INACTIVATION OF 17-HYDROXYCORTICOSTEROIDS IN THE LIVER OF HEALTHY DOGS AND DOGS EXPOSED TO IONIZING RADIATION

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The liver assumes an active role in corticosteroid metabolism [8]. The hepatic process of hormone inactivation apparently is coordinated with the rate of corticosteroid secretion by the adrenals. It is thought that the blood level of the hormones is a resultant of the equilibrium between the gland and the hormone inactivating organs, among which the liver plays the leading part [12].

The literature contains no information concerning the condition of the hormone inactivation process in the liver following damage with ionizing radiation. Moreover, the extent of hormone regulation by means of inactivating mechanisms assumes special importance under conditions of the endocrine disfunction peculiar to radiation sickness.

The problem in the present work was an investigation into the inactivation of adrenal cortical hormones in the liver of healthy dogs and in dogs in the course of acute radiation sickness produced by external γ-radiation.

METHODS

The work was carried out with mongrel dogs weighing 23-28 kg. The animals were subjected to surgery for the placement of angiostomy cannulas on the portal vein and the hepatic vein (according to I. A. Pigalev).

The γ-radiation was given in the ÉGO-2 apparatus at a dose level of 350 r. The animals developed typical symptoms of radiation sickness and died by the end of 2 weeks after exposure.

The level of free 17-hydroxycorticosteroids in the blood plasma was determined by the Silber and Porter method as modified by N. A. Yudaev and Yu. A. Pankov. Cortisone (0.1 g) was fed to the dogs with a small amount of meat. The blood for analysis was obtained from the portal and hepatic veins before giving the cortisone and at 1 and 2 h thereafter. The rate of 17-hydroxycorticosteroid inactivation in the liver was assessed through the difference in the steroid content of blood entering the liver (via the portal vein) and of the blood leaving the liver (via the hepatic vein).

RESULTS

As a preliminary, the changes in peripheral venous blood plasma with respect to 17-hydroxycorticosteroids were followed after oral administration of 0.1 g cortisone in 6 dogs. In 14 of 20 experiments similar typical curves were obtained showing a maximum rise in the blood corticosteroid level at 2 h and a return to the original value at 4 h after loading (see Fig.). It was found in 4 of the experiments that the highest blood corticosteroid content was reached at 1 h and in 2 other experiments the maximum was reached at 3 h after administering the cortisone. In most cases, the blood content of free 17-hydroxycorticosteroids reached a maximum level of 12-24 μg % above the starting value.

Loading with cortisone results in an increased urinary output of the 17-hydroxycorticosteroid fraction (to 0.5-1.2 mg per day) and of 17-ketosteroids (to 2-6.5 mg per day).

Level of Free 17-Hydroxycorticosteroids in Blood Plasma and the Effectiveness of Hormone Retention by the Liver of γ-Irradiated (350 r) Dogs After Administration of Cortisone (0.1 g) Via the Stomach

Conditions of experiment	No. of dog	Before cortisone administration				1 h later				2 h later			
		Portal vein	Hepatic vein	Difference	Effectiveness of retention(%)	Portal vein	Hepatic vein	Difference	Effectiveness of retention(%)	Portal vein	Hepatic vein	Difference	Effectiveness of retention(%)
		In μg %				In μg %				In μg %			
Before irradiation	Average values	10,4 (4,3—23,5)	2,7 (2,0—3,6)	7,7 (2,3—21,0)	67,7 (53,5—89,5)	24,3 (10,0—54,3)	9,5 (5,0—21,8)	14,8 (5,0—32,5)	57,6 (39,3—75,1)	30,6 (16,6—59,2)	12,8 (3,9—27,6)	17,8 (7,4—35,8)	56,7 (40,0—80,3)
After irradiation:													
In 1 h	1	3,7	0,85	2,85	77,0	26,6	14,7	11,9	44,7	17,3	11,3	6,0	34,7
» 1 »	2	4,4	2,0	2,4	54,5	9,6	6,0	3,6	37,5	18,2	7,0	11,2	61,5
» 1 »	3	5,6	2,5	3,1	55,3	17,9	8,8	9,1	50,8	43,6	13,3	30,3	69,5
» 5 days	3	5,6	4,4	1,2	21,4	23,2	18,6	4,6	19,8	19,6	17,5	2,1	10,7
» 9 »	1	3,6	1,8	1,8	50,0	13,1	12,2	0,9	6,9	25,9	14,6	11,3	43,6
» 9 »	2	7,2	5,9	1,3	18,1	—	—	—	—	19,3	12,5	6,8	35,2
» 10 »	3	15,3	12,1	3,2	20,9	20,9	16,6	4,3	20,6	17,6	15,6	2,0	11,3

