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The Effects of Potassium Bromate and Resveratrol on Fatty Acid Levels in Heart, Muscle and Brain of Wistar Rats

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ABSTRACT

The aim of this study was to examine the effects of antioxidant resveratrol and carcinogen KBrO₃ on the level of fatty acids in heart, muscle and brain of old female Wistar rats. In this study Wistar rats were randomly divided into three groups: 1. Control (C), 2. KBrO₃ (P) (80 mg/kg, i.p. single dose) 3. Resveratrol+KBrO₃ (Res) (80 mg/kg KBrO₃ i.p. single dose, 33 mg/kg resveratrol, every other day, for 35 days). In heart, muscle and brain, fatty acid levels were measured by gas chromatography.

In the present study, palmitoleic acid (16:1) and oleic acid (18:1) levels were significantly increased in the P and Res groups ($p<0.05$, $p<0.001$, respectively). Stearic acid (18:0) and docosahexaenoic acid (22:6) levels were significantly decreased in the P and Res groups ($p<0.01$, $p<0.05$, respectively) in the heart. Palmitoleic acid (16:1), oleic acid (18:1) and linolenic acid (18:3) levels were significantly increased in the P and Res groups ($p<0.01$, $p<0.001$, $p<0.05$, respectively). Docosahexaenoic acid (22:6) level was decreased in the P and Res groups ($p<0.05$) in the muscle. Palmitoleic acid (16:1) and stearic acid (18:0) levels were decreased in the Res group ($p<0.05$) in the brain. Our results confirm that resveratrol and KBrO₃ treatment were affected the amount of important fatty acids which substrates in fatty acids metabolism of heart, muscle and brain of Wistar rats.

Key Words: Resveratrol, KBrO₃, Heart, Muscle, Brain

1. INTRODUCTION

Resveratrol (3,5,4'-trihydroxystilbene) is a naturally occurring phytoalexin found in juice and wine from dark skinned grape cultivars, which has been reported to exert a variety of pharmacological effects [1]. Originally, this molecule attracted interest as the likely active ingredient of wine that might explain the "French paradox", i.e. the apparent compatibility of a high fat diet with a low incidence of coronary atherosclerosis [2]. Its inhibitory effect on the pathogenesis of atherosclerosis was attributed to the protection, *in vitro*, of human LDL against copper-catalyzed oxidation. This protection resulted greater than that exerted by the natural chain-breaking antioxidant α -tocopherol [3-5]. The *in vitro* efficiency of resveratrol was found to be more due to its copper chelation than to free radical

scavenging [6,7]. However, recent results obtained *in vivo*, cast doubts on resveratrol effectiveness in preventing serum lipid peroxidation [8,9].

Potassium bromate (KBrO₃) is an oxidizing agent and this compound has been reported to be carcinogenic in rats, in renal tumors [10,11]. In addition, it has been determined that the level of 8-oxodeoxyguanosine (8-OH-deoxyguanosine, 8-oxodG) in the kidney DNA of treated rats. Sai *et al.* (1991) suggested that enhanced formation of 8-OH-dG in kidney DNA due to KBrO₃ is closely related to the increase in lipid peroxidation levels [12]. KBrO₃ is known to cause to the kidney by oxidative damage but not to other organs. With a single dose of KBrO₃ (80 mg/kg), activity in the kidney was found to increase significantly at 3 h in comparison to that at zero time [13]. KBrO₃ is carcinogenic in the rat

kidney, thyroid, and mesothelium and is a renal carcinogen in male mice [14,15].

Fatty acids are used as major substrates for the synthesis of various kinds of lipid including phospholipids, triacylglycerol and cholesterol esters. Oleate is the most abundant monounsaturated fatty acid found in triacylglycerol, cholesterol esters, wax esters and phospholipids [16]. The ratio of stearic acid to oleic acid has been implicated in the regulation of cell growth and differentiation through effects on membrane fluidity and signal transduction [17]. Monounsaturated fatty acids also influence apoptosis and may have some role in mutagenesis of some tumors [18].

The aim of this study was to examine effects of resveratrol and carcinogen potassium bromate on the level of fatty acids in heart, muscle and brain tissue of Wistar albino rats.

