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INFLUENCE OF HAPLOGENIN – 7 – GLYCOSIDE ON RESPIRATION AND OXIDATIVE PHOSPHORYLATION OF RAT LIVER MITOCHONDRIA

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Abstract:
It has been established that haplogenin – 7 – glycoside increases mitochondrial respiration of rat liver. Thus the ADP/O quotient increases slightly by glutamate, and by succinate on the contrary, decreases imperceptibly.

Keywords: haplogenin-7-glycoside, mitochondria, respiration, oxidative phosphorylation, liver, biological effects, substrates.

1. Introduction. It is known that in mitochondria occur processes as a result which energy accumulates in cells and these organelles possess all main functions of independent organism such as reduction, ion transportation and heredity. It allows considering that mitochondria are rather complete substances of a living matter preserving their basic properties. If this so, a response of isolated mitochondria - their metabolic stations - should correspond to physiological laws of influence of living organisms on external actions. Differently, it is possible to believe that there is a correlation between metabolic station of isolated mitochondria and such stations, as excitation and braking. These terms often use for the description of system reactions of the whole organism. We use them in that sense in what they are applied in physiology to a designation of the basic laws of influence of a living tissue on external actions.

It's established that flavonoids possess anti-inflammatory, antiatherogenic, antivirus, anticytotoxic, membrane – stabilization, anti-cancer, cytoprotective, neurocytoprotective immune-modulation properties. However, the questions, concerning influences haplogenin-7-glycoside on structure and functions of mitochondrial membranes still are not studied.

Research of effect of haplogenin-7-glycoside on respiration and oxidative phosphorylation is of interest not only from a position of clarification of physiological and biochemical mechanisms the regulation of an organism activity, but also for an establishment of pathogenic importance of these parameters at various stress conditions and diseases.

2. Materials and Methods. Mitochondria were isolated from cells of rat liver according to a method. Velocity of mitochondrial respiration at a various metabolic states was registered polarographically with the help of the rotating platinum electrode. Reactions were started with addition of a mitochondrial suspension into polarographic cell. An incubation medium has the following composition: sucrose – 0.25 M, KH_2PO_4 – 5 mM, tris-HC1 – buffer – 10 mM (pH 7,4). As oxidizing substrata were used 10 mM of succinate (pH 7,4) and 10 mM glutamate (pH 7,4). Mitochondrial respiration and oxidative phosphorylation were analyzed at the consecutive addition 200 mcM of haplogenin-7-glycoside and ADP, 5.10^5 M of 2.4 - dinitrophenol (DNP). Herewith the following velocity of respiration chemicals were determined: V_2 – state 2 before the addition of ADP, V_3 – active phosphorylation state, V_4 – state 4 after an exhaustion of ADP in a cell; ADP/O ratio and respiration control quotient were calculated by a method of Chance and Williams (V_3:V_4). Rate of the substrata oxidation at a various metabolic states was expressed in nanogram atom oxygen min/mg of mitochondrial protein. Protein was defined by a method of Lowry et al.

Experiments were carrying out in absence of flavonoids and with addition haplogenin-7-glycoside into a polarographic cell in vitro. Haplogenin-7-glycoside was used in a manner of glycerin solution. The specified flavonoids were put into polarographic cell in final concentration 20, 40, 60 mcgr/mg mitochondrial protein and studied the features of change of mitocondrial functional state. Haplogenin-7-glycoside has been kindly given by officials-professors Z. Khushbaktova and V.Syrov of Institute of Plant substances' chemistry.

3. Analysis of results.

3.1. Influence of haplogenin-7-glycoside on glutamate oxidation and oxidative phosphorilation of mitochondria

Table 1

Influence Of Haplogenin-7-Glycoside On Glutamate Oxidation And Oxidative Phosphorilation Of Liver Mitochondria (M±m; n= 8-12).

