STEROID HORMONE LEVELS IN PATIENTS WITH PRIMARY BILIARY CIRRHOSIS OF THE LIVER

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Many aspects of the problem of the origin of primary biliary cirrhosis of the liver (PBC) still remain unsolved. In particular, we have no clear idea why predominantly women suffer from this disease. Is it the result of a disturbance of sex hormone metabolism? Many investigations have shown that some women develop intrahepatic cholestasis after taking oral contraceptives [12, 16, 17] or during pregnancy [12, 13, 14, 17]. The appearance of cholestasis in these women has been linked with a raised estrogen level [13, 17]. Administration of estrogens to laboratory animals leads to depression of synthesis and excretion of bile acids [11, 16]. In hamsters, ethinyl estradiol reduced activity of cholesterol 7α-hydroxylase, a key enzyme in the conversion of cholesterol into bile acids [7, 9]. However, it is not yet clear whether changes take place in the levels of sex and steroid hormones in primary biliary cirrhosis of the liver and whether there is some connection between the disturbance of biosynthesis of bile acids occurring in PBC and the levels of these hormones. Information about these matters is very important for the elucidation of the mechanism of development of the disease and, consequently, for pathogenetic treatment of patients with PBC also.

EXPERIMENTAL METHOD

An investigation was conducted on 82 women aged from 30 to 62 years, suffering from primary biliary cirrhosis of the liver. The comparative group consisted of patients with diseases of the gastrointestinal tract but with no clinical, biochemical, or morphological evidence of liver damage (chronic gastritis, gastric or duodenal ulcer, reflux esophagitis, or dyskinesia of the biliary passages). The women forming the comparative group were aged from 24 to 56 years. Steroid hormone levels in the blood plasma were determined in 10-ml samples of venous blood shaken into test tubes each containing 100 μl of 6% EDTA solution. The contents of the tube were thoroughly mixed and centrifuged for 10 min at 3000g on a TsUM-1 centrifuge at 4°C. The supernatant (blood plasma) was collected into clean test tubes and stored at −20°C until required for determination of steroid hormone levels. The concentrations of steroid hormones in the blood plasma were determined by radioimmunoassay using standard kits of reagents: aldosterone — with a kit from "CEA Sorin" (France); cortisol, progesterone, testosterone, and estradiol — with kits of Soviet origin, marketed by the Institute of Bio-organic Chemistry, Academy of Sciences of the Belorussian SSR.

EXPERIMENTAL RESULTS

Investigation of plasma levels of progesterone, cortisol, aldosterone, testosterone, and estradiol in patients with PBC and subjects of the comparative group showed that in both groups they were within normal limits, as specified in the instructions with the kits (Table 1). However, as Table 1 shows, the plasma cortisol level of patients with PBC was significantly lower than its concentration in the blood plasma of the comparative group. A tendency also was noted for the plasma testosterone level in patients with PBC to be depressed to the lower limit of normal. The mean concentrations of progesterone, aldosterone, and estradiol in the blood plasma of the two groups was about equal, and did not differ significantly.

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TABLE 1. Concentrations of Progesterone, Cortisol, Aldosterone, and Estradiol in Blood Plasma of Patients with Primary Biliary Cirrhosis of the Liver and Subjects of the Comparative Group ($M \pm m$)

Hormone	Normal limits of hormone concentrations	Control comparative group	Patients with PBC
Progesterone, nmoles/liter			
follicular phase	0,1—6,4	18,75±2,98	15,65±3,12
luteal phase	10—40	(n=10)	(n=34)
Cortisol, nmoles/liter	230—750	599,6±62,6* (n=39)	348,7±26,9* (n=82)
Aldosterone, nmoles/liter	0,122—0,582	0,424±0,068 (n=14)	0,372±0,038 (n=39)
Testosterone, mg/ml	0,2—1,0	0,274±0,06 (n=7)	0,198±0,021 (n=31)
Estradiol, pmoles/liter			
follicular phase	110—330		
ovulatory phase	477—1174		
luteal phase	257—734	268,4±83,3	232,1± ±43,6**
menopause	36,7—147	(n=9)	(n=21)

Legend. *$p < 0.001$, **) The cycle was disturbed in patients with PBC, and for that reason the results were averaged and are not shown relative to the phase of the cycle. To determine plasma estradiol levels for comparison, women were selected from the group with follicular and luteal phases of the cycle.

