Liver Function in Physically Trained Subjects

Galactose Elimination Capacity, Plasma Disappearance of Indocyanine Green, and Aminopyrine Metabolism in Long-Distance Runners

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Physical exercise and physical training are known to affect several aspects of hepatic metabolism. To assess whether adaptation to long-lasting exercise modifies microsomal drug metabolism, 8 long-distance runners were compared with a group of medical students having significantly lower maximal rates of oxygen consumption. At rest the hepatic galactose elimination capacity and the indocyanine green plasma disappearance rate used as reference methods were the same in both groups. The plasma clearance of ([^{14}C]dimethylamine) aminopyrine and the kinetics of $^{14}CO_2$ in breath did not differ either. It is concluded that adaptation to long-lasting exercise can occur without evidence for changes in hepatic galactokinase activity, liver blood flow, or microsomal metabolism of aminopyrine.

Rates of microsomal drug metabolism are subject to many endogenous and exogenous influences and therefore to much individual variation. Among the modifying factors, genetic determinants, age, disease, diet, and exposure to xenobiotics have been found relevant in man (8–10, 21, 30). A recent study in our laboratory suggested the possibility that physical training may also be important (12). Physical exercise in man is known to affect hepatic energy metabolism, increasing at least the uptake of oxygen and of substrates such as lactate, pyruvate, and alanine (25, 31). Physiological studies of the liver carried out in physically trained rats at rest revealed changes of both energy and protein metabolism (11, 22).

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We therefore set out to investigate the influence of physical training on liver function and more specifically on microsomal drug metabolism. For this purpose, three tests were applied in a comparison of long-distance runners with a control group of untrained students. The galactose elimination capacity (GEC) is thought to measure one of the metabolic functions of the liver (28, 29), and the plasma disappearance rate of indocyanine green (k_{ICG}) may be considered as an index of hepatic blood flow (24). In order to assess hepatic drug metabolism, [^{14}C]aminopyrine was chosen as test compound because its kinetics may be simultaneously evaluated in plasma and by breath analysis (1, 5, 6, 13, 15, 26).

MATERIALS AND METHODS

Subjects. Studies were carried out in 14 male volunteers, aged 20 to 31 years. They were divided by their history into two groups on the basis of criteria related to physical training. The first group consisted of 8 well-

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trained long-distance runners, 7 of them belonging to the Swiss track team. The second group consisted of 6 untrained students, essentially leading a sedentary life. None of these volunteers were smokers, and none had been on medication for at least two weeks prior to the study. Most of them took alcohol only rarely, and then not exceeding 12 g/day. Their good health, as determined by a complete physical examination, was confirmed by normal results of blood counts, serum electrophoreses, and serum levels of the glutamic oxaloacetic transaminase, alkaline phosphatase, and creatinine.

Procedures. All subjects were allowed a breakfast consisting of tea and toast, and a lunch of two sandwiches and tea the day of the experiments. An intracath was placed in an antecubital vein. The volunteers were kept at rest for the duration of the galactose, ICG, and aminopyrine tests, which were always started at 8, 9, and 10 AM, respectively.

The galactose elimination capacity was assessed according to Tygstrup's procedures using venous blood samples (28). Galactose concentrations in plasma were measured enzymatically using Hjelm's methods (16).

Indocyanine green (Cardio-Green®) was injected intravenously in a dose of 0.5 mg/kg body weight, within a period of 10 sec and measured photometrically at 800 nm in venous plasma samples collected after 3, 6, 9, 12, 15, and 18 min (24). As described by Scherrer et al (26), crystalline aminopyrine (9 mg/kg body weight) mixed with 2 μCi of [^{14}C]aminopyrine was given by mouth; breath and blood samples were collected at intervals for 8 hr. The maximal oxygen uptake of the subjects was determined by bicycle or treadmill spiroergometry according to the procedures reported previously (18, 27).

Calculations. The galactose elimination capacity (GEC) was calculated using Tygstrup's methods modified for venous blood samples by using a correction factor of 5 min (28, 29). The plasma disappearance rate constant of ICG (k_{ICG}) was calculated by log-linear regression analysis. Pharmacokinetic parameters for aminopyrine, plasma disappearance rate constant (k_P), plasma clearance (Cl_{tot}), and disappearance rate constant of specific activity of $^{14}CO_2$ in breath (k_B), were obtained as described previously (26).

Group comparisons were made by the Wilcoxon rank test and regarded as statistically significant if $P < 0.05$.

