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Peculiarities of Action of Catecholamines and their Metabolites in the Regulation of Cardiomyocyte Enzymes

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Abstract

BACKGROUND: Myocardial ischemia is accompanied by a significant increase in adrenaline content in the heart. By its nature, sympathetic hyperactivation is accompanied by increased formation of products of enzymatic and nonenzymatic metabolism of adrenaline and its analogs, which can change the use of ATP by cells, change the activity of mitochondrial and cytosolic enzymes, contributing to disruption of bioenergetic adaptation, antioxidant defense system and levels of intercellular modulators such as AMP and adenosine.

AIM: The study objective was to explore the features of adrenaline and its analogs in the regulation of the activity of mitochondrial and cytoplasmic enzymes of cardiomyocytes.

METHODS: The experiment was carried out on 65 3-month-old male Wistar rats weighing 60–190 g. To study the effects of catecholamines and their metabolites in the regulation of mitochondrial and cytoplasmic enzymes activity of cardiomyocytes, experimental rats were put to death by intraperitoneal injection of 10% ketamine in an amount of 0.25 mg/100 g. Activity of mitochondrial succinate dehydrogenase, cytochrome c oxidase, mitochondrial DNP-activated ATPase, adenosine deaminase (AD), AMP deaminase (AMPD), glutathione reductase, and glutathione peroxidase were determined.

RESULTS: Dopamine has the greatest activating effect on cardiac mitochondrial ADH, adrenaline on CHO, and adrenochrome and adrenoxyl on ATPase. Isadrine and dopamine reduce cardiac AMPase activity. An activating effect on cardiac mitochondrial AMPD was found only in norepinephrine.

CONCLUSION: In cardiomyocytes, adrenaline, activates cytosolic enzymes of purine nucleotide metabolism AD and AMPD, as well as increases the level of lipid peroxidation (MDA and DC). This proves that adrenaline acting on adrenoreceptor mechanisms leads the body into a state of oxidative stress. Hormone-mediators of the sympatho-adrenal system adrenaline, dopamine, noradrenaline, isadrine, and catecholamine metabolites (adrenochrome and adrenoxyl), changes the activity of mitochondrial respiratory chain enzymes of cardiomyocytes, also regulate tissue respiration processes, putting mitochondria into the state of "loose" coupling of respiration and phosphorylation.

Introduction

Catecholamines such as dopamine (DA), norepinephrine (NE), and epinephrine (EPI) are important neurotransmitters and hormones with a variety of essential functions in the body. Besides other functions, catecholamines regulate cardiac action by local neuroendocrine secretion [1].

Already in the 1930's it has been hypothesized that catecholamines might be important regulators of the heart rate even before the inception of nerval control [2]. In embryonic chick hearts, catecholamines (NE and EPI) were detected as early as day 3, and L-DOPA and DA were already present from day 1 on [3]. Intrinsic cardiac adrenergic cells were later identified in rat [4], mouse [5], and human [6] heart tissue and primary cardiomyocyte isolates.

Currently, in cardiology, to develop adequate methods for the treatment of cardiovascular diseases, it is highly relevant to establish the mechanisms of disturbances in adaptation processes observed in case of sympathetic hyperactivation. As many studies show, myocardial ischemia is accompanied by a significant increase in adrenaline content in the heart. By its nature, sympathetic hyperactivation is accompanied by increased formation of products of enzymatic and non-enzymatic metabolism of adrenaline and its analogs, which can change the use of ATP by cells, change the activity of mitochondrial and cytosolic enzymes, contributing to disruption of bioenergetic adaptation, antioxidant defense system and levels of intercellular modulators such as AMP and adenosine.

The control of metabolism and physiological activity of all body cells is carried out by means of a complexly organized specific multifunctional hormonal ensemble [7], [8]. In this regard, for a more meaningful understanding and use of catecholamines in clinical practice, the work set a goal: to study the features of adrenaline and its analogs in the regulation of the activity of mitochondrial and cytoplasmic enzymes of cardiomyocytes. A significant part of the data in this direction has been published by us earlier [9].

Materials and Methods

Study design and procedures

1. To comparatively study the peculiarities of DA, noradrenaline, adrenaline, isadrine, adrenoxyl, and adrenochrome effect on the activity of mitochondrial processes of cardiomyocytes.
2. To determine the functional specificity of adrenaline in the regulation of cytoplasmic enzymes activity of cardiomyocytes and blood.

