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EFFECT OF *Bryonia alba* ROOT EXTRACT ON LIPID PEROXIDATION IN THE LIVER OF RATS WITH ALLOXAN DIABETES

K. G. Karagezyan, G. S. Vartanyan, and A. G. Panosyan

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KEY WORDS: diabetes; rat liver; *Bryonia alba* root extract; lipid peroxidation; fatty acid composition.

In previous investigations [14] the writers showed that in experimental alloxan diabetes (AD) an extract of *Bryonia alba* roots has a hypoglycemic action, due to the fraction of trihydroxyoctadecadienoic acids, which exhibit prostaglandin-like activity.

In diabetes depression of insulin secretion is accompanied by specific disturbances in fatty acid and prostaglandin metabolism [8, 9], and the role of special factor regulating the secretion of the hormone is ascribed to phospholipase A_2 [12]. The polyenic fatty acids set free are not only transformed into prostaglandins, but also are oxidized into monohydroperoxides, which subsequently break down to form hydroxy and epoxy acids [7]. The trihydroxyoctadecadienoic acids are C-18 homologs of the end products of the lipoxygenase pathway of oxidation of arachidonic and icosa-8, 11, 14-trienoic acids. Their precursors – the corresponding monohydroperoxides – can inhibit prostacyclin biosynthesis in blood vessel walls [6], and this is regarded as one possible cause of the development of atherosclerotic complications that are characteristic of diabetes [10], accompanied by a simultaneous rise in the blood lipid peroxide (LP) level [15].

The object of the present investigation was to study the effect of *Bryonia alba* root extract (BAE) on the formation of lipid peroxidation products in homogenates and the microsomal fraction of the liver (MFL) of albino rats with AD, and also on the fatty acid composition of individual phospholipids (PL).

EXPERIMENTAL METHOD

Diabetes was induced by the method described previously [3]. From the 7th day of the disease the animals were given a daily intramuscular injection of an aqueous solution of BAE in a dose of 5 mg/kg body weight. The MFL was isolated by differential centrifugation. The malonic dialdehyde (MDA) content was determined by the method in [2]. Total and individual PL and free fatty acids were isolated by the standard methods [5]. Gas–liquid chromatography (Pye Unicam) was done on 1200 × 3 mm, 180C columns, with 8% PEGA and 3% E-30 on the Gas Chrom Q instrument.

EXPERIMENTAL RESULTS

The results indicate an increase in MDA formation both in homogenates and in MFL of rats with AD (Table 1), in agreement with data on the increase in the LP level in various pathological states [2]. These changes were accompanied

Laboratory of Lipid Biochemistry, Institute of Biochemistry, Academy of Sciences of the Armenian SSR, Erevan.
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TABLE 1. MDA Content in Homogenates (in μmoles/g tissue) and Microsomes (in nmoles/mg protein) in Liver of Rats with AD before and after Injection of BAE (M ± m)

Test object	MDA		
	control	diabetes	diabetes + BAE
Homogenate	2,90 ± 0,06	4,35 ± 0,21 $P<0,001$	3,19 ± 0,17 $P<0,001$
Microsomes, ascorbate-dependent peroxidation system	13,27 ± 0,43	20,16 ± 0,72 $P<0,001$	14,15 ± 0,79 $P<0,001$
Microsomes, NADPH-dependent peroxidation system	10,98 ± 0,32	14,26 ± 1,08 $P<0,01$	10,89 ± 0,70 $P<0,05$

Legend. Number of experiments in parentheses.

TABLE 2. Fatty Acid Composition (in %) of Individual PL in Liver of Rats with AD before and after Injection of BAE (M ± m)

Acid	Phosphatidylcholines			Lysophosphatidylcholines			Lysophosphatidylethanolamines		
	control	diabetes	diabetes+BAE	control	diabetes	diabetes+BAE	control	diabetes	diabetes+BAE
16:0	22,40	30,28	25,94	23,96	30,17	57,14	—	52,67	50,27
16:1	1,34	0,23	1,80	2,40	1,27	5,71	—	2,43	3,32
18:0	31,36	50,92	27,73	28,22	61,15	17,14	—	36,47	34,55
18:1	8,06	13,76	15,51	8,57	7,01	20,00	—	7,83	8,12
18:2	8,06	1,14	7,50	6,00	—	—	—	—	3,01
20:4	27,77	3,67	23,01	30,85	—	—	—	0,60	0,73

Legend. Here and in Tables 3 and 4 mean values of 2 or 3 determinations are given.

