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Effects of Ethanol and Caffeine Intake on Di (2-Ethylhexyl) Phthalate (DEHP) Toxicity in Rats

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Abstract

Background: *Mono(2-ethylhexyl) phthalate (MEHP), a metabolite of di(2-ethylhexyl) phthalate (DEHP), stimulates peroxisome proliferator-activated receptors and disrupts carbohydrate and lipid metabolism. The oxidative stress generated may be closely related to the toxicity of DEHP. The authors report on the effects of simultaneous consumption of drinking water containing the hydroxyl radical scavengers' ethanol or caffeine on diet-mediated DEHP toxicity.*

Method: *Four-week-old male SD rats were divided into control, DEHP, DEHP+ethanol and DEHP+caffeine groups (6 rats per group). The treatment groups were fed 1% (w/w) DEHP diet and tap water or 5% (v/v) ethanol or 0.05% (w/w) caffeine-containing water for 1 week.*

Result: *Dietary exposure to DEHP resulted in a slight decrease in body weight, a significant decrease in testicular weight, and a significant increase in liver weight. There was a significant negative correlation between plasma MEHP concentration and final body weight of the rats; ethanol and caffeine administration slightly suppressed the decrease in testicular weight. The relative testicular weights (% of body weight) of the control and DEHP groups showed a strong negative correlation with testicular MEHP concentration. In contrast, the relative testicular weights of the DEHP+ethanol and DEHP + caffeine groups showed weak negative correlation with testicular MEHP concentration, and the slope of the regression line was more moderate than that of the control and DEHP alone groups. However, ethanol and caffeine administration did not significantly suppress the increase in liver weight.*

Plasma glucose levels were significantly lower in the DEHP-only group than in the control group, but were slightly improved by ethanol or caffeine administration. Plasma lipid-related markers such as total cholesterol, high-density lipoprotein cholesterol, and triglycerides were lower in all DEHP-treated groups than in controls and were not improved by concurrent ethanol or caffeine administration.

Conclusion: *Ethanol and caffeine were found to improve testicular atrophy and hypoglycemia caused by DEHP. This effect may be due to the oxidant scavenging ability of ethanol and caffeine.*

Keywords: Ethanol Caffeine, Hydroxyl Radical Scavenger, DEHP, Testicular Atrophy, Hypoglycemia, Oxidative Stress

1. Introduction

Di(2-ethylhexyl) phthalate (DEHP), the most widely used plasticizer for polyvinyl chloride, has now become a ubiquitous contaminant; DEHP has been shown in animal studies to adversely affect the testes, liver, kidney, and endocrine system, and there is concern that environmental exposure may adversely affect human health. Although the mechanism of toxicity is not fully understood, it is thought to be closely related to the fact that phthalate metabolite mono(2-ethylhexyl) phthalate (MEHP) stimulates peroxisome proliferator-activated receptors and disrupts the carbohydrate and lipid metabolic systems generating oxidative stress. The authors reported the effects of dietary DEHP exposure on testes, liver, and blood biochemical parameters in rats and the effects of concurrent consumption of drinking water containing the hydroxyl radical scavengers' ethanol or caffeine [1-15].

2. Materials and Methods

2.1 Chemicals and Animal Diet

DEHP, ethanol, caffeine was purchased from Wako pure chemical industries Ltd. (Osaka, Japan). The chemical purities of DEHP, ethanol and Caffeine were found to be >97%,>99.7% and 98.0%, respectively. CE-2 diets (Clea,

Tokyo, Japan) containing DEHP by 1 w/w% were prepared by Oriental Yeast Company (Chiba, Japan). MEHP was purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). All other chemicals were the highest grade from commercial sources.

2.2 Animals and Ethics

Male Sprague-Dawley rats aged three-week-old purchased from Charles River (Kanagawa, Japan) were housed at the Laboratory Animal Center of Kagawa University. They were acclimated at 22–24 °C and 50–60% relative humidity with a 12-h light/dark cycle. The experiment protocols had the approval by the Kagawa University Animal Committee.

2.3 Experimental Design

Four-week-old rats weighing 116.6 ± 3.4 g were divided into control and treatment groups (6 rats per group). The treatment group received 1% (w / w) DEHP feed and tap water, or 0.05% (w / w) water with caffeine, or 5% (v / v) ethanol water for 1 week. At the end of the experiment, rats were sacrificed under ether anesthesia. Testes, livers, and kidneys were removed and weighed. Testes were frozen at -40°C until MEHP analysis. Blood samples from the heart were collected in heparinized tubes, and plasma was separated from whole blood by centrifugation at 1500 g and frozen at -40°C until MEHP and biochemical parameters were determined.

