CHOLESTEROL METABOLISM, ACETYLATION PROCESSES, AND THIAMINE

Yu. M. Ostrovskii

From the Department of Biochemistry (Head: Yu. M. Ostrovskii), Grodno Medical Institute
(Presented by Active Member AMN SSSR V. V. Parin)
Translated from Byulleten'Éksperimental'noi Biologii i Meditsiny, Vol. 52, No. 7,
pp. 62-64, July, 1961
Original article submitted July 15, 1960

Practically the whole of the carbon skeleton of cholesterol is made up of acetyl residues, which are condensed initially to give the aliphatic hydrocarbon squalene. This is then converted, by an oxidocyclization reaction, into the phenanthrene ring system of cholesterol [12]. The synthesis of cholesterol proceeds in practically all of the tissues of homeotherms, and the first stage of this process is closely bound up with generation of active acetyl groups, produced by other metabolic processes. In the oxidative degradation of carbohydrates, an intermediate product in the formation of acetyl coenzyme A is a compound of a two-carbon fragment with thiamine pyrophosphate [15]. There are grounds for believing that this intermediate may function as an acetylating agent, transferring ready-made acetyl to coenzyme A to the pyruvate oxidase system [11, 14]. Coenzyme A would here function merely in the secondary role of carrier. This formulation would to some extent explain why incorporation of C^{14}– acetate into cholesterol is unaffected by pantothenate deficiency [13]. The existence of a dependence of the process of acetylation of sulfanilamide on the state of thiamine metabolism has been reported [2]. We have shown, on the other hand, that diversion of acetyl residues for acetylation of isoniazid has an appreciable effect on cholesterol synthesis [5].

Published data on the effect of thiamine on cholesterol metabolism are both scanty and contradictory. I. A. Myasnikova [4] found that a single injection of thiamine into patients caused a fall in the level of blood cholesterol, whereas prolonged administration had the opposite effect. Thiamine retards the development of experimental hypercholesterolemia in rabbits [3]. The rate of synthesis of cholesterