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Thyroxine-Binding Globulin: Investigation of Microheterogeneity*

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ABSTRACT. Preparation of T₄-binding globulin (TBG) from human serum was performed using only two affinity chromatography steps. Purity of the protein was demonstrated by a single band in overloaded disc and sodium dodecyl sulfate electrophoresis, equimolar binding to T₄, and linearity in sedimentation velocity run. The molecular weight was calculated to be 60,000 ± 3,000 daltons (n = 3), the sedimentation coefficient was 3.95S, and the Stokes' radius was 37 Å. The amino acid composition was found to be in good agreement with the calculations of other authors. By isoelectric focussing (IEF), pure TBG showed four main bands at pH 4.25, 4.35, 4.45, and 4.55 together with several fainter bands. The N-acetylneuraminic acid (NANA) content of the four TBG bands isolated by preparative IEF was found to decrease from 10.2 mol NANA/mol TBG in the band at pH 4.25 to 4.8 mol NANA/mol TBG in the band at pH 4.55. No significant difference in the affinity constants of the TBG bands to T₄ was found. The affinity constants for TBG ranged from 3.1 × 10⁹ to 7.2 × 10⁹ M⁻¹. Sequential kinetic desialylation of pure TBG

resulted in a progressive tendency toward one major band at pH 6.0.

In native sera, microheterogeneity of TBG was detected after IEF on polyacrylamide gel plates by immunofixation. The typical TBG patterns shown by pure TBG were also found in normal subjects. Characteristic deviations from this pattern were found in the sera of females during estrogen therapy or pregnancy, where there was a gradual increase in density of the band at pH 4.25 and the appearance of an additional band at pH 4.15. In sera from patients with liver disease and elevated TBG levels, there was a fading of the acidic bands, whereas the more alkaline band at pH 4.55 was intensified.

It is therefore proposed that microheterogeneity of TBG is caused by differences in NANA content and that variations of TBG patterns in native sera may reflect altered TBG synthesis or degradation. A genetically related microheterogeneity of TBG could not be demonstrated after examination of 800 sera, including 2 families with quantitative TBG deficiency. (*J Clin Endocrinol Metab* 52: 657, 1981)

SINCE its discovery by Gordon *et al.* (1) in 1952, T₄-binding globulin (TBG) has been a subject of intensive research. When affinity chromatography was introduced in 1969 by Marshall and Pensky (2) for purification of TBG, most of the physicochemical properties of the isolated protein could be confirmed (3-6). It is well established that TBG binds equimolar quantities of T₄ and T₃ (5) with affinity constants of approximately 10¹⁰ and 10⁹ M⁻¹, respectively (7). TBG is an inter- α -globulin with a molecular weight of about 60,000 daltons and a carbohydrate content of approximately 15% (8). It is composed of a single polypeptide chain (9) and four carbohydrate side chains (10).

In 1973, Marshall *et al.* (11) first demonstrated a microheterogeneity of isolated TBG by isoelectric focusing (IEF), and this has been confirmed in our laboratories (5, 12, 13). The cause of this microheterogeneity is still controversial but is generally assumed to be produced by genetically determined variation in amino acid composition

of TBG (11) or by an irreversible transition of TBG near its isoelectric point (14).

In this paper, we used a mild and rapid two-step purification procedure for TBG from human serum (13), a convenient method for detecting microheterogeneity patterns of TBG in native sera (12), and the preparative IEF technique to examine whether microheterogeneity of TBG is an artifact or might be explained by a difference in N-acetylneuraminic acid (NANA) content. Simultaneously, we screened for evidence of genetic variations in the TBG polypeptide chain.

Materials and Methods

Source of serum for TBG preparation and investigation of TBG microheterogeneity

Human serum for isolation of TBG was obtained from healthy donors. Sera were pooled, frozen at once, and stored at -24 C. For examination of the microheterogeneity of TBG, individual sera were either stored at -24 C or used freshly. No preservatives were added to the sera.

Preparation of TBG

T₃ (600 mg; Henning, Berlin, Germany) were dissolved in 5 ml 1 M NaOH, then 10 ml dimethyl-sulfoxide and 10 ml 0.1 M

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borate buffer were added and the pH was adjusted to pH 10.0 with 1 M HCl. [¹²⁵I]T₃ (1 ml; Hoechst AG, Frankfurt, Germany), purified by chromatography on alkaline Sephadex G-25 superfine (Pharmacia Fine Chemicals, Piscataway, NJ), was then added for later calculation of bound T₃. Moist Epoxy-activated Sepharose 6B (45 ml; Pharmacia) was then added to the T₃ solution, and the gel suspension was gently shaken overnight at room temperature. After the gel was filtered and washed once with 0.01 M NaOH, it was shaken for an additional 4 h in 200 ml 1 M ethanolamine to saturate free oxirane groups. After washing the gel alternatively with 1 liter 0.1 M acetate buffer, pH 4.0, and 1 liter 0.1 M glycine NaOH buffer, pH 9.0, each containing 0.5 M NaCl, the T₃-Sepharose 6B was counted for bound radioactivity. On the average, 150 mg T₃ were linked to 45 ml Epoxy-Sepharose 6B.