The experiment was carried out on 65 3-month-old male Wistar rats weighing 60–190 g. The rats were purchased from the Kazakh Scientific Center for Quarantine and Zoonotic Diseases, Almaty, Kazakhstan. The animals were kept in the vivarium of the research laboratory of the Semey Medical University Nonprofit Joint Stock Company with free access to the basic diet and tap water and fed a balanced diet specially designed for laboratory animals, containing all the necessary ingredients. The experiment was reviewed and approved by the Ethical Committee of the State Medical University of Semey, Kazakhstan (№2 protocol 21.12.2016), in accordance with the Directive of the European Parliament on the protection of animals used for scientific purposes. Conducting experiments on animals and withdrawal of animals from the experiment were conducted in accordance with the "Rules for conducting preclinical, medical and biological experiments and clinical trials in the Republic of Kazakhstan." Ministry of Health of the Republic of Kazakhstan from July 25, 2007 №442.

To study the effects of catecholamines and their metabolites in the regulation of mitochondrial and cytoplasmic enzymes activity of cardiomyocytes, experimental rats were put to death by intraperitoneal injection of 10% ketamine in an amount of 0.25 mg/100 g. After killing, blood sampling was performed and the heart of experimental rats was taken. The hearts of the animals were washed with saline and homogenized with a Teflon pestle in a medium containing 0.25 M sucrose. Tissue homogenates were filtered through 2 layers of gauze and centrifuged for 10 min (0°–2°C) at 800 g to remove cell debris and nuclear fraction. The supernatant after centrifugation was used for the study. Mitochondria were isolated from cardiac homogenates by differential centrifugation at 8500g for 15 min.

Activity of mitochondrial succinate dehydrogenase (SDH) was determined in incubation medium containing 0.05 M phosphate buffer solution, pH = 7.4, 10 μM 0.05 M $MgCl_2$ solution, KCL 2.5 μM 1.0 M solution, 50 μM succinate and 0.5 ml of 1% 2.3.5.triphenyltetrazolium chloride solution.

Activity of cytochrome c oxidase (CCO) was determined by the monometric method in a Warburg apparatus in a medium containing 1.4 ml of 0.05 M borate buffer, 0.2 ml of 0.2% dimethyl paraphenylenediamine solution. The activity was expressed in mcats of oxygen per mg of protein.

Activity of mitochondrial dinitrophenol (DNP)-activated ATPase was determined by increasing of inorganic phosphorus in medium containing 30 μm Tris-buffer pH = 7.5, 2 μM $MgCl_2$, 50 μM α-DNP, 0.1 ml 0.2% ATP solution.

The activity of adenosine deaminase (AD), AMP deaminase (AMPD) was determined according to the method of S.O. Tapbergenov [10] and expressed as nmol ammonia per mg protein per minute in tissues or nmol/ml in blood. The activity of 5'-nucleotidase (5'H) was estimated from the rate of hydrolysis of AMP to adenosine and phosphoric acid and expressed as μmol H_3PO_4 per mg of protein per minute. The amount of protein was determined by the commonly used Lowry's method.

Activity of glutathione reductase (GR) and glutathione peroxidase (GPO) was determined according to the method of Vlasova *et al*. [11], catalase activity according to the method of Korolyuk *et al*. Determination of MDA amount was performed according to the method of Uchiyama and Mihara [12], [13], diene conjugates (DC) by the method of Gavrilov *et al*. [14]. Protein amount was determined by the standard Lowry's method.

Statistical analysis

The results of the study were processed using Student's t-criterion. Mean data ± standard deviation (X ± SD) are used for quantitative data presentation in case of distribution tended to be symmetrical and median with 25^{th} and 75^{th} quartile were used in case of skewed distribution. Mann-Whitney test was used to analyze nonparametric data. Differences were considered significant at $p < 0.05$.

Ethical standards

The experiment was approved by the ethical committee of the State Medical University of Semey in accordance with the Directive of the European Parliament on the protection of animals used for scientific purposes (№2 protocol 21.12.2016).

Results

It is known that neurogenic stress caused by electric stimulation of the aortic arch [15] and accompanied by the release of endogenous catecholamines causes significant changes in the activity of cardiac mitochondrial respiratory chain enzymes (Table 1).

