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EFFECT OF TRIHYDROXYOCTADECADIENOIC ACIDS ON BLOOD LEVELS OF PROSTAGLANDINS E_2 AND $F_{2\alpha}$ AND OF 5-HYDROXYEICOSATETRAENOIC ACID IN RATS WITH ALLOXAN DIABETES

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It was shown previously that the fraction of trihydroxyoctadecadienoic acids (THODA), isolated from the roots of *Bryonia alba* L. (Cucurbitaceae), causes the blood glucose level to fall in rats with alloxan diabetes [2]. C_{20}-homologs of the THODA of *Bryonia* are formed in platelets from 12-hydroperoxyeicosatetraenoic acid (12-HPETE), a product of lipoxygenase oxidation of arachidonic acid (AA). This process is observed in the presence of high concentrations of AA and subsides in the presence of glucose, for activation of the hexose monophosphate shunt leads to the formation of reduced glutathione, and then to reduction of 12-HPETE into 12-hydroxyeicosatetraenoic acid [5, 6].

The eicosanoids, as we know, are modulators of secretion of the hormones involved in regulation of the blood glucose level [4, 9]. In particular, leukotrienes B_4, C_4, and E_4 [11], 5-hydroxyeicosatetraenoic acid (5-HETE) [15], and 12-HPETE [9] are stimulators of insulin secretion. We also know that when the blood glucose concentration falls, there is a sharp increase in synthesis of both thromboxane A_2 and prostacycline [12], whereas when the glucose concentration in the medium rises, biosynthesis of prostaglandins E_2 and $F_{2\alpha}$ (PGE_2 and $PGF_{2\alpha}$, respectively) is inhibited [14]. Meanwhile, in diabetes biosynthesis of prostacycline [12] is stimulated and synthesis of leukotriene B_4 is depressed [8]. The formation of these various eicosanoids, in turn, has a decisive role in the vascular disturbances accompanying diabetes [7, 13].

In connection with the facts described above, the effect of the THODA fraction on blood levels of some eicosanoids and, in particular, of PGE_2, $PGF_{2\alpha}$, and 5-HETE in rats with alloxan diabetes was studied.

EXPERIMENTAL METHOD

The THODA fraction was isolated from *Bryonia* roots by the method described previously [3]. Experiments were carried out on noninbred albino rats weighing 170-220 g. Diabetes was induced by a single intraperitoneal injection of alloxan (150 mg/kg). Starting from the 7th day after injection of alloxan, when the group of animals had a blood glucose concentration of not less than 10 mM, an aqueous solution of the sodium salt of THODA was injected intramuscularly in a dose of 0.05 mg/kg daily. Animals of the control group received injections of the corresponding volumes of isotonic NaCl solution. The hungry animals were decapitated on the 21st day after injection of alloxan, under superficial ether anesthesia.

Concentrations of PGE_2, $PGF_{2\alpha}$, and 5-HETE in peripheral blood plasma were determined by radioimmunoassay, using kits from the firms Seragen and Clinical Assays (USA). To assess the loss of substances during extraction and chromatography, $^3H_8$-PGE_2 (140-170 Ci/mmole), $^3H_8$-$PGF_{2\alpha}$ (160-180 Ci/mmole), from Amersham Corporation (England), and $^3H_8$-5-HETE (from Seragen) were used. The yield of PGE_2, $PGF_{2\alpha}$, and 5-HETE was 80, 72, and 85%, respectively.

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TABLE 1. Plasma PGE_2, $PGF_{2\alpha}$, and 5-HETE Levels in Albino Rats with Alloxan Diabetes and after Injection of THODA

Parameter	Control	Diabetes	Diabetes + THODA
PEG_2, pg/ml	786,1±59,7	1052,3±80,8*	1296,1±104,0
$PEG_{2\alpha}$, ng/ml	15,4±1,1	2,3±0,1	20,6±1,7*
5-HETE, pg/ml	95,4±15,5	71,4±22,2	251,8±24,6*

Legend. *P < 0.05. Number of experiments 7-8.

Radioactivity of the samples was determined on an SL-4221 spectrophotometer (Roche Bioelectronique, France), using Bray's scintillator.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that the $PGF_{2\alpha}$ concentration in the blood plasma of rats with alloxan diabetes was reduced by 85%, and the 5-HETE concentration by 25%, whereas the PGE_2 level rose by 34%.

After injection of the THODA fraction into the diabetic animals a sharp increase was observed in the concentration of 5-HETE, which stimulates insulin secretion [15], and also in the concentration of $PGF_{2\alpha}$ above the control level. A similar but weaker effect was produced by the THODA fraction on PGE_2, whose blood level also was raised.

Since the free AA concentration in the blood of diabetic rats is lowered by the action of THODA [1], it can be concluded from the results described above that the hypoglycemic action of THODA is connected with activation of oxidative metabolism by AA.

To shed light on relations of cause and effect with respect to the effects of THODA described above, further investigations are needed; these will perhaps enable a fresh approach to be made to the search for hypoglycemic agents and will contribute to a better understanding of the role of the various eicosanoids in regulation of the blood glucose level.

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