STRESS IN RATS WITH ALLOXAN DIABETES

I. I. Ivanova and V. F. Lapshina

UDC 616.379-008.64-092.9-06:616.45-001.1/.3

In rats with alloxan diabetes, unlike in control animals, stress does not reduce but increases the corticosterone concentration in the adrenals. Secretion of the hormone into the blood in response to stress is not reduced in diabetic animals.

There is evidence in the literature of the effect of diabetes on adrenocortical function [2-5, 6, 8-10]. However, the principles governing the response to stress in diabetes have not been elucidated.

In the investigation described below the corticosteroid content in the adrenals and in blood draining from them was studied in rats with alloxan diabetes.

EXPERIMENTAL METHOD

Male albino rats weighing initially 267-285 g were used. Alloxan was injected subcutaneously into the rats in a dose of 12 mg/100 g in the first experiments and 20 mg/100 g in the second. Throughout the experiments the diuresis was systematically determined for 3-5 h and the blood sugar concentration was estimated colorimetrically [11]. Animals receiving alloxan and the control rats were divided into two groups. In the rats of one group the concentration of corticosteroids in the adrenals was determined in the resting state (rapid decapitation of the animals) 24 h after injection of alloxan in the first experiment and 66 days after its injection in the second. In the animals of the second group, a stressor response was induced 22-23 days after injection of alloxan in the first experiment and 57-60 days after its injection in the second. The factors producing stress were tying the animals to the bench, ether anesthesia, introduction of a cannula into the renal vein, and collecting blood flowing from the adrenal gland. In the animals exposed to stress the corticosteroid concentration was determined in the blood from the adrenal vein and in the adrenal glands themselves by a chromatographic method, in which the chromatograms were stained with blue tetrazolium. When corticosteroids were determined in the adrenals, the glands from 2 rats were pooled. At the end of the experiments the blood sugar was estimated in all the animals by the method of Crecelus-Seifert [12].

EXPERIMENTAL RESULTS AND DISCUSSION

After injection of alloxan the rats developed an increased diuresis with glucosuria and hyperglycemia. In the first experiment the mean blood sugar concentration was 178.6 mg% compared with a control level of 86.59 mg%. The diuresis of individual animals with the severest diabetes was increased by 14.7 times, while the sugar concentration in the urine rose to 14%. In the second experiment individual indices were analyzed. In this way it could be shown that diabetes developed to different degrees in different animals. In 16 of the 38 rats the diabetes was more marked than in the rest. In rats with marked diabetes, 46-54 days after injection of alloxan the mean diuresis was increased by 4-5 times, 7.4% sugar was found in the urine, and the blood sugar level (after 57-60 days) exceeded 300 mg%. In the animals with less marked (latent) diabetes the diuresis was indistinguishable from normal, the sugar concentration in the urine was 0.2-0.9%, and the blood sugar was only slightly, but significantly, increased (Table 1).

Department of Human and Animal Physiology, N. G. Chernyshevskii Saratov University. (Presented by Academician of the Academy of Medical Sciences of the USSR N. A. Yudaev.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 74, No. 10, pp. 25-28, October, 1972. Original article submitted March 24, 1971.

TABLE 1. Response to Stress in Animals with Alloxan Diabetes

Expt. No.	Experimental conditions	No. of animals	Body wt. (in g)	Blood sugar (in mg %; M ± m)	Weight of adrenals: mg	Weight of adrenals: mg/100 g (M ± m)	Weight of adrenals: %	Corticosterone in adrenals: µg/100 mg (M ± m)	Corticosterone in adrenals: %	Corticosterone in adrenals:	Corticosterone in blood (in µg/100 ml; M ± m)
1	Control	30	292,33	86,59±1,85	33,70	11,53±0,35	100	7,96±1,40	100		196,43±58,54
	Stress	8	269,25	184,48±23,05 $P<0,001$	32,25	11,98±0,79	103,90	4,43±0,44 $P<0,05$	55,65		
	Diabetes	13	260,85	178,61±28,88 $P<0,002$	35,77	13,71±1,25 $P<0,05$	118,91	4,70±0,60 $P<0,05$	59,05	100	
	Diabetes + Stress	10	227,10	320,33±40,11 $P<0,001$	37,70	16,60±2,33 $P<0,05$	143,97	5,30±0,64	66,59	112,76	284,47±31,18
2	Stress	16	273,93	165,36±22,14 $P<0,001$	30,80	11,24±0,49	97,48	6,49±0,62	81,53		
	Latent diabetes	12	297,92	106,61±2,82	38,83	13,03±0,33 $P<0,05$	113,01	7,51±2,42	94,35	100	270,68±19,36
	Latent diabetes + stress	10	293,90	268,50±17,39 $P<0,001$	38,12	12,97±0,58 $P<0,05$	112,49	6,08±0,34	76,38	80,96	270,07±28,12
	Frank diabetes	8	249,00	326,45±22,86 $P<0,001$	41,00	16,46±1,16 $P<0,001$	142,76	4,23±0,19 $P<0,02$	53,14	100	
	Frank diabetes + stress	8	215,00	358,27±24,66 $P<0,001$	36,87	17,15±1,44 $P<0,001$	148,74	7,84±0,88	98,49	185,34 $P<0,01$	332,44±92,92