TBG was extracted batchwise by gently shaking T₃-Epoxy-Sepharose 6B in human serum (9 ml Epoxy-Sepharose/liter serum) diluted 2:1 with 0.1 M barbital buffer, pH 8.6, at room temperature for 1 h. After sedimentation of the Sepharose at 4 C, the supernatant was decanted and the T₃-Sepharose was packed in a 2 × 15-cm column. Alternatively, TBG from 500 ml human serum or less was extracted quantitatively by affinity chromatography on a 45-ml T₃-Epoxy-Sepharose column. From here on, all steps were performed at 4 C and monitored at 280 nm with Uvicord II (LKB-Produkter, Bromma, Sweden). Unspecific bound proteins were eluted from the T₃-Epoxy-Sepharose 6B by extensive washing with 500 ml 0.1 M barbital buffer, pH 8.6, containing 1 M NaCl-500 ml 0.1 M Tris-HCl buffer, pH 8.6, with 2 M NaCl-500 ml 0.05 M NaPO₄-buffer, pH 6.8, with 2 M NaCl-500 ml 0.1 M Tris-HCl-buffer, pH 8.6.

TBG was then eluted specifically with 200 ml of a 10 mg/dl T₄ solution. T₄ (10 mg; Henning) was dissolved in 100 ml 0.1 M Tris-HCl buffer, pH 8.6, containing 0.1 g human serum albumin (HSA) purchased from Behring-Werke AG (Frankfurt, Germany). The HSA had to be rechromatographed on Concanavalin A (Con A)-Sepharose (Pharmacia) because of contamination with other proteins. To remove endogenous HSA and the HSA from the T₄ solution, the TBG peak was applied to a 2 × 50-cm Con A-Sepharose 4B column. After washing with 300 ml 0.05 M Tris-HCl buffer, pH 7.4, containing 0.5 M NaCl, TBG was eluted with 0.03 M α-methyl-D-mannoside in 0.05 M Tris-HCl buffer, pH 7.4, containing 0.5 M NaCl. Desalting was performed by chromatography on a Sephadex G-25 coarse (Pharmacia) column, followed by dialysis.

Characterization of TBG

Disc electrophoresis was performed in 7.5% (wt/vol) or 5% (wt/vol) acrylamide and 0.24% (wt/vol) N,N'-methylene-bisacrylamide in Tris-glycine buffer, pH 8.9. Sodium dodecyl sulfate (SDS) electrophoresis was performed in 7.5% (wt/vol) acrylamide and 0.24% (wt/vol) N,N'-methylene-bisacrylamide in Tris-glycine buffer, pH 8.9. SDS electrophoresis was performed in 7.5% (wt/vol) acrylamide and 0.24% (wt/vol) N,N'-methylene-bisacrylamide in Tris-glycine buffer, pH 8.9, containing 0.1 g/100 mg SDS. Slab gels of 0.5 × 15.5 cm were used.

IEF on slab gels (0.5 × 17.5 cm) was carried out in 5.06% (wt/vol) acrylamide and 0.2% (wt/vol) N,N'-methylene-bisacrylamide containing 2.16% ampholine (LKB and Pharmacia,

respectively).

For tracer studies, TBG, preincubated with [¹²⁵I]T₄ or [¹²⁵I]T₃, was focussed in slab gel IEF, and then gels were cut in 1-mm slices and counted for radioactivity.

Staining of gels was performed with Coomassie blue R 250, bromphenol blue, or periodic acid Schiff's solution. The molecular weight was determined by sedimentation equilibrium (15, 16).

Analytical amino acid and hexosamine determinations were performed on an amino acid autoanalyzer (Durum D 100). Samples of TBG were hydrolyzed for 24 h at room temperature in 1 M HCl, with correction being made for amino acid loss during hydrolysis. The carbohydrate content was determined with anthron using glucose as the reference standard.

The sialic acid content of TBG was determined by the thiobarbituric acid method (17) after hydrolysis in 0.1 N H₂SO₄ for 1 h at 80 C or cleavage by neuraminidase preparations from *Clostridium perfringens*, *Vibrio cholerae*, or influenza virus (Behring-Werke) (18-20).

The TBG RIA was performed as described earlier (5). [¹²⁵I]TBG was prepared with chloramine-T. Separation of antibody-bound and free TBG was performed using a double antibody method.

Methods for characterization of TBG microheterogeneity

The incubation medium for enzymatic desialylation was 50 μl 0.1 M acetate buffer (pH 5.6), 50 μl 50 mg/dl TBG, and 50 μl neuraminidase in different concentrations. For kinetic studies, incubation times varied from 2 min to 24 h. The enzymatic reaction was stopped by the addition of 50 μl 0.15 M glycine-NaOH buffer, pH 11.0. Desialylation of TBG with the neuraminidase preparation from *Vibrio cholerae* was performed in 0.1 M acetate buffer, pH 5.6, containing 9 mg/ml NaCl and 1 mg/ml CaCl₂.

To examine nonspecific effects, either of the proteases possibly contaminating the neuraminidase preparations or of the acidic hydrolysis of TBG in the incubation medium, control experiments were performed by adding Aprotinin, a protease inhibitor (Trasylol, Bayer; 400 KIU/ml), or by incubation of TBG in the incubation medium without neuraminidase.

IEF on flat bed polyacrylamide gels (PAG plates) was carried out in 4.8% (wt/vol) acrylamide and 0.15% (wt/vol) N,N'-methylene-bisacrylamide containing 2% (wt/vol) ampholine and 12.5 g/dl sucrose. Plates of 235 × 105 × 1 mm were poured, and polymerization was catalyzed by riboflavin (3.3 × 10⁻⁵ g/dl). Samples were applied by filter paper (5 × 10 mm; Whatman, Inc., Clifton, NJ) placed on the PAG plates. For IEF, the LKB Multiphor 2117 chamber and the LKB power supply 2103 were used. Running conditions were limited power (20 watts), voltage (1000 V), and temperature (10 C) for 2 h. Focused protein bands were detected either by staining of the gel with Coomassie brilliant blue R 250 or immunofixation (21). Cellulose acetate strips (Millipore ESW P050 F0, Millipore Corp., Bedford, MA) were soaked with diluted TBG antiserum for 15 min, placed on the focussed PAG plates for 2 min, washed thoroughly in tap water overnight to remove nonprecipitated proteins, and then stained with Coomassie brilliant blue R 250.

Densitometric evaluation of the stained protein bands was

carried out with Multiphorese Equipment (Fa. Vogel, Gießen, Germany). TBG antiserum was produced by immunization of rabbits with pure TBG. Monospecificity was demonstrated by immunoelectrophoresis according to the methods of Grabar and Williams (22) and Clarke and Freeman (23).

For preparative IEF, 4.0 g Sephadex G-75 fine (Ultradex, LKB) were mixed with 100 ml distilled water and 5 ml 40% (wt/vol) ampholine (pH 3.5–5.0). In a trough (230 × 110 × 5 mm), gel was allowed to evaporate to exactly 73% (wt/vol) of its initial weight. Running conditions were limited power (8 watts), voltage (1000 V), and temperature (10 C) for 20 h. Then, the pH range from pH 4.0–4.7 (measured by a surface pH electrode, lot 403-30-80, Ingold, Germany) was cut off, the moist gel was diluted with distilled water (0.73:0.27, wt/vol), poured again in a clean trough, and then allowed to evaporate to exactly 73% (wt/vol) of the initial weight. Samples were dissolved in 3 ml 1% (wt/vol) ampholines and applied. The single focussed TBG bands were harvested using LKB equipment and quantified by TBG RIA.

Binding analyses of T_4 to TBG were carried out in microcells with Dianorm equilibrium dialysis apparatus (24, 25). One hundred microliters of T_4 standards (from 0.313–20 $\mu\text{g}/\text{dl}$ T_4) and 100 μl [^{125}I] T_4 (containing 1.2 $\mu\text{g}/\text{dl}$ T_4) were filled into the first cell; 200 μl 0.025 mg/dl TBG were filled into the other cell. The T_4 content of TBG had been determined by RIA and amounted to 0.3 μg T_4 /0.025 mg TBG. This T_4 concentration was taken into consideration when the affinity constant was calculated. All substances were dissolved in 0.1 M Tris-HCl buffer, pH 8.6. The cells were separated by a semipermeable membrane. Dialysis was allowed to take place overnight at 4 C; when equilibrium was reached, fractions were counted for radioactivity (correction was made for loss at the membranes). Association constants (K_a) and molar binding ratios were calculated using a Scatchard plot (26).

Results

On the average, 60% of total serum TBG could be extracted in batches by the T_3 -Epoxy-Sepharose 6B, and 95% could be extracted by affinity chromatography. During the washing steps, a further purification was effected by varying hydrogen ion concentration and ionic strength, demonstrated by additional protein peaks in the eluted material. None of these protein peaks contained immunoreactive TBG. After specific elution of TBG with the T_4 -HSA-solution, only TBG and HSA were detected in disc electrophoresis. The HSA contamination could be quantitatively removed by further affinity chromatography on Con A-Sepharose (Fig. 1). The overall yield of pure TBG was about 40% by batchwise treatment and about 60% of total serum TBG (estimated by TBG RIA) by affinity chromatography.

The prepared TBG gave one single band in overloaded disc electrophoresis at two polyacrylamide concentrations (7.5% and 5%). The molar binding ratio of T_4 to TBG, calculated from Scatchard plot, was 1:1. The purity of the TBG was further confirmed by a single band in

overloaded SDS electrophoresis and by linearity in the sedimentation velocity run. The sedimentation coefficient was calculated to be 3.95S, the molecular weight was $60,000 \pm 3,000$ daltons ($n = 3$), and the Stokes' radius was 37 Å. Analysis of amino acid composition was in good agreement with recently published data. In accordance with Gershengorn *et al.* (14), 22 residues of glucosamine, but no galactosamine, were found. The total carbohydrate content was estimated to be 15%.

