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How Does Resveratrol Change Some Metabolic and Circulatory Parameters? A Preliminary Study*

Zmiany niektórych wskaźników krążenia i metabolicznych wywołane przez resveratrol – badanie wstępne

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Abstract

Objectives. Resveratrol is a natural polyphenol present in red wine and various foods. The aim of this study was to investigate its effects on body weight, several biochemical parameters, blood pressure, and heart rate in rats.
Material and Methods. In this preliminary study, rats were divided into two equal groups according to body weight (n = 20 each) to investigate the effects of resveratrol on two different weight groups, one relatively higher than the other. The first group constituted 10- to 12-week-old male Sprague-Dawley rats with a mean body weight of 235 g and the second rats weighing approximately 284 g. Both groups were divided into control (n = 10) and experimental (n = 10) groups. In the two experimental groups, resveratrol was administered (20 mg/kg) in drinking water for 24 weeks. After one week of training, systolic arterial blood pressure and heart rate were recorded in all the groups. Changes due to resveratrol administration in body weight and blood glucose, total cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and uric acid (UA) levels were compared with the controls.
Results. There were statistically significant decreases in weight gain, total cholesterol, and blood pressure in both experimental groups. In the lighter group, ALT level ($p = 0.003$) and in the heavier ALP ($p = 0.049$) and UA levels ($p = 0.030$) were decreased slightly compared with the controls.
Conclusions. The results suggest that resveratrol ameliorated total cholesterol levels and decreased body weights with subsequent changes in systolic blood pressure while not leading to any deterioration in biochemical parameters (**Adv Clin Exp Med 2009, 18, 4, 323–328**).

Key words: resveratrol, cholesterol, blood pressure, heart rate, body weight.

Streszczenie

Cel pracy. Resveratrol jest naturalnym polifenolem obecnym w czerwonym winie i produktach spożywczych. Celem pracy była ocena jego wpływu na masę ciała, wskaźniki biochemiczne, ciśnienie krwi i tętno u szczurów.
Materiał i metody. We wstępnym badaniu szczury podzielono na 2 grupy odpowiadające pod względem masy ciała (n = 20), aby ocenić wpływ resveratrolu na 2 różne grupy mas, jedna istotnie większa od drugiej. Do pierwszej grupy włączono 10–12-tygodniowe szczury Sprague-Dawley ze średnią masą ciała 235 g, a do drugiej szczury ważące średnio 284 g. Obie grupy podzielono na kontrolną (n = 10) i badaną (n = 10). W obu grupach badanych resveratrol (20 mg/kg) podawano przez 24 tygodnie w wodzie pitnej. Po tygodniu treningu zmierzono skurczowe ciśnienie krwi i tętno we wszystkich grupach. Zmiany wywołane podaniem resveratrolu masy ciała, glukozy we krwi, całkowitego cholesterolu, aminotransferazy asparaginianowej AST, aminotransferazy alaninowej ALT, fosfatazy alkalicznej ALP, gamma-glutamylotransferazy GGT, kwasu moczowego porównano z grupą kontrolną.
Wyniki. Zanotowano istotnie statystycznie zmniejszenie masy ciała, całkowitego cholesterolu i ciśnienia krwi w obu grupach badanych. W grupie z mniejszą masą ciała stężenie ALT (p = 0,003), a w grupie z większą masą ALP (p = 0,049) i kwas moczowy (p = 0,30) były mniejsze w porównaniu z grupą kontrolną.
Wnioski. Wyniki sugerują, że resveratrol poprawił stężenie całkowitego cholesterolu i zmniejszył masę ciała wraz z następującymi zmianami skurczowego ciśnienia krwi, ale nie doprowadził do pogorszenia wskaźników biochemicznych (**Adv Clin Exp Med 2009, 18, 4, 323–328**).

Słowa kluczowe: resveratrol, cholesterol, ciśnienie krwi, tętno, masa ciała.

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Resveratrol (3,4,5-trihydroxystilbene) belongs to a class of polyphenolic compounds called stilbenes [1]. Some types of plants produce resveratrol and other stilbenes in response to stress, injury, fungal infection, and ultraviolet (UV) radiation [2]. Significant reductions in cardiovascular disease risk have been associated with moderate consumption of red wine [3, 4]. This "French Paradox", i.e. the observation that mortality from coronary heart disease is relatively low in France despite relatively high levels of dietary saturated fat and cigarette smoking, led to the idea that the regular consumption of red wine might provide additional protection from cardiovascular disease [5, 6].