RESULTS

As shown in Table 1, both groups of subjects were well matched for age, height, and body weight. Their maximal oxygen uptake, expressed in ml/min/kg body weight varied from 56 to 78 in the physically trained and from 43 to 51 in the untrained control subjects. These values are in good agreement with those generally found in long-distance runners with a mean training distance of 100 km per

TABLE 1. MAXIMAL OXYGEN UPTAKE (V_{O_2max}), GALACTOSE ELIMINATION CAPACITY (GEC), PLASMA DISAPPEARANCE RATE CONSTANT FOR INDOCYANINE GREEN (k_{ICG}) AND AMINOPYRINE DISPOSITION IN PHYSICALLY TRAINED AND UNTRAINED SUBJECTS

Subject	Age (yr)	Height (cm)	Weight (kg)	V_{O_2max} (ml/min/kg)	GEC (mg/min/kg)	k_{ICG} (%/min)	Aminopyrine* k_p (%/hr)	Aminopyrine† Cl_{tot} (ml/min/kg)	Aminopyrine‡ k_B (%/hr)
Trained subjects									
H.R.	20	170	64	78.0	7.8	23	55	8.2	26
G.F.	26	172	60	73.5	6.9	15	34	4.2	19
U.R.	27	177	68	67.5	6.2	16	34	4.5	18
K.B.	22	175	67	65.8	6.0	21	33	4.2	14
F.N.	22	183	73	65.8	7.4	19	39	6.0	22
R.H.	20	179	64	65.7	10.0	19	30	5.0	19
F.W.	27	180	68	63.7	6.4	16	45	6.5	27
R.R	20	174	59	56.6			39	6.1	21
$\bar{X}$	23	176	65.4	67.1§	7.24	18.43	38.6	5.6	20.8
SD	±3.16	±4	±4.6	±6.4	±1.38	±2.94	±8.1	±1.4	±4.3
Untrained subjects									
B.M.	23	168	60	51.4	8.1	22	36	3.8	20
K.H.	23	185	70	50.9	6.1	19	39	5.6	20
R.L.	31	186	72	46.1	7.8	19	40	7.0	21
G.O.	26	182	70	45.9	6.5	21	64	8.3	23
Z.M.	24	174	59	42.8	6.6	21	31	6.7	24
H.C.	29	191	88	42.7	7.6	21	27	3.3	15
$\bar{X}$	26	181	69.8	46.6§	7.12	20.5	39.5	5.8	20.5
SD	±3.35	±8	±10.8	±3.8	±0.82	±1.22	±13.0	±1.9	±3.2

*Plasma disappearance rate constant.
†Plasma clearance.
‡Disappearance rate constant of specific activity of $^{14}CO_2$ in breath.
§Difference between trained and untrained subjects statistically significant, $P < 0.001$.

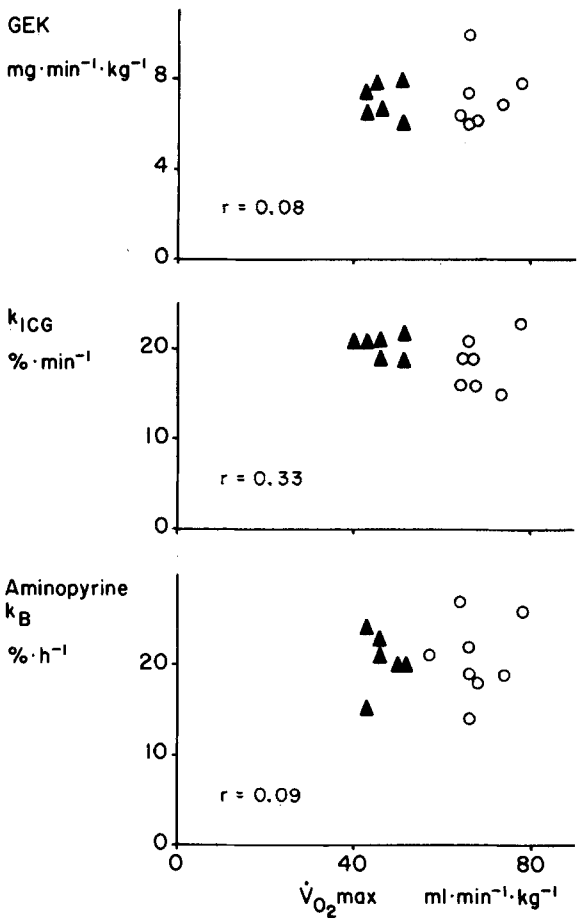

Fig 1. Relation between maximal oxygen uptake (V_{O_2max}) and liver function. The latter has been investigated by galactose elimination capacity (GEC), plasma disappearance rate constant of indocyanine green (k_{ICG}), and the disappearance rate constant of specific activity of $^{14}CO_2$ in breath (k_B) after administration of [^{14}C]aminopyrine. The open circles indicate physically trained subjects and the closed traingles untrained control persons.

week and in subjects having no regular physical exercise, respectively (17). The difference between the two groups is highly significant statistically ($P < 0.001$). These figures therefore provide good evidence for efficient physical training and for lack of such training in the appropriate test subjects.