Several TBG preparations from pooled human sera were found to show three distinct and (depending on the quantity of focussed TBG) one to three less intensive bands in slab gel IEF in the pH area from pH 4.1–4.6. These bands coincided, regardless of the method of staining, with the radioactivity peaks obtained from the run of a TBG preincubated with [^{125}I] T_4 or [^{125}I] T_3 (Fig. 2). This indicated that all bands represented glycoproteins which bound thyroid hormones.

The same microheterogeneity pattern of isolated TBG was obtained from PAG plate IEF either stained in the gel by Coomassie blue or identified by the immunofixation technique. Comparable TBG patterns, only detectable by immunofixation, were found in native sera from normal subjects. In addition, no change in TBG pattern in the same individuals was found when fresh or frozen serum was investigated.

Kinetic *in vitro* desialylation studies with pure TBG performed using different neuraminidases showed similar results. After a short incubation time (2 min), microheterogeneity increased immediately, showing new alkaline bands. Subsequently, dependent on incubation time, TBG bands migrated stepwise to more basic positions, finally reaching a characteristic end point. Most of the desialylated TBG focussed in a strong band at pH 6.0; additional faint bands were found at pH 5.4, 5.7, 6.2, and 6.3 (Fig. 3). Treatment with all three neuraminidase preparations resulted in the same TBG pattern, differing only in their kinetics.

Nonspecific effects of neuraminidases and incubation conditions could be excluded by control experiments.

Radioimmunological determination of TBG with different degrees of desialylation documented the independence of immunoreactivity of TBG from its degree of sialylation. The recovery of different sialylated TBG in the TBG RIA was within the coefficient of variation. We found no significant loss of TBG when a TBG standard was incubated with neuraminidase and after desialylation was determined by TBG RIA.

Simultaneous measurement of enzymatically removed NANA resulted in an increase parallel to incubation time and reached a maximum of 6 mol NANA/mol TBG at the end of desialylation. The total NANA content of TBG derived from hydrolysis with 0.1 N H_2SO_4 was 6.5 mol NANA/mol TBG.

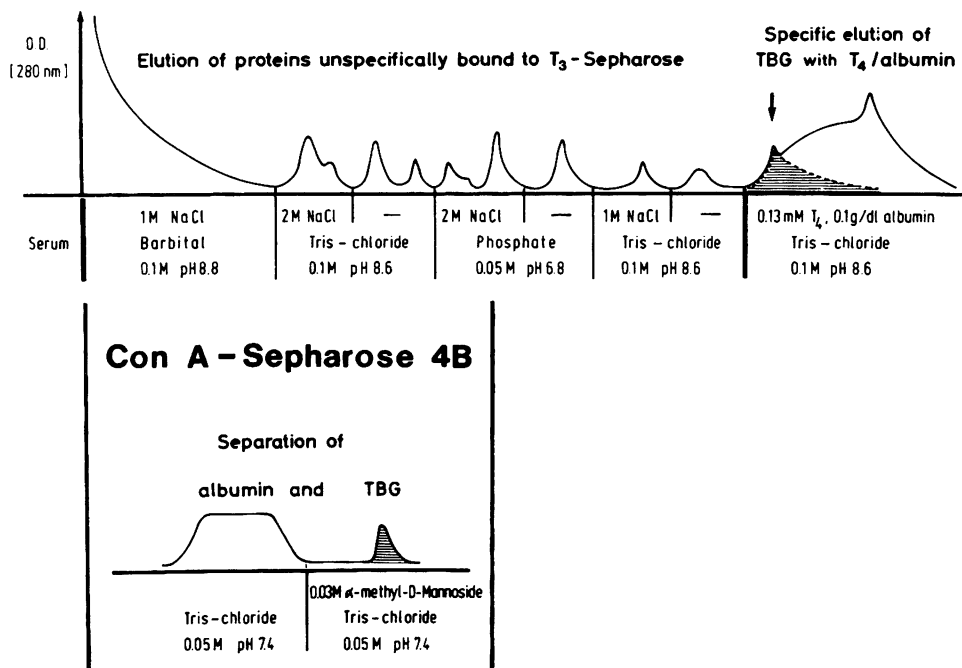
T₃ - (12 carbon spacer) Sepharose 6B

FIG. 1. Two-step purification of TBG from human serum. TBG was extracted by affinity chromatography on T₃-Epoxy-Sepharose 6B. Nonspecifically bound serum proteins were removed by washing with different buffer solutions. TBG was specifically eluted with 10 mg/dl T₄-HSA-0.1 M Tris-HCl buffer, pH 8.6. Endogenous HSA and HSA from the buffer were removed by a further affinity chromatography step using Con A-Sepharose 4B. The shaded area shows immunoreactive TBG (determined by RIA).

