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Original Article

Resveratrol attenuates the development of nitro-oxidative stress in the liver of rats exposed to round-the-clock lighting and a high-carbohydrate-lipid diet

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Abstract

The aim of this study is to investigate the effects of resveratrol on nitro-oxidative stress in the liver of rats exposed to round-the-clock lighting (RCL) and kept on the high-carbohydrate-lipid diet (HCLD). The experiment was performed on 21 Wistar white male rats weighing 215–255 g. Control animals (Group 1) were fed standard chow and kept on a 12/12 hour light/dark cycle. Rats of the Group 2 were kept on HCLD (20% aqueous fructose solution for drinking and an appropriate ration) for 8 weeks and exposed to RCL, thus simulating MS development. The animals of the Group 3 received resveratrol in a daily dose of 5 mg/kg intragastrically starting on the 30th day of the experiment. We evaluated the production of the superoxide anion radical ($\bullet O_2^-$), total NO-synthase (NOS) activity, the activity of its constitutive and inducible NOS isoforms (cNOS/iNOS) and the concentration of peroxynitrites of alkali and alkali-earth metals. As a result, the administration of resveratrol under experimental conditions reduces the following nitro-oxidative stress indicators as the $\bullet O_2^-$ production by microsomal monooxygenases, cNOS, mitochondrial respiratory chain, and phagocytic NADPH oxidase, the NOS activity (total and its inducible isoenzyme), and peroxynitrites concentration under the growing activity of the cNOS and its coupling index. In conclusion, the administration of resveratrol under constant impact of adverse factors of the Western lifestyle (a diet rich in fats and carbohydrates, disruptions of circadian rhythm) is an effective means to restrict the production of reactive oxygen and nitrogen species in the liver tissues.

Keywords: resveratrol, metabolic syndrome, nitro-oxidative stress, reactive oxygen and nitrogen species, liver.

Introduction

Nowadays, considerable attention has been paid to the role of circadian system disruption in the pathogenesis of the different metabolic disorders implicated in such chronic diseases as type 2 diabetes mellitus and cardiovascular pathology. There is increasing evidence regarding circadian rhythm disturbances as one of the key components of metabolic syndrome (MS) and the number of related comorbidities, including liver diseases and, in particular, non-alcoholic steatohepatitis [1, 2]. In the liver, a number of nuclear receptors or transcriptional factors (REV-ERB, ROR, PPAR, ATF6, NF-κB and Nrf2) regulated by the circadian clock and reactive oxygen and nitrogen species (ROS/RNS) serve as direct links between nitro-oxidative stress and circadian metabolism [2, 3].

The mechanisms of metabolic disorders, systemic inflammatory response, arterial hypertension, endothelial dysfunction, and nitro-oxidative stress are

substantially associated with the development of hypomelatoninemia, which results from the infringement of the central circadian oscillator suprachiasmatic nucleus of the hypothalamus and a decrease in pineal melatonin production under altered light/dark cycle [4].

Recent reports have shown that diet and nutrients can modulate the fluctuations in melatonin [5]. The combined action of round-the-clock lighting (RCL) and prolonged keeping on the high-calorie carbohydrate-lipid diet (HCLD) in experiments on rats led to more pronounced metabolic disorders (hypomelatoninemia, hyperinsulinemia, dyslipoproteinemia, hypo-α-lipoproteinemia, hypertrialcylglycerolemia, and increased visceral fat) than under the separate actions of the factors mentioned above [6].

To some extent, the administration of melatonin under these conditions can only mitigate manifestations of metabolic disorders and signs of nitro-oxidative stress in skeletal muscles and the liver, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) does not change considerably [7]. Obviously, replenishing melatonin levels is not enough to correct metabolic disorders under these conditions.