Resveratrol has antioxidant and anti-aging effects on obese laboratory mice. High supplemental doses of resveratrol prevented nearly all negative health changes caused by eating high-calorie diets [7]. Reports on the potential of resveratrol to inhibit the development of cancer and extend lifespan in cell culture and animal models have continued to generate scientific interest [8, 9]. The results of some animal studies suggest that oral doses of resveratrol could decrease the risk of cardiovascular diseases [10, 11]. Atherosclerosis is now recognized as an inflammatory disease, and several measures of inflammation are associated with increased risk of myocardial infarction [12]. Resveratrol has been found to inhibit the activity of several inflammatory enzymes *in vitro* [13–15]. In some studies it was shown that polyphenolics may increase the metabolic rate and may also increase fat oxidation, implicating their potential use in anti-obesity treatment. However, the mechanisms by which red wine phenolics benefit the cardiovascular system in humans remain unclear [16].

The aim of this study was to determine the effects of resveratrol in rats on body weight, biochemical parameters, blood pressure, and heart rate in two different body-weight groups. This study showing the effects of resveratrol in a broad spectrum may provide a useful point of view during the treatment of cardiovascular and cerebrovascular disease, diabetes, and obesity.

Material and Methods

In this preliminary study, rats were divided into two equal groups according to body weight (n = 20 each). The first group constituted 10- to 12-week-old Sprague-Dawley rats with a mean body weight of 235 g and the second group rats weighing approximately 284 g. The two groups were divided into control (n = 10) and experimental (n = 10) groups. In the experimental rats of both groups, resveratrol was administered (20 mg/kg) in drinking water for 24 weeks. After a one-week training period, systolic arterial blood pressures and heart rates were recorded in the controls and experimental groups. Changes due to resveratrol administration on body weight and blood glucose, total cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and uric acid (UA) levels were also evaluated compared with the controls.

During the surgical procedures, combinations of ketamine (80 mg/kg) and xylazine (8 mg/kg) i.p. were used to produce anesthesia in the rats lasting 30 minutes. Blood samples were collected for a variety of biochemical analyses into heparinized tubes. While withdrawing the 2 ml of blood, the researchers obeyed the "Guide for the Care and Use of Laboratory Animals".

Comparisons of variables among the groups were analyzed by the Mann-Whitney *U* test or Kruskal Wallis ANOVA. When the *p* value from the Kruskal-Wallis test statistics was statistically significant, the multiple comparison test differed from the others [17]. A *p* value less than 0.05 was considered significant.

Results

The results showed that in the two different body-weight groups, weight gains were statistically significantly ($p = 0.017$, $p = 0.033$) lower in the experimental groups than in the controls. In the first group, with a mean body weight of 235 g, decreases in blood glucose, ALT, ALP, GGT, and UA were observed after resveratrol administration, by which the decrease in ALT level was statistically significant ($p = 0.003$). In the second group, with a mean body weight of 284 g, decreases in blood glucose, AST, ALT, ALP, GGT, and UA were detected after resveratrol administration, whereby the decreases in ALP and UA levels were found to be statistically significant ($p = 0.049$, $p = 0.03$, respectively). Also, in the resveratrol-administered groups, total cholesterol and systolic arterial blood pressure were found to be lower than in their own controls (first group: $p = 0.000$, $p = 0.006$, second group: $p = 0.034$, $p = 0.009$, respectively). In the first group the heart rates were also slightly lower. All data are expressed as mean ± *SD* and median (minimum-maximum) and shown in Tables 1–4.

Discussion

Resveratrol has been found to exert a number of potentially cardioprotective effects *in vitro*, includ-

Table 1. Body weights of the first group

Tabela 1. Masa ciała grupy pierwszej

	Controls (Grupa kontrolna)	Experimental group (Grupa badana)	*P*
First day – g (Dzień pierwszy – g)	237.9 ± 13.1 243.5 (208–250)	230.5 ± 17.4 239.5 (200–247)	0.289
Last day – g (Dzień ostatni – g)	313.5 ± 21.0 312.5 (280–340)	284.5 ± 17.6 285 (260–305)	0.017*

All data are expressed as mean ± *SD* and median (range).

Dane wyrażone jako średnia ± *SD* i mediana (zakres).

Table 2. Body weights of the second group

Tabela 2. Masa ciała grupy drugiej

	Controls (Grupa kontrolna)	Experimental group (Grupa badana)	*P*
First day – g (Dzień pierwszy – g)	287.2 ± 18.4 280.5 (270–323)	281.4 ± 21.0 273.5 (265–320)	0.150
Last day – g (Dzień ostatni – g)	344.2 ± 19.4 345 (310–370)	321.0 ± 22.8 325 (290–350)	0.033*

All data are expressed as mean ± *SD* and median (range).