Readings	Respiration rate, nanogram atom oxygen/min mg of protein			
	Haplogenin-7-glycoside,mcg/mg of protein			
	0	20	40	60
V_2	18.0±1.2	18.6±1.4	19.0±1.2	20.5±1.6
%	100	103.3	105.5	113.9
V_3	54.5±1.8	57.4±2.2	60.3±1.9*	73.0±1.8***
%	100	105,3	110,6	133,9
V_4	17.6±1.4	17.8±1.4	17.9±1.3	20.8±1.7
%	100	101.1	101.7	118.2
V_{DNP}	68.8±1.8	75.5±2.2	80.0±2.4*	96.5±2.4****
%	100	109,7	116.3	140.2
RC_{Ch} (V_3:V_4)	3.09±0.10	3.22±0.10	3.37±0.09*	3,51±0,10**
%	100	104.2	109.0	113,6
ADP/O	2.37±0.09	2.81±0.13**	3.00±0.14***	2.85±0.10**
%	100	118.4	126.4	120.3

A note: Here and in the table 2 the quotient authenticity was marked:*, *P<0.05; **P <0.002; ***P < 0.01;****P < 0.001.

Haplogenin-7-glycoside, in low concentrations (20 mcg/mg of protein) wasn't influence on glutamate oxidation and a respiration control value by Chance, however rose ADP/O quotient up to 18.4%. It has known that if a respiration control value by Chance reflects the degree of relationship of transformation processes and energy accumulation by mitochondria with energetic processes in the cell, that ADP/O value characterizes the functional organization of mechanisms, defining an ADP phosphorylation process in mitochondrial membrane and their relationship with activity of a terminal respiratory chain. The more a value of ADP/O, the less oxygen spent to phosphorylation, that accordingly higher mitochondrial coefficient of efficiency from energy storage point of view for further intracellular metabolic processes. The increase of haplogenin-7-glycoside concentration entered into a cell of a polarograph twice oxidative phosphorylation of glutamate (V3) raises on 10.6 % from control level. As a result, the value of the respiratory control on Chance and

ADP/O quotient raised on 9.0 and 26.4 %, respectively, from control level. The further increase of haplogenin-7-glycoside concentration (60 mkg/mg of protein) raises glutamate oxidation in various metabolic conditions of mitochondria.

Thus, a mitochondrial respiration in V_2, V_3 and V_4 states increases on 13.9; 33.9 and 18.2% respectively, in comparison with control. Increase of respiration in phosphorylation condition leads to increase of value of the respiratory control by Chance and ADP/O quotient on 13.6 and 20.3 %. It means that haplogenin-7-glycoside is a respiratory activator and especially, ATP synthesizing function of mitochondria at oxidation of NAD - dependent substrata.

3.2. Influence of haplogenin-7-glycoside on succinate oxidation and oxidative phosphorylation of liver mitochondria.

In low concentration (20 mkg/mg of protein), haplogenin-7-glycoside slightly (on 12.9%) increases oxidative phosphorylation of succinate. At the same time respiration of mitochondria in V2 and V4 metabolic states and value of respiration control by Chance hasn't change, however ADP/O quotient decreases to 12,1%. The increase of haplogenin-7-glyoside concentration, entered into a polarograph cell in two times leads to increase of oxidative phosphorylation of succinate (V3) to 24.9 % from control level, and respiration of mitochondria at the calm state (V4) - to 24.9 %. Thus, value of the respiratory control on Chance does not change, however the ADP/O quotient raises on 16.0 %. The further increase of haplogenin-7-glycoside concentration (60 mkg/mg of protein) leads to increase of succinane oxidation in various metabolic states of mitochondria. Thus, respiration of mitochondria in V2, V3 and V4 states increases in comparison with control on 16.7; 39.8 and 34.7%, respectively. It means that haplogenin-7-glyoside is the activator of the respiratory functions of mitochondria at oxidation of succinate oxidation pathway. Thus, the value of the respiratory control on Chance does not change, however ADP/O quotient decreases on 17.6%.

