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Subacute Toxicological Study of Neosugar

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Technicians;
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Time Period;
Jan. 15, 1982～Apr. 30, 1982

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Experiment 1 Oral administration study

1 Materials and Methods

Male Wistar rats (SPF) at the age of 8 weeks, purchased from Nichi-ido Co., were used in groups of 18 animals each.

Neosugar (GF; trace, GF2; 30.9%, GF3; 55.0% and GF4; ..1%) and Neosugar G (a mixture of 51% of Neosugar, 38% of monosaccharides and 11% of sucrose) dissolved with distilled water was used as the test sample solution. Sucrose and glucose were used as control saccharides. Sample solution was orally dosed daily at the level of1.5, 3.0 and 4.5 g of Neosugar per kg of bodyweight in 2.0 ml for a rat.

Six blood samples of respective groups were collected for general hematological tests from the inferior vena cava under anesthesia with Nembutal at 2, 4 and 6 weeks. Immediately after collection of blood samples, organs, ver, adrenal and pancreas were collected. Other organs, kidny, cerebrum, cerebellum, hypophysis', heart, lung, spleen and testis, were also obtained at 6 weeks and pathologically observed.

2. Results

1) Mortality and General condition;

None of rats died during the period and no abnormality in general condition was found in every animal.

2) Body weight

Body weight of animals in Neosugar 3g/kg group, 4.5g/kg group and Neosugar G 3g/kg group were slightly less than that of untreated group at 6 weeks. Body weight changes of other groups were the same to the untreated group (Fig. 1).

3) Hematological tests

Significant differences from the untreatment were scatteringly found in every sugar group (Table 1).

4) Necropsy findings

Distension of caecum was found in 4 rats of Neosugar 4.5g/kg group, one rat of Neosugar G 3g/kg group and 4.5g/kg group at 4 weeks. Other abnormality was not found.

3. Discussion

Although there were some significant differences in hematological tests, they scattered in every dose level and every test period. So these differences seemed not to be caused by sample administration. Thus, we estimated that there were no remarkable toxicity in test samples.

Experiment 2; Mixed diet administration study

1 Materials and Methods

Male Wistar rats (SPF) at the age of 6 to 7 weeks, purchased from Nichi-ido Co., were used in groups of 18 animals each.

Neosugar (GF; trace, GF2; 30.9%, GF3; 55.0% and GF4; 14.1%) and Neosugar G (a mixture of 51% of Neosugar, 38% of monosaccharides and 11% of sucrose) were added to a commercially available powdered diet (Oriental Yeast Industry Co.) in concentrations of 5 and 10%. Five % of sucrose was minused for the 5% mixed diet and 5% sucrose and 5% starch were minused for the 10% mixed diet from the basal diet. Sucrose, glucose and sorbitol were used as control saccharides.

Rats were fed on the mixed diets ad libitum for 6 weeks and six blood samples of respective groups were collected for general hematological tests from the ıferior vena cava under anesthesia with Nembutal at 2, 4 and 6 weeks.
Immediately after collection of blood samples, organs, liver, adrenal and pancreas were collected. Other organs, kidny, cerebrum, cerebellum, hypophysis', heart, lung, spleen and testis, were also obtained at 6 weeks and HE-stained samples were examined histologically under an optical microscope.

2. Results

') Mortality and General condition;

Diarrhea was observed in rats of sorbitol group on about 3day and in rats of Neosugar group on about 10day. No remarkable abnormality in general condition was found after that. None of rats died during the test period.

2) Body weight

Body weight of Neosugar and sorbitol group were less than that of normal diet group until 5 weeks but they recovered finally. Body weight of Neosugar G group altered below the level of normal group troughout the study (Fig. 2).

3) Hematological tests

Significant differences from the normal group found in scattering items. Cholesterol level of Neosugar and Neosugar G group tended to be lower than normal group (Table 2 and Figure 3).

4) Necropsy findings

Distension of caecum was found in Neosugar and sorbitol group at 2 weeks and Neosugar, Neosugar G and sorbitol group at 6 weeks.