Table 1: The influence of neurogenic stress (electric stimulation of aortic arch) on activity of cardiac mitochondrial enzymes (n = 12)

Series	SDH	COX	Mg-ATPase	AMP deaminase
Control	29.04 ± 1.84	17.78 ± 0.72	46.29 ± 4.07	73.20 ± 5.52
Neurogenic stress	54.61 ± 5.90*	31.73 ± 1.85*	59.70 ± 1.51*	148.73 ± 15.25*

*p < 0.05 in comparison with control.

Due to the main direction in the function of catecholamines to ensure the formation of the organism's stress response, a comparative analysis of the effects of various catecholamines and their metabolites on the main mitochondrial and cytosolic enzymes of cardiomyocytes was performed [16].

Effect of catecholamines and their metabolites on the main mitochondrial enzymes

SDH activity

Amber acid is produced in human and animal cells and is responsible for energy metabolism. A healthy body synthesizes succinate in sufficient quantities. However, as a result of unfavorable factors, in particular under intensive physical strain, stress, there appears tension in metabolic processes, the expenditure of succinic acid increases. One of the most resistant to damage is the succinic acid oxidation system, which, for example, in myocardial infarction is damaged to a lesser extent and restored more completely than the system of NAD-dependent dehydrogenases [17]. Oxidation of succinic acid is the main energy-generating process that replenishes the damage of macroergic stores in stress-induced myocardial lesions. Our studies found that DA injected into animals at a dose of 1.5 mg/100 g 15 min before cardiac DA study activates this enzyme in the heart mitochondria. Noradrenaline injected in animals at a dose of 0.5 mg/100 g and adrenaline at a dose of 0.015 mg/100 g also cause activation of SDH in the heart (Table 2). It can be assumed that the effects of the major catecholamines on SDH are to some extent related to adrenoreception. Using isadrine as a specific beta-adrenagonist, a similar effect to that of DA and NE has been established for SDH activation in cardiac mitochondria.

Studies of the effect of catecholamine quinoid oxidation products on mitochondrial ADH showed that adrenoxyl (adrenochrome monosemicarbozone) at a dose of 0.2 mg/100 g injected 30 min before the study, like DA and noradrenaline, causes activation of ADH in the heart Similar effect on ADH also has adrenochrome itself (Table 2). DA, adrenochrome, then adrenoxyl, and isadrine have the greatest activating effect on cardiac mitochondrial ADH.

Table 2: Effect of catecholamines on cardiac mitochondrial enzyme activity (n = 12)

Series	SDH	COX	Mg-ATPase	AMP deaminase
Control	24.84 ± 0.59	16.24 ± 0.72	59.60 ± 3.96	86.59 ± 2.28
Dopamine (1.5 mg/100 g)	48.32 ± 4.42*	19.83 ± 1.41*	27.19 ± 1.51*	78.40 ± 2.72*
Norepinephrine (0.5 mg/100 g)	30.34 ± 2.01*	16.59 ± 1.80	38.83 ± 4.17 *	104.98 ± 1.31*
Adrenaline (0.15 mg/100 g)	29.40 ± 2.17*	27.62 ± 1.36*	40.51 ± 2.38*	-
Izadrin (0.1 mg/100 g)	34.04 ± 2.04*	19.92 ± 0.37*	25.88 ± 2.12*	39.65 ± 7.88*
Adrenoxyl (0.2 mg/100 g)	35.07 ± 3.01*	20.16 ± 1.26*	45.45 ± 3.00*	71.90 ± 3.96*
Adrenochrome (0.2 mg/100 g)	43.06 ± 3.00*	28.76 ± 4.64*	47.79 ± 2.81*	86.10 ± 12.66

*p < 0.05 compared to control.

Cytochrome c-oxidase activity

Cytochrome c-oxidase (CP 1.9.3.1) catalyzes electron transfer from cytochrome C to oxygen, causing activation of the latter. Cytochrome c-oxidase (COX) is localized in the inner membrane of mitochondria [18]. Our studies have shown that DA increases the activity of CCO in cardiac mitochondria (Table 2). Since DA can be converted to NE under the influence of DA-beta-hydroxylase, we could assume a similar effect of NE. However, NE does not cause an increase in cardiac mitochondrial activity. At the same time, adrenaline as an agonist of alpha- and beta-adrenoreceptors, the stabilized product of adrenaline quinoid oxidation adrenoxyl, and adrenochrome activate CHO in the heart (Table 2). Adrenaline has the greatest activating effect on cardiac mitochondrial COX.