In the experiment, the administration of ammonium pyrrolidine dithiocarbamate, an NF-κB inhibitor, considerably improves carbohydrate and lipid metabolism, inhibits the development of systemic inflammatory response [8] and reduces the ROS/RNS generation in tissues [9]. However, this specific NF-κB inhibitor demonstrates a number of adverse effects, and genotoxicity is among them [10]. There is no such disadvantage in natural herbal NF-κB inhibitors, such as bioflavonoids (*e.g.*, quercetin and epigallocatechin-3-gallate) and other polyphenols [11–14]. Natural phytoalexin resveratrol (3,4',5-trihydroxy-trans-stilbene) can also suppress NF-κB signaling pathways by reducing the sirtuin 1 (Sirt1) dependent acetylation of NF-κB subunit RelA/p65 [15]. Compared to quercetin, resveratrol has been shown to be a more effective means of correcting endothelial dysfunction and pro-inflammatory hypercytokinemy in patients with coronary artery disease [16, 17].

Protein deacetylation by Sirt1 is known as a leading mechanism of the pharmacological action of resveratrol. Studies have confirmed its capability to suppress signs of nitro-oxidative stress and systemic inflammatory response caused by tumor necrosis factor-α (TNF-α) [15]. Moreover, resveratrol can lower oxidative stress by activating the nuclear factor-E2-related factor-2 (Nrf2), antagonistic to NF-κB. Nrf2 serves as a regulator of numerous genes encoding antioxidant and phase II-detoxifying enzymes [18]. Among the other resveratrol targets, there are such Sirt1-dependent transcription factors as FOXO 1 and 3, STAT-3, p53, HEY2, and PPARγ [19].

The main clinical and experimental studies give grounds to suggest that resveratrol can impact MS signs via multiple mechanisms, attenuating effects on oxidative stress, inflammation, and adipokines [20]. Resveratrol has been found to be a highly effective means in the therapy of non-alcoholic steatohepatitis, but the mechanisms of its action have not been fully elucidated yet [21].

This study aims to investigate the effects of resveratrol on nitro-oxidative stress in the liver of rats exposed to round-the-clock lighting and kept on a diet rich in carbohydrates and lipids.

Material and methods

Animals data and ethics statement

The experiment was performed on 21 Wistar white male rats weighing 215–255 g kept under standard vivarium conditions (air temperature: +22±2°C, air humidity: 30–60%). Control animals (Group 1, n=7) were fed standard chow and kept on a 12/12 hour light/dark cycle. Rats of Group 2 (n=7) were kept on an HCLD for 8 weeks and exposed to RCL to simulate MS development. The animals of Group 3 (n=7) received resveratrol in a daily dose of 5 mg/kg [22] intragastrically via gavage starting on the 30th day of the experiment. Resveratrol was administered together with carbohydrates (20% aqueous solution of fructose), which increased the solubility and bioavailability of stilbenoids [23]. Instead of receiving resveratrol, rats of the first two groups were given 1 ml of 20% fructose solution intragastrically as "placebo".

The experiment complied with the requirements of the European Convention for the protection of vertebrate animals used for research and other scientific purposes (Strasbourg, 1986) and the European Union Directive 2010/10/63 EU on animal experiments. The Commission on Bioethics of Petro Mohyla Black Sea National University did not find any violations of moral and ethical norms during this study. We removed animals from the experiment under ether anesthesia by decapitation. The liver was removed and rinsed with 0.9% sodium chloride solution. Then it was homogenized with 0.1 M Tris buffer (pH 7.4) in cold to obtain 10% tissue homogenate.

The experimental model of metabolic syndrome

To simulate MS, the rats were kept on HCLD for 2 months: the animals received a 20% aqueous fructose solution for drinking and a diet containing refined wheat flour (45%), skimmed milk powder (20%), starch (10%), table margarine with fat content 72–82% (20%) peroxidized sunflower oil (4%), sodium chloride (1%). Since the 30th day of the experiment, the rats were exposed to RCL with an intensity of 1500 lx over the next 30 days [24].