5) Optical microscopic findings

Mild necrosis of the hepatic cell's and round cell infiltration was observed in 1 or 2 cases for each group. Degeneration and decollement of the proximal renal tubural epithelial cell's ,was observed for every sugar diet group and the extent was stronger for sucrose and sorbitol group. Dilation of the distanal renal tubules was found in some cases for Neosugar, Neosugar G and glucose group. Calcium deposition in the inside of cortex was found in 1 or 2 cases for normal and Neosugar and sorbitol group (Table 3).

3. Discussion

For Neosugar and Neosugar G group, body weight suppression, serum cholesterol reduction, distension of the caecum were observed and degeneration of hepatic and kidney cell were also found in some rats.

The occurrence ratio of caecum distension was equal to or less than that of sorbitol group and degenaration of the liver cells were also found in other sugar diet groups. Degeneration of the proximal renal tubural cells was milder than that of sucrose group and calcium deposition was found also in normal diet group. Thus, we concluded

that Neosugar or Neosugar G did not show stronger toxicity than sucrose glucose and sorbitol.

The body weight suppression and reduction of serum cholesterol seemed not to be caused by toxicity of Neosugar but to be caused by its low bioavailability because other studies suggested Neosugar did not increase serum glucose level.

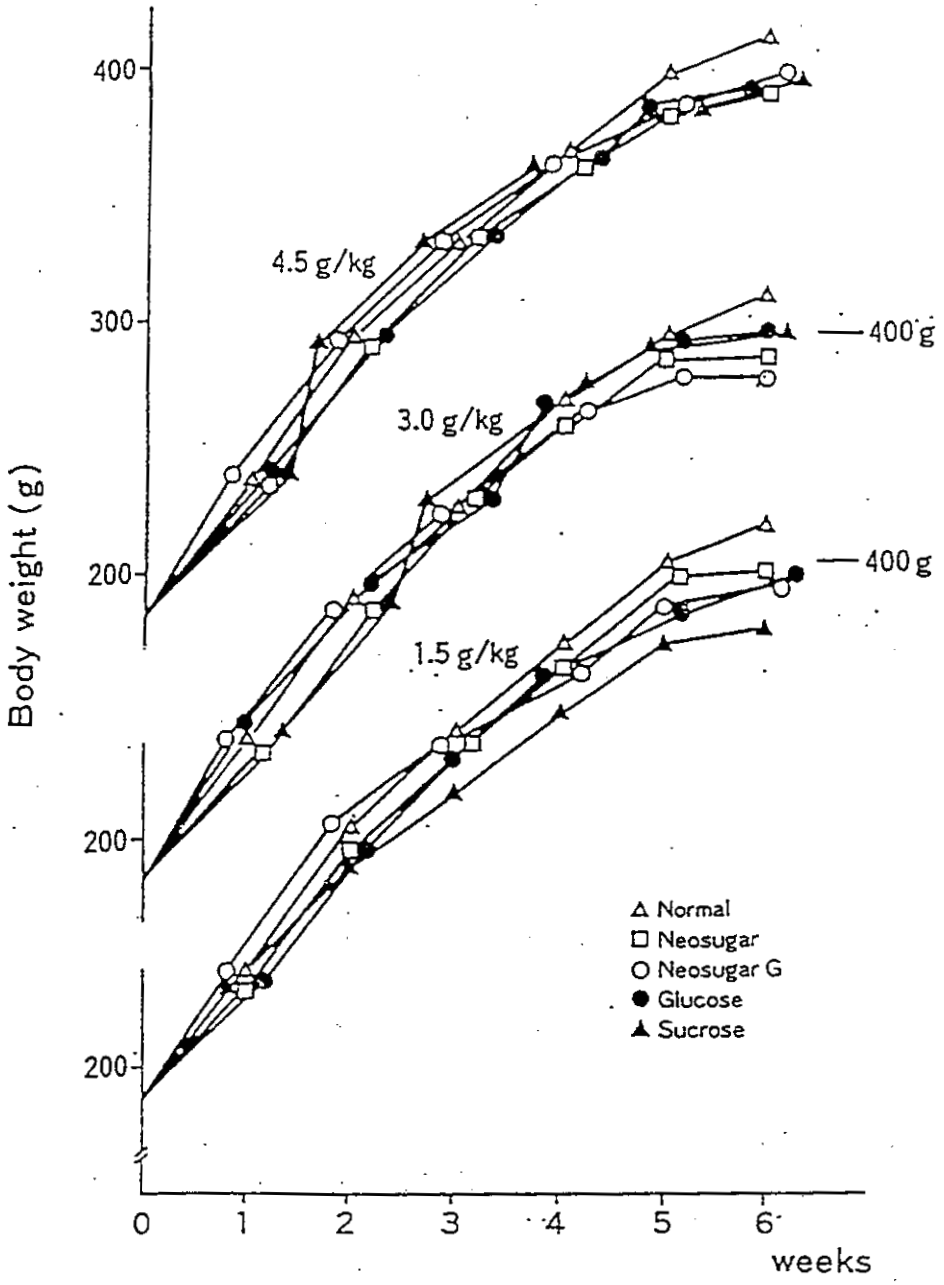

Figure 1 Mean body weight changes in 6-week oral toxicity studies in male rat.

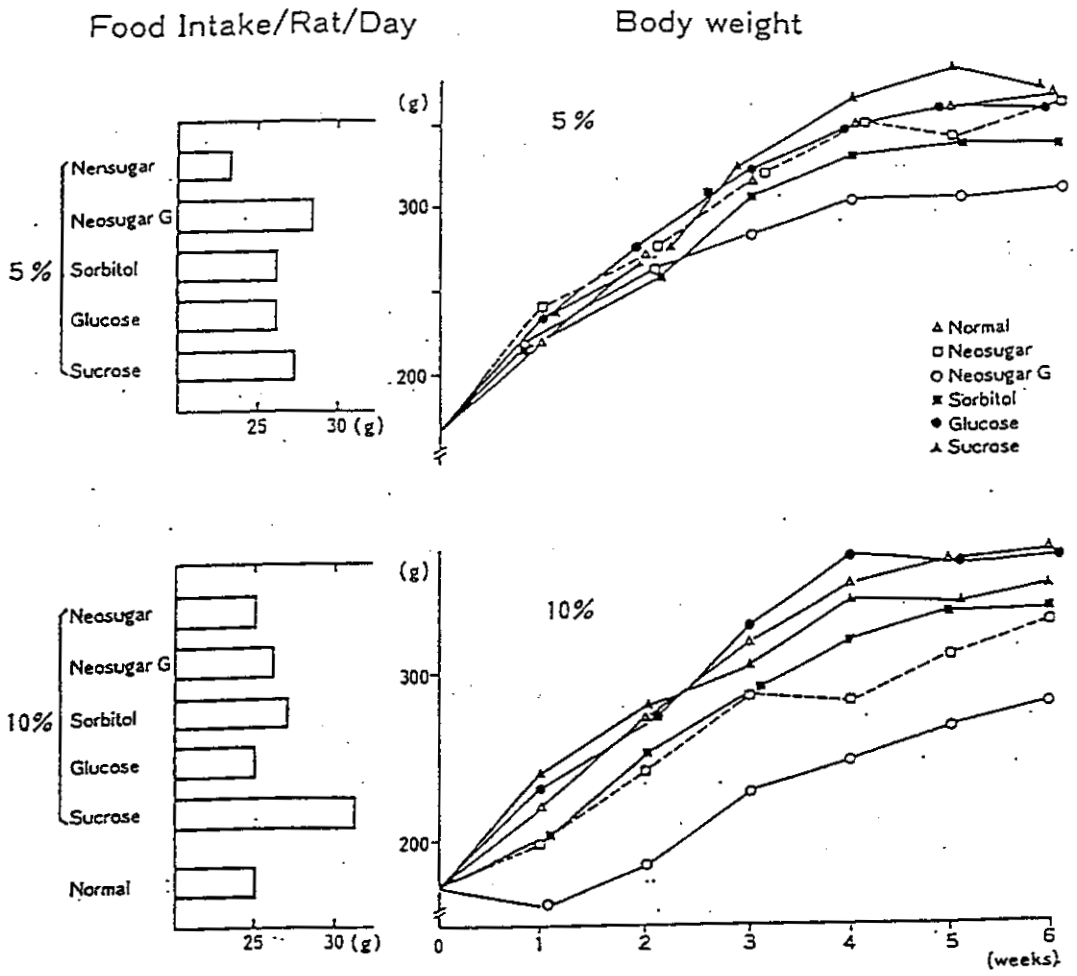

Figure 2 Mean bodyweights and food consumptions in rat 6-week feeding toxicity studies.

