ECOLOGY

Isoforms of Thyroxin-Binding Globulin as Markers of Ecologically Induced Pathologies

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The content of thyroxin-binding globulin isoforms differing by the carbohydrate constituent is significantly increased in the blood of coronary patients and patients with insulin-dependent diabetes mellitus compared to normal and is comparable to that in cancer patients. Enhanced biosynthesis of abnormal proteins due to structural and functional reorganization of plasma membranes is probably responsible for accumulation of thyroxin-binding globulin isoforms.

Key Words: *thyroxin-binding globulin; plasma membranes; atherosclerosis; diabetes mellitus; cancer*

Biological functions of glycoproteins are numerous: they act as sensory molecules in protein-protein and cell-cell interactions, participate in protection of the organism from infections and dehydration, and are involved in the transport of some lipophilic molecules. Fucosylated isoforms of glycoproteins are now regarded as molecular markers of cancer. Abnormally fucosylated serum proteins were detected in some neoplastic processes: α_1-proteinase inhibitor in breast and ovarian cancer [7], α-fetoprotein in liver cancer [5], haptoglobin in ovarian cancer [9], and immunoglobulins in myeloma [8]; fucose binding by serum albumin from cancer patients was also reported [4].

We detected molecular variants of thyroxin-binding globulin (TBG) differing by the structure of its carbohydrate component in the blood of patients with tumors of different locations [2].

In this study we investigated serum concentrations of TBG isoforms differing by glycosylation pattern in coronary heart disease and insulin-dependent diabetes mellitus (IDDM), *i.e.,* pathologies associated with unfavorable environmental factors.

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MATERIALS AND METHODS

Adolescents from most ecologically favorable regions of Minsk (n=22, reference group), coronary patients (n=23, mean age 15 years, boys and girls), diabetics (n=15, mean age 14 years) hospitalized at Research and Clinical Institute of Radiation Medicine and Endocrinology (Aksakovshchina settlement) in 2000, and cancer patients (8 with lung cancer and 9 with breast cancer) were examined. Groups of adolescents with CHD and IDDM were formed on the basis of patients' age.

The content of molecular variants of TBG: TBG-1 (N-acetyl lactose amine type) and fucosylated TBG (FTBG) was measured as described elsewhere [2] by affinity chromatography on concanavalin A-Sepharose and lentil-Sepharose 4B, respectively.

RESULTS

We previously revealed increased content of minor molecules characterized by aberrant glycosylation patterns in the blood of clinically healthy adolescents with pronounced euthyroid syndrome from Khoiniki town (^{137}Cs pollution 185-555 kBq/m^2, Republican Catalogue) [2]. Blood content of FTBG in these ado-

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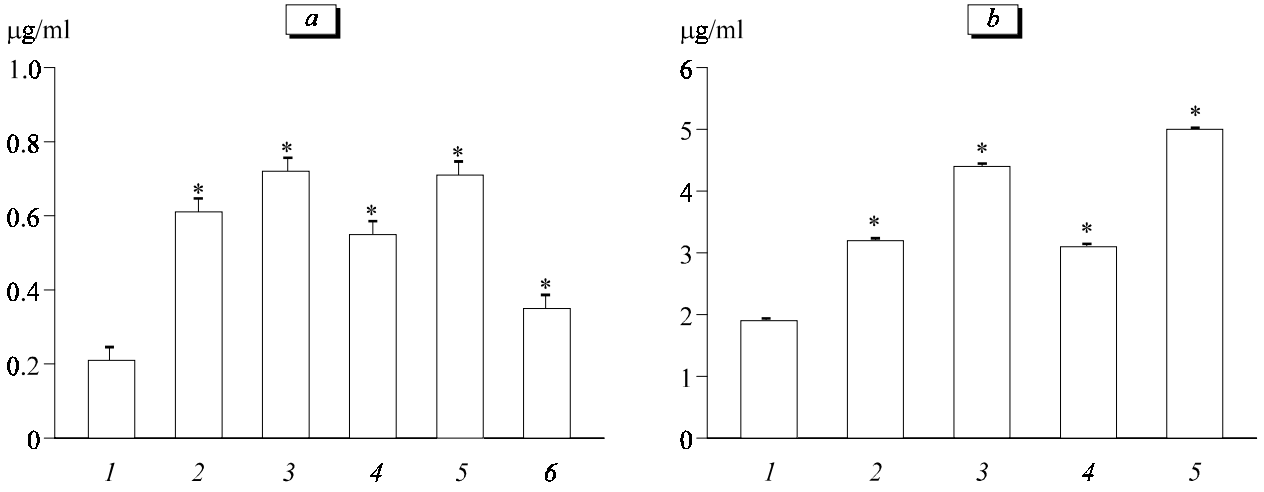