Note: The limits of variation are shown in parentheses.

The dogs that reacted with greatest uniformity to cortisone administration, attaining a maximum rise in corticosteroid level in 2 h were subjected to agiostomy and 8 experiments were performed on them (see table).

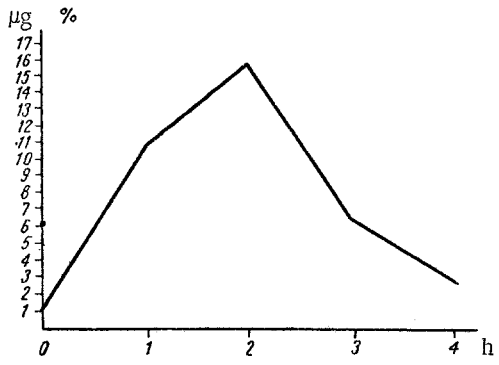
Before giving cortisone, the blood level of free 17-hydroxycorticosteroids in the portal vein was invariably higher than it was in the hepatic vein (respectively 4.3-23.5 and 2-3.6 μg %). The mean difference in hormone concentration was 7.7 μg %. Consequently, the processes of corticosteroid inactivation operate continuously in the liver even under conditions of physiological rest when natural low hormone concentrations prevail in the blood. The liver retains and apparently converts or binds from 53.5 to 89.5% (average 67.6%) of the 17-hydroxycorticosteroids delivered to it by the portal vein blood.

Loading with cortisone elevated the blood level of 17-hydroxycorticosteroids in the blood and almost always in the portal vein blood (after 1 h to an average of 13.9 μg % and after 2 h to 20.2 μg %). In response to the elevated blood corticosteroid concentration, there was a significant increase in hormone retention by the liver. In one h after cortisone administration, the difference in blood 17-hydroxycorticosteroid concentration in the portal vein, compared with that in the hepatic vein, had risen in the mean to 14.8 μg % and after 2 h the difference reached 17.8 μg %. The adequacy of reaction by the liver is of interest; the proportionality of the elevation of corticosteroids in the blood and the retention of these substances by the liver is demonstrated by the mean values for the hormone retention by the liver. Before administration of cortisone, the retention was 67.7%, 1 h after giving cortisone it was 57.6% and after 2 h 56.7%.

The data we have obtained are in agreement with those of other workers [12] indicating that the rate of hormone inactivation is determined not so much by capacity of the hormone-inactivating enzyme system in the liver, but by the quantity of hormone entering the liver. In other words, it is a matter of the adaptive quality of the hepatic enzyme system for inactivation of the corticosteroids.

We have previously observed a similar reaction of the liver to elevated levels of one or another component in the blood in studies of carbohydrate and nitrogen metabolism [3,4]. Apparently, the inactivation process relating to corticosteroid inactivation conforms to the general regulatory behavior of the liver in maintaining homeostasis.

