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Increased liver glucose-6-phosphatase activity after cortisone administration*

The behavior of liver glucose-6-phosphatase under physiological and pathological conditions has been under investigation in this laboratory. Studies of the glucose-6-phosphatase reaction in normal fasting animals[1], and in precancerous, neoplastic[2], regenerating, foetal and new born liver[3] have focussed our attention on the regulation of this enzymic activity in tissues.

It has been known that high doses of cortisone resulted in permanent diabetes in rat[4], characterized by hyperglycemia and glycosuria. Insulin resistant "cortisone diabetes" showing very high blood sugar levels and glycosuria was also described in human[5]. The increase in the quantity of carbohydrate after cortisone administration has been attributed to increased gluco-neogenesis and there is also evidence that some phases of the carbohydrate utilization are inhibited[6]. Recently however, it was demonstrated that cortisone administration caused a striking increase in the rate of glucose production[7]. Since glucose production from the liver is related to the rate of hydrolysis of the glucose-6-phosphate ester, it seemed of interest to study the glucose-6-phosphatase reaction in the liver of animals treated with high doses of cortisone. The preliminary results of this investigation are reported here.

Young male Wistar rats of 100 grams of weight were injected with 1 ml (25 mg) of cortisone acetate ("Cortone", Merck**) intramuscularly, daily for five days and were killed by decapitation on the sixth day. Control animals received injection of the vehicle**, in which the cortisone is dissolved. Animals were maintained on Purina Fox Chow and water *ad libitum* until sacrificed. Livers were pooled and the homogenates were prepared for enzymic studies as described in a previous communication[2]. The glucose-6-phosphatase activity was measured by the method of CORI AND CORI[8] using a 15 minutes incubation time. Liver glycogen was determined by the method of GOOD, KRAMER AND SOMOGYI[9] employing the NELSON'S adaptation of the SOMOGYI method for glucose[10]. The enzymic activities are expressed per wet weight, nitrogen, per average cell basis and also per liver weight/body weight ratio. Total nitrogen was determined by the micro-Kjeldahl procedure. Nuclear counts were done by the method of PRICE AND LAIRD[10] as modified by ALLARD *et al.*[11]. Blood glucose was determined by the method of FOLIN-WU.

The preliminary results are shown in Figs. 1 and 2. The results are presented as percentage changes from the control values which are taken arbitrarily as 100%.

Fig. 1 shows that cortisone injection increased the blood glucose level by 78%. The well known glycogenic effect of cortisone on the liver is also illustrated in Fig. 1. When liver glycogen is expressed on per cell basis the increase in glycogen content after cortisone administration is higher than when data are expressed on the conventional gram per cent wet weight basis.

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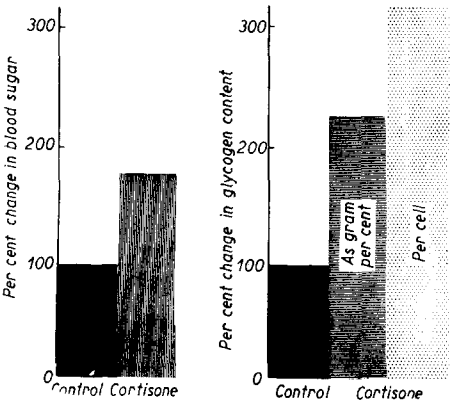

Fig. 1. The effect of cortisone administration on liver glycogen and blood sugar. The control values are taken as 100%.

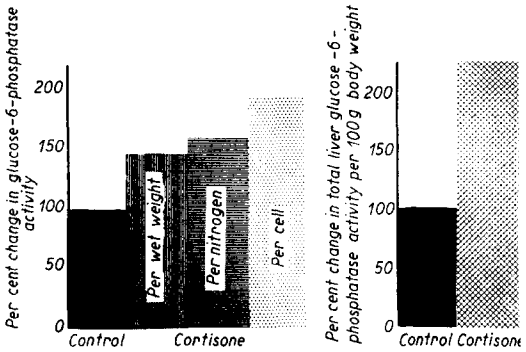

Fig. 2. The effect of cortisone administration on liver glucose-6-phosphatase activity and on total liver glucose-6-phosphatase activity per 100 g body weight. The control values are taken as 100%.

Fig. 2 shows that cortisone caused a marked increase in the glucose-6-phosphatase activity of rat liver homogenate. This increase is 49% on wet weight basis, 62% on nitrogen basis and 95%, when expressed on per cell basis.

The effect of cortisone on the total liver glucose-6-phosphatase activity per 100 g body weight is shown in Fig. 2. There is 146% more liver glucose-6-phosphatase activity present in the cortisone treated animals than in the control rats.

In vitro, cortisone has no effect on the glucose-6-phosphatase activity of normal liver homogenate.

The highly increased liver glucose-6-phosphatase activity may explain, partly at least the high blood glucose levels in cortisone treated animals. This finding supports the report of WELT *et al.*[7] on the great increase in the rate of glucose production after cortisone treatment. The high liver glucose-6-phosphatase level also agrees well with the recent data of increased liver glucose-6-phosphatase activity in alloxan diabetic rats[12].

A complete report on these studies including the effect of cortisone on the intracellular distribution of liver glucose-6-phosphatase will be published later.

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