Activity of mitochondrial ATPase

Mitochondrial ATPase (KF 3.6.1.3), unlike plasma and synaptic membrane ATPase, is activated by magnesium ions, is sensitive to DNP, is not only a factor controlling ATP synthesis but also a generator of membrane potential energy [19]. As shown by our studies on the effect of catecholamines on Mg-activated, DNP-stimulated mitochondrial ATPase, DA, noradrenaline, and adrenaline reduce the activity of ATPase in cardiac mitochondria (Table 2).

Injection of the beta-adrenoceptor agonist izadrine (0.1 mg/100 g) 15 min before the study causes similar changes in the activity of ATPase in the heart mitochondria as DA and NE. Administration of adrenoxyl (0.2 mg/100 g) to animals 30 min before the study causes the same changes in mitochondrial ATPase activity as DA and NE. The quinoid oxidation product of adrenaline, adrenochrome, 2 h after its administration also decreases mitochondrial ATPase activity in cardiac mitochondria. Adrenochrome, adrenoxyl, then adrenaline, and noradrenaline have the greatest activating effect on cardiac mitochondrial ATPase. Isadrine and DA decrease cardiac AMPase activity.

AMPD activity

Our studies have shown that DA and yzadrine decrease cardiac AMPD activity in mitochondria (Table 2). In contrast to DA, noradrenaline increases AMPD activity in cardiac mitochondria. Administration of adrenoxyl, a stabilized quinoid oxidation product of adrenaline, 30 min before the study leads to a decrease of AMPD activity in cardiac mitochondria. In general,

studies have shown that neither alpha- nor beta-adrenoreceptor apparatus is used for catecholamine control of AMPD activity.

An activating effect on cardiac mitochondrial AMPD was found only in NE. To a greater extent, cardiac mitochondrial AMPD activity decreases under the influence of isadrine. Then adrenoxyl and DA.

Oxidative phosphorylation in cardiac mitochondria

Administration of adrenaline to animals at a dose of 0.1 mg/100 g 60 min before the study, there was some activation of respiration and decrease of P/O ratio in cardiac mitochondria (Table 3).

Table 3: Effect of adrenaline on oxidative phosphorylation in cardiac mitochondria (n = 12)

Group	ATP synthase (mcat P)	Succinatoxidase (mcat O_2)	Coefficient P/O
Control	2.46 ± 0.23	1.69 ± 0.07	1.68 ± 0.14
Adrenaline *in vivo* at a dose of 0.1 mg/100 g in 60 min	2.75 ± 0.48	2.25 ± 0.33*	1.27 ± 0.20*
Adrenaline *in vitro* (10 μg/1 ml of incubation medium. preincubation time 2 min)	2.23 ± 0.45	1.93 ± 0.29	1.1 ± 0.12*

*p < 0.05 compared to control.

A decrease in the intensity of the oxidative phosphorylation process in the heart by administration of adrenaline has also been shown by other researchers. Adrenaline administered to cardiac mitochondria reduces the level of P/O phosphorylation coefficient. The nonuniformity of the effects of catecholamines on oxidative phosphorylation processes suggests the possibility that their effects are superimposed on the quinoid metabolite and monoamine oxidase pathway of mediator hormones. This ability of catecholamines to alter the activity of respiratory chain enzymes determines their action in the regulation of tissue respiration and oxidative phosphorylation [20].

Accelerated degradation of AMP against the background of reduced ATPase activity by quinoid products and oxidation of succinate and other substrates stimulated by catecholamines and quinoid metabolites can lead mitochondria to a state of “loose” coupling of respiration and phosphorylation. However, the energy of the oxidized substrates is transformed into membrane electrochemical potential, primarily into thermal energy. At the same time, ATP accumulation is not disturbed, but it recedes into the background, which is the mechanism of the caloriogenic effect of catecholamines. In this case, the degree of oxidative phosphorylation (P/O Coefficient) decreases, but the intensity of succinate oxidation and mitochondrial respiration increases, which leads to the phenomenon of “oxygen leakage.”