2.4 Plasma and Testicular MEPH Analysis

The MEHP levels in organs and plasma were determined by high performance liquid chromatography [16-38].

2.5 Plasma Biochemical Parameter Measurements

Plasma levels of glucose, total cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (TCH) and triglyceride (TG) were measured using an automated biochemical analyzer, Hitachi 7600 (Hitachi, Japan).

2.6 Statistical Analysis

Results were expressed as means ± standard deviations (SD). Statistical analysis was performed by one-way ANOVA test followed by Dunnett's post analysis test for multiple comparisons. $p < 0.05$ was considered as statistically significant.

3. Results

Table 1 shows body, organ weights, plasma and testicular MEHP concentrations for each treatment group; the DEHP treatment group gained less weight than the control group. Figure 1 shows a significant negative correlation between plasma MEHP concentration and final body weight: the DEHP treatment group had significantly heavier liver weight and significantly lighter testicular weight than the control group, while the DEHP diet and drinking water containing ethanol and caffeine slightly suppressed the decrease in testicular weight. However, ethanol and caffeine administration did not significantly suppress the increase in liver weight. There was no significant difference in kidney weight. The relative testicular weights (% of body weight) of the control and DEHP groups showed a strong negative correlation with testicular MEHP concentration. In contrast, the relative testicular weights of the DEHP+ethanol and DEHP+caffeine groups showed weak negative correlation with testicular MEHP concentration, and the slope of the regression line was more moderate than that of the control and DEHP groups (Figure 2). DEHP doses estimated from food intake and mean body weight during the treatment period ranged from 0.9 to 1.0 grams/kg/day in the DEHP administered groups.

Plasma biochemical parameters are shown in Table 2. Plasma glucose levels in the DEHP-treated group were significantly lower than those in the control group, but were slightly improved in the groups with simultaneous ethanol or caffeine intake. Plasma lipid-related markers such as TCH, LDL-C, HDL-C, and TG of all treatment groups on the DEHP diet were significantly and equally lower than controls [39, 40].

Table 1. Body, organ weights, plasma and testicular MEHP concentrations. *p < 0.05, **p < 0.01, ***p < 0.001as compared to control. #p < 0.05, ##p < 0.01, ###p < 0.001 as compared to 1%DEHP-only group. BDL: below the detection limit.

Group		Control		DEHP		DEHP+Ethanol		DEHP+Caffeine	
	n	6		6		6		6	
Initial body weight (g)	mean	116.5		118.3		118.3		113.8	
	SD	3.4		3.1		2.8		2.2	
Final body weight (g)	mean	181.8		169.0		168.6		170.0	
	SD	10.3		3.9		11.6		7.0	
Testes (g)	mean	1.62	###	0.99	***	1.20	*	1.12	**
	SD	0.10		0.24		0.19		0.31	
Relative testicular weight (%)	mean	0.90	###	0.58	***	0.71	*	0.65	**
	SD	0.08		0.14		0.08		0.17	
Kidneys weight (g)	mean	1.74		1.62		1.71		1.70	
	SD	0.13		0.12		0.11		0.15	
Relative kidney weight (%)	mean	0.96		0.96		1.02		1.00	
	SD	0.06		0.09		0.11		0.06	

Group		Control		DEHP		DEHP+Ethanol		DEHP+Caffeine	
	n	6		6		6		6	
Initial body weight (g)	mean	116.5		118.3		118.3		113.8	
	SD	3.4		3.1		2.8		2.2	
Final body weight (g)	mean	181.8		169.0		168.6		170.0	
	SD	10.3		3.9		11.6		7.0	
Testes (g)	mean	1.62	###	0.99	***	1.20	*	1.12	**
	SD	0.10		0.24		0.19		0.31	
Relative testicular weight (%)	mean	0.90	###	0.58	***	0.71	*	0.65	**
	SD	0.08		0.14		0.08		0.17	
Kidneys weight (g)	mean	1.74		1.62		1.71		1.70	
	SD	0.13		0.12		0.11		0.15	
Relative kidney weight (%)	mean	0.96		0.96		1.02		1.00	
	SD	0.06		0.09		0.11		0.06	