Dane wyrażone jako średnia ± *SD* i mediana (zakres).

Table 3. The results of the first group (mean body weight: 235 g)

Tabela 3. Wyniki grupy pierwszej (średnia masa ciała: 235 g)

	Controls (Grupa kontrolna)	Experimental group (Grupa badana)	*P*
Blood glucose – mg/dl (Glukoza we krwi – mg/dl)	185.1 ± 20.3 179 (160–220)	181.4 ± 28.4 186.5 (117–212)	0.940
AST (IU/l)	133.6 ± 53.5 136 (71–232)	144.8 ± 31.0 139.5 (109–197)	0.545
ALT (IU/l)	85.1 ± 14.6 81 (70–120)	62.1 ± 13.1 61 (49–87)	0.003*
ALP (IU/l)	274.2 ± 83.9 291 (140–400)	203.8 ± 61.1 187 (116–300)	0.058
GGT (IU/l)	2.7 ± 0.9 2 (2–4)	2.0 ± 0.8 2 (1–3)	0.132
UA (mg/dl)	1.8 ± 0.5 1.75 (1.1–2.5)	1.7 ± 0.4 1.75 (1.1–2.5)	0.675
Total cholesterol – mg/dl (Cholesterol całkowity – mg/dl)	123.3 ± 22.0 124 (90–155)	69.4 ± 18.3 60 (54–99)	< 0.001*
Systolic arterial blood pressure – mm Hg (Skurczowe ciśnienie krwi – mm Hg)	156.4 ± 48.4 151 (96–2240)	113.4±16.6 115.5 (86–148)	0.034*
Heart rate – beats/min Tętno (uderzeń/min)	360.8 ± 40.8 356.5 (300–440)	342.1 ± 58.2 324.5 (241–431)	0.406

* Statistically significant.
All data are expressed as mean ± *SD* and median (range).
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), uric acid (UA).

* Istotne statystycznie.
Dane wyrażone jako średnia ± *SD* i mediana (zakres).
AST – aminotransferaza asparaginowa, ALT – aminotransferaza alaninowa, ALP – fosfataza alkaliczna, GGT – gamma-glutamylotransferaza, UA – kwas moczowy.

Table 4. The results of the second group (mean body weight: 284 g)

Tabela 4. Wyniki grupy drugiej (średnia masa ciała: 284 g)

	Controls (Grupa kontrolna)	Experimental group (Grupa badana)	*P*
Blood glucose – mg/dl (Glukoza we krwi – mg/dl)	231.8 ± 44.9 219 (189–300)	212.4 ± 29.5 216.5 (160–247)	0.596
AST (IU/l)	181.0 ± 43.7 170 (130–260)	153.9 ± 30.6 148 (118–220)	0.150
ALT (IU/l)	74.1 ± 16.6 71.5 (55–97)	63.4 ± 9.6 64 (49–76)	0.150
ALP (IU/l)	290.0 ± 100.1 290 (160–420)	199.3 ± 41.9 206 (137–280)	0.049*
GGT (IU/l)	1.4 ± 0.5 1 (1–2)	1.3 ± 0.5 1 (1–2)	0.648
UA (mg/dl)	1.7 ± 0.4 1.7 (1–2.1)	1.3 ± 0.2 1.25 (0.9–1.6)	0.030*
Total cholesterol – mg/dl (Cholesterol całkowity – mg/dl)	67.3 ± 9.7 65 (55–86)	54.7 ± 6.9 56 (43–65)	0.006*
Systolic arterial blood pressure – mm Hg (Skurczowe ciśnienie krwi – mm Hg)	161.7 ± 40.0 164.5 (106–233)	116.2 ± 22.9 110.5 (80–153)	0.009*
Heart rate – beats/min Tętno (uderzeń/min)	364.1 ± 24.5| 373 (317–389)	365.7 ± 53.0 366.5 (275–440)	0.910

* Statistically significant.
All data are expressed as mean ± *SD* and median (range).
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), uric acid (UA).

* Istotne statystycznie.
Dane wyrażone jako średnia ± *SD* i mediana (zakres).
AST – aminotransferaza asparaginowa, ALT – aminotransferaza alaninowa, ALP – fosfataza alkaliczna, GGT – gamma-glutamylotransferaza, UA – kwas moczowy.

ing the inhibition of platelet aggregation, promotion of vasodilation by enhancing NO production, and inhibition of inflammatory enzymes [18, 19].