In all subjects, results of galactose and ICG tests were within the range of those found in normal volunteers in our laboratory and elsewhere (19, 20, 24). It may be noted that the k_{ICG} tended to be lower in physically trained subjects. The difference, however, was not significant statistically. All parameters reflecting aminopyrine metabolism showed satisfactory agreement among themselves. The disappearance of $^{14}CO_2$ from breath expressed as k_B correlated well with k_P ($r = 0.63$, $n = 14$) and with the total plasma clearance of aminopyrine, Cl_{tot} ($r = 0.80$, $n = 14$). Similarly, k_P was correlated with Cl_{tot} ($r = 0.81$, $n = 14$). Neither of the three methods revealed a difference between trained and untrained subjects.

If the different tests of hepatic function are correlated with the maximal oxygen uptake (Figure 1), no relationship can be detected.

DISCUSSION

Physical training is known to influence skeletal and cardiac muscle cells as well as heptaocytes (3, 4, 23). Increased numbers of mitochondria and ribosomes, and increased activity of some enzymes have been described in liver cells of rats exposed repeatedly to strenuous exercise. In particular glycerol phosphate dehydrogenase, succinate dehydrogenase, and concentrations of cytochromes, *a*, *b*, and *c* were augmented (22). Increases in some functions of the liver were, therefore, expected also in physically trained men, for instance in long-distance runners having augmented rates of maximal oxygen uptake. None of the quantitative liver function tests, however, revealed a statistically significant difference between the runners and the untrained control subjects.

The lack of difference in liver function related to physical training may be due to methodological limitations of the study. Since the subjects could not be used as their own controls, two independent samples had to be examined. Consequently individual variations might have obscured minor differences due to training. Furthermore, the functions of the liver measured by galactose elimination capacity, plasma disappearance of ICG, and aminopyrine metabolism may not be relevant for the adaptation which occurs as a result of physical training. Nevertheless, in view of the well-documented difference in maximal oxygen consumption in the two groups of investigated subjects, the results deserve due consideration.

The galactose elimination capacity as determined with Tygstrup's method is independent of hepatic blood flow and assesses one of the metabolic functions of the liver (29). Since all hepatocytes are thought to participate maximally in the removal of galactose, the test has been regarded as a measure of the functioning liver cell mass (Lm) (28). This concept has been supported by the proportional reductions in galactose elimination capacity and BSP

elimination in patients with liver diseases (7, 20). If the galactose elimination capacity indeed represents the functioning cell mass, the results of this test suggest that adaptation of the liver to long-lasting exercise occurs without a change in liver cell mass.

When small amounts of indocyanine green are rapidly injected intravenously, hepatic blood flow is the predominant rate-limiting factor for its plasma disappearance. The k_{ICG} is then considered to be a reflection of hepatic plasma flow (24). The 10% reduction in average k_{ICG} in long-distance runners, therefore, suggests a corresponding decrease in hepatic plasma flow. This finding is not statistically significant.

Aminopyrine is a well-established test compound for the measurement of microsomal drug metabolism in vitro and in vivo (1, 6). The recent introduction of breath analysis of $^{14}CO_2$ after oral administration of appropriately labeled [^{14}C]aminopyrine has further increased its usefulness. Alterations of aminopyrine metabolism have been observed in patients with cirrhosis and after in vivo inhibition of microsomal enzymes by disulfiram or by ethanol (2, 5, 14). Increases due to enzyme induction have also been well documented (14). The lack of differences in k_B, k_P, and Cl_{tot} between trained and untrained subjects seems to indicate that adaptation to long-lasting exercise may occur without changes in microsomal drug metabolism as revealed by this test compound. We therefore found no evidence to suggest that physically trained subjects such as long-distance runners need higher or lower doses of those drugs which are metabolized in the liver.

The data of the present study seem to suggest that adaptation of the liver to long-lasting physical exercise occurs as a relatively specific process. The physiological phenomena measured by the quantitative tests of hepatic function used in the investigated long-distance runners do not appear to participate. Development of other investigative procedures is therefore needed to better understand these aspects of liver physiology.

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