The exposure of animals to fatal doses of γ-radiation produced characteristic changes in the hepatic activity of hormone inactivation. One h after irradiation, before loading with cortisone, it was observed that the level of corticosteroids fell in all 3 dogs in comparison with the mean control values (see table). Moreover, the rate of steroid retention by the liver at this time was not outside the normal limits. After administering cortisone in dog No. 1 after 2 h



Changes in the venous blood (femoral vein) concentration of free 17-hydroxycorticosteroids following administration of 0.1 g of cortisone via the stomach.

and in dog No. 2 after 1 h, the intensity of hormone retention by the liver was somewhat diminished (34.7 and 37.5%, respectively), but on the whole it may be noted that the hormone inactivation activity during the first 3 h after irradiation remained essentially unchanged. Thereafter, a substantial decrease occurred in the ability of the liver to retain the adrenal cortical hormones.

It is of interest also that the disturbance in the ability of the liver to inactivate the hormones was evident in the resting state as well as under loading test conditions.

The difference between the portal and hepatic vein blood plasma with respect to free 17-hydroxycorticosteroid concentrations in these experiments was less (1.2-3.2 µg %) than it was before irradiation (2.3-21 µg %). The capacity of the liver to retain the steroids varied from 18.1 to 50%. A similar picture prevailed after cortisone administration; only in 1 case, 2 h after administering the hormone, (dog No. 1, ninth day),was the function of hormone inactivation within the range of the normal lower limit (43.6%), and in this case the difference in corticosteroid levels was 11.3 µg %. In all other cases, the values did not attain the lower limits of normal.

The lowered capacity of liver tissue, after irradiation, to retain corticosteroids may be brought about by 2 causes.

First of all, it may be theorized that the processes of conversion and binding of the hormone by the liver are suppressed. It is known that individuals suffering from liver disorders show a disturbance in the hepatic processes of hormone inactivation; labeled hydrocortisone is catabolized more slowly [6] and the formation of 17-ketosteroids in the liver tissue is inhibited [7]. Considering that in acute radiation sickness there are pathological disturbances in functional activity of the liver [1-4], it may be thought with considerable certainty that the decreased inactivation of corticosteroids in the liver of the irradiated animal is associated with a suppression of activity of the enzyme systems involved. Of course, such a proposed mechanism requires direct experimental confirmation.

The second reason for the decrease in retention capacity of the liver for corticosteroids may be the increased utilization of the steroids by other tissues in the organism. The opinion is held by some [9,10] that the requirement for adrenal cortical hormones is greatly elevated in the tissues of the irradiated animals. In such a case, the decreased retention of hormone by the liver must be viewed as a regulatory act directed toward the compensation of damaged functions in the organism. Such an assumption is supported by data in the literature [11] showing that liver, removed from an organism in a condition of stress, has depressed capacity to inactivate hormones.

The second theory is supported by the findings in our experiments which indicate that there is practically no increase in the blood level of free 17-hydroxycorticosteroids in irradiated dogs, despite the considerable weakening of the hepatic barrier and the greater bulk of cortisone entering into the blood because of this.

It should also be kept in mind that disturbance of blood flow to the liver, which occurs in acute radiation sickness [5], is a possible factor which could influence the hepatic retention of corticosteroids.

LITERATURE CITED

1. G. D. Gubin, Radiobiologiya, 4, 553 (1962).
2. A. E. Ivanov and N. N. Kurshakova, Byull. éksp. biol., 7, 58 (1960).
3. T. A. Fedorova and V. P. Fedotov, Vopr. med. khimii, 5, 497 (1960).
4. V. P. Fedotov, Med. radiol., 6, 46 (1958).
5. V. P. Fedotov, Radiobiologiya, 2, 240 (1962).
6. D. Biancalana and G. Pagni, Minerva nucl., 7, 174 (1963).
7. M. Faggiano and M. Minozzi, Endocr. Sci. Cost., 26, 421 (1960).
8. O. Hechter, M. M. Soloman, and E. Caspi, Endocrinology, 53, 202 (1953).
9. S. Katsh and A. Edelmann, Fed. Proc., 10, 73 (1951).
10. R. H. Mole, Brit. J. exp. Path., 37, 528 (1956).
11. M. Perrini, Folia endocrinol. (Roma), 7, 641 (1954).
12. Z. Stary and M. Arnaki, Med. Mschr., 10, 285 (1956).