CORTICOSTEROID RESPONSE TO STRESS IN EXPERIMENTAL TOXIC HEPATITIS

B. L. Lempert, M. B. Sheikman,
T. S. Petrova, and M. G. Zaslavskaya

UDC 616.36-002-092.9-06:616.45-001:1/.3-07:616.453-008.6-072.7

After a single exposure to stress (tying down abdomen uppermost for 1 h) the response of an increase in the total unconjugated 11-hydroxycorticosteroids in the peripheral blood observed in intact animals was inhibited in rats with toxic hepatitis. This inhibition was evidently due to an increase in the initial level of 11-hydroxycorticosteroids not bound with the plasma proteins in hepatitis.

In lesions of the liver parenchyma the intensity of enzymic inactivation of the steroid hormones is reduced and interaction between the hormones and plasma proteins is disturbed [3, 4, 6, 7, 12, 13]. This leads to an increase in the concentration of the physiologically active form of corticosteroids, not bound with plasma proteins, in the peripheral blood. At the same time, the concentration of corticosteroids conjugated with the plasma proteins is reduced, so that the total level of conjugated corticosteroids in the peripheral blood remains within normal limits.

In experimental toxic hepatitis induced in rats by administration of CCl_4, there is a significant decrease in the corticosterone-binding capacity of the plasma proteins and in the glucocorticoid-inactivating function of the liver [6, 7]. These changes are also observed in experimental allergic hepatitis [1, 2]. The increase in concentration of the active form of the hormone in the blood in hepatitis might be expected to reduce the synthesis of the hormone in the adrenals through a feedback mechanism operating through the hypothalamus–pituitary–adrenal cortex system, as occurs after injection of an excess of active glucocorticoid hormones. In this way, in hepatitis the usual response of the adrenal cortex, as observed during exposure to stress, would be reduced.

The object of this investigation was to study the concentration of unconjugated 11-hydroxycorticosteroids, bound and not bound with proteins, in the peripheral blood and to examine complex formation between corticosterone and plasma proteins and the ability of liver homogenates to inactivate corticosterone during stress in intact rats and in rats with toxic hepatitis.

EXPERIMENTAL METHOD

Male albino rats weighing 250-300 g were kept on the ordinary laboratory diet. Toxic hepatitis was produced by subcutaneous injection of CCl_4 in a dose of 0.3 ml/100 g body weight, and tests were carried out 48 h after the injection. Control rats received the same dose of physiological saline at the same times. Stress was produced by Selye's method by tying the rats down, abdomen uppermost, on an operating table for 1 h. The rats were deprived of food for 18 h before the beginning of the experiment. The animals were decapitated and the following determinations made: the content of lipids in the liver by extraction of liver powder, dried to constant weight, with dichloroethane in a Soxhlet apparatus (as a test of liver damage); the corticosterone-binding capacity of the plasma proteins by the method of De Moor et al. [10]; the concentration of unconjugated 11-hydroxycorticosteroids, bound and not bound with proteins in the blood

Laboratory of Pathochemistry of Lipid Metabolism, Department of Pathophysiology, Central Postgraduate Medical Institute. Academic Research Group of Academician G. P. Rudnev. (Presented by Academician of the Academy of the Medical Sciences of the USSR G. P. Rudnev.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 71, No. 4, pp. 21-24, April, 1971. Original article submitted May 11, 1970.

TABLE 1. Effect of a Single Exposure to Stress on Indices of Corticosterone Metabolism in Intact Rats and Rats with Toxic Hepatitis (M±m)

Group of animals	Liver lipids (in g% per dry weight)	Intensity of enzymic inactivation of corticosterone in liver homogenates (in μg steroid/g fresh wt/10 min incubation at 37°C)	Corticosterone-binding capacity of plasma proteins (in μg bound hormone/100 ml plasma/15 min incubation at room temperature)	Unconjugated 11-hydroxycorticosteroids in blood plasma (in μg/100 ml)		
				not bound with plasma proteins	bound with plasma proteins	total 11-hydroxycorticosteroids
1) Intact rats	16.9±0.3 (20)	175.94±4.3 (44)	37.24±0.49 (38)	1.30±0.27 (20)	19.31±0.74 (20)	20.61±0.71 (20)
2) Intact rats in a state of stress	17.5±0.4 (19)	153.55±5.06 (16)	35.05±1.12 (16)	23.12±2.25 (16)	24.50±1.55 (16)	47.62±3.02 (16)
		$P_{2-1} < 0.001$	$P_{2-1} > 0.05$	$P_{2-1} < 0.001$	$P_{2-1} < 0.01$	$P_{2-1} < 0.001$
3) Rats with toxic hepatitis	26.5±0.7 (34)	105.7±3.80 (43)	23.10±0.77 (43)	9.50±0.95 (14)	11.81±1.04 (14)	21.31±1.30 (14)
		$P_{3-1} < 0.001$	$P_{3-1} < 0.001$	$P_{3-1} < 0.001$	$P_{3-1} < 0.001$	$P_{3-1} > 0.1$
4) Rats with toxic hepatitis and stress	26.7±0.6 (37)	95.71±3.73 (43)	21.94±1.20 (22)	13.03±1.11 (15)	11.49±0.96 (15)	24.52±1.69 (15)
		$P_{4-3} > 0.05$	$P_{4-3} > 0.1$	$P_{4-3} < 0.05$	$P_{4-3} > 0.1$	$P_{4-3} > 0.1$

Note. Number of animals shown in parentheses.

plasma by fractionation on a column with sephadex G-50 followed by spectrofluorometric estimation of both fractions by the method of Usvatova and Pankov [5]; the rate of enzymic inactivation of corticosterone in the liver homogenates by a modified method of Yates et al. [17]. Statistical analysis of the results was carried out by the Fisher-Student method.