2. MATERIAL AND METHODS

2.1. Materials

Resveratrol, n-hexane, sulphuric acid and methanol were obtained from Sigma Chemical Co. (USA). Isopropyl alcohol was obtained from Fluka BioChemica (Switzerland). Potassium bromate, KCl and NaCl were obtained Merck (Germany).

2.2. Animals

The following experiments were approved by the Ethical Committee of Firat University for the care and use of laboratory animals. In this study, total 30 old female Wistar rats were used. The animals were housed in cages where they had *ad libitum* rat chow and water in an air-conditioned room with a 12-h light/12-h dark cycle, and were randomly divided into three groups. The first group was used as a Control (C), the second group potassium bromate (P), and third group Resveratrol+KBrO₃ (Res). Rats in the P and Res groups were injected intraperitoneally a single dose potassium bromate 80 mg/kg in the physiologic saline buffer (0.9% NaCl) [13]. After administration of KBrO₃ for two days, the rats in Res group was injected intraperitoneally resveratrol 33 mg/kg four times per week. In addition, physiological saline was injected to C group rats. These treatments were continued for five weeks, after which time each experimental rat was decapitated and blood samples were collected and stored in -85 °C prior to biochemical analysis.

2.3. Lipid Extraction

Total lipids were extracted with hexane-isopropyl alcohol (3:2 v/v) by the method of Hara and Radin [19]. The tissue samples were homogenized. Two hundred mg heart, one thousand mg muscle and three hundred mg brain of the homogenized tissue samples were taken and mixed with 5 ml hexane- isopropyl alcohol (3:2, v/v) in a mixer. Non-lipid contaminants in lipid extracts were extracted into 0.88% KCl solution. The extracts were evaporated in a rotary evaporator flask, and then stored at 25 °C.

2.4. Fatty Acid Analysis

Fatty acids in the lipid extracts were converted into methyl esters including 2% sulphuric acid (v/v) in methanol [20]. The fatty acid methyl esters were extracted three times with n-hexane. Then the methyl esters were separated and quantified by gas chromatography and flame-ionization detection (Shimadzu GC 1.7 Ver.3) coupled to a Glass GC 1.0 software computing recorder. Chromatography was performed with a capillary column (25m in length) and 0.25mm in diameter, Permabound 25, Machery-Nagel, Germany using nitrogen as a carrier gas (flow rate 0.8 ml/min). The temperatures of the column, detector and injection valve were 130–220, 240, 280 °C, respectively. Identification of the individual methyl esters was performed by frequent comparison with authentic standard mixtures that were analyzed under the same conditions.

2.5. Statistical analysis

The experimental results were reported as mean ± S.E.M. Statistical analysis was performed using SPSS Software. Analysis of variance (ANOVA) and an LSD test were used to compare the experimental groups with the controls.

3. RESULTS

In this study, the levels of fatty acids in heart, muscle and brain of old female Wistar rats by resveratrol and KBrO₃ were examined.

3.1. The Fatty Acid Composition of Heart

The fatty acid composition of heart is shown in Table 1. In respect our results, palmitic acid (16:0) level was lower than C group in the Res group ($p < 0.05$). Palmitoleic acid (16:1), oleic acid (18:1) and MUFA levels were significantly increased in the P and Res groups when compared to C group ($p < 0.05$, $p < 0.001$, $p < 0.05$ respectively). Stearic acid (18:0) and docosahexaenoic acid (22:6) levels were significantly decreased in the P and Res groups when compared to C group ($p < 0.01$, $p < 0.05$, respectively). PUFA and n-3 fatty acids levels were significantly decreased in the P and Res groups when compared to C group ($p < 0.05$).