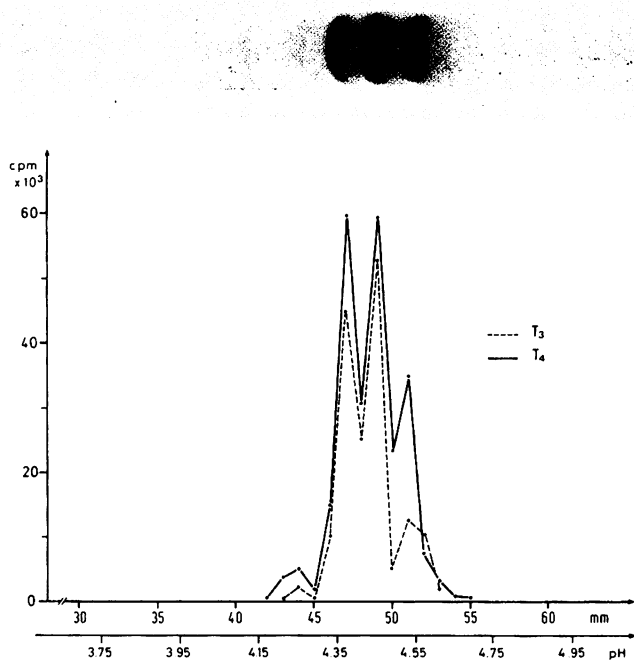


FIG. 2. IEF on slab gels with a pH gradient from pH 3.5-5.0 (top). TBG was preincubated with [¹²⁵I]T₄ or [¹²⁵I]T₃. Gels were either stained with bromophenol blue or cut in 1-mm slices and counted for radioactivity (bottom).

Using preparative IEF, pure TBG derived from pooled serum of normal donors could be separated into four main constituents with pIs at pH 4.25, 4.35, 4.45, and 4.55. When pure TBG derived from females treated with

estrogens was used, a fifth constituent with a pI of 4.15 was obtained (Fig. 4). The single TBG bands were examined for NANA content and affinity constants to T₄. The NANA content was 10.2 mol NANA/mol TBG (obtained from normal donors) for the most acidic TBG band (pI = 4.25), decreasing to 4.8 mol NANA/mol TBG for the most alkaline band (pI 4.55) (Table 1). The TBG band at pH 4.15 has not yet been examined for its NANA content because of its low concentration. The affinity constants were almost independent of the degree of sialylation ($3.1-7.2 \times 10^9 \text{ M}^{-1}$). Even completely *in vitro*, desialylated TBG had a K_a of $3.3 \times 10^9 \text{ M}^{-1}$, which was not significantly different from those of isolated untreated TBG fractions.

Using analytical flatbed IEF, followed by immunofixation, about 800 native sera were examined for their patterns of microheterogeneity. All healthy examinees showed very similar IEF patterns, having the same pI and intensity as shown in preparative and slag gel IEF from pure TBG.

In sera of patients suffering from thyroid diseases (hyperthyroidism, hypothyroidism, and euthyroid goiter), significant variations of microheterogeneity patterns could not be detected.

Two main groups of patients differing from this normal pattern were observed. The first group, suffering from liver diseases, revealed an intensified band at pH 4.55, with a relatively diminished band at pH 4.25 [Figs. 5 and 6 (G and H)]. In a second group of patients with elevated estrogen levels, the band at pH 4.55 almost disappeared,

Desialylation of isolated TBG
(Clostridium perfringens)

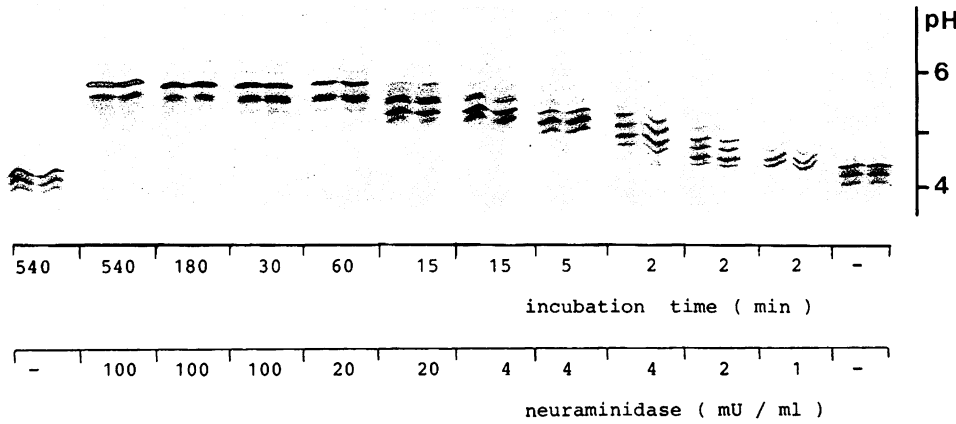


FIG. 3. Sequential desialylation of pure TBG. Pure TBG (50 µg) was incubated with different neuraminidase concentrations from 0-100 mU/ml for 0-540 min in 0.1 M acetate buffer, pH 5.6. After IEF on PAG plates (pH gradient from 3.5-10.0), TBG was detected by immunofixation.

