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Effect Of Cinoroside And Thermopsoside On Respiration And Phosphorylation Of Mitochondria

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ABSTRACT

This article presents the results of a study of the effect of cynoroside and thermopsoside on respiration and oxidative phosphorylation of mitochondria in vitro. It has been established that cynoroside increases mitochondrial respiration, especially during glutamate oxidation, and, on the contrary, decreases with succinate.

KEYWORDS

Flavonoids, Cynoroside, Thermopsoside, Oxidative Phosphorylation, Glutamate, Succinate.

INTRODUCTION

A characteristic feature of flavanoids is the ability to block transport systems that carry toxic compounds, reducing their negative effect on the human body [2, 3, 4]. Another feature is their property (in particular, silibinin) - to inhibit the synthesis of acetaldehyde, an intermediate product of the metabolism of ethyl alcohol [1, 5]. A characteristic feature of flavanoids is their membrane stabilizing effect [4, 6]. Membranes play a leading role in biotransformation and neutralization of endogenous toxins and xenobiotics, incl. side effects of drugs [7]. Flavanoids contribute to the stabilization and normalization of membrane function by direct biochemical interaction with them, and inhibit the activity

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of phosphodiesterase, which contributes to the accumulation of cyclic adenosine monophosphate in the cell [1, 8].

In this regard, within the framework of a program for studying the molecular mechanisms of action of flavonoids, it seems essential to investigate the effect of various representatives of these compounds on one of the energy supply systems of the cell - the system of respiration and phosphorylation of mitochondria.

In this work, we present data on some features of the energy metabolism of rat liver mitochondria in the presence of thermopsoside and cynoroside.

METHODS

Mitochondria were isolated from rat liver cells as described in [9]. The respiration rate of mitochondria was studied under various metabolic states: V2 - before the addition of ADP, V3 - in the presence of ADP, V4- at rest, and Vdnf - uncoupled respiration. The indicators were recorded polarographically using a rotating platinum electrode. The reaction was started by adding a suspension of mitochondria to a polarographic cell. The composition of the incubation medium: sucrose — 0.25M, KH_2PO_4 —5 mM, Tris — HCl — buffer — 10 mM (pH 7.4). Respiration and phosphorylation were analyzed with the sequential addition of flavones, 200 mkM ADP, 2,4-dinitro-phenol (DNP) - 5.105 M. The ADP / O ratio and the respiratory control coefficient were calculated using the Chance and Williams method (DCch-V3: V4) [10]. The substrates for oxidation were 10 mM succinate and 10 mM glutamate. The rate of oxidation of substrates at various metabolic states was expressed in nanograms oxygen atom / min mg of protein. Protein was determined by the method of Lowry et al. [11].

As can be seen from the above data, the introduction of cynoroside into the suspension of mitochondria (Table 1) leads to an increase in the rate of glutamate oxidation in metabolic state 2, without significant changes in respiration in states 3 and 4. In this case, the ADP / O coefficient slightly increases, and the DCch value does not changes. Cinoroside slightly increases dinitrophenol-stimulated oxidation of glutamate. In low doses, this flavonoid does not affect the oxidation of succinate. However, with an increase in its concentration, mitochondrial respiration in states 2 and 4 gradually increases and the efficiency of oxidative phosphorylation is impaired. Therefore, if in the presence of 60 mkg of cynoroside per mg of protein in V2 and V4, the rate increases by 20.7 and 16.0%, respectively, then the DCch value and the ADP / O coefficient, on the contrary, decrease by 9.2 and 10.5 % of the original level. In the presence of 70 mkg / mg protein in the V2 and V4 states, mitochondrial respiration increases by 26.5 and 24.4%, and the DCch value and the ADP / O coefficient decrease by 14.3 and 20.9%.

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Table 1.

Effect of cynoroside on respiration and oxidative phosphorylation of mitochondria (M±m; n= 8-12).

Mkg / mg protein	Respiration rate, nanogram oxygen atom / min mg protein				DK_{ch} (V_3:V_4)	**ADF/O**
	V_2	V_3	V_4	V_{dnf}		
	Glutamate					
0	18,0±1,2	61,4±2,1	13,4± 0,9	63,3±2,7	4,58±0,15	2,78±0,10
10	19,6±1,4	62,6±2,4	13,3±1,0	65,4±3,1	4,70± 0,16	2,85±0,09
20	22,3±1,3	61,4±2,5	13,4±1,1	70,5±3,3	4,58±0,15	2,90±0,10
30	24,8±0,9	60,7±2,6	13,0±1,2	75,0± 2,8	4,67±0,14	2,98±0,11
40	25,6±1,1	61,0±2,8	13,4±1,1	73,6±3,2	4,55±0,13	2,96±0,12
50	26,8±1,2	60,5±2,7	13,6±1,3	74,4±3,4	4,49±0,12	2,99±0,11
	Succinate					
0	48,2±2,4	136,6±3,8	40,6±2,2	180,9±5,0	3,36±0,13	1,82±0,08
20	46,0±2,6	137,0±4,5	41,0±2,6	183,0±5,2	3,42±0,12	1,88±0,07
30	50,8±2,7	138,9±4,5	40,7±2,9	186,4±5,1	3,41±0,12	1,82±0,09
40	52,4±2,8	138,4±4,3	40,8±3,1	184,5±4,8	3,40±0,10	1,80±0,08
50	55,7±3,1	141,6±4,4	43,2±3,4	190,2±5,2	3,28±0,09	1,72±0,07
60	58,2±3,3	143,8±4,5	47,1±3,3	194,8±5,5	3,05±0,08	1,63±0,10
70	61,0±3,0	145,5±4,8	50,5±3,2	198,0±5,4	2,88±0,09	1,44±0,12