Fig. 1. Concentrations of thyroxin-binding globulin-1 (*a*) and fucosylated thyroxin-binding globulin (*b*) in reference group (*1*), adolescents with CHD (*2*), IDDM (*3*), patients with lung cancer (*4*) and breast cancer (*5*), and adolescents from Khoiniki (*6*, published data [2]). *$p<0.05$ compared to the control.

lescents was lower (1.92±0.24 μg/ml) that in cancer patients (2.45±0.25 μg/ml, breast cancer), but higher than in intact controls (1.54±0.02 μg/ml). This prompted us to refer these adolescents to a high risk group for cancer. Increased heterogeneity of serum proteins differing by the structure of the carbohydrate constituent and, especially, the appearance of fucosylated proteins were regarded as a process associated with carcinogenesis. We analyzed blood concentrations of some cancer markers in these adolescents: β_2-microglobulin (used for the diagnosis of lymphoproliferative diseases), carcinoembryonic antigen (the concentration of this marker sharply increases in mammary, testicular, and lung cancer), and antibodies to thyroglobulin (used for the diagnosis of Hashimoto goiter, Graves' disease, and thyroid cancer). The data were compared with the corresponding values in the control group consisting of age-matched adolescents living in Minsk (Table 1). Serum concentrations of all cancer markers in the high risk group adolescents were within normal.

Environmental factors play a crucial role in the pathogenesis of atherosclerosis and diabetes mellitus.

TABLE 1. Serum Concentrations of Molecular Markers of Cancer in Healthy Adolescents Living in Khoiniki Settlement (*M*±*m*)

Marker	Control (*n*=22)	Adolescents from Khoiniki (*n*=20)
β_2-microglobulin, mg/liter	1.60±0.09	1.8±0.2
Antibodies to thyroglobulin, IU/ml	58.90±6.65	61.10±5.94
Carcinoembryonic antigen, mg/liter	2.87±0.43	3.67±0.61

It was interesting to measure blood concentrations of TBG isoforms in adolescents with CHD and IDDM, because epidemiological screening in Gomel and Mogilev regions of Belarus showed a stable increase in the incidence of CHD, rheumatoid arthritis, and IDDM in adolescents from these territories. Moreover, increasing morbidity in younger age groups reflecting the early aging syndrome was noted.

Of particular interest is activation of abnormal TBG glycosylation in diabetics: the concentration of minor TBG variant (TBG-1) in these patients was statistically higher than in the reference group. Similar trends to selective intensification of TBG-1 synthesis were observed in adolescents with CHD (Fig. 1, *a*).

Serum concentrations of FTBG in coronary and diabetic adolescents were comparable with those in cancer patients (Fig. 1, *b*). Intensive fucosylation of serum glycoproteins can be due to increased fucose concentration in the blood of these patients.

Hence, not only cancer, but also atherosclerosis and IDDM are associated with the presence of TBG variants (TBG-1 and FTBG) differing by the structure of carbohydrate component. Changes in serum protein glycosylation in cancer, IDDM, and atherosclerosis can be due to impairment of cell membranes induced by environmental factors.

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