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CORRECTION OF HORMONAL-METABOLIC DISTURBANCES IN RATS BY NATURAL ADAPTOGENS DURING DEVELOPMENT OF AN ADAPTATION SYNDROME AND FUNCTION TESTS WITH DEXAMETHASONE AND ACTH

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UDC 613.863-092.9-085.322.547.
972.3]-036.8-072.7:615.357

KEY WORDS: stress; pituitary-adrenal system; dexamethasone; ACTH; adaptogens of plant origin

Adaptogens and, in particular, those of them which belong to the group of natural origin, have been used in the combination treatment of various diseases characterized by a nonspecific component of their pathogenesis [6, 7]. The ability of these substances to control disturbances of the hormonal-metabolic status of an individual observed during the development of the adaptation syndrome is well known, but the mechanism of these effects is largely unexplained. It has been shown that the main pathogenetic stages in the formation of this group of disturbances are the successively developing (stages of anxiety and exhaustion of the stress reaction respectively) manifestations of loss of hypothalamic sensitivity to regulatory homeostatic signals and exhaustion of adrenocortical function [2, 5]. It is logical to suggest that the regulatory effects of adaptogens are largely connected with their action on this mechanism. One method of assessment of disturbances of function of the pituitary-adrenal system and, consequently, of discovering the mechanisms of the corrective effects of adaptogens, is to perform loading function tests with dexamethasone (DM) and with adrenocorticotrophic hormone (ACTH) [2, 4].

The aim of this investigation was to study the effect of adaptogens of natural origin, in the form of an extract of Baikal skullcap (*Scutellaria baicalensis*) (EBS) and its active principle – the flavonoid baikalin, on parameters of the hormonal-metabolic status of rats during the development of an adaptation syndrome, and during function tests with DM and ACTH.

Research Institute of Pharmacology, Tomsk Scientific Center, Academy of Medical Sciences of the USSR. (Presented by Academician of the Academy of Medical Sciences of the USSR E. D. Gol'dberg.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 112, No. 12, pp. 599-601, December, 1991. Original article submitted April 10, 1991.

0007-4888/91/0012-1739$12.50

TABLE 1. Effect of Natural Adaptogens in Extract of Baikal Skullcap (EBS) and of Baikalin (B) on Parameters of Hormonal-Metabolic Status of Rats Exposed Once to Stress, during Function Tests with Dexamethasone (DM, M ± m)

Experimental conditions	Glucose, mmoles/liter	Urea, mmoles/liter	Insulin, U/ml	ACTH, pg/ml	ACTH/ insulin
Intact animals	8,24±0,91	8,90±0,95	25,6±7,5	195,6±50,3	1,0
EBS	7,35±0,84	7,90±0,96	43,7±9,4	313,4±126,7	0,94
B	8,56±0,94	8,34±0,92	35,9±8,7	286,0±79,5	1,04
Stress	5,80±0,62(1)	10,8±1,30(1)	6,4±1,34(1)	483,0±91,4(1)	9,84
Stress + ESB	7,50±0,84(4)	9,21±1,30	12,4±3,12	290,0±132,2(4)	3,17
Stress + B	7,96±0,82(4)	8,80±1,10(4)	14,4±2,84	425,5±121,5	3,88
DM	9,52±1,32	8,70±0,94	39,5±9,73	92,3±19,9(1)	0,31
EBS + DM	8,24±0,96	8,11±1,18	30,9±6,5	314,0±118,0	1,33
B + DM	8,43±1,13	7,89±8,37	26,9±7,3	239,5±115,0	1,16
Stress + DM	6,07±0,75	11,2±1,43	11,6±3,2	461,3±76,4	5,22
Stress + EBS + DM	7,84±0,93 (10)	10,3±1,14	30,0±5,7 (10)	242,8±87,2 (10)	1,06
Stress + B + DM	8,92±0,97	9,9±1,20	25,4±6,7(10)	242,0±19,5(10)	1,27

Legend. Here and in Table 2 serial numbers of groups with whose parameters differences are significant at the $p \leq 0.05$ level are shown in parentheses.

TABLE 2. Effect of Natural Adaptogens in Extract of Baikal Skullcap (EBS) and of Baikalin (B) on Parameters of Hormonal-Metabolic Status of Rats during Seven Exposures to Stress and Functions Tests with ACTH (M ± m)

Experimental conditions	Glucose, mmoles/liter	Urea, mmoles/liter	Insulin, U/ml	11-OHCS, µg/ 100 ml	11-OHCS/ insulin ratio
Intact animals	8,62±0,74	9,13±0,97	22,9±6,7	14,4±2,5	1,0
EBS	8,12±0,92	10,55±1,41	21,0±5,4	9,0±1,7	0,45
B	7,30±1,24	7,42±0,81	25,9±5,2	22,8±3,3	1,41
Stress	5,64±0,82	11,85±2,31 (1)	38,4±8,3 (1)	16,1±2,7	0,67
Stress + EBS	6,37±0,72	12,07±1,64	40,2±9,7	9,6±1,3	0,38
Stress + B	7,12±1,25	9,4±0,75 (4)	23,7±3,4 (4)	19,7±4,5	1,32
ACTH	6,28±0,74	11,1±1,45	26,5±4,2	22,8±4,7 (1)	1,36
EBS + ACTH	7,12±0,85	8,80±0,94 (7)	26,9±5,3	11,3±2,5 (7)	0,67
B + ACTH	6,44±0,71	10,95±1,38	26,0±4,7	36,3±3,2	2,15
Stress + ACTH	5,50±0,68	14,73±1,65 (4,7)	30,8±4,3	15,4±2,8	0,80
Stress + EBS + ACTH	6,80±0,75	11,31±1,66	24,3±3,5	36,4±5,2 (10)	2,52
Stress + B + ACTH	6,32±0,70	10,2±1,34 (10)	25,6±4,5	27,6±3,4 (10)	1,34

