a statistically significant increase in the level of MDA by 72.2% compared to the control group (p<0.001). In group III, there was an increase in the level of MDA by 116.6 % in relation to the control indicators (p<0.001) (Table 1).

Table 2.

Daily KA excretion and MAO activity in practically healthy patients and patients with FH, (P<0.001)

Group	**A, mcg/day**	**NA, mcg/day**	**DA, mcg/day**	**DOPA, mcg/day**	**MAO, mcg/day**
I- Control				46,4±0,6	0,07±0,001
Free	4,5±0,1	9,9±0,1	140,4±5,2		
Conjugated	3,8±0,1	8,7±0,1	152,8±5,5		
Total	8,3±0,2	18,8±0,2	292,2±9,4		
II- FH without IHD				48,5±0,8	0,05±0,003
Free	5,6±0,1	11,1±0,1	152,4±6,3		
Conjugated	4,9±0,1	10,4±0,1	167,0±5,2		
Total	10,5±0,2	21,5±0,4	319,4±10,0		
III- FH with IHD				36,2±0,6	0,038±0,003
Free	3,1±0,1	6,8±0,1	68,6±3,2		
Conjugated	2,9±0,1	6,5±0,1	81,1±4,1		
Total	6,0±0,2	13,3±0,2	149,7±7,4		

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Thus, the problem of the functional state of SAS in patients with IHD, its relationship with the features of the course of the disease, the formation of complications is the subject of discussion. One of the central places in the complex interaction of various regulatory systems belongs to SAS, which is associated with the widest range of its effects (6). Activation of SAS, through direct trophic effects, is accompanied by a number of structural changes, primarily in the vascular wall and myocardium. Structural changes in blood vessels are directly involved in the formation of myocardial ischemia, stroke, and damage to other target organs [10].

An increase in the activity of SAS in familial hypercholesterolemia can be regarded as compensatory, ensuring the mobilization of the body's defenses, increasing the energy supply of the myocardium. The further increase in the stress of SAS activity is aimed at mobilizing the internal reserves of the body. However, at one of the stages of this process, the catabolic direction of the effects of SAS begins to manifest itself, and a further increase in the activity of which becomes one of the main elements of the formation of IHD and its complications.

The results of the conducted studies showed that in FH there is a moderate activation of SAS, associated with an increase in the excretion of catecholamines: A, NA, and DOPA by 1.27; 1.14; 1.05 times, respectively ($p<0.001$), and by 1.09 times ($p<0.05$) in relation to healthy people. These data coincide with the data of L. M. Doborgiginidze, N. A. Graziansky and co-authors, A. I. Nesterova (2000). In turn, in patients with chronic forms of IHD, there is an equivalent decrease in the daily excretion of catecholamines: A, NA, DA in 1.38; 1.41; 1.96 times, respectively ($p<0.001$), DOPA 1.28 times ($p<0.05$) in relation to the control. In patients with FH with chronic forms of IHD, the inhibition of SAS activity is manifested by a decrease in the hormonal and mediator link, and there is also a decrease in reserve capabilities due to a decrease in the release of DOPA ($p<0.05$) and dopamine ($p<0.001$). It is known that a decrease in the level of catecholamines in cardiovascular diseases can be a predictor of the development of arrhythmias, asystoles, and the threat of sudden death in stressful situations [10]. Currently, it is reliably known that the activation of peroxide free radical processes underlies the pathogenesis of many diseases of the internal organs. LPO processes cause the accumulation of oxidized LDL, which leads to impaired microcirculation [10]. From this point of view, it was particularly interesting to study the processes of LPO in FH, since the main biochemical indicator of blood is an increase in LDL. It was found that in IHD and atherosclerosis, there is an increase in LPO. The intensity of LPO reflects the degree of metabolic disorders in the body (8). The results obtained by us indicate an increase in the LPO processes in FH without IHD by 1.72 times ($p<0.001$), and the most pronounced intensification of the LPO processes is observed in chronic forms of IHD, exceeding the control indicators by 2.16 times ($p<0.001$).

As is known, under conditions of lipid peroxidation, the key enzyme of biogenic amine oxidation, MAO, can undergo a significant transformation of its catalytic properties, which reduces its activity to monoamines [7]. We studied the activity of MAO in healthy and FH patients with IHD and without clinical manifestations of IHD, during the observation it was revealed that the functional activity of MAO undergoes significant changes depending on the degree of manifestation of cardiovascular pathology. Thus, in patients with FH without clinical forms of IHD, there is a decrease in MAO activity by 1.4 times ($p<0.001$). And in patients with FH with IHD, the lowest activity of the enzyme is noted, which is 1.75 times ($p<0.001$) lower than the indicators of the control group, which confirms the qualitative violation of its catalytic properties.

Thus, the obtained data revealed that the development and progression of IHD in is accompanied by disorders of the functioning of the SAS. Increased sympathetic tone leads to a number of metabolic, trophic, and hemodynamic changes, which is accompanied by an increased risk of cardiovascular disasters in FH. The results of our studies, to some extent, can show the important role of violations of the activity of SAS and the processes LPO in the development of IHD and its complications in FH. Determining the parameters of lipid metabolism, studying the state of SAS, MAO activity, and LPO processes can provide additional information for the early diagnosis of IHD and atherosclerosis in relatives with IHD, and assessing the severity of IHD and atherosclerosis in IHD.

CONCLUSIONS:

1. A comprehensive study of individuals with FH without clinical manifestations of IHD showed an increased excretion of adrenaline, noradrenaline, dopamine, DOPA on 26,5%, 14,4%, 9,3%, 4,5% accordingly in relation to

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the healthy what he says about activating the hormonal link of SAS, in which requires early correction to prevent development of IHD.

2. A comprehensive study of FH patients with chronic forms of IHD showed a reduction of urinary excretion of adrenaline, noradrenaline, dopamine, DOPA on 27,7%, 29,3%, 48,8%, 22,0% respectively relative to the control group, talking about lowering the hormone activity, neurotransmitter level, and the reserve capacity of SAS.

3. In the subjects with FH, there is a significant decrease in MAO activity in relation to healthy subjects, which indicates a qualitative change in the catalytic properties of the enzyme.

4. In FH, there is a significant intensification of LPO, possibly contributing to the development of oxidative stress, a sharp decrease in antioxidant protection, and the early development of IHD.

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