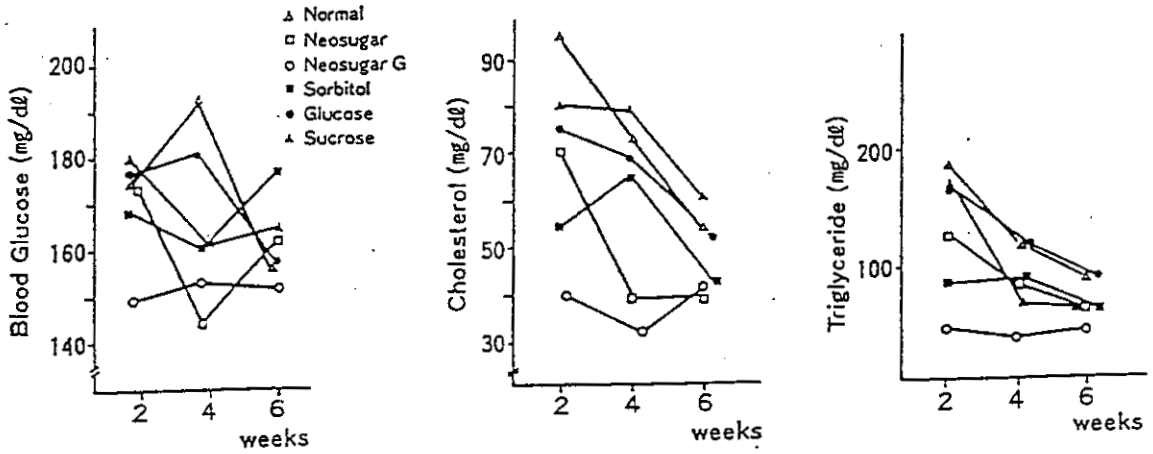

Figure 3 Changes in blood glucose, cholesterol and triglyceride in rat 6-week feeding toxicity studies.

Table 1 · · Summarized Table of Serum Biochemistry in Rat 6-week Oral Toxicity Studies

Weeks	Groups (g/kg)		Serum															
	Item		GPT	GOT	LAP	ChE	Al-P	LDH	CPK	BUN	CRE	TP	Alb	Ca	Chol	TG	Glu	A/G
2	Neosugar	1.5						⇩	⇩									
		3.0																
		4.5																
	Neosugar G	1.5																
		3.0																
		4.5						⇩										
	Glucose	1.5																
		3.0																
		4.5																
	Sucrose	1.5																
		3.0				⇧												
		4.5						⇩	⇩									
4	Neosugar	1.5																
		3.0								⇩								
		4.5																
	Necsugar G	1.5									⇩					⇩		
		3.0																
		4.5			⇧													
	Glucose	1.5																
		3.0																
		4.5																
	Sucrose	1.5										⇧						
		3.0								⇩								
		4.5								⇩								
6	Neosugar	1.5																
		3.0																
		4.5																
	Necsugar G	1.5								⇩								
		3.0					⇩											
		4.5																
	Glucose	1.5								⇩								
		3.0																
		4.5	⇩															
	Sucrose	1.5																
		3.0																
		4.5								⇩								

⇧ (Increase), ⇩ (Decrease)·····Significantly different from Untreatment $P<0.01$

Table 2 Summarized Table of Serum Biochemistry in Rat 6-week Feeding Toxicity Studies