EXPERIMENTAL METHOD

Experiments were carried out on 144 male Wistar rats weighing 180-200 g. Stress was induced in the animals by fixation for 12 h: once or seven times daily in order to reproduce the stages of anxiety or exhaustion of the adaptation syndrome respectively [4]. EBS and baikalin, produced by the Khar'kov All-Union Research Institute of Chemical Technology of Therapeutic Substances, were used in doses of 1 ml/kg and 15 mg/kg respectively, daily perorally, starting with the 7th day before stress. The test with DM (the "short DM test") was conducted after a single exposure to stress. DM (Dexason, from Galenika, Yugoslavia) was used in a dose of 5 µg/100 g intramuscularly in the morning, and the rats were decapitated 30 min later. The test with ACTH (corticotrophin, USSR) was given after seven exposures to stress. ACTH was injected intramuscularly in a dose of 1 U/kg in the morning, and the animals were decapitated 1 h later. The distribution of the animals by groups is shown in Tables 1 and 2. The concentrations of urea and glucose were determined in the blood serum by means of "Lachema" kits (Czechoslovakia). Insulin and ACTH levels were determined by radioimmunoassay, using test kits from IBOKh (USSR) and CIS (France). The radioactivity of these samples was measured on "Clinigamma-1272, Single" counter (LKB, Sweden). The 11-OHCS concentration was determined fluorometrically by means of a "Hitachi" spectrofluDrometer (Japan), and the ratios ACTH/insulin and 11-OHCS/insulin were calculated [5]. The results were subjected to statistical analysis by nonparametric tests [1].

EXPERIMENTAL RESULTS

In rats exposed once to stress, the various changes in the parameters of homeostasis, namely a sharp increase in the ACTH level and ACTH/insulin ratio, and an increase in the urea concentration, indicating activation of catabolism, all suggests that the animals were in the alarm phase of the adaptation syndrome (Table 1). Meanwhile, the parallel fall of the insulin and glucose concentrations is a sign of the phase of resistance, but following its least favorable, exhausting type of course [5].

Injection of DM into intact rats caused a regular fall of the ACTH level, which can be explained by activation of a negative feedback mechanism between the secretory activity of the hypothalamus and the blood glucocorticoid level. Meanwhile, in animals exposed to stress, no significant changes in the ACTH level could be found in response to administration of the hormone, evidence that they had developed total a reactivity of the hypothalamus.

The preparations studied had effects of different severity both in intact and in stressed rats; in the latter, moreover, they were mainly regulating in character, and were exhibited to the greatest degree toward parameters of hormonal metabolism, in which they took the form of a sharp reduction of the ACTH/insulin ratio (from 9.8 to 3.2-3.9). The results of the positive test with DM in the stressed animals, receiving adaptogens, suggested that an essential role in the mechanism of these regulatory effects of the preparations is played by their ability to restore normal hypothalamic reactivity.

During exposure to stress 7 times, the rats developed a raised insulin level and also high activity of catabolic processes, judging by the increased urea concentration (Table 2). These changes, along with the negative test with ACTH, can be regarded as signs of a strain on the compensatory-adaptive systems of the animal, characteristic of the exhaustion stage of the adaptation syndrome [5].

In rats receiving the preparations no significant differences were found between the parameters studied and their background values; the results of the test with ACTH, moreover, proved to be positive both in intact animals and in those treated with baikalin.

During exposure of the rats to stress after administration of adaptogens, activation of catabolic processes were not observed, and when baikalin was used, elevation of the insulin level likewise was not observed. The test with ACTH was positive when both preparations were used, suggesting that they stabilized adrenocortical function, and this was probably manifested mainly as a protective effect.

Thus the results of the investigations suggest that the effects of the natural adaptogens EBS and baikalin relative to parameters of hormonalmetabolic homeostasis in rats in the alarm or exhaustion stage of the adaptation syndrome, are characterized by definite rules, manifested as a tendency toward normalization of the majority of parameters studied, irrespective of the direction of their changes.

These regulatory effects, which have frequently been observed also for other adaptogens, are evidently characteristic of the mechanism of action of these preparations, and they probably obey the physiological rule known as the initial level rule (the Wilder–Leites rule) [3, 8]. As regards the mechanism of action of the preparations studied, judging by the results of the positive tests with DM and ACTH, an essential role may be played by regulation of the functional activity of the hypothalamus and adrenal cortex by these adaptogens, bearing in mind that these are the principal homeostatic structures, whose disturbance is primarily responsible for the series of changes characteristic of formation of the stress reaction.

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