3.2. The Fatty Acid Composition of Muscle

The fatty acid composition of muscle is shown in Table 2. According to our results, 16:1, 18:1 and linolenic acid (18:3) levels were significantly increased in the P and Res groups when compared to C group ($p < 0.01$, $p < 0.001$, $p < 0.05$, respectively). 22:6 level was decreased in the P and Res groups when compared to C group ($p < 0.05$). Eicosenoic acid (20:1) level was decreased in the Res group when compared to C group ($p < 0.05$). Docosadienoic acid (22:2) level was decreased in the P group when compared to C group ($p < 0.05$). Docosapentaenoic acid (22:5) level was increased in the Res group when compared to C group ($p < 0.05$). Docosatetraenoic acid (22:4) and MUFA levels were significantly increased in the P and Res group when compared to C group ($p < 0.01$, $p < 0.001$, respectively). PUFA, n-3 and n-6 fatty acids levels were significantly decreased in the P and Res groups when compared to C group ($p < 0.001$, $p < 0.05$, $p < 0.01$, respectively).

3.3. The Fatty Acid Composition of Brain

The fatty acid composition of brain is shown in Table 3. In the brain, 16:1, 18:0 and n-6 fatty acids levels were decreased in the Res group when compared to C group ($p<0.05$). 18:1, 20:1 and MUFA levels were increased in the Res group when compared to C group ($p<0.05$). Linoleic acid (18:2) level was increased in the P group when compared to C group ($p<0.05$).

4. DISCUSSION

Experimental studies pointed beneficial effects of resveratrol such as, improvement of lipid profile and

lipoprotein metabolism [21,22], enhanced insulin sensitivity [23,24], antioxidant activity [25-27] and prolonged survival [28].

Ajmo *et al.* (2008) indicated that resveratrol treatment led to reduced lipid synthesis and increased rates of fatty acid oxidation [29].

Gnoni and Paglialonga (2009) reported show in isolated hepatocytes from normal rats a resveratrol-induced short-term inhibition of fatty acid and triacylglycerol synthesis occurs. This finding may represent a potential mechanism contributing to the reported hypolipidemic effect of resveratrol [30].

Table 1. The Fatty Acids Composition of Heart Lipids (%).

Fatty Acids	Control (C)	KBrO ₃ (P)	KBrO ₃ +R (Res)
16:0	15.48±0.41 ^a	16.25±0.28 ^a	17.16±0.54 ^b
16:1 n-7	1.65±0.39 ^a	2.57±0.13 ^b	2.56±0.36 ^b
18:0	17.68±0.88 ^a	15.47±0.34 ^c	14.89±0.54 ^c
18:1 n-9	7.54±0.91 ^a	11.18±0.29 ^d	12.38±0.65 ^d
18:2 n-6	24.13±0.74 ^a	24.06±0.86 ^a	23.67±0.57 ^a
20:4 n-6	12.78±0.73 ^a	11.77±0.34 ^a	11.14±0.93 ^a
22:5 n-3	1.90±0.12 ^a	1.48±0.13 ^a	1.70±0.13 ^a
22:6 n-3	15.78±0.91 ^a	12.27±0.64 ^b	11.78±0.17 ^b
ΣSaturated	32.03±1.17 ^a	32.45±0.50 ^a	33.04±0.70 ^a
ΣUnsaturated	68.57±0.29 ^a	68.07±1.27 ^a	67.86±0.99 ^a
ΣMUFA	16.31±2.51 ^a	18.89±0.44 ^b	18.81±1.30 ^b
ΣPUFA	52.25±2.75 ^a	49.18±1.19 ^b	49.04±1.15 ^b
Σn-3	16.42±1.61 ^a	13.76±0.67 ^b	14.07±0.20 ^b
Σn-6	35.83±1.29 ^a	35.41±0.78 ^a	34.92±1.15 ^a

