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THE STREPTOZOTOCIN-PROSTAGLANDIN INTERACTION IN GOLGI APPARATUS OF RAT LIVER

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16,16'-Dimethylprostaglandin E_2 was administered to rats in three doses: 30 min prior and 24 h and 48 h after a single intraperitoneal injection of streptozotocin. The Golgi membrane fraction was analyzed 6 days after streptozotocin injection. It has been found that prostaglandin restores the Golgi membrane fraction and the activity of UDP-Gal→GlcNAc transferase, both significantly decreased upon treatment with streptozotocin alone. Morphology of the liver Golgi apparatus studied by the electron microscopy was similar to that of control from untreated rats although streptozotocin alone significantly decreased the size of this organelle.

Alterations in protein pattern and lower yield of Golgi-rich membrane fraction [1] as well as diminished UDP-Gal→GlcNAc transferase activity [10] were previously observed in our laboratory in streptozotocin-diabetic rats on the 10th or 11th day after drug injection. This was accompanied by morphologic changes of liver Golgi apparatus *in situ* demonstrated by electron microscopic observations [2]. None of the alterations described above were found in alloxan-diabetic rat livers [3]. Stachura *et al.* [4, 5] found that certain cytotoxic effects of galactosamine in rats could be prevented by treatment with prostaglandin. The effect of prostaglandin on the changes induced by streptozotocin in Golgi apparatus was studied six days after streptozotocin-prostaglandin administration since upon short term action of streptozotocin given in diabetogenic dose the blood sugar level was not elevated and both the enzymatic and morphological symptoms were not yet established [6].

MATERIALS AND METHODS

Animal material. Female Wistar rats weighing 190-230 g and aged above 6 months were fed *ad libidum* commercial pelleted food and tap water. The rats were divided into four groups: 1, control group, rats without any treatment (6 animals); 2, the animals received subcutaneously 3 injections of 16,16′-dimethylprostaglandin E_2 (dm PGE_2) in a dose of 5 μg/kg body weight, dissolved in 0.5 ml of isotonic saline at time 0, and 24 h and 48 h after the first injection (6 animals); 3, the animals received streptozotocin intraperitoneally in a single dose of 65 mg/kg body weight in citrate buffer, pH 4.5. Only the rats with blood sugar levels higher than 250 mg/100 ml (250-370 mg per 100 ml) were used for the experiments (6 animals) 4, the animals were injected with streptozotocin as in group 3. In addition, they received dm PGE_2 as group 2 except that the first injection was given 30 min prior to streptozotocin injection. The level of free blood sugar was in three animals higher and in three lower than 150 mg/100 ml (6 animals).

Animals from groups 3 and 4 were killed on the 6th day after streptozotocin injection. All animals were anaesthetized with ether, exsanquinated, and small pices of liver were immediately taken for morphological analysis of the Golgi apparatus. Liver ultra-thin sections were prepared as previously described [7, 2] and examined with Philips EM 300 electron microscope. The remaining liver tissue was rinsed in saline, weighed and immediately used for isolation of Golgi-rich membrane fraction by the Fleischer method [8]. In all investigated groups the rats were not starved in order to reduce the effect of factors other than prostaglandin or streptozotocin. As observed elsewhere [9] starvation has no effect on galactosyltransferase activity, but alters the yield of Golgi-rich membrane fraction.

Assay of galactosyltransferase. The activity of this enzyme was determined according to Fleischer [8] as previously described in detail [10].

Analytical methods. Blood sugar was estimated by the method of Somogyi & Nelson [11] and protein according to Lowry *et al.* [12] with crystalline serum albumin as a standard.

RESULTS AND DISCUSSION

In Table 1 blood sugar levels, liver weights and yields of Golgi-rich membrane fraction from four investigated groups of rats are presented. In comparison with control, the rats injected with prostaglandin or streptozotocin showed lower yield of Golgi-rich membrane fraction expressed in mg of protein per 1 g of liver. Statistically significant differences were found in the second group and on the bordeline of significance in the third