Weeks	Groups(%) \ Item		Serum															
			GPT	GOT	LAP	ChE	Al-P	LDH	CPK	BUN	CRE	TP	Alb	Ca	Chol	TG	Glu	A/G
2	Neosugar	5																
		10						⇩							⇩			
	Neosugar G	5												⇩				
		10									⇧			⇩	⇩	⇩	⇩	⇧
	Sorbitol	5						⇩	⇩							⇩	⇧	
		10												⇩	⇩	⇩		
	Glucose	5													⇩			
		10		⇩				⇩	⇩						⇩			
	Sucrose	5															⇧	
		10						⇩										
4	Neosugar	5																
		10												⇩	⇩		⇩	
	Neosugar G	5				⇩									⇩		⇩	⇧
		10							⇧		⇧			⇩	⇩	⇩	⇩	⇧
	Sorbitol	5															⇩	
		10											⇧				⇩	
	Glucose	5										⇧	⇧				⇩	
		10																
	Sucrose	5																
		10										⇧	⇧	⇧		⇩	⇩	
6	Neosugar	5																
		10																⇧
	Neosugar G	5		⇩											⇩	⇩	⇧	⇧
		10			⇩											⇩		⇧
	Sorbitol	5														⇩		⇧
		10														⇩	⇧	⇧
	Glucose	5		⇩				⇩									⇧	
		10										⇧						
	Sucrose	5		⇩				⇩										
		10						⇩									⇧	

⇧ (Increase), ⇩ (Decrease)……Significantly different from Normal $P<0.01$

Table 3 Microscopicfindings in Rat 6-week Feeding Toxicity Studies

Weeks	Organs	Findings \ Groups (%)		Normal	Neosugar		Neosugar G		Sorbitol		Glucose		Sucrose	
					5	10	5	10	5	10	5	10	5	10
2	Liver	NAD		6	6	6	5	6	6	6	6	4	5	4
		Necrosis of the hepatic cell's and round cell infiltration	±	0	0	0	1	0	0	0	0	2	1	2
	Adrenal	NAD		6	6	6	6	6	6	6	6	6	6	6
	Pancreas	NAD		6	6	6	6	6	6	6	6	6	6	6
4	Liver	NAD		5	5	6	6	6	6	6	6	6	6	6
		Necrosis of the hepatic cell's and round cell infiltration	±	1	1	0	0	0	0	0	0	0	0	0
	Adrenal	NAD		6	6	6	6	6	6	6	6	5	6	6
		Focal necrosis in the zona fasciculata		0	0	0	0	0	0	0	0	1	0	0
	Pancreas	NAD		6	6	6	6	6	6	6	6	6	6	6
6	Liver	NAD		6	6	5	4	6	4	5	6	5	6	6
		Necrosis of the hepatic cell's and round cell infiltration	±	0	0	1	2	0	2	1	0	1	0	0
	Adrenal	NAD		6	6	6	6	6	6	6	6	6	6	6
	Pancreas	NAD		6	6	6	6	6	6	6	6	6	6	6
	Kidney	NAD		4	6	3	0	5	0	2	2	5	5	0
		Round cell infiltration interstitute	±	0	0	1	0	0	0	0	0	0	0	0
		Degeneration of the proximal renal tubular epithelial cells'	±	0	0	1	0	0	0	0	0	0	0	0
		Degeneration and decollement of the proximal renal tubural epithelial cells'	±	0	0	0	2	0	3	2	2	0	0	0
			+	0	0	0	2	1	2	2	2	0	1	0
			++	0	0	0	0	0	1	0	0	0	0	6
		Dilatation of the distanal renal tubules	±	0	0	3	2	0	0	0	0	1	0	0
		Calsium deposition in the inside of cortex	±	0	0	0	2	0	0	0	0	0	0	0
			+	2	0	0	1	0	1	0	0	0	0	0
			++	0	0	0	0	1	0	0	0	0	0	0
	Cerebrum	NAD		6	6	6	6	6	6	6	6	6	6	6
	Cerebellum	NAD		6	6	6	6	6	6	6	6	6	6	6
	Hypophysis'	NAD		6	6	6	6	6	6	6	6	6	6	6
	Heart	NAD		6	6	6	6	6	6	6	6	6	6	6
	Lung	NAD		6	6	6	6	6	6	6	6	6	6	6
	Spleen	NAD		6	6	6	6	6	6	6	6	6	6	6
	Testis	NAD		6	6	6	6	6	6	6	6	6	6	6