EFFECT OF PREDNISONE ON SECRETION OF ENZYMES IN THE ALIMENTARY TRACT

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Because of the widespread use of preparations of the adrenal cortical hormones in the treatment of many different diseases, their effect on the state of the organism must be carefully examined. Besides their positive therapeutic action, these preparations may lead to undesirable changes or serious complications. One of these side effects is a disturbance of the activity of the digestive system, resulting in the development of heartburn, nausea, and gastro-intestinal hemorrhage [9, 11, 12]. The action of adrenal cortical hormones on the function of the gastro-intestinal tract and, in particular, on its enzyme secreting function, requires further study.

According to some authors, removal of an adrenal gland in experimental animals leads, as a rule, to a decrease in the secretory activity of the digestive glands. Experiments on rats, in conditions approaching those of acute experiments, revealed that adrenalectomy diminished the secretion of gastric juice and lowered its acidity [13, 14, 15]. In cats, adrenalectomy led to a fall in the amylase content of the pancreatic tissue and blood [2]. Chronic experiments on dogs showed that unilateral, and more especially bilateral, adrenalectomy caused changes in the character of the secretion of intestinal juice from isolated segments of intestine and a sharp decrease in the concentration of enzymes such as enterokinase and saccharase in the juice [7].

Conversely, administration of certain adrenal cortical hormones, and also of ACTH which stimulates the production of these hormones, to intact animals was followed by an increase in the volume of gastric [5, 12, 17, 18] and intestinal juice [4]. This action has not always been observed in clinical conditions [10, 16].

The digestive glands play an active part in the production of many specific enzymes. The character of their secretion and the mechanism of its regulation differ, so that the study of the changes in the enzyme-secreting function after the experimental administration of adrenal cortical hormone is of considerable interest.

Experiments were carried out to study the effect of prednisone on the enzymic function of the principal digestive glands. Prednisone, a member of the delta-gluco-corticoid group, possesses higher therapeutic activity and gives rise to less marked side effects than cortisone.

EXPERIMENTAL METHOD

Experiments were conducted on six adult dogs on which a preliminary operation was performed to create an isolated stomach pouch and a fistula of the pancreatic duct by Pavlov's method and an isolated segment of duodenum by Thiry's method. To prevent pathological conditions associated with the loss of pancreatic juice, the method of I. M. Dzhakson and T. F. Milyushevich [1] was used successfully after slight modification.

Gastric and intestinal juice was obtained by administration of food stimuli. The volume of juice secreted during intervals of 1 h and the total volume secreted in 5 h were determined. In the pancreatic juice the following determinations were made: the pepsin content by Gross's method, the free HCl and total acidity by titration with 0.02N NaOH solution, the content of amylase, lipase, and trypsin by the methods used in our laboratory. In addition its alkalinity was titrated and expressed as milliliters of 0.1N HCl/ml juice, and its pH was measured on a potentiometer, using a glass electrode. Intestinal juice was collected during periodic secretion for 5 h. The volumes of the liquid and solid portions of the juice (the mucous floccules) were measured, after which the juice was homogenzied