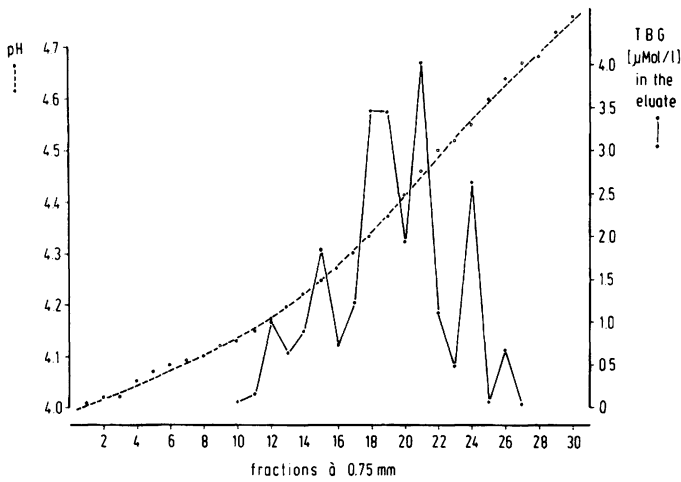


FIG. 4. Preparative IEF of pure TBG. IEF was performed on flatbed gel (Ultradex, LKB). TBG concentrations of the fractions were determined by TBG RIA; the corresponding pH values were measured with a pH electrode.

TABLE 1. NANA content and affinity constants to T₄ of the single TBG constituents isolated by preparative IEF of pure TBG

	pI	NANA:TBG ratio (mol/mol)	K _a (× 10 ⁹ M ⁻¹)
Isolated TBG		6.5	6.1
Separated in	4.25	10.2	3.1
	4.35	7.2	5.9
	4.45	5.0	7.2
	4.55	4.8	5.0
desialylated	6.2	—	3.3

whereas the band at pH 4.25 was intensified. In sera from the latter group of subjects with higher TBG levels (3.5 mg/dl), an additional band at pH 4.15 appeared [Fig. 6 (F and I)].

These changes in microheterogeneity patterns were

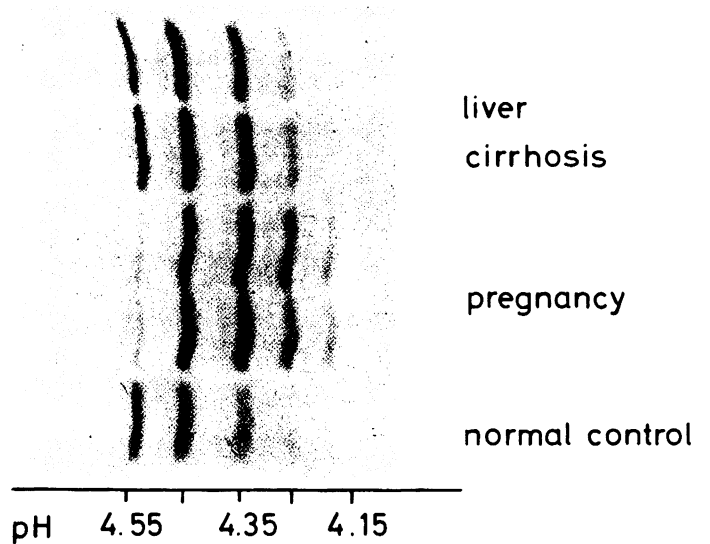


FIG. 5. Immunofixation of TBG after IEF on PAG plates (pH 3.5-5.0). The TBG pattern of a female suffering from liver cirrhosis is compared with those of a pregnant woman (28th week of pregnancy) and a normal control.

shown to be variable in several women during pregnancy and 1 week after delivery. During pregnancy, the patterns changed parallel to the increase of TBG levels, as described above [Figs. 6 (D-F) and 7]. One week after delivery, when TBG levels had not yet changed significantly, the most acidic band had disappeared, whereas the band at pH 4.55 intensified again.

The sera of members from two families with congenital TBG deficiency were examined, but no variation in the microheterogeneity pattern could be detected compared with that in normal subjects. In these families, an x-autosomal pattern of inherited low serum immunoreactive TBG levels (0.2-0.4 mg/dl) was found.

Euthyroid healthy newborns at term had elevated

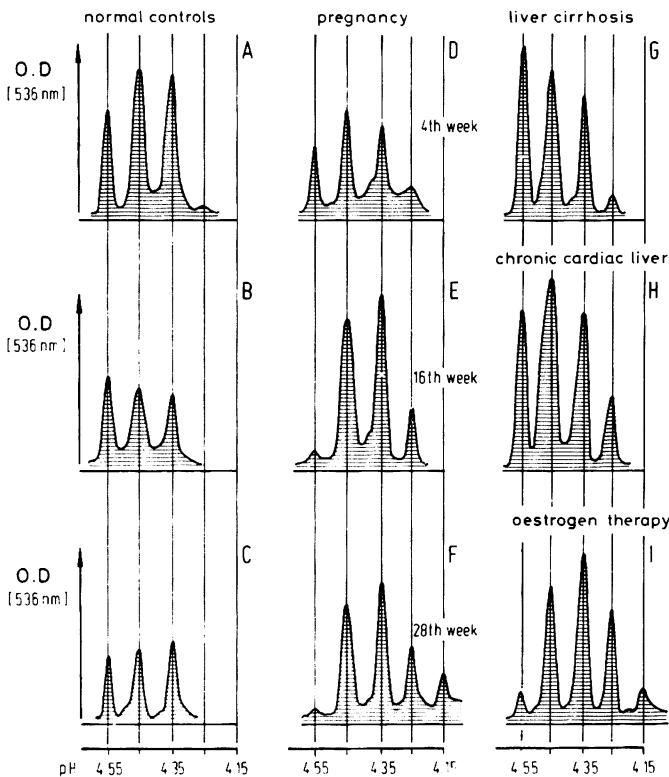


FIG. 6. Densitometric evaluation [optical density (O.D.), 536 nm] of some typical TBG patterns after IEF on PAG plates (pH 3.5-5.0), followed by immunofixation.