How can the significant fall in the plasma cortisol concentration in patients with PBC compared with its plasma level in the comparative group be explained? This is possible either by acceleration of catabolism in the liver or by slowing of biosynthesis in the adrenal cortex. We know that cortisol catabolism takes place in the liver with reduction initially to dihydrocortisol, and then to tetrahydrocortisol [2]. Damage to the liver (the chief organ for inactivation of cortisol) in PBC may lead to disturbance of its catabolism. Moreover, to lower the plasma cortisol concentration, reduction processes must be accelerated and excretion of cortisol metabolites with the urine increased. However, as Genes [2] points out when the liver is damaged in various diseases the quantity of 17-ketosteroids excreted with the urine is reduced, partially on account of their reduced formation from cortisol. Consequently, the inactivating function of the liver for cortisol is depressed by liver damage. The significant fall of the cortisol concentration in the blood plasma of patients with PBC within normal limits can be explained mainly by depression of its biosynthesis in the adrenals. In turn, the lowering of the level of cortisol biosynthesis in the adrenals can be assumed to take place through lowering of activity of the enzyme 17α-hydroxylase. This suggestion is based on analysis of the scheme of steroid hormone biosynthesis from cholesterol (Fig. 1). As Fig. 1 shows, pregnenolone is the substrate for biosynthesis of cortisol and aldosterone. Four principal enzymes participate in both these pathways of biosynthesis, three of which are common to both pathways. The two pathways differ with respect to the 4th enzyme. In the case of aldosterone biosynthesis this is 18-hydroxylase, whereas in the case of cortisol biosynthesis, it is 17α-hydroxylase. These enzymes determine the differences between the two pathways of cortisol and aldosterone biosynthesis. Progesterone is an intermediate during steroid hormone biosynthesis. As Table 1 shows, the plasma concentrations of progesterone and aldosterone in patients with PBC is just the same as in the comparative group, so that it can be concluded that aldosterone biosynthesis is not disturbed in these patients. Does this mean that activity of the enzymes involved in its biosynthesis are evidently unchanged? If this is so, the fall in the plasma cortisol concentration in patients with PBC can be attributed only to hypoactivity of adrenal 17α-hydroxylase. A direct answer to this question can be given by determination of adrenal 17α-hydroxylase activity. Unfortunately, however, it is not yet possible to determine the activity of this enzyme in the adrenals of patients with PBC.