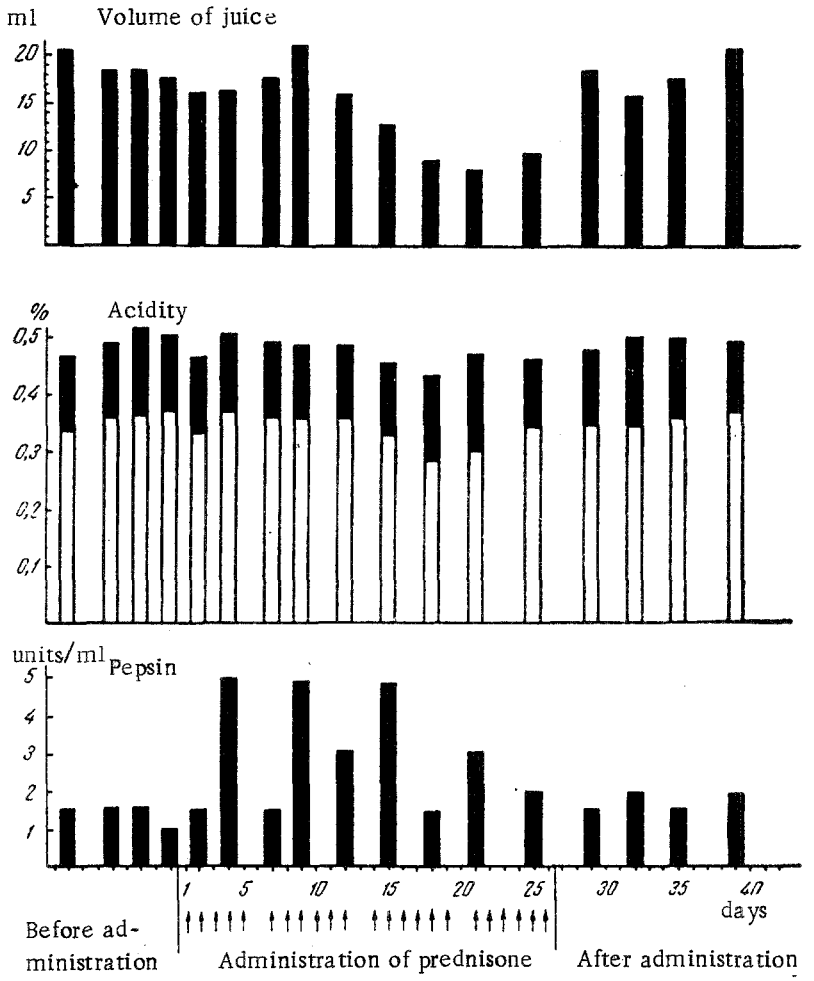

Fig. 1. Effect of prednisone on the secretory function of the stomach. In the middle part of the figure the whole column denotes the total acidity and the unshaded part the free hydrochloric acid.

and its content of intestinal enzymes (enterokinase, alkaline phosphatase, lipase, saccharase) determined by quantitative methods.

The dogs received prednisone by mouth, once daily in the morning for 4 weeks, in a dose of 0.3 mg/kg body weight. This corresponds to the dose suggested by A. I. Nesterov for the treatment of patients with rheumatoid arthritis [3]. During the 1st week, dogs Nos. 1, 2, 5, and 6 each received 5 mg daily and dogs Nos. 3 and 4 received 7.5 mg daily, during the 2nd week, all the animals received 5 mg each daily, during the 3rd week each received 2.5 mg daily, and during the 4th week 1.24 mg daily. This scheme is close to that used for hormone therapy in clinical practice.

EXPERIMENTAL RESULTS

Throughout the period of administration of the hormone in the doses specified above the general behavior and condition of the dogs remained unchanged. The animals retained their usual appetite and weight. Blood investigations revealed no changes in the erythrocyte and leukocyte counts and hemoglobin concentration, although in four dogs a transient eosinopenia was observed.

Obvious changes were observed, however, in the secretory function of the various parts of the alimentary tract. Observations on the function of the gastric glands showed no change in the latent period as a result of administration of prednisone. Both before and after administration of the hormone the latent period in experiments in which meat was given as the stimulus was between 6 and 9 min in different dogs. Administration of prednisone caused a reduction in the volume of juice secreted, which did not appear immediately but in the course of the third week of treatment or, in some cases, after administration of the hormone had been discontinued. As a rule this reduction in volume lasted not longer than 7-10 days.