Thus, analyzing our data on the effect of catecholamines and their metabolites on the activity of cardiac mitochondrial enzymes, we can consider that the metabolism of sympatho-adrenal system mediator hormones is a regulatory factor of mitochondrial processes of energy transformation in the cell.

Effect of adrenaline on cytosolic enzymes of cardiomyocytes and blood

Taking into account peculiarities about mitochondrial effects of catacholamines, *we set a goal to study* the state of cytosolic enzymes of cardiomyocytes and in blood plasma - enzymes of purine nucleotide metabolism. The enzymes of purine nucleotide metabolism include AMPD, AD, 5’H, antioxidant defense enzymes - catalase, GR and GPO, and levels of MDA and DC.

It was found that in serum adrenaline at a dose of 4 mg/kg administered to animals in 60 min of study (Table 4) caused activation of the enzymes of purine nucleotide metabolism AMPD, AD, 5’H and the enzyme of antioxidant protection HPO, increase in DA level as an integrated indicator of lipid peroxidation.

Table 4: Changes in the activity of purine nucleotide metabolism enzymes and antioxidant system in blood serum during administration of adrenaline

Study groups	N	Me	Interquartile range		Mann-Whitney criterion		
			Q1	Q3	U	Z	P
GR μmol NADPH/g/min							
Adrenaline	15	3.54	3.22	3.75	54	−0.45	0.34
Control	20	3.13	3.05	3.91			
GPO μmol oxidized glutathione/g min							
Adrenaline	15	570.09	540.91	590.3	28	−1.37	0.05
Control	20	469.08	432.39	482.9			
Catalase mol/g min							
Adrenaline	15	80.62	78.50	84.66	27	−2.58	0.43
Control	20	81.85	67.57	82.13			
MDA nmol/g							
Adrenaline	15	0.63	0.44	0.76	56	−0.93	0.35
Control	20	0.73	0.63	0.85			
DC ounce/mL							
Adrenaline	15	1.60	0.91	1.73	64	−0.46	0.05
Control	20	1.18	0.99	1.23			
AD μmol/mg min							
Adrenaline	15	1309.2	1287.2	1334.8	29	−1.74	0.05
Control	20	532.67	513.1	568.0			
AMPD μmol/mg min							
Adrenaline	15	558.29	542.2	575.4	37	−1.58	0.05
Control	20	419.83	411.8	425.0			
5’H μmol/mg min							
Adrenaline	15	0.07	0.00	0.08	27	−2.08	0.15
Control	20	0.06	0.01	0.07			
AD+AMPD/5’H							
Adrenaline	15	2.34	1.81	3.23	25	−2.68	0.01
Control	20	1.26	1.15	1.35			

Previously, we found that administration of adrenaline at a dose of 4 mg/kg for 60 min of study, accompanied by an increase in the total number of leukocytes, lymphocytes and a decrease in the number of T-suppressors. At the same time, adrenaline (Table 4) causes an increase in the “B” coefficient (AD/AMPD activity ratio), indicating the activation of the functional relationship between the cellular and humoral parts of immunity [7].

According to the results of the study in the heart (Table 5), administration of adrenaline to animals is accompanied by activation of the enzymes of purine nucleotide metabolism AD, AMPD, a decrease in 5’H activity and an increase in the ratio of activities of AD+AMPD/5’H enzymes. The increase in the ratio of the activities of the enzymes of purine nucleotide metabolism AD+AMPD/5’H is directed toward an increase in the deamination of adenosine and AMP with the formation of inosine and IMF. At the same time, due to the appearance of toxic forms of oxygen during oxidation of inosine to uric acid, there is an increase

Table 5: Changes in the activity of purine nucleotide metabolism enzymes and antioxidant system in the heart during adrenaline administration