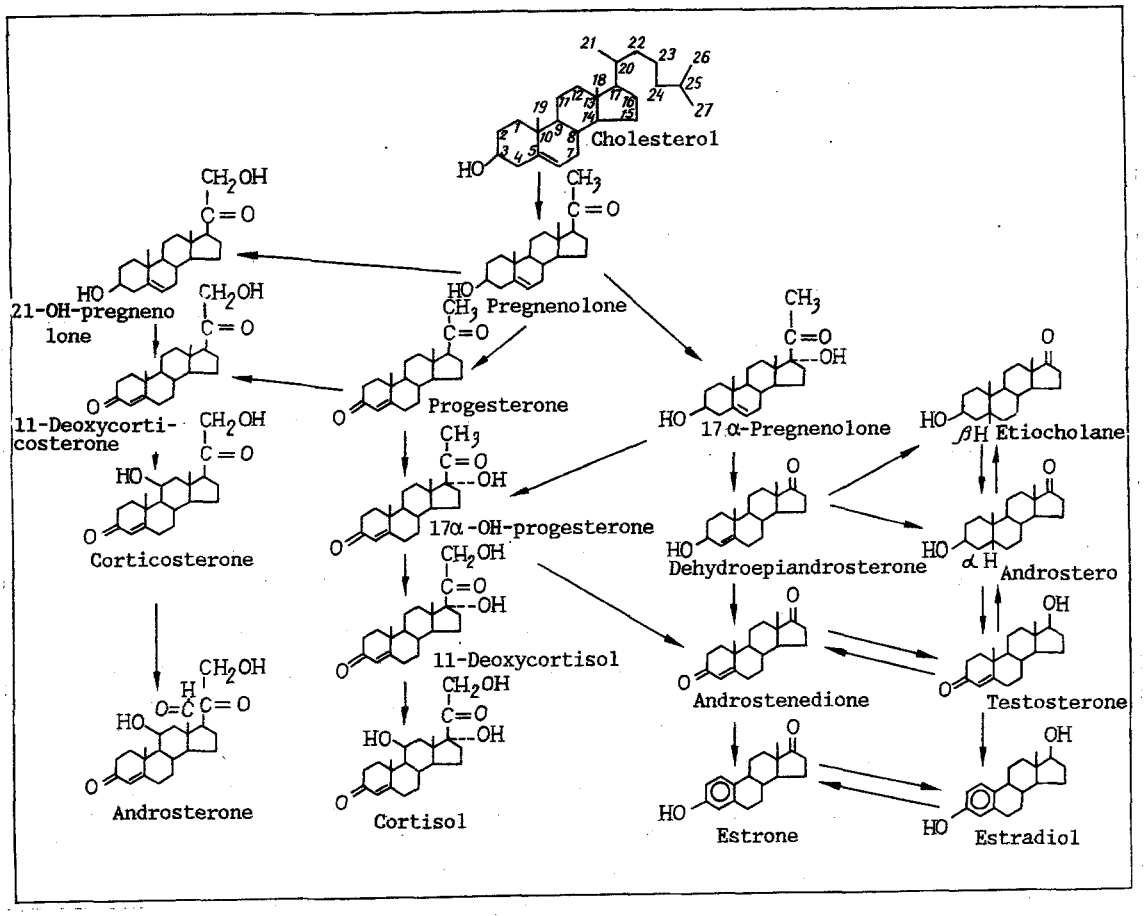

Fig. 1. Scheme of steroid hormone biosynthesis (after Horst, 1982).

In PBC processes of cortisol inactivation are depressed, evidently because of liver damage, so that the cortisol level in these patients is maintained within normal limits despite a simultaneous significant reduction in its concentration in the comparative group.

These results also indicate that the development of the disease is evidently unconnected with a disturbance of estrogen biosynthesis and a change in plasma estrogen levels. Accordingly the question why mainly women suffer from this disease remains unanswered. Admittedly, recent investigations [4-6, 8] have shown that many functions (of the liver, for example) exhibit sexual differentiation. It is possible that this may also account for the development of disturbance of the liver functions in primary biliary cirrhosis in women.

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EFFECT OF NAPHTHENE HYDROCARBONS OF NAPHTHALAN ON CAPILLARY PERMEABILITY

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The study of the effect of certain components of naphthalan (NPH) on physiological functions has shown that they possess high biological activity [1, 5, 8]. To characterize the therapeutic action of factors of NPH, it is essential to study their effect on the state of the capillary and vascular permeability.

Investigations have shown that NPH and some of its components have a definite effect on the permeability of animal tissues and cells [6]. There is evidence that under the influence of cyclopentane–perhydrophenanthrene (CPPP) naphthene hydrocarbons the permeability of erythrocyte membranes and of the blood-brain barrier for various substances is increased [7, 9].

Considering that changes in vascular and capillary permeability may lie at the basis of many physiological and pathological processes, we studied the state of two-way capillary permeability in animals under the influence of a course of injections of CPPP naphthene hydrocarbons, which are among the active principles of NPH [1, 2, 8].

EXPERIMENTAL METHOD

Experiments were carried out on rats. The radioactive isotope of phosphorus was used as indicator. CPPP naphthene hydrocarbons, dissolved in vegetable oil, were injected intramuscularly in a dose of 150 mg/kg daily for 10 days. Control animals received corresponding injections of vegetable oil.

Vascular permeability was investigated in the blood–tissue system by determining the dynamics of outflow of an intravenously injected solution of $Na_2H^{32}PO_4$ (5 μCi) from the bloodstream. Blood samples (0.05 ml each) were taken from the caudal vein after 1, 5, 15, 30, 45, 60, and 120 min. The radioactivity of the dried blood samples was determined on PP-8 and DP-100 instruments with a T-25-BFL end-window counter, with thin mica window in lead housing. The investigations were carried out 1 and 10 days after the end of a course (10-12 days) of injections of the preparation.

Capillary permeability in the direction from tissue to blood (^{32}P clearance) was determined in 24 rats by measuring the rate of 50% resorption of the intravenously injected isotope (0.1 ml). Radioactivity above the site of injection of the isotope was counted every minute for 8-14 min by means of an end-window β-shunt with an MST-17 counter on a B-2 apparatus. The half-elimination time of the isotope from the skin depot ($T_{1/2}$) was determined and the velocity constant of resorption calculated by

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