Biochemical assays

We evaluated the production of the superoxide anion radical ($\bullet O_2^-$) using a spectrophotometer Ulab 101 (China) by estimating the concentration of diformazan, formed in the reaction of $\bullet O_2^-$ with nitroblue tetrazolium (IUPAC name: 2,2'-bis(4-Nitrophenyl)-5,5'-diphenyl-3,3'-(3,3'-dimethoxy-4,4'-diphenylene) ditetrazolium chloride, "Sigma Aldrich") [25]. In order to assess the influence of the electron transport chains (ETCs) of cellular organelles (mitochondria, endoplasmic reticulum) and tissue phagocytes, specific reaction conditions described in [25] were used. We applied β-nicotinamide adenine dinucleotide reduced disodium salt hydrate (NADH, ≥97%, "Sigma Aldrich") as an inductor of the $\bullet O_2^-$ generation by the mitochondrial ETC; β-nicotinamide adenine dinucleotide 2'-phosphate reduced tetrasodium salt hydrate (NADPH, 97%, "Sigma Aldrich") to evaluate $\bullet O_2^-$ production by endoplasmic reticulum and NO-synthases (NOS, EC 1.14.13.39), and *Salmonella typhi* lipopolysaccharide (Pyrogenalum, "Medgamal", Russia) was used to assess $\bullet O_2^-$ generation by phagocytic NADPH oxidase (EC 1.6.3.1).

Total NOS activity was evaluated by an increase in NO_2^- concentration following the incubation of homogenated tissue samples for 30 min in the incubation solution (2.5 ml 0.1 M Tris buffer, 0.3 ml 320 mM L-arginine ("Sigma Aldrich") water solution, and 0.1 ml 1 mM NADPH solution as described in [26]. In addition to this method, to determine the activity of constitutive NOS isoforms (cNOS), we added 0.1 ml of 1% (weight/volume) aminoguanidine hydrochloride solution (98%, "Sigma Aldrich") to the first aliquot (0.2 ml of 10% homogenate and the aforementioned incubation solution) as described in [27]. Inducible NOS isoform (iNOS) activity was evaluated by subtracting the cNOS activity from the total NOS activity. Protein concentration was determined by the Biurette method.

The cNOS coupling index was calculated as the ratio between the cNOS activity and the $\bullet O_2^-$ generation rate by the NADPH-dependent ETCs [28].

The concentration of peroxynitrites of alkali and alkali-earth metals was measured by using its reaction with potassium iodide (≥99.0%, "Sigma Aldrich") under pH 7.0 in 0.2 M phosphate buffer with the same pH [26].

Statistical analysis

The findings obtained were statistically processed by applying the Microsoft Office Excel software package with the Real Statistics 2019 extension using the Shapiro-Wilk test to check the normality of variances. Basic statistics, such as arithmetic mean (M) and standard error of the mean (m), were calculated. As far as all samples had normal distribution, we applied the ANOVA parametric analysis of variance, followed by a pairwise comparison of groups by Student's t-test for independent samples and Tukey's HSD (Honestly Significant Difference) analysis. The Dunn – Šidák correction was used to avoid the phenomenon of multiple comparisons. The differences between arithmetic means were considered significant at $p<0.05$.

Table 1: The effect of resveratrol on the superoxide anion radical production in the liver of rats exposed to round-the-clock lighting and kept on a high-carbohydrate-lipid diet.

Parameters	Groups		
	Control (Group 1), n=7	Group 2 (HCLD+RCL), n=7	Group 3 (HCLD+RCL+ Resveratrol), n=7
Superoxide anion radical generation, nmol/s per g of tissue			
From microsomal ETC and NOS	22.05±0.66	42.57±0.81 *	24.81±0.70 *, **
From mitochondrial ETC	26.98±0.74	50.95±0.92 *	32.53±1.25 *, **
From phagocytic NADPH oxidase	1.37±0.07	2.74±0.06 *	1.81±0.07 *, **

Note: * – P<0.05 compared to findings in the control group; ** – P<0.05 compared to findings in the rats of Group 2. ETC – electron transport chain; NOS – NO-synthase; NADPH – reduced nicotinamide adenine dinucleotide phosphate.

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Results

ROS formation in the liver tissue of rats significantly elevated under their RCL exposure with an intensity of 1500 lx and keeping on HCLD. The $\cdot O_2^-$ generation (Table 1) by NADPH-dependent microsomal monooxygenases and NOS exceeded the respective parameters in Group 1 by 1.93 times; its production by mitochondria grew 1.89 times, and by phagocytic NADPH oxidase rose twofold.