Study groups	N	Me	Interquartile range		Mann-Whitney criterion		
			Q1	Q3	U	Z	P
GR μmol NADPH/g/min							
Adrenaline	15	35.31	30.52	36.75	43	−0.32	0.05
Control	20	32.13	30.05	32.91			
GPO μmol oxidized glutathione/g min							
Adrenaline	15	3.22	3.11	3.32	18	1.22	0.05
Control	20	2.59	2.39	2.93			
Catalase mol/g min							
Adrenaline	15	69.85	53.45	66.87	21	−2.58	0.05
Control	20	81.58	76.18	87.21			
MDA nmol/g							
Adrenaline	15	0.05	0.04	0.06	59	−0.85	0.05
Control	20	0.04	0.04	0.04			
DC ounce/mL							
Adrenaline	15	0.02	0.02	0.02	61	−0.38	0.25
Control	20	0.02	0.02	0.02			
AD μmol/mg min							
Adrenaline	15	0.26	0.18	0.43	28	−1.76	0.05
Control	20	0.19	0.05	0.23			
AMPDμmol/mg min							
Adrenaline	15	0.13	0.08	0.15	37	−1.58	0.05
Control	20	0.09	0.08	0.11			
5'H μmol/mg min							
Adrenaline	15	0.01	0.00	0.08	27	−2.08	0.05
Control	20	0.02	0.01	0.07			
AD+AMPD/5'H							
Adrenaline	15	39.02	37.1	3.23	24	−2.66	0.05
Control	20	14.26	13.5	14.35			

in MDA level and activation of antioxidant protection enzymes catalase and HPO.

Simultaneously, adrenaline administration is accompanied by activation of the enzymes of antioxidant protection of GPO and catalase, an increase in the level of lipid peroxidation products of MDA.

It is known that catabolism of adenosine and AMP in xanthine oxidase reaction is accompanied by the appearance of toxic oxygen forms, which leads to activation of antioxidant protection enzymes of HPO and catalase, which we found in the heart during adrenaline administration. These data indicate that cytosolic enzyme level shifts occur in the heart when adrenaline is injected, approximating the oxidative stress state.

Discussion

Our studies have shown that DA and adrenochrome have the greatest activating effect on cardiac mitochondrial ADH, followed by adrenoxyl and azadrine; adrenoxyl, adrenoxyl, then adrenaline and noradrenaline have the greatest activating effect on cardiac mitochondrial COX; adrenochrome, adrenoxyl, then adrenaline and noradrenamine have the greatest activating effect on cardiac mitochondrial ATP-ase. Isadrine and DA reduce cardiac AMPase activity [21].

An activating effect on cardiac mitochondrial AMPD was found only in NE. To a greater extent, cardiac mitochondrial AMPD activity is decreased under the influence of isadrine. Then adrenoxyl and DA [22].

The nonuniformity of the effects of catecholamines on mitochondrial enzymes and on oxidative phosphorylation in cardiomyocytes suggests the possibility of an overlap between their effects of quinoid and monoamine oxidase metabolites of adrenaline and noradrenaline. This ability of catecholamines and their metabolites to change the activity of respiratory chain enzymes determines their action in the regulation of the process of tissue respiration and oxidative phosphorylation [23].

Thus, against the background of reduced activity of ATP-ase by quinoid products and oxidation of succinate and other substrates stimulated by catecholamines and quinoid metabolites and accelerated destruction of AMP by deamination, lead mitochondria to the state of "loose" coupling of respiration and phosphorylation. The energy of oxidized substrates is transformed into membrane electrochemical potential and then into other forms of energy of living systems, and, first of all, into heat energy [24].

In blood, adrenaline at a dose of 4 mg/kg injected into animals over 60 min of the study causes activation of enzymes of purine nucleotide metabolism AMPD, AD, 5'H and antioxidant protection enzyme GPO, increase in DC level as an integrated indicator of lipid peroxidation. At the level of cytosolic enzymes in the heart, administration of adrenaline at a dose of 4 mg/kg 60 min before the study increased the activity of antioxidant protection enzymes GPO, catalase, and enzymes of purine nucleotide metabolism AD and AMPD and increased the level of lipid peroxidation indicators [25].

Conclusion

1. In cardiomyocytes adrenaline, by activating cytosolic enzymes of purine nucleotide metabolism AD and AMPD, increasing the level of lipid peroxidation (MDA and DA), increases the activity of antioxidant protection enzymes GPO and catalase, indicating that adrenaline leads the body to oxidative stress through adrenoreceptor mechanisms.
2. Sympatho-adrenal system mediator hormones adrenaline, DA, noradrenaline, isadrine, and catecholamine metabolites (adrenochrome and adrenoxyl), changing the activity of mitochondrial respiratory chain enzymes of cardiomyocytes, regulate tissue respiration processes, putting mitochondria into a "loose" coupled state of respiration and oxidative phosphorylation.

Authors Contributors

All authors have contributed to manuscript writing and review, and have approved the final version.

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