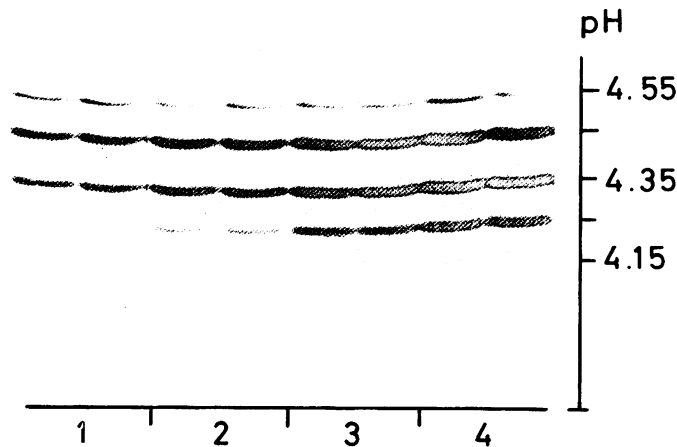


FIG. 7. Immunofixation of TBG after IEF on PAG plates (pH 3.5-5.0). TBG patterns during the course of pregnancy from one individual are shown. TBG microheterogeneity is shown in the 4th (1), 16th (2), 28th (3), and 35th (4) weeks of pregnancy.

serum TBG levels of 2.76 ± 0.5 mg/dl ($n = 12$) and normally distributed microheterogeneity bands, with the most alkaline one ($pI = 4.55$) slightly intensified.

The sera of four 1- to 5-day-old premature newborns, two of whom were twins, however, revealed microheterogeneity patterns not seen up to this point. In addition to the three main bands (pI 4.55, 4.45, and 4.35), there

were faint bands close to the normal bands, giving a picture of double bands. Six months later when the TBG pattern of one of these infants was reinvestigated, it was found to be comparable to the patterns of euthyroid normal mature newborns (Fig. 8).

Discussion

Since the introduction of affinity chromatography for the TBG preparation from human serum by Marshall and Pensky (2) in 1969, various procedures for isolation of TBG have been reported, all requiring at least two further chromatographic steps, including ion exchange chromatography (4, 5). The authors have succeeded in establishing a rapid, mild, two-step TBG purification procedure using T_3 -Epoxy-Sepharose 6B and Con A-Sepharose 4B affinity chromatography. The overall yield of about 60% pure TBG by this preparation was approximately 3 times the yield described by other authors (2-5). A high yield of pure TBG was the requirement for further characterization of TBG microheterogeneity.

Microheterogeneity of isolated TBG was first demonstrated in slab gel IEF (11). That the observed microheterogeneity was not related to the purification procedure has been confirmed by examination of individual native sera. The microheterogeneity bands of isolated TBG coincided with radioactivity peaks in slab gel IEF after preincubation of serum with $[^{125}I]T_4$ or $[^{125}I]T_3$ and with the immunofixation precipitation lines of native sera after PAG plate IEF. To exclude artifacts in IEF, different agents were used for polymerization of acrylamide (riboflavin and ammoniumpersulfate) and different commercial ampholines (from LKB and Pharmacia) were used with different pH gradients and different modes of sample application (anodal and cathodal) either on slab gels or PAG plates. In each case, identical microheterogeneity patterns were seen. This was in contrast to the findings of Marshall *et al.* (11), who detected four bands

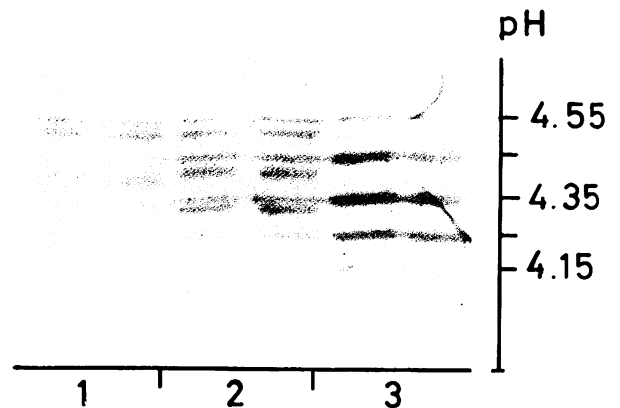


FIG. 8. Immunofixation of TBG after IEF on PAGE plates (pH 3.5-5.0). The TBG patterns of two premature 5-day-old newborns (1, 2) are shown; one of them was reinvestigated 6 months later (3).

when using ammonium persulfate for polymerization of acrylamide, but at least nine bands in the pH area from 4.2–5.2 when using photopolymerization with riboflavin. These differences probably are related to the fact that we added samples to the unpolymerized gel suspension only after the polymerizing agent had been removed by a short prerun.