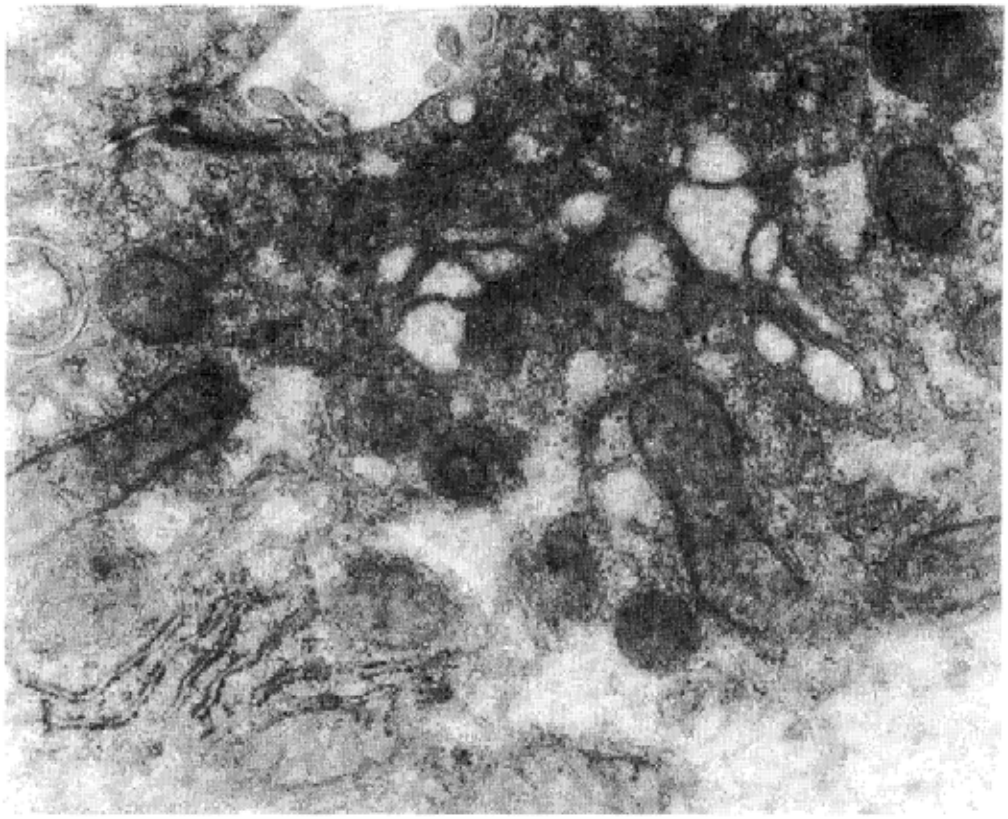

Plate. I. Ultra-thin section of the Golgi apparatus region from rat liver after 16,16'-dimethylprostaglandin F_2 and streptozotocin administration. Magnification ×32000. For details see Material and Methods.

group. However, the lowest yield was found in group 3, i.e. in rats showing, after streptozotocin injection, blood glucose concentration above 250 mg/100 ml.

In this group the activity of UDP-Gal→GlcNAc calculated in nmol of Gal transferred per 1 h and per 1 g of liver was significantly ($0.01 < p < 0.05$) decreased.

It appears that diabetic rats examined on the 6th day after streptozotocin administration showed changes in galactosyltransferase activity similar to those observed in rats 10-11 days after streptozotocin injection [10].

Table 1

Blood sugar levels, liver weights and yields of the Golgi-membrane fraction 6 days after prostaglandin or/and streptozotocin administration.

Mean values ± SD and the range of values are given; t and p values calculated by Student's t test. For details see Material and Methods.

Experimental	n	Blood sugar level (mg/100 ml)	Liver weight (g)	Yield of Golgi-rich membrane fraction (mg protein/g liver)
1. Control	6	127 ± 17 107 - 154	7.2 - 10.4	0.83 ± 0.12
2. Prostaglandin	6	179 ± 70 102 - 272	4.1 - 7.5	0.63 ± 0.19*
3. Streptozotocin	6	302 ± 43 250 - 370	6.0 - 8.2	0.46 ± 0.39**
4. Prostagladin + Streptozotocin	6	210 ± 134 84 - 432	4.6 - 8.0	0.73 ± 0.21

** Significant at the level of $p \leq 0.05$

* at the level of $0.05 < p < 0.1$

The increased blood sugar level (Table 1) in rats from group 2 is directly related to dm PGE_2 influence on insulin and glucagon secretion [3]. In our experiments this drug caused a lower yield of Golgi-rich membrane fraction ($0.01 < p < 0.05$), whereas galactosyltransferase activity calculated both per 1 g and per whole liver was similar to that of control one (Fig. 1).