TABLE 3. Fatty Acid Composition (in %) of Liver Microsomes of Rats with AD before and after Injection of BAE (M ± m)

Acid	Control	Diabetes	Diabetes + BAE
16	1,49	4,19	2,77
16:0	25,61	37,23	30,38
16:1	4,12	1,83	3,01
18:0	22,88	25,55	23,42
18:1	23,61	12,43	16,78
18:2	12,81	6,54	7,14
20:4	14,92	11,68	14,40
22:6	4,57	0,55	1,10

TABLE 4. Composition and Content (in %) of Free and Lipid-Bound Fatty Acids in Liver of Rats with AD before and after Injection of BAE (M ± m)

Acid	Control		Diabetes		Diabetes + BAE	
	free fatty acids	bound fatty acids	free fatty acids	bound fatty acids	free fatty acids	bound fatty acids
16	5,79	0,99	1,30	0,40	2,66	1,07
16:0	48,19	23,79	39,61	29,55	48,36	30,30
16:1	9,98	2,13	8,44	2,61	5,74	3,21
18:0	12,17	24,96	11,69	20,10	11,27	19,82
18:1	14,03	21,49	19,48	26,26	17,21	21,92
18:2	7,67	7,25	12,99	4,90	9,84	0,73
20:4	2,17	19,21	6,49	16,18	4,92	18,36
22:6	—	—	—	—	—	4,59

by a fall in the relative percentage of arachidonic and docosahexaenoic acids, the main substrates in peroxidation reactions [13], in the composition of the microsomal lipids. The writers showed previously [1] that in AD the relative percentage of polyunsaturated fatty acids in the composition of some PL fractions is reduced, and this is accompanied by considerable abnormalities in the composition of the liver PL [3], and, in particular, by a twofold increase in the content of lysophosphatidylcholines, and by the appearance of lysophosphatidylethanolamines, which were not found in the liver of the control animals. In the composition of the lysophospholipids, linoleic acid was totally absent, and arachidonic acid was detected in trace quantities only in the composition of the lysophosphatidylethanolamines (Table 2). The changes in the composition and content of PL noted above, on the one hand, and the increase in the relative percentage of unsaturated fatty acids in the composition of the free fatty acids (Tables 3 and 4), with a simultaneous increase in their absolute content, on the other hand, are evidence of increased phospholipase A_2 activity in diabetes. The possibility cannot be ruled out that the increase in the content of free fatty acids may also be due both to inhibition of activity of the enzymes responsible for their esterification, and also the involvement of L-α-glycerophosphate in the reaction of dihydroxyacetone phosphate formation. This takes place by the action of glycerophosphate dehydrogenase, whose activity in diabetes has been shown to be appreciably increased [3], in agreement with data in the literature on intensification of gluconeogenesis in the liver in diabetes [4].

Injection of BAE was accompanied both by a decrease in the free fatty acid content and by restoration of the original glycerophosphate dehydrogenase activity. In the writers' view, this can be interpreted as a special manifestation of the normalizing effect on liver function, together with regulation of the LP level and the fatty acid composition of individual PL (Tables 1-4). A fact of special interest is the maximal normalization of the fatty acid composition of the phosphatidylcholines which, as we know, play the role of principal carriers of polyunsaturated fatty acids and play an active role in the structural organization of biological membranes and in regulation of the activity of the most important enzyme systems of the cell organelles, especially the liver microsomes [11].

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ACTION OF CYCLIC AMP ON GLYCOLYSIS AND GLYCOGENOLYSIS IN THE ALBINO RAT LIVER AND ADRENALS

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L. E. Panin and T. A. Tret'yakova

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The rate of glycolysis in different tissues is modified in different ways under the influence of subextremal and extremal factors: It is slowed in the liver, muscles, and heart, but is unchanged, for example, in the brain [3]. Glycogenolysis undergoes phasic changes: Activation in the initial period of action of an extremal stimulus is followed by inhibition, but no such changes are found in the brain [3]. Inhibition of glycolysis (and glycogenolysis) during stress is associated with an increase in production of catecholamines and glucocorticoids, which act indirectly through cyclic AMP-dependent mechanisms [3-5]. The cyclic AMP content in the adrenals is increased under the influence of ACTH [6]. A similar situation arises during stress, when a decrease in the rate of glycolysis and glycogenolysis would inhibit steroid production as a result of insufficient formation of glucose-6-phosphate (G6P) and, consequently, of NADPH. Activity of phosphorylase and glucose-6-phosphate dehydrogenase in the adrenals rises during stress [1, 7]. Conditions enabling different physiological effects to be produced by the action of the same hormones are thus formed in different tissues in the course of differentiation. Changes in the direction of action of a hormone in the same hormone depending on the conditions are also possible [3, 4]. However, these conditions are as yet unknown.

The object of this investigation was to study changes in glycolysis and glycogenolysis in two organs with high functional specialization – the liver and adrenals – during stress and to examine the role of cyclic AMP in these changes.

Laboratory of Biochemistry, Institute of Clinical and Experimental Medicine, Siberian Branch, Academy of Medical Sciences of the USSR, Novosibirsk.

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