a: $p>0.05$ b: $p<0.05$ c: $p<0.01$ d: $p<0.001$

In our results of the heart tissue, while 16:0 and 18:0 fatty acid levels were decreased in the P group, 16:1 and 18:1 fatty acid levels were increased in the P and Res groups when in comparison to C group (Table 1). According to these results, the decreasing of 18:0 and the increasing of 18:1 in the P and Res groups can be explained by the increasing of Stearoyl-CoA desaturase (SCD) enzyme activity. The desaturating enzymes, Δ^9 -desaturase (also referred to as stearoyl-CoA-desaturase (SCD)), Δ^6 -desaturase (Δ^6D) and Δ^5 -desaturase (Δ^5D), introduce cis-double bonds in the carbon chain of long chain fatty acids [31]. These enzymes catalyze the synthesis of the long chain monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), which are needed to maintain membrane structures, to participate in cellular communication and differentiation, for eicosanoid signaling and to regulate gene expression [31,17]. SCD is an endoplasmic reticulum enzyme that catalyzes the biosynthesis of monounsaturated fatty acid from saturated fatty acids, and it is a rate-limiting enzyme in the biosynthesis of monounsaturated fatty acids. SCD expression affects the fatty acid composition of membrane phospholipids, triacylglycerol and cholesterol esters, resulting in changes in membrane fluidity, lipid metabolism and obesity [31]. SCD can convert the 18:0 fatty acids to the 18:1 fatty acids [32,33]. Therefore, the levels of MUFA were increased in the P and Res groups of the heart

tissue. The decreasing of 16:0 and 18:0 fatty acids levels may be explained decreasing activity of elongase enzyme. Elongase catalyzes the conversion of the 16:0 fatty acids to the 18:0 fatty acids [33]. Thus, the levels of 16:0 and 18:0 fatty acids were decreased due to the reduction of this enzyme activity in the heart tissue. According to our estimates, the cause of highly levels of 16:1 and 18:1 in the heart may be the application of KBrO₃. We think that this event may be caused by damaging of enzymes and other molecules which the fatty acids converting to more advanced metabolites, because the similar results were observed in the P and Res groups. These results indicated that the administrations of resveratrol and potassium bromate affected the activities of enzymes in fatty acids metabolism and this result was harmonious with enzyme activities. In the heart, the levels of 22:6, PUFA and n-3 fatty acids were decreased in the P and Res groups. Lipids, especially PUFA are preferential targets of oxidative damage [34]. *In vitro* experiments have shown that the more double bonds a polyunsaturated fatty acid has, the more vulnerable to peroxidation it is [35]. This event was indicated that the administration of potassium bromate may be caused to polyunsaturated fatty acids oxidations and their levels were decreased in the P and Res groups.

Table 2. The Fatty Acids Composition of Muscle Lipids (%).

Fatty Acids	Control (C)	KBrO ₃ (P)	KBrO ₃ +R (Res)
16:0	24.32±0.42 ^a	23.85±0.48 ^a	24.13±0.55 ^a
16:1 n-7	2.87±0.26 ^a	4.46±0.26^c	4.92±0.62^c
18:0	9.79±0.43 ^a	8.44±0.53 ^a	8.45±0.75 ^a
18:1 n-9	11.76±0.44 ^a	15.86±0.93^c	17.01±1.98^d
18:2 n-6	17.59±0.57 ^a	17.79±0.61 ^a	17.66±0.42 ^a
18:3 n-6	0.29±0.05 ^a	0.59±0.06^b	0.48±0.03^b
20:1 n-9	0.58±0.06 ^a	0.49±0.01 ^a	0.39±0.02^b
20:3 n-6	0.63±0.03 ^a	0.51±0.06 ^a	0.51±0.05 ^a
20:4 n-6	7.82±0.61 ^a	6.24±0.32 ^a	6.08±0.80 ^a
20:5 n-3	0.56±0.04 ^a	0.47±0.05 ^a	0.45±0.03 ^a
22:2	0.43±0.05 ^a	0.24±0.06^b	0.38±0.07 ^a
22:4	0.65±0.08 ^a	0.90±0.05^b	0.98±0.06^c
22:5 n-6	0.22±0.01 ^a	0.28±0.01 ^a	0.36±0.01^b
22:5 n-3	1.69±0.11 ^a	1.55±0.19 ^a	1.50±0.14 ^a
22:6 n-3	15.01±0.71 ^a	12.43±0.69^b	12.38±1.46^b
ΣSaturated	34.53±1.16 ^a	34.01±0.60 ^a	34.23±0.26 ^a
ΣUnsaturated	66.30±0.76 ^a	67.82±1.53 ^a	66.88±0.34 ^a
ΣMUFA	18.29±1.70 ^a	26.78±1.48^d	26.64±2.54^d
ΣPUFA	48.00±2.54 ^a	40.89±1.02^d	40.23±2.75^d
Σn-3	17.74±0.79 ^a	15.62±1.10^b	14.82±1.61^b
Σn-6	29.46±1.91 ^a	25.72±0.73^c	25.57±1.08^c