Table 1: Body, Organ Weights, Plasma and Testicular MEPH Concentrations

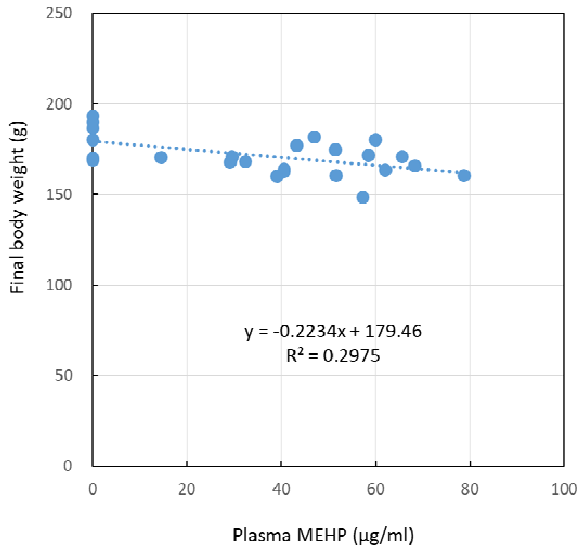

Figure 1: Relationship Between Final Body Weight and Plasma MEHP Concentration

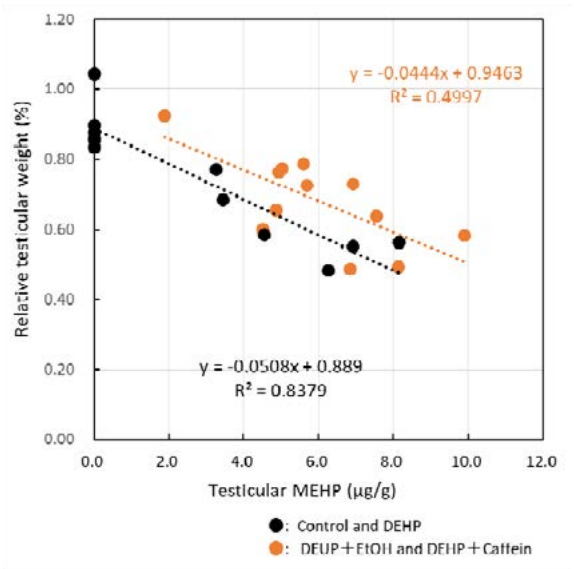

Figure 2: Relationship Between Relative Testicular Weight and Testicular MEHP Concentration

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Group		Control		DEHP		DEHP+Ethanol		DEHP+Caffeine	
	n	6		6		6		6	
Glucose (mg/dl)	mean	171.5	#	72.7	*	117.2		97.0	
	SD	46.8		34.3		40.2		10.2	
TC (mg/dl)	mean	87.8	##	66.8	**	58.2	**	64.8	**
	SD	13.9		12.5		5.6		7.5	
HDL-C (mg/dl)	mean	34.2	###	24.2	***	23.8	***	25.5	***
	SD	5.8		2.6		2.3		2.8	
TG (mg/dl)	mean	84.8	###	30.8	***	25.5	***	30.2	***
	SD	43.8		3.7		6.9		3.5	

Table 2: Plasma Biochemical Parameters

Table 2. Plasma Biochemical Parameters. *p < 0.05, **p < 0.01, ***p < 0.001as compared to control. #p < 0.05, ##p < 0.01, ###p < 0.001as compared to 1%DEHP-only group.

4. Discussion

Orally administered DEHP is rapidly metabolized to MEHP by lipase in the gastrointestinal tract MEHP stimulates peroxisome proliferator-activated receptors, disrupting carbohydrate and lipid metabolism and generating oxidative stress. Dietary exposure to DEHP resulted in a slight decrease in body weight, a significant decrease in testicular weight, and a significant increase in liver weight. The body weight suppression and testicular atrophy observed in this experiment were both MEHP-dependent, and therefore may be the result of oxidative stress generated by MEHP. MEHP-induced oxidative stress may damage thyroid tissue and reduce thyroid hormones, which play an important role in the process of skeletal muscle formation [21-32].

The weight loss may be due to MEHP-induced thyroid dysfunction. However, simultaneous administration of hydroxyl radical scavengers, ethanol, and caffeine, improved testicular atrophy but not body weight suppression. This suggests that the weight suppression is not due to MEHP-induced hydroxyl radicals. It also indicates that the increase in liver weight is merely the result of MEHP-stimulated peroxisome proliferation. Plasma glucose, TCH, LDL-C, HDL-C, and TG were significantly lower in the DEHP-exposed group. Administration of ethanol and caffeine slightly improved DEHP-induced hypoglycemia. MEHP-induced PPAR-γ promotes lipid metabolism, and the generated reactive oxygen species may promote insulin secretion. Hydroxyl radical scavengers' ethanol and caffeine may regulate insulin hypersecretion and prevent tissue damage caused by hypoglycemia-induced oxidative stress [45-50].

5. Conclusion

Ethanol and caffeine were found to improve testicular atrophy and hypoglycemia caused by DEHP. This effect may be due to the oxidant scavenging ability of ethanol and caffeine.

Compliance with Ethical Standards

Acknowledgments

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Disclosure of Conflict of Interest

There is no conflict of interest in this work.

Statement of Ethical Approval

The experiment protocols had the approval by the Kagawa University Animal Committee.

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