Table 2 **Influence of haplogenin-7-glyoside on succinate oxidation and oxidative phosphorylation in liver mitochondria (M±m; n= 8-12).**

Readings	Velocity of respiration, nanogram atom oxygen/min mg of protein haplogenin-7-glycoside,mcg/mg of protein			
	0	20	40	60
V_2	40.0±2.4	40.9±2.7	42.4±3.2	46.7±4.0
%	100	102.2	106.0	116.7
V_3	112.0±3.6	126.5±4.4*	144.4±5.7***	156.6±6.5****
%	100	112.9	128,9	139.8
V_4	32.5±2.5	34.8±3.0	40.6±3.5*	43.8±3.7**
%	100	107.0	124.9	134.7
V_{DNP}	130.6±5.6	144.5±6.0	180.0±6.4***	200.0±7.7****
%	100	110.6	137.8	153.1
RC_{Ch} (V_3:V_4)	3.44±0.13	3.63±0.12	3.55±0.12	3.57±0.09
%	100	105.5	103.2	103.8
ADP/O	1.82±0.09	1.71±0.08	1.53±0.11*	1.50±0.08**
%	100	87.9	84.0	82.4

Depending on dose, haplogenin-7-glyoside raises dinitropenolstimulative oxidation of substrata. So, if at the entering of haplogenin-7-glycoside into a polarograph cell in a dose of protein of 20 mkg/mg mitochondria, glutamate and succinate oxidation raise on 9.7 and 10.6 % from control level, at the entering of protein of 40 mkg/mg – 16.3 and 37.8 %, and 60 mkg/mg of protein – 40.2 and 53.1 %. Thus, haplogenin-7-glyoside increases transport of electrons from substrata to molecular oxygen along respiratory chain of mitochondria, and it considerably occurs on succinate oxidation pathway.

Analyzing the obtained results, it is possible to conclude that haplogenin-7-glycoside considerably raises mitochondrial respiration of rat liver. Thus, the ADP/O quotient with glutamate considerably raises, on the contrary, decreases with succinate.

At the analysis of oxidizing capability of mitochondria, the attention has been paid to characteristics of their conditions corresponding to a certain tissue activity. Now it became obvious that at functioning of mitochondria in vivo in quietness the main bulk of mitochondria are in a state 4 on Chance. This condition is characterized by good supply of mitochondria with oxygen and substrates. However, respiratory activity is suppressed because it is integrated to phosphorylation processes, and in a based tissue, the basic exchange fund of adenylic nucleotides, using for

intracellular transport of energy, appears in the form of ATP. Absence of corresponding acceptors of phosphate is the basic brake of cellular respiration. Increase of cell activity leads to energy expenses and ATP hydrolysis. Occurrence of phosphate acceptors in the form of ADP leads to activation of respiratory activity of mitochondria, and it will proceed until cell will spend energy of macroergic phosphoric connections and deliver of ATP to mitochondria. At presence of haplogenin-7-glycoside, mitochondria pass from one metabolic state in higher metabolic state. In our opinion, high intensity of metabolism can be supported animals, received haplogenin-7-glycoside at the expense of a mitochondrial activation system of various tissues and, most likely, inner organs. Increase of mitochondrial respiration by haplogenin-7-glycoside can be connected with increase of translocase activity. It has shown that, exchange of adenine nucleotides (ATP^{4-}/ADP^{3-}) between mitochondrial matrix and cytosol performed by special transport system – translocase, determines total speed of respiration. With use of fluorescence probe has been shown coexistence in a membrane not only not-mobile transmitting agents (a fixated portal pore) but also mobile ones, carrying out rotate and lateral diffusion in a membrane surface. The most essential line of translocase is electrogenity. It means that in energized mitochondria transport of nucleotides is performed always in one direction: ADP from cytosol into mitochondria, ATP - from mitochondria into cytosol, and K_M moreover, in 100 times higher for exogenous ATP than for exogenous ADP; relation ATP/ADP of cytosol: mitochondrial ATP/ADP is in direct linear dependence on the sizes of a membrane potential. Translocase-adenine nucleotide, working synchronously with ATF-synthase and oxidizing enzymes system be under the control inner-mitochondrial pool of adenine nucleotides and linearly depends on the sizes of this pool.