EXPERIMENTAL RESULTS

The results given in Table 1 show that, as reported previously [6, 7], in rats with toxic hepatitis the intensity of inactivation of corticosterone in liver homogenates and the corticosterone-binding capacity of the plasma proteins are reduced, while the total (bound and not bound with proteins) level of unconjugated 11-hydroxycorticosteroids in the peripheral blood was unchanged. In intact animals subjected to stress of this type, an increase in the total level of unconjugated 11-hydroxycorticosteroids was found in the peripheral blood (it was more than doubled). An increase in the plasma concentration of corticosteroids has been observed experimentally in other types of stress [8, 11, 14]. The increase in concentration of unconjugated 11-hydroxycorticosteroids took place mainly on account of the fraction not bound with plasma proteins (this fraction was increased on the average by 20 times, whereas the fraction of protein-bound 11-hydroxycorticosteroids was increased on the average by 1.25 times). This type of stress also decreases the intensity of inactivation of corticosterone in liver homogenates, as is observed during exposure to other forms of stress [9]. Elevation of the 11-hydroxycorticosteroid level in this type of stress was thus evidently due, not only to stimulation of the hormone-synthesizing function of the adrenals, but also to a decrease in the intensity of their inactivation. No significant change in the corticosterone-binding capacity of the plasma proteins was observed under these circumstances, merely a tendency for this parameter to decrease.

When stress was produced in the rats with toxic hepatitis, with a raised initial level of 11-hydroxycorticosteroids not bound with plasma proteins, by contrast with the intact rats the concentration of total unconjugated 11-hydroxycorticosteroids in the peripheral blood was not increased. As Table 1 shows, there was a small (on the average by 1.36 times) increase in the concentration of the fraction of 11-hydroxycorticosteroids not bound with plasma proteins, but this increase was many times less than in the intact rats (in which the average increase was by 17.8 times).

The rate of secretion of adrenocortical hormones is known to be coordinated with the rate of their inactivation, which takes place mainly in the liver. In animals after partial hepatectomy, inactivation of corticosterone is reduced, secondary atrophy of the adrenal cortex develops [16], and the weight of the adrenals falls [15]. A direct relationship has been found between the size of the

adrenals and the ability of the liver to saturate the A ring of the glucocorticoid molecule with hydrogen [18]. The results of the present experiments, indicating a sharp decrease in the intensity of the reaction to stress, give direct evidence of the depressed state of the adrenal cortex in the presence of a lesion of the liver parenchyma. Changes in the corticosterone-binding capacity of the plasma proteins under the influence of stress were not observed in the rats with hepatitis. By contrast with the intact rats, under the influence of stress only a tendency for the corticosterone-inactivating function of the liver to diminish was observed in the rats with hepatitis. The reason for this, like the mechanism of the decrease in intensity of inactivation of corticosterone in the liver during stress in intact rats still remains unexplained.

The observed decrease in reactivity of the adrenal cortex to the action of stress in rats with toxic hepatitis may to some extent explain the lowering of the nonspecific resistance of the animal to various pathogenic agents in diseases accompanied by lesions of the liver parenchyma, and they attract attention to the need for hormonal correction when such patients are exposed to stress.

LITERATURE CITED

1. F. Ya. Groisberg, in: Mechanisms of Some Pathological Processes [in Russian], No. 1, Rostov-on-Don (1967), p. 201.
2. V. I. Pytskii and Yu. L. Gulyi, Pat. Fiziol., No. 4, 12 (1968).
3. V. B. Rozen and A. V. Antonichev, Probl. Éndokrinol., No. 4, 76 (1966).
4. G. P. Rudnev, M. B. Sheikman, and G. E. Latsinnik, Klin. Med., No. 1, 72 (1970).
5. I. Ya. Usvatova and Yu. A. Pankov, in: Current Methods of Estimation of Steroid Hormones in Biological Fluids [in Russian], Moscow (1968), p. 38.
6. M. B. Sheikman, T. S. Petrova, B. L. Lempert, et al., Abstracts of Sectional Proceedings of the 2nd All-Union Biochemical Congress, Section 15 [in Russian], Tashkent (1969), p. 264.
7. M. B. Sheikman, T. S. Petrova, B. L. Lempert, et al., in: Proceedings of a Conference on Current Problems in Gastroenterology [in Russian], Dushanbe (1969), p. 183.
8. N. A. Yudaev, Yu. A. Pankov, and N. P. Surikova, Probl. Éndokrinol., No. 1, 20 (1957).
9. D. L. Berliner et al., Endocrinology, 8, 621 (1961).
10. P. K. De Moor et al., J. Clin. Invest., 41, 816 (1962).
11. K. M. Knigge and K. M. Hoar, Proc. Soc. Exp. Biol. (New York), 113, 623 (1963).
12. P. Milquom and E. Baulien, in: Foie et Glandes Endocrines, Paris (1967), p. 99.
13. B. P. Murphy and C. J. Pattee, J. Clin. Endocrinol., 23, 450 (1963).
14. R. F. Timmer, Proc. Soc. Exp. Biol. (New York), 108, 615 (1961).
15. P. Urquhart et al., Endocrinology, 64, 816 (1959).
16. T. Williams, Endocrinology, 48, 651 (1951).
17. F. Yates et al., Am. J. Physiol., 194, 65 (1958).
18. F. Yates, Am. J. Physiol., 194, 373 (1958).