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The introduction of thermopsozide into the suspension of mitochondria (Table 2) leads to a dose-dependent decrease in the rate of glutamate oxidation. In states 3 and 4 at doses of 20, 30, 40, and 50 mkg / mg of protein in V3, it decreases by 11.8, respectively; 18.1; 21.5 and 33; 8%, V4 - by 12.7; 19.1; 20.7 and 17.5%,), without significant changes in respiration in state 2. At the same time, the value of DCch does not change, but the ADF / o ratio increases by 21.1; 21.1; 27.7 and 14.4%. It should be noted that in the presence of thermopsoside, a decrease in the rate of phosphorylating oxidation of glutamate correlates with a decrease in dinitrophenol-stimulated mitochondrial respiration. Low concentrations of thermopsozide do not affect the oxidation of succinate. However, with an increase in the dose of the drug, the respiratory rate increases in state 4 at a dose of 50.60 and 70 mkg / mg of protein, it was higher than the initial value, respectively, by 20.1; 26.6 and 33.9%.

As a result, oxidative phosphorylation is suppressed, the DCch value decreases by 16.9; 21.8 and 27.3%, and the ADF / O ratio by 9.8; 18.1 and 33.6%. These changes correlate with the concentration of thermopsoside used. Since high concentrations of thermopsozide inhibit dinitrophenol-stimulated respiration of mitochondria, it follows that thermopsozide inhibits mitochondrial respiration, especially in the NAD-dependent part of the respiratory chain.

Table 2.

Effect of thermopsoside on respiration and oxidative phosphorylation of mitochondria (M±m; n= 8-12).

Mkg / mg protein	Respiration rate, nanogram oxygen atom / min mg protein				DK_{CH} (V_3:V_4)	**ADF/O**
	V_2	V_3	V_4	V_{dnf}		
	Glutamate					
0	18,0±1,0	61,9±1,6	13,2±1,0	63,0±2,0	4,69±0,15	2,78±0,09
10	18,4±1,2	60,0±1,5	12,6±1,1	62,3±1,8	4,76±0,13	2,92±0,09
20	19,3±1,1	54,6±1,4	11,0±0,9	58,6±1,6	4,96±0,14	3,18±0,08
30	20,6±1,0	50,7±1,3	10,2±0,8	52,0± 1,4	4,97±0,13	3,37±0,07

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40	21,2±1,0	48,6±1,2	10,0±0,7	48,5±1,3	4,86±0,15	3,55±0,08
50	20,2±1,1	41,0±1,2	10,4±0,9	43,4±1,5	3,95±0,16	3,18±0,06
	Succinate					
0	46,5±2,4	138,0±3,8	44,8±2,5	186,8±5,2	3,08±0,09	1,88±0,09
20	46,5±2,5	138,8±4,1	44,9±2,6	183,2±5,5	3,09±0,10	1,82±0,08
30	46,7±2,6	139,3±4,0	46,6±2,7	178,6±5,1	2,99±0,12	1,80±0,09
40	47,2±2,5	140,6±4,4	49,4±3,0	174,4±4,8	2,84±0,11	1,76±0,10
50	47,3±2,7	138,8±4,2	54,2±2,9	170,6±4,2	2,56±0,10	1,70±0,09
60	47,4±2,6	136,9±3,9	56,7±2,9	166,3±3,7	2,41±0,10	1,54±0,08
70	47,5±2,6	134,4±3,1	60,0±2,8	161,5±3,4	2,24±0,09	1,25±0,09

Analyzing the data obtained, it can be concluded that cynoroside increases mitochondrial respiration, especially during the oxidation of NAD-dependent substrates. In this case, the values of oxidative phosphorylation of glutamate slightly increase, while succinate, on the contrary, decrease.

Thermopsozide inhibits the rate of phosphorylating and dinitrophenol-stimulating oxidation of glutamate. Low concentrations of thermopsozide do not affect the oxidation of succinate. However, with an increase in the dose of the drug, the respiration rate in state 4 increases, as a result of which oxidative phosphorylation of mitochondria is suppressed. High concentrations of thermopsozide inhibit dinitrophenol-stimulated mitochondrial respiration.

CONCLUSION

The physiological meaning of the inhibition of respiration and the preservation of the parameters of oxidative phosphorylation by flavones can be seen in the fact that, under these conditions, in mitochondria, metabolism is generally transferred to a more economical mode in terms of the expenditure of substrates and energy. We have previously shown that antihypoxants and antioxidants - benzonal, catacin, gutimine, cavergal and serotonin - stabilize membranes and suppress mitochondrial respiration without uncoupling oxidative phosphorylation [12, 16, 18, 19].

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