The administration of resveratrol under the experiment conditions led to a considerable decrease in NADPH- and NADH-induced $\cdot O_2^-$ generation in the liver tissues by 41.7% and 36.2%, respectively, compared to Group 2. Lipopolysaccharide-induced $\cdot O_2^-$ production by phagocytes fell by 33.9%.

RCL exposure elevates the total NOS activity in the liver tissues of the rats kept under HCLD by 2.35 times and the iNOS activity by 2.57 times compared with Group 1 (Table 2). The cNOS activity, on the contrary, goes down 1.7 times. cNOS coupling index under the experiment subsided 1.83 times. The concentration of peroxynitrite of alkaline and alkaline earth metal peroxynitrites in liver tissues elevated 1.68 times.

Resveratrol administered during exposing rats to RCL and keeping them on HCLD reduced total NOS activity in the liver tissues by 44.4%, iNOS activity – by 47.4% compared with the respective values in Group 2. cNOS activity under these conditions was thrice as much.

The administration of this polyphenol under the conditions of RCL and HCLD lowered total NOS activity in liver tissues by 44.4% and iNOS activity by 47.4% compared to the corresponding Group 2 values.

The use of resveratrol substantially improved the cNOS coupling, as their coupling index increased under the resveratrol administration 4.83 times compared with the results in Group 2. The concentration of peroxynitrites of alkali and alkali-earth metals concentration under applying resveratrol in the experiment fell by 34.3% compared to the respective values.

Discussion

The results confirmed that RCL and HCLD, which included a 20% aqueous fructose solution and special ration, cause a significant increase in ROS generation. NF-κB nuclear translocation is an important mechanism of the initiation of oxidative stress: it results in the expression of genes responsible for coding biosynthesis of pro-inflammatory and pro-oxidant proteins (cytokines, gp91 phox, iNOS, Cyp7b, Cyp2E1, Cyp2C11 monooxygenases, xanthine oxidoreductase, cyclooxygenase 2, and 5-lipoxygenase) [29]. On the one hand, this is facilitated by HCLD components such as non-esterified fatty acids that can induce NF-κB signaling through sequential activation of Toll-like receptors 2 and 4, as well as IκB kinase complex [30]. The presence of fructose in the diet accelerates this process by the increased expression of fatty acid synthase genes, acyl-coenzyme A carboxylase, sterol coenzyme A desaturase-1, as well as by decreased activity of peroxisome proliferator-activated receptor γ coactivator 1α/β (PGC-1α/β) [31]. On the other hand, NF-κB activation is possible due to RCL-induced changes in the circadian oscillator gene expression [2].

Table 2: The effect of resveratrol on the reactive nitrogen species formation in the liver of rats under round-the-clock lighting and a high-carbohydrate-lipid diet.

Parameters	Groups		
	Control (Group 1), n=7	Group 2 (HCLD+RCL), n=7	Group 3 (HCLD+RCL+ resveratrol), n=7
NOS activity, μmol (NO_2^-)/min per g of protein			
Total	8.42±0.88	19.84±1.28 *	11.03±1.80 **
cNOS	0.81±0.03	0.24±0.02 *	0.72±0.02 *, **
iNOS	7.61±0.87	19.6±1.28 *	10.31±1.80 **
cNOS coupling index	0.037±0.002	0.006±0.001 *	0.029±0.001 *, **
Peroxynitrites of alkali and alkali-earth metals concentration, μmol/g of tissue	1.42±0.05	2.39±0.08 *	1.57±0.06 **

Note: * – P<0.05 compared to findings in the control group; ** – P<0.05 compared to findings in the rats of Group 2. NOS – NO-synthase; cNOS – constitutive NOS isoforms; iNOS – inducible NOS isoform.

Our previous studies have demonstrated that $\cdot O_2^-$ generation by microsomal and mitochondrial ETCs and phagocytic NADPH oxidase considerably grows under hypomelatoninemia and can be corrected by using an inhibitor of NF-κB activation – 4-methyl-N1-(3-phenylpropyl)-1,2-benzenediamine [32]. According to our data, the combined effect of RCL and HCLD reduces the melatonin concentration in the blood serum by 55.6% compared with the results obtained in the animals exposed to the RCL only [6]. This creates the conditions for reducing the direct antioxidant activity of melatonin as $\cdot O_2^-$ and •OH scavengers [33].