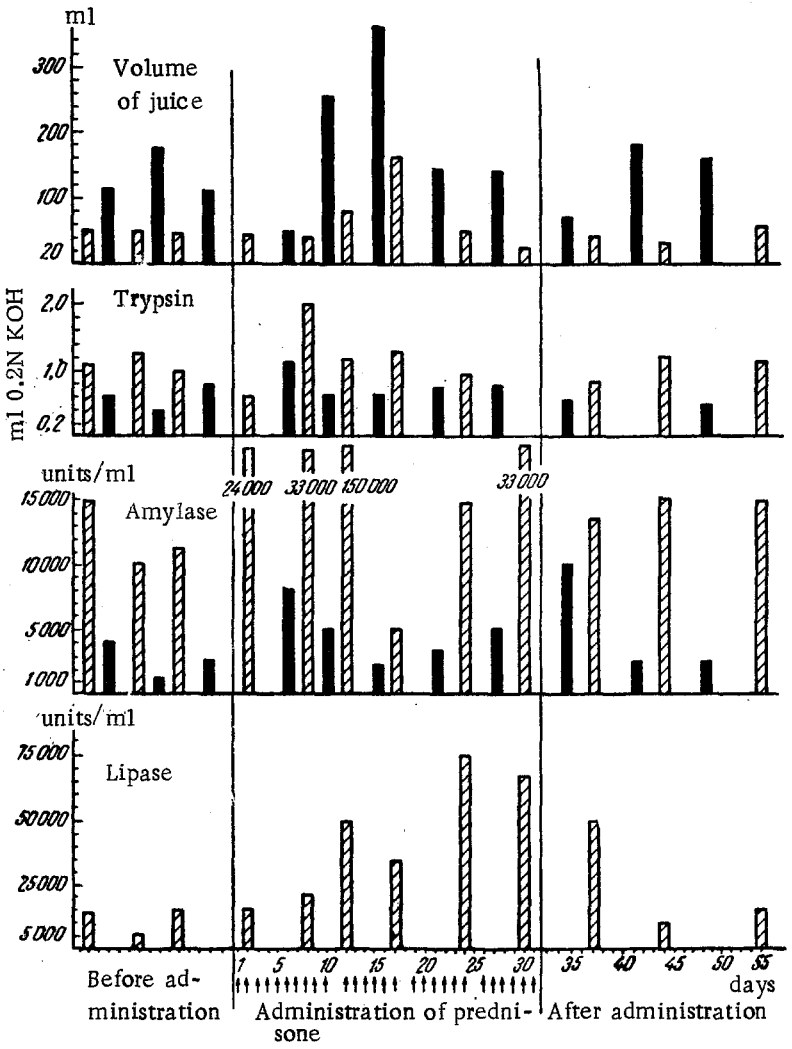

Fig. 2. Changes in the secretion of pancreatic enzymes under the influence of prednisone. The black and shaded columns show the results of experiments in which meat and fat respectively were used to stimulate secretion.

Analysis of the secretory process in the gastric glands, the activity of which is very clearly under combined nervous and neurohumoral control, revealed no marked change in the secretion pattern in favor of the first (1st hour) or second (2nd-5th hour) phase. Only in dog No. 2 was the volume of juice secreted during the neurohumoral phase increased during the administration of prednisone compared with the volume secreted during the nervous phase of gastric secretion.

The concentration of free HCl and the total acidity of the gastric juice showed no significant change after administration of the hormone. An increase in the pepsin content was observed, reaching on some days four times its initial level, as a result of administration of prednisone.

Typical results of the investigation of the secretion of gastric juice in one of the dogs are shown in Fig. 1. The volume of gastric juice secreted in response to feeding the animal with meat before administration of the hormone was between 17.2 and 20.7 ml during the 5 h experiment. From the 15th day after administration of the hormone began, its level began to fall, and it remained low until the end of this period (7.9-12.4 ml). After the animal ceased to receive the hormone, the volume of juice secreted during the experiment was the same as before administration of the hormone.

The concentration of free hydrochloric acid initially was 0.335-0.380%, and the total acidity was 0.460-0.525%. During administration of prednisone to the animals these values remained essentially unchanged, except on the days when the volume of juice was reduced. At these times the concentration of free acid in some experiments fell to

