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Research Article

Effects of monosaccharides administration on rat DEHP toxicity

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Abstract

Di(2-ethylhexyl) phthalate (DEHP), a suspected endocrine disruptor, causes hepatomegaly, testicular damage, and other toxic effects in oral administration experiments using rats. MEHP, a DEHP metabolite, is directly responsible for these toxicities; the potent oxidative stress generated by MEHP is thought to be closely involved.

To elucidate the relationship between the hydroxyl radical scavenging activity of monosaccharides, including rare sugars, and DEHP toxicity, D-glucose, D-fructose, D-allulose, D-allose and allitol were mixed 1.0 w/v% in drinking water and administered to 4-week-old male SD rats for 1 week with 1% w/w DEHP mixed food.

D-Allulose had a strong inhibitory effect on testicular atrophy, and D-Allose had a significant inhibitory effect on hepatomegaly. Furthermore, plasma ALT levels in the D-allulose and D-allose-treated groups were significantly lower than those in the control group and the group treated with DEHP alone. These results may be due to the anti-inflammatory and anti-cell death effects of the monosaccharides through their hydroxyl radical scavenging action. Although allitol did not prevent DEHP-induced hepatomegaly and testicular atrophy, but prevented DEHP-induced reduction in weight gain. MEHP induced oxidative stress can disrupt thyroid hormones, which plays an important role in the process of skeletal muscle formation. The weight loss may be due to MEHP-induced thyroid dysfunction. Allitol may counteract MEHP-induced thyroid dysfunction.

Keywords: D-glucose; D-fructose; D-allulose; D-allose; allitol; DEHP

Introduction

Di(2-ethylhexyl) phthalate (DEHP), a suspected endocrine disruptor, is used as a plasticizer in polyvinyl chloride (PVC) in ratios ranging from a few percent to tens of percent [1-3]. DEHP is known to cause hepatic peroxisome proliferation and testicular atrophy in rats as an oral toxicity of DEHP [4-11]. However, recently, toxic effects on the testes have been observed at even lower concentration levels than those conventionally used for detection, and there is growing concern about the health effects of exposure to low concentrations of DEHP [13].

In oral administration experiments using rats and other animals, DEHP itself is hardly absorbed into the body, but mono(2-ethylhexyl) phthalate (MEHP), which is hydrolyzed by lipase in the digestive tract, is absorbed and distributed in the body, and is thought to be involved in the development of toxicity in the testes and liver [14-16]. Recently, the involvement of reactive oxygen species (ROS) in the mechanism of germ cell apoptosis induction by MEHP has been clarified [17, 18].

On the other hand, many monosaccharides, including rare sugars, are known to exhibit antioxidant effects based on hydroxyl radical scavenging [19-24], and may have a protective effect against DEHP-induced testicular toxicity and liver toxicity.

Therefore, the authors investigated the effects of some monosaccharides, including rare sugars on DEHP toxicity in animal experiments.

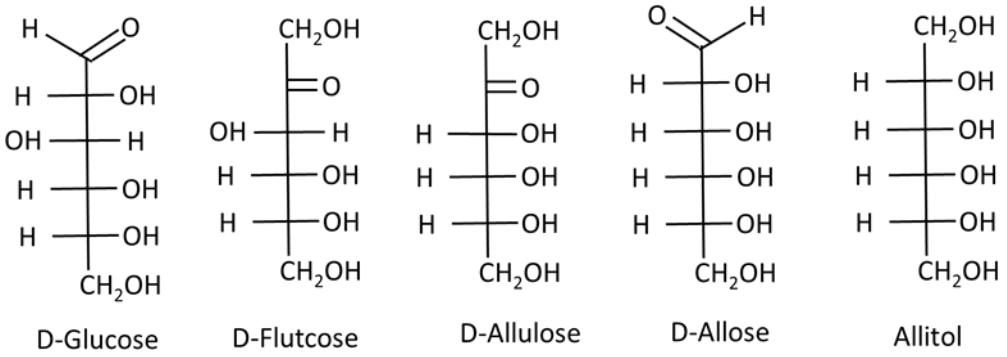

Figure 1. Molecular structures of D-glucose, D-fructose, D-allulose, D-allose and allitol.

2. Methods

2-1. Experimental Animals and Reagents

Male Charles River Sprague-Dawley (SD) rats were used as experimental animals, and were fed a rat diet made by Oriental Yeast and a diet mixed with DEHP (97% or higher purity). Rare sugars (98% or higher purity) were provided by the Kagawa University Rare Sugar Research Center. Other ingredients were commercial grade reagents.

2-2 Oral administration of DEHP and sugars

The experiments were conducted under the conditions of 22-24℃ of temperature and 50-60% relative humidity at the Laboratory Animal Center of Kagawa University. The experiment protocols had the approval by the Kagawa University Animal Committee. D-glucose, D-fructose, D-allulose, D-allose and allitol (Figure 1) were mixed 1.0 w/v% in drinking water and administered to 4-week-old male SD rats for 1 week with 1% w/w DEHP mixed food. The administration experiment was repeated in units of 6 rats per group.