The administration of resveratrol, capable of inhibiting NF-κB, has shown the capability to reduce $\cdot O_2^-$ generation in the liver tissues considerably. As mentioned above, microsomal monooxygenases and phagocytic NADPH oxidase synthesis depend on the NF-κB activation. Therefore, NF-κB suppression with resveratrol regularly restrains ROS formation. Moreover, resveratrol has powerful antioxidant properties and the capability to reduce mitochondrial ROS generation by promoting Sirt3 enrichment within the mitochondria and subsequent upregulation of forkhead box O3A (FoxO3A)-mediated mitochondria-encoded gene expression of ATP synthase 6, cytochrome *c* oxidase pseudogene 1, cytochrome *b*, NADH dehydrogenase 2 and 5 [34].

Our study has demonstrated that RCL exposure elevates the total NOS and iNOS activity in the liver tissues of the rats kept under HCLD. It is known that iNOS gene expression is regulated by NF-κB [29], and this process is controlled by melatonin [35]. Therefore, under RCL-induced hypomelatoninemia, the iNOS level and its activity naturally increase.

We have found out that the cNOS coupling index subsiding under the experiment confirms the role of NADPH-dependent ETCs used by NOS in the generation of $\cdot O_2^-$ additional amount. Uncoupled cNOS generates $\cdot O_2^-$ instead of nitric oxide (NO), which usually occurs due to the lack of the critical for enzyme functioning substrates (L-arginine, O2) and tetrahydrobiopterin [36].

Simultaneous excessive formation of $\cdot O_2^-$ and NO is accompanied by an increase in the concentration of peroxynitrite, a very dangerous RNS, as indicated by a significant growth in the concentration of alkaline and alkaline earth metal peroxynitrites in the liver tissues.

The use of resveratrol substantially improves the cNOS coupling. The previous investigation has shown that resveratrol prevents $\cdot O_2^-$ production from uncoupled endothelial NOS by up-regulating the tetrahydrobiopterin-synthesizing enzyme GTP cyclohydrolase I [37].

The consequence of restraining $\cdot O_2^-$ and NO generation is a decrease in the concentration of peroxynitrites. This mitigates the risk of RNS-related cytotoxicity and enhances the functioning of NO as a signaling molecule [38].

In addition to the effects described above, resveratrol can restrict the ROS/RNS level in tissues as a direct scavenger of a number of free radicals. However, this action of resveratrol is relatively negligible [37]. The antioxidant properties of resveratrol *in vivo* are more likely to be attributable to its effect as a gene regulator. Moreover, resveratrol increases the expression of various antioxidant enzymes. Some of the gene-regulating effects of resveratrol are mediated not only by Sirt1 but Nrf2 as well [18] that regulates the expression of a battery of genes, which can coordinate a protective response against a variety of oxidative stressors, in particular, genes of glutathione peroxidase 2, glutathione S-transferases, glutathione reductase 1, thioredoxin and sulfiredoxin [39].

The capability of resveratrol to restrict nitro-oxidative stress in the liver tissue under the experimental conditions provides grounds for the further investigation of resveratrol as a safe means in the therapy and prevention of liver diseases that may be caused by the impact of adverse factors of Western lifestyle (a diet rich in fats and carbohydrates, disruptions of circadian rhythm).

Conclusions

Thus, the administration of resveratrol under experimental metabolic syndrome, modeled by carbohydrate-lipid diet and round-the-clock lighting, reduces such nitro-oxidative stress indicators as the $\cdot O_2^-$ production in the liver tissues by microsomal monooxygenases, cNOS, mitochondrial respiratory chain and phagocytic NADPH oxidase, the activity of NO-synthase (total and its inducible isoenzyme) and peroxynitrites concentration under the growing activity of the cNOS and its coupling index that indicates the restoration of the coupling state of this isoenzyme. Thus, the administration of resveratrol under the constant impact of adverse factors of the Western lifestyle (a diet rich in fats and carbohydrates, disruptions of circadian rhythm) is an effective means to restrict the production of reactive oxygen and nitrogen species in the liver tissues.

Conflict of interest

The authors declare no conflict of interest.

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