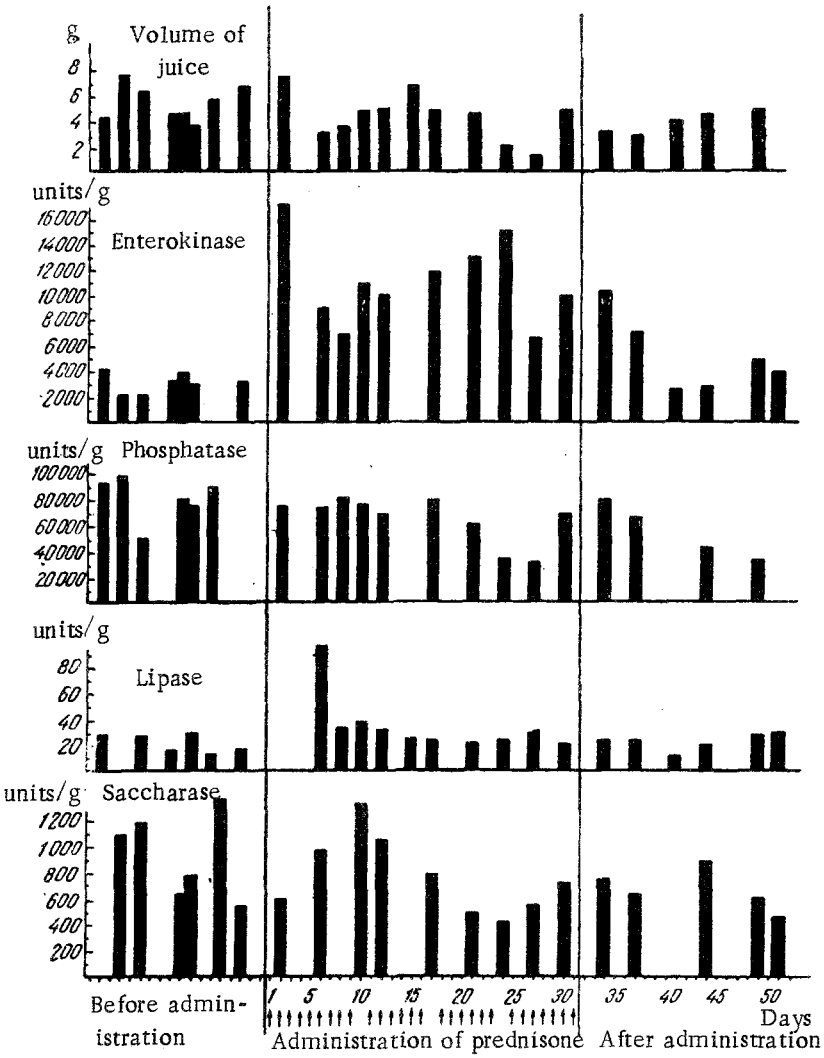

Fig. 3. Secretion of intestinal juice and enzymes during administration of prednisone.

0.277% and the total acidity to 0.430%. The pepsin level during administration of prednisone rose from 1.0-1.5 to 3-5 units/ml.

During the administration of prednisone, the pancreatic secretory function varied as follows. After the second week, the volume of juice increased, although this change did not last long and it was followed by a normal process of secretion. At the end of the period of administration of the hormone and during the first few days after its withdrawal, the secretory activity of the pancreas diminished, so that the volume of juice secreted became the same as during the initial period. Changes took place not only in the total volume of juice secreted, but also in the character of the secretion pattern during each hour of the experimental period. Whereas in the control experiments, when the animals were fed on meat the maximum of secretion fell as a rule at the 1st hour, and when they were fed on oil, at the 3rd hour, during the administration of prednisone the pattern of secretion of juice was different and the course of secretion from hour to hour in most cases was abnormal. The typical curve of secretion of juice for the food stimulus lost its distinguishing features and became indeterminate. When the administration of the hormone ceased, these changes in the activity of the pancreas were quickly normalized.

Determination of the enzyme content of the pancreatic juice in the initial period showed that this varied with the nature of the food stimulus. Feeding on fat is known to cause a sharp increase in the secretion of enzymes and in their concentration in the juice. For instance, the trypsin content of the juice obtained during feeding the dogs with meat was 0.6-0.8 ml 0.2 N KOH, and when feeding them with oil, 1.2-1.7 ml. The concentration of lipase and amylase in the juice from animals fed on fat was between 3 and 4 times higher than when meat was given. These findings are

in harmony with the view that fat is a special type of stimulus exerting a neurotrophic action on the pancreas, as a result of which the secretion of enzymes is increased [6]. During administration of prednisone, the concentration of amylase and lipase in the pancreatic juice was increased; a small increase in the concentration of trypsin was observed. The quantitative differences in the enzyme content of the pancreatic juice obtained in response to the different food stimuli stood out even more clearly than in the initial period. The concentration of amylase and lipase in the juice increased more during the administration of oil to the animals than during feeding with meat (Fig. 2).

No appreciable changes were found in the values of indices of the qualitative composition of the pancreatic juice, such as the pH and titrational alkalinity. For example, in various dogs both before and during the administration of prednisone, the pH of the juice obtained in response to meat varied from 8.0 to 8.4, and in response to oil from 7.3 to 8.1. The titrational alkalinity was 1.25-1.50 ml 0.1N HCl/ml of juice secreted during feeding with meat, and 1.12-1.36 ml during feeding with oil.

During the administration of prednisone the periodic character of the secretion of intestinal juice was not disturbed. The periods of secretion of juice from the isolated segments of the intestine recurred after the same intervals of time as in the initial period of observation. There was likewise no change in the external appearance of the juice.