In presence of haplogenin-7-glycoside increasing of ADP/O quotient by succinate and decreasing by glutamate in liver mitochondria is connected with an “anatropic electron transfer” phenomenon (restored NAD). In 1957, it has been found the phenomenon, which has entered into bioenergetics under the name “oxidative phosphorylation convertibility”, or, “anatropic transport of electrons” [26]. Succinate, added to mitochondrial suspension, invoked fast reduction of mitochondrial pyridine nucleotides. After addition of ADP pyridine nucleotides acidified and only after full phosphorylation ADP, they became reduced once again. The phenomenon of anatropic transport of electrons has found a rational

explanation in frameworks of Mitchell's chemiosmotic theory. It is known that from three proton pumps of a respiratory chain (respiratory complexes 1, 3, 4) two (respiratory complexes 1 and 3) function reversible.

In vitro, for example can be created following conditions: at succinate oxidation, when the stream of protons, pumped out two proton pumps of a respiratory chain (3 and 4), will be pump inside by the proton pump I. Anatropic transport of protons correlated with anatropic transport of the electrons moving against gradient of redox potential of isopotential groups of respiratory transmitting agents at the energy expense of an electrochemical gradient of protons on a mitochondrial membrane. Thus, in this case, succinate acts both as the donor of protons, pumped out by the pumps 3 and 4, and it is inversely to protons pumped in by the pump I. As a result, it can be registered by optical methods restoration of NAD^+. It is obvious that anatropic transport of electrons can carry out only by "energized" mitochondria, i.e. possessing an electrochemical gradient of protons on a membrane.

Thus, haplogenin-7-glycoside enhancing anatropic transport process of electrons raises ATP synthesis in mitochondria. Physiologically, that process is very expediently. It is known [29] that on each NAD.H molecule, oxidized by oxygen, ten protons carry through a membrane. Interrelation H^+/O, equals to 10. It responses to value of P/O for NAD-dependent substrates, succinate and ascorbate 10: 3 = 3, 3, 6: 3 = 2 and 4: 3 = 1, 3 respectively. It is known that extra membrane synthesis ATP from ADP and phosphate demands transport of three protons into mitochondrial matrix.

It is considered that transport of two protons is necessary for synthesis of one molecule of intra-mitochondrial ATP, while transport of one more proton provides by antiport energy $(ADP^{3-})_{outer} + (H_2PO_4^-)_{outer} / (ATP^{4-})_{inner}$.

Commutation of succinate oxidation to NAD-dependent substrates at presence of haplogenin-7-glucoside represents the mechanism providing the possibility of completion of damage in high-energy compounds depot in a tissue, which has arisen after excitation.

That commutation has an important power consequence. Considering that succinate oxidation rate is higher than NAD-dependent substrates, and transport intensity of high – energy compounds by respiration chain is higher at its burning (oxidation). This mechanism reacts as a spring, automatically backtracking abovementioned system and is created by irritation. According to the modern biochemical reports,

for realization of protein and lipid synthesis it is necessary, especially high power potential of mitochondria. Succinic acid, as it is known, has no competitors in building of a high level of high-energy bonds and reduced pyridine nucleotide [30]. Therefore, it should possess specific function of plasticity maintenance. It has been shown that at succinate use observed more complete cycle of mitochondrial changes with connection of ion transport, than at use of other substrates. It is possible to think that this commutation represents the buffer system, giving the chance to keep on the high levels of native state.

Differently, at any normal physiological activity that biochemical mechanism should be involved first.

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