Administration of prostaglandin and streptozotocin raised both the yield of Golgi-rich membrane fraction and the activity of galactosyltransferase to the values observed in the control group (Fig. 1 and Table 1).

These results are consistent with morphological analysis. The electron-microscope micrograph (Plate 1) shows that the morphology of the rat liver Golgi apparatus following the combined streptozotocin-prostaglandin treatment remains within the range of normal variations of healthy animals.

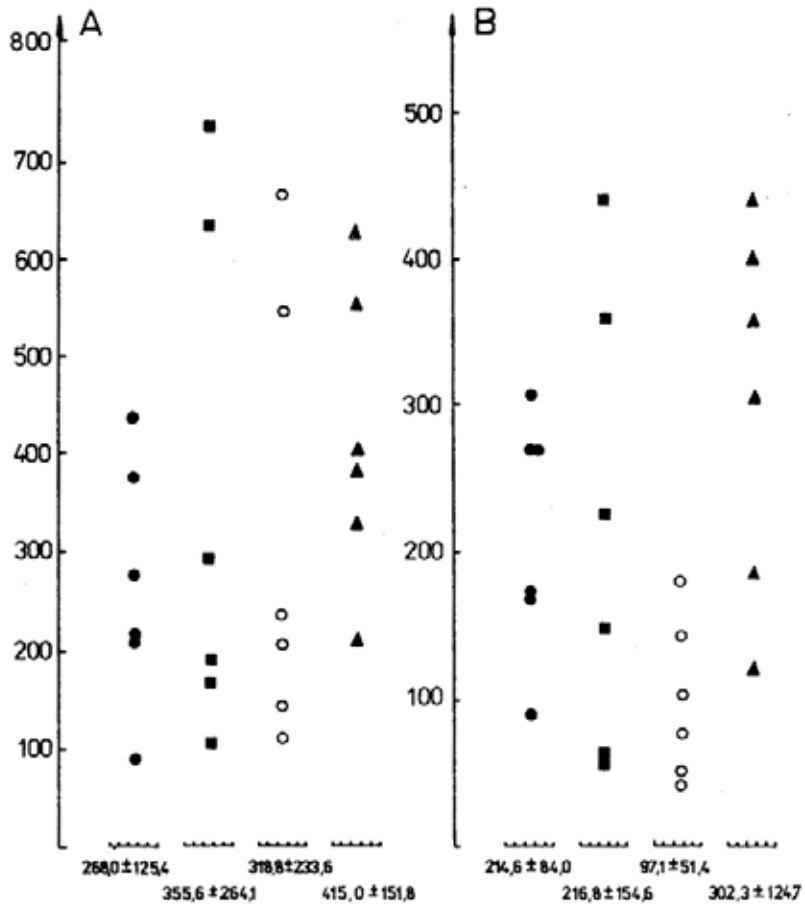

Fig. 1. Activity of UDP-Gal→GlcNAc transferase in Golgi-rich membrane fraction isolated from the liver of control ●, 16,16′-dimethylprostaglandin E_2 treated ■, streptozotocin--diabetic , and 16,16′-dimethylprostaglandin E_2 and streptozotocin treated rats ▲. For details see Material and Methods. The activity is expressed in nanomole of galactose transferred per h and per mg of protein A; and per h and per g of liver B; $t = 2.921$. $0.01 < p < 0.05$ between ● and groups calculated by Student's t test.

Stachura *et al.* [4. 5] reported that in rats dm PGE_2 protected the liver not only from cytotoxic action of large doses of galactosamine but also prevented gastric necrosis caused by ethanol. HCl. NaOH. hypertonic NaCl solution or thermal stress [14]. Also Lichtenberger *et al.* [15] observed cytoprotection by dm PGE_2 in acid-induced gastric ulcerogenesis and bleeding rats; they suggested an interesting mechanism of prostaglandin action to account for this effect.

Despite objections discussed above concerning direct comparison of groups 3 and 4. the results obtained are compatible with the idea that

dm PGE_2 protects the Golgi apparatus of rat liver from toxic effects of streptozotocin.

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