a: p>0.05 b: p<0.05 c: p<0.01 d: p<0.001

According to our results of the muscle tissue, 16:1 and 18:1 fatty acid levels were increased in the P and Res groups when compared to C group (Table 2). The increasing of 16:1 and 18:1 in the P and Res groups can be explained by the increasing of SCD enzyme activity. Therefore, the level of MUFA was increased in the P and Res groups of the muscle tissue. 18:1 and 16:1 fatty acids are the most abundant fatty acids found in triacylglycerol, cholesterol esters, wax esters and phospholipids [16]. These fatty acids are synthesized by SCD. Cohen *et al.* (2001) have reported that the monounsaturated fatty acids increase as a result of increased SCD activity [36]. There are the multiple roles of monounsaturated fatty acids, variation in SCD activity in mammals would be expected to affect a

variety of the key physiological variables, including differentiation, insulin sensitivity, metabolic rate, adiposity, atherosclerosis, cancer and obesity [17]. In the muscle, the levels of 22:6, PUFA, n-3 and n-6 fatty acids were decreased in the P and Res groups. This event was indicated that the application of potassium bromate may be caused to these fatty acids oxidations and their levels were decreased in these groups. Because, lipids especially PUFA are preferential targets of oxidative damage [34].

In the brain tissue, while 16:1, 18:0 and n-6 fatty acids levels were decreased, 18:1 and MUFA levels were increased in the P group (Table 3).

Table 3. The Fatty Acids Composition of Brain Lipids (%).

Fatty Acids	Control (C)	KBrO ₃ (P)	KBrO ₃ +R (Res)
16:0	18.18±0.32 ^a	18.30±0.34 ^a	17.61±0.20 ^a
16:1 n-7	1.98±0.03 ^a	2.06±0.06 ^a	1.78±0.07 ^b
18:0	20.73±0.63 ^a	19.97±0.27 ^a	19.35±0.25 ^b
18:1 n-9	21.07±0.49 ^a	21.55±0.36 ^a	22.35±0.29 ^b
18:2 n-6	0.88±0.04 ^a	1.27±0.08 ^b	0.89±0.06 ^a
20:1 n-9	2.38±0.21 ^a	2.31±0.29 ^a	3.16±0.22 ^b
20:3 n-6	0.45±0.01 ^a	0.45±0.01 ^a	0.42±0.04 ^a
20:4 n-6	9.65±0.31 ^a	9.27±0.16 ^a	8.76±0.40 ^a
22:5 n-5	2.67±0.08 ^a	2.54±0.09 ^a	2.45±0.09 ^a
22:6 n-3	16.55±0.30 ^a	16.20±0.27 ^a	15.57±0.50 ^a
24:0	0.48±0.02 ^a	0.53±0.04 ^a	0.51±0.06 ^a
ΣSaturated	39.40±0.76 ^a	38.97±0.44 ^a	38.05±0.26 ^a
ΣUnsaturated	61.75±0.56 ^a	62.04±0.42 ^a	62.64±0.43 ^a
ΣMUFA	31.59±0.84 ^a	32.64±0.87 ^a	33.92±0.68 ^b
ΣPUFA	30.15±0.45 ^a	29.83±0.49 ^a	28.72±0.95 ^a
Σn-3	16.55±0.30 ^a	16.03±0.15 ^a	15.94±0.54 ^a
Σn-6	13.68±0.39 ^a	13.67±0.33 ^a	12.45±0.46 ^b

a: p>0.05 b: p<0.05 c: p<0.01 d: p<0.001

We have not found any study about the effect of potassium bromate on fatty acids. Our results showed that the application of potassium bromate and resveratrol affected the amounts of important fatty acids that the substrates of fatty acid metabolism on duty enzymes in the heart, muscle and brain.

5. ACKNOWLEDGEMENT

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