The volume of intestinal juice secreted fell at the beginning aof administration of prednisone, and during the 2nd and 3rd weeks it was approximately the same as in the initial period, after which a further decrease in the secretion of juice occurred at the end of the course (4th week). It should be noted that the total volume of intestinal juice changed in these circumstances as a result of a change in the secretion of its fluid part. A characteristic example of the state of the intestinal secretion in dogs during administration of prednisone is shown in Fig. 3.

During administration of prednisone marked changes took place in the content of certain enzymes in the intestinal juice. This applied particularly to changes in the enterokinase content. It will be apparent from Fig. 3, that on the second day of the administration of prednisone the enterokinase content of 1 g of the solid portion had risen to four times its initial value, and that throughout the experiment it remained at twice or three times its initial level. Immediately after the administration of prednisone to the animal ceased, the enterokinase content was normalized. Changes affected not only the concentration of this enzyme, but also the volume secreted per hour. For example, in dog No. 5, before the experiment, 175-530 units were secreted in 1 h, while during administration of the hormone 540-4500 units were secreted; the corresponding figures for dog No. 6 were 260-880 and 540 to 2600 units.

During administration of prednisone, an increase was also observed in the lipase content of the intestinal juice, although only in the first week, and in the case of dog No. 6 (see Fig. 3), only on one or two days during the experiment. It was possible that this change could have been due to an increase in the blood lipase level as a result of an increase in the secretion of this enzyme by the pancreas. So far as the alkaline phosphatase andsaccharase of the intestinal juice are concerned, no significant changes in their concentration were observed.

The findings described above demonstrate that prednisone has a marked effect on the activity of the principal digestive glands.

A common feature of the action of prednisone on the glands in the different parts of the gastro-intestinal tract is its ability to cause an increased production of enzymes, although the changes in the enzyme secreting function of these various parts that were tested also showed certain peculiarities.

The results of our experiments concur with those of other workers reporting an increase in the secretion of pepsin in animals receiving certain adrenal corticosteroid hormones or ACTH [5, 17], although in the present experiments no increase in the acidity of the gastric juice was observed.

The distinctive features of the secretion of enzymes by the pancreas during administration of prednisone were that if oil was used to stimulate secretion in the animals the concentration of lipase and amylase in the juice rose to a greater degree than when meat was given. The fact that the production of some enzymes was increased more than the production of others by administration of prednisone demonstrates that the adrenal cortical hormones are intimately concerned in the adaptation reactions of the pancreatic glands to the nature of food stimuli.

Furthermore, the changes in the content of trypsin, lipase, and amylase did not follow a parallel course: the trypsin level changed only on certain days and to a lesser degree than the lipase or amylase levels. This fact must be taken into consideration during clinical investigation of the secretroy function of the pancreas, for it is not sufficient to determine the activity of only one enzyme to indicate the level of enzyme production as a whole.

Our experiments confirmed the essential role of the adrenal cortical hormones in the enzymes secreting function of the intestine. In particular, adrenalectomy in dogs lowers the level of the enzymes in the intestinal juice [7], while administration of prednisone raises this level. This applies above all to enterokinase, an enzyme whose concentration changes primarily in response to changes in the external and internal environments of the organism [8].

It should be noted that although enzyme production increased during the administration of prednisone, the secretion of the digestive juices was reduced after its administration for 2-3 weeks. This fact agrees with the hypothesis that these processes are independent and that the administration of prednisone effects them differently.

It is concluded, therefore, that prednisone, which causes changes in the external secretory activity of the glands of the gastro-intestinal tract, has a marked influence on the production of the digestive enzymes.

SUMMARY

The effect produced by prendisone on the secretion of digestive juices and enzymes was studied. Experiments were staged on dogs, in which isolated stomach pouches and fistulae of the pancreas were formed after Pavlov, and intestinal segments were isolated. Prednisone was given once a day/os (0.3 mg/kg of body weight). The hormone was administered for 4 weeks according to the hormone therapy scheme accepted at the clinic. During the administration of the preparation there was a rise of pepsin concentration in the gastric juice, of amylase and lipase – in the pancreatic juice, and of enterokinase – in the intestinal juice. The secretion of digestive juices decreased, as a rule, by the end of the 3rd-4th week.

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