In the rats with diabetes the weight of the adrenals was definitely increased, and the longer the duration of the diabetes the greater that increase (2nd experiment). In the presence of manifest diabetes the corticosterone concentration in the adrenals was reduced by 41-47%. In latent diabetes the corticosterone concentration in the adrenals was unchanged, despite the increase in weight of the glands.

It might be supposed, from the decrease in corticosteroid production estimated in vitro in rats with alloxan diabetes, which is described in the literature [13], that in the present experiments the synthesis of adrenocortical hormones was depressed in the rats with diabetes. Meanwhile the decrease in the corticosterone concentration in the adrenals of these animals could also be attributed to increased liberation of the hormone from the adrenals into the blood stream.

In the rats with an intact pancreas exposed to stress the concentration of corticosterone in the adrenals was reduced, evidently because of an increase in its liberation into the blood stream not made good by synthesis of the hormone. The response to stress followed a similar course in the rats with latent diabetes. The corticosterone level in the adrenals of these animals fell to the same degree as in the animals with a normal pancreas, while the concentration of the hormone in the blood from the adrenal vein increased. In the rats with manifest diabetes, on the other hand, the corticosterone concentration in the adrenals after exposure to stress was higher than at rest. This increase was particularly marked when the duration of the diabetes was longer (2nd experiment), when it reached 85.3%.

The corticosterone concentration in the blood flowing from the adrenal was not lower in the rats with manifest diabetes exposed to stress than in animals with an intact pancreas similarly exposed. In rats with diabetes the secretion of corticosterone from the adrenals into the blood stream is thus not reduced in response to stress, whereas the concentration of the hormone in the adrenals themselves rises.

Presumably whereas during the response of normal animals to stress liberation of the hormone from the adrenals into the blood stream is not compensated by an increase in its synthesis (leading to a decrease in its level in the glands) in rats with manifest diabetes the synthesis of corticosterone is activated to a greater degree, so that its level in the adrenals is higher than in rats with diabetes at rest. These results agree with reports in the literature that the response to ACTH is preserved in diabetic patients [14].

According to some reports changes in adrenocortical function in diabetes mellitus depend on the duration of the disease. An increase in the function of these glands is found at the beginning of the disease, with a subsequent

return to normal if the disease is of long duration [8]. The results of the present investigation show that both in the initial period of the disease (after 3 weeks) and later in its course (2 months) the ability of the adrenals to respond to stress is at any rate not reduced.

Stress was accompanied by elevation of the blood sugar both in animals with an intact pancreas and in diabetic rats. Only in rats with manifestations of severe diabetes, with a high blood sugar concentration (326.45 mg%) was the sugar level increased only slightly (by 10%) in response to stress. Elevation of the blood sugar during stress in normal and diabetic rats has been described in the literature [1]; hyperglycemia is regarded as characteristic of the acute phase of the response to stress [7].

LITERATURE CITED

1. M. F. Bondarenko, Probl. Éndokrinol., No. 2, 92 (1970).
2. L. I. Geller and Z. P. Kozlova, Probl. Éndokrinol., No. 6, 32 (1969).
3. S. G. Genes, Ter. Arkh., No. 7, 3 (1965).
4. S. G. Genes, in: Problems in Neuro-endocrine Regulation [in Russian], Moscow-Leningrad (1966), p. 38.
5. E. Z. Gincherman, Probl. Éndokrinol., No. 6, 16 (1960).
6. I. F. Krivoruchko, and E. M. Kunina, Vrach. Delo, No. 10, 132 (1967).
7. I. T. Kurtsin, (Editor), Problems in Neuro-endocrine Regulation [in Russian], Moscow–Leningrad (1966).
8. L. Sh. Orkodashvili, Probl. Éndokrinol., No. 5, 34 (1968).
9. L. Sh. Orkodashvili, Probl. Éndokrinol., No. 1, 13 (1969).
10. G. M. Povolotskaya and T. P. Bezverkhaya, Probl. Éndokrinol., No. 3, 29 (1969).
11. V. E. Predtechenskii, V. M. Borovskaya, and L. T. Margolina, Laboratory Methods of Investigation [in Russian], Moscow (1950).
12. A. Gitter and L. Heilmeyer, Reference Book on Clinical Function Tests [Russian translation], Moscow (1966).
13. N. Kalant, Am. J. Physiol., 182, 503 (1955).
14. J. Lederer and J. Bataille, Ann. Endocrinol. (Paris), 27, 228 (1966).