During sequential desialylation studies of isolated TBG, we observed a change in the mobility of microheterogeneity bands to alkaline pH, with subsequent reduction to one main band at pH 6.0 and several faint bands which remained in more alkaline and acidic positions even when the desialylation conditions were intensified. Control experiments with a protease inhibitor (Aprotenin-Trasyolol) or in simple buffer (without neuraminidase) excluded artifacts due to the desialylation treatment *per se*. Despite this, a single TBG band in IEF was never achieved by desialylation, leading us to the hypothesis that a variable NANA content could be the cause of the microheterogeneity observed in pure TBG preparations as well as in the individual native sera. The single isolated TBG bands differed from one another in sialic acid content.

The results from the desialylation studies are in disagreement with those of Marshall *et al.* (11), whose desialylation studies resulted in an alkaline displacement of the microheterogeneity pattern without any reduction in the number or intensity of the bands. To explain the nondisappearance of the faint bands after the desialylation procedure described here, it is supposed that the stability of the residual carbohydrate chains or of the whole molecule may be diminished after desialylation, so that the incubation in acetate buffer, pH 5.6, for several hours may cause mild hydrolysis of the carbohydrate residues.

The total NANA content of pure TBG was found to be from 6.0–6.5 mol/mol TBG. Zinn *et al.* (10) found 9 mol NANA/mol TBG and believed that these were located at the terminal groups of the four carbohydrate side chains. Since the different TBG bands found on isoelectric focussing contained amounts of NANA varying from 4–10 mol/mol TBG, the mean content of 6.5 mol NANA/mol pure TBG found seems reasonable. Data for the NANA content of TBG found in the literature vary from 0–10 mol NANA/mol TBG. Since sialic acid is the most labile of any of the serum carbohydrates, the differences of NANA content in the literature may be due to variations in the methods of handling the serum, including collection and purification.

As microheterogeneity of TBG was investigated using only isolated TBG from pooled serum, variations of individual TBG microheterogeneities have remained undetected until now. IEF on PAG plates, followed by immunofixation, is a simple and rapid method for inves-

tigating the individual TBG microheterogeneities in large numbers of different sera. Almost all sera, including those from individuals with inborn TBG deficiency or different thyroid diseases, revealed microheterogeneity patterns comparable with that of TBG prepared from pooled sera.

Striking changes were found in states known to influence glycoprotein synthesis and degradation. The influence of elevated estrogens on liver protein synthesis, as occurs during pregnancy or estrogen therapy, resulted in the appearance of an additional TBG band with a pI of 4.15 and a simultaneous reduction in the intensity of the band at pH 4.55. Sequential investigations in several women during pregnancy showed that this phenomenon paralleled the increase in the TBG level in serum. Glinier *et al.* (27, 28) observed an estrogen-stimulated TBG production rate in rhesus monkeys 2.9 times normal and a degradation rate 0.9 times normal. The additional acid band observed in our investigations is interpreted as an expression of the increased production rate, with a more sialylated TBG circulating in serum. According to our findings, the degradation rate must also be increased, as demonstrated by the fading alkaline band representing the more desialylated TBG.

Like other glycoproteins, TBG is assumed to be desialylated by peripheral neuraminidases and then to be bound to receptors (for desialylated glycoproteins) on the liver cell membrane for further degradation (29–33). Marshall *et al.* (30) demonstrated that less TBG from the serum of patients with liver cirrhosis is bound to hepatocellular membranes *in vitro* than TBG from serum of healthy donors. It is assumed that the increase of alkaline bands of TBG from patients with liver cirrhosis and elevated TBG levels which we found using the immunofixation technique is an indication of reduced degradation caused either by a reduction in the number of liver receptors for desialylated glycoproteins or a relative saturation of these receptors by other glycoproteins.

The double band microheterogeneity seen in premature newborns was normalized 6 months after birth, indicating a change in TBG sialylation or glycosylation during maturation. In sera of healthy newborns at term, this double band configuration was not found. A higher degree of sialylation of glycoproteins in fetal liver as well as in primary liver cell carcinoma has been described (34); an altered sialylation of TBG in the premature liver resulting in these double configured TBG bands is possible. However, since the distance between the bands is smaller than that observed by the removal of 1 mol NANA, an altered carbohydrate composition in this premature TBG other than sialic acid is possible and, therefore, worth further investigation.

In the present study, affinity constants of the single TBG bands for T_4 were not found to differ from one another. Cheng *et al.* (35) also found a slightly diminished

affinity constant of deglycosylated TBG to T_4 . However, Marshall *et al.* (29) and Refetoff *et al.* (31) have reported that even completely *in vitro* desialylated TBG was not found to change its affinity constant to T_4 . From the clinical point of view, it is important to note that even marked changes in the microheterogeneity of TBG in different metabolic states do not affect the T_4 to TBG ratio (36).

Acknowledgments

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