In the present study the results showed that in both experimental groups there were significant decreases in body weight gain ($p = 0.017$, $p = 0.033$). Similar effects were observed by other investigators; absolute and relative body and ovary weights were decreased in resveratrol-administered female rats [20]. In another study, resveratrol administration (5 and 25 mg/kg) led to a decrease in body weight [21]. On the other hand, conflicting data were also reported; for example, resveratrol treatment had no significant effect on body weight, serum cholesterol, or messenger RNA levels for insulin-like growth factor I [22].

In the first group of the present study, only blood ALT levels ($p = 0.003$) and in the second group ALP ($p = 0.049$) were significantly decreased after resveratrol treatment. The highly specific effects of resveratrol on NF-κB leading to cytokine production inhibition may have a role in this condition. [23, 24]. In another study it was shown that resveratrol has an immunosuppressive property as well as a protective effect on hepatocytes [25]. In some reports, resveratrol also decreased liver laboratory parameters and liver damage, probably as a result of the diminished release of proinflammatory cytokines such as interleukin-1 (IL-1) [26, 27]. It was reported that any toxicologically significant changes in rat livers were detected even with a single dose of 2000 mg resveratrol per kilogram body weight [28]. In one study with resveratrol administration, mice also maintained normal liver functions and had relatively low levels of glucose [29]. In the present study, blood glucose levels were also slightly decreased and no adverse effects were seen.

The present study showed that resveratrol has a significant effect on total cholesterol because the levels were found to be decreased significantly in both experimental groups ($p < 0.0001$, $p = 0.006$). Resveratol was considered to have a cholesterol-decreasing effect. Some reports have shown that as an antioxidant, resveratrol effectively scavenges free radicals and other oxidants and inhibits LDL oxidation [30, 31, 32]. In one study it was suggested that red wine polyphenolics inhibit lipoprotein production and secretion from the liver and intestine, thereby decreasing circulating concen-

trations of LDL. It was demonstrated that red wine can also increase hepatic LDL receptor activity and HMG-CoA reductase activity in cultured liver cells. Consistent with the present authors' studies, red wine phenolics led to significant decreases in cholesterol levels [32–34]. Pal et al. also showed that with resveratrol treatment there was a significant delay in fat absorption [33]. In another study, plasma total triglyceride and cholesterol levels were also decreased by 13 and 25%, respectively. Hamsters fed dealcoholized wine had significantly less atherosclerosis (–22%) than control hamsters. In some reports the effects of red wine on LDL metabolism were measured and red-wine polyphenols attenuated cardiovascular risk by modulating LDL. Whether red wine polyphenolics benefit the cardiovascular system by decreasing the production of proatherogenic lipoproteins and increasing their clearance from the liver via the LDL receptor warrants further investigation [33, 35, 36].

In the present study, significant decreases in systolic blood pressure were also observed in both experimental groups ($p = 0.034$, $p = 0.009$). Trans-resveratrol appears to be able to protect against increased SBP and subsequent cardiac hypertrophy *in vivo*. In one study, after 4 weeks of resveratrol administration (50 mg/kg), SBP, ET-1, and Ang II concentrations decreased and the mechanisms responsible may involve, at least in part, modulation of NO, AngII, and ET-1 production [37]. The antioxidants promoted the recovery of stable NO metabolites in rat serum and maintained the expression of endothelial NO synthase at a normal level. These effects were confirmed by correction of blood pressure and endothelium-dependent vascular dilation [38]. Chronic resveratrol administration significantly improved endothelium-dependent relaxation to acetylcholine. Spontaneously hypertensive rats (SHRs) were administered the red wine polyphenol resveratrol in drinking water at 0, 0.448, or 4.48 mg/l (control, low, or high, respectively) for 28 days and, interestingly, the results of this study provided novel evidence of improved endothelium-dependent vasorelaxation in hypertensive, but not in normotensive, animals as a result of chronic resveratrol consumption mimicking dosages resulting from moderate red wine consumption. This response was not dependent on increases in eNOS expression, but was dependent on improved NO bioavailability by the reduction of hydrogen peroxide, which was reduced in the SHR thoracic aorta by a high dosage of resveratrol [39].

In conclusion, this preliminary study suggests that as an antioxidant and anti-aging compound, resveratrol ameliorated total cholesterol with beneficial effects on body weight and blood systolic pressure and that its administration does not lead to any deterioration in biochemical parameters.

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