At the first week after administration, blood was drawn from the heart under ether anesthesia, and the testes, liver, and other organs were removed and weighed.

Plasma isolated from rat blood was used to measure the following parameters:

Plasma levels of glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, HDL cholesterol, triglycerides.

The analyzer was a Hitachi Model 7600 Automated Analyzer (Hitachi).

2-3 Statistical Analysis

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

3. Results

Body weight and organ weights are shown in Table 1, 2 and 3, and blood biochemical test results are shown in Table 4, 5 and 6. Final body weights of DEHP alone and DEHP plus D-glucose, D-fructose, D-allulose or D-allose, were statistically significantly lower than those of the control group. Significant inhibition of weight suppression was observed in the DEHP plus allitol group. As shown in Table 2, the degree of testicular atrophy of DEHP in terms of relative testicular weight (testes/body weight %) was DEHP (0.62) ≈ DEHP plus allitol (0.58) > D-glucose (0.75) ≈ D-allose (0.72) > D-allulose (0.82) ≈ control (0.88). D-allulose showed the strongest and statistically significant inhibition of testicular atrophy. As shown in Table 3, the degree of DEHP hepatomegaly in terms of liver weight (relative weight %) was DEHP (7.8) ≈ DEHP+D-allitol (7.7) ≈ D-glucose (7.6) ≥ D-allulose (7.3) > DEHP+D-allose (6.9) versus control (4.8). D-allose significantly suppressed hepatomegaly, while D-allulose showed insignificant suppression (p=0.052).

Group	n	Initial body weight (g)			Final body weight (g)		
		mean	SD		mean	SD	
Control	18	97.1	4.3		159.2	9.1	###
DEHP	18	94.3	5.0		141.3	8.4	***
DEHP+Glucose	6	94.0	4.8		136.2	5.9	***
DEHP+Fruktose	6	99.0	3.6		145.7	5.3	**
DEHP+Allulose	12	95.1	4.5		137.0	4.6	***
DEHP+Allose	12	96.7	4.4		135.0	10.6	***
DEHP+Allitol	6	99.0	3.0		153.9	6.5	##

*p<0.05, **p<0.01, ***p<0.001, as compared to control.
#p<0.05, ##p<0.01, ###p<0.001, as compared to DEHP alone.

Table 1. Initial and final body weights

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Group	n	Testes (g)			Relative testicular weight (%)		
		mean	SD		mean	SD	
Control	18	1.40	0.11	###	0.88	0.05	###
DEHP	18	0.87	0.20	***	0.62	0.15	***
DEHP+Glucose	6	1.02	0.24	***	0.75	0.15	
DEHP+Fruktose	6	0.99	0.20	***	0.68	0.13	**
DEHP+Allulose	12	1.13	0.22	**, ##	0.82	0.16	##
DEHP+Allose	12	0.97	0.25	***	0.73	0.18	**
DEHP+Allitol	6	0.89	0.12	***	0.58	0.10	***

*p<0.05, **p<0.01, ***p<0.001, as compared to control.
#p<0.05, ##p<0.01, ###p<0.001, as compared to DEHP alone.

Table 2: Testicular weights

Group	n	Liver (g)			Relative liver weight (%)		
		mean	SD		mean	SD	
Control	18	7.67	0.64	###	4.82	0.24	###
DEHP	18	10.99	1.25	***	7.77	0.69	***
DEHP+Glucose	6	10.32	0.51	***	7.59	0.47	***
DEHP+Fruktose	6	11.83	0.66	***	8.12	0.30	***
DEHP+Allulose	12	10.00	0.51	***, ###	7.31	0.45	***
DEHP+Allose	12	9.37	0.90	***, ###	6.95	0.35	***, ###
DEHP+Allitol	6	11.83	0.66	***	7.70	0.54	***

*p<0.05, **p<0.01, ***p<0.001, as compared to control.
#p<0.05, ##p<0.01, ###p<0.001, as compared to DEHP alone.

Table 3. Liver weights

As shown in Table 4, plasma glucose levels were significantly suppressed in the group treated with DEHP alone compared to the control. D-glucose and D-allulose restored plasma glucose levels, while D-allose and allitol did not. DEHP alone and DEHP plus monosaccharide treatments had significantly lower triglycride levels than controls. As shown in Table 5, plasma total-cholesterol and HDL-cholesterol in the DEHP alone and DEHP plus monosaccharide treated groups were significantly lower than controls.

Plasma ALT levels in the DEHP plus D-allulose, or D-allose treated groups were significantly lower than controls and DEHP alone (Table 6).

Group	n	Glucose (mg/dL)			Triglycerides (mg/dL)		
		mean	SD		mean	SD	
Control	18	206.2	56.7	#	46.2	21.5	###
DEHP	18	174.2	27.8	*	24.8	9.5	***
DEHP+Glucose	6	185.0	15.8		19.7	4.3	**
DEHP+Fruktose	6	-	-		-	-	
DEHP+Allulose	12	183.8	23.7		26.0	8.5	**
DEHP+Allose	12	167.8	15.1	*	31.0	12.9	*
DEHP+Allitol	6	170.5	11.5	*	24.8	9.5	**

*p<0.05, **p<0.01, ***p<0.001, as compared to control.
#p<0.05, ##p<0.01, ###p<0.001, as compared to DEHP alone.

Table 4. Plasma levels of glucose and triglycerides

Group	n	AST (U/L)			ALT (U/L)		
		mean	SD		mean	SD	
Control	18	202.6	155.3		56.4	16.0	
DEHP	18	160.6	86.9		57.7	16.8	
DEHP+Glucose	6	134.8	41.8		44.0	5.8	
DEHP+Fruktose	6	-	-		-	-	
DEHP+Allulose	12	121.6	48.5		43.9	8.6	#
DEHP+Allose	12	138.8	107.3		41.5	7.6	*, ##
DEHP+Allitol	6	116.3	25.8		44.8	6.3	

*p<0.05, **p<0.01, ***p<0.001, as compared to control.
#p<0.05, ##p<0.01, ###p<0.001, as compared to DEHP alone.

Table 5. Plasma levels of ALT and AST

Group	n	Total-cholesterol (mg/dL)			HDL-cholesterol (mg/dL)		
		mean	SD		mean	SD	
Control	18	90.1	14.1	###	36.4	4.2	###
DEHP	18	65.2	5.0	***	26.4	3.3	***
DEHP+Glucose	6	65.8	5.2	***	24.5	2.2	***
DEHP+Fruktose	6	-	-		-	-	
DEHP+Allulose	12	66.1	9.7	***	26.3	3.3	***
DEHP+Allose	12	70.8	8.2	***	28.3	4.0	***
DEHP+Allitol	6	72.8	14.4	**	28.7	4.7	***

*p<0.05, **p<0.01, ***p<0.001, as compared to control.
#p<0.05, ##p<0.01, ###p<0.001, as compared to DEHP alone

Table 6. Plasma levels of total cholesterol and HDL cholestero

4. Discussion

After oral administration, DEHP, distributed in the body primarily as MEHP, stimulates peroxisome proliferator-activated receptors and increases carbohydrate and lipid metabolism. The oxidative stress produced may be closely related to DEHP toxicity, including hepatomegaly and testicular atrophy [4-12]. In the present oral administration experiments of DEHP and monosaccharides, D-Allulose showed the strongest and significant testicular atrophy inhibitory effect, suggesting that D-allose, D-glucose, and D-fructose have a slight inhibitory effect on testicular atrophy. The liver weights of the D-allose-treated groups were significantly lower than those of the group treated with DEHP alone. Furthermore, plasma ALT levels in the D-allulose and D-allose-treated groups were significantly lower than those in the control and the group treated with DEHP alone. These results may be attributed to the anti-inflammatory and anti-cell death effects of monosaccharides due to their hydroxyl radical scavenging action. Plasma glucose concentrations were significantly lower in the group treated with DEHP alone than in the control group, but not in the D-allulose-treated group. This suggests that D-allulose inhibits DEHP -induced glycemic suppression; MEHP -induced PPAR-γ can promote lipid metabolism, while the reactive oxygen species produced can promote insulin secretion [25-27]. The antioxidant D-allulose may regulate insulin hypersecretion and protect pancreatic function [28, 29].

Allitol did not prevent DEHP-induced hepatomegaly and testicular atrophy, but prevented DEHP-induced reduction in weight gain. MEHP induced oxidative stress can damage thyroid tissue and lower thyroid hormones [30-33] which plays an important role in the process of skeletal muscle formation [34]. The weight loss may be due to MEHP-induced thyroid dysfunction. Allitol may counteract MEHP-induced thyroid dysfunction.

5. Conclusion

D-Allulose had a strong inhibitory effect on testicular atrophy, and D-Allose had a significant inhibitory effect on hepatomegaly. Furthermore, plasma ALT levels in the D-allulose and D-allose-treated groups were significantly lower than those in the control group and the group treated with DEHP alone. These results may be due to the anti-inflammatory and anti-cell death effects of the monosaccharides through their hydroxyl radical scavenging action. Although allitol did not prevent DEHP-induced hepatomegaly and testicular atrophy, but prevented DEHP-

induced reduction in weight gain. MEHP induced oxidative stress can disrupt thyroid hormones, which plays an important role in the process of skeletal muscle formation. The weight loss may be due to MEHP-induced thyroid dysfunction. Allitol may counteract MEHP-induced thyroid dysfunction.

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Disclosure of conflict of interest

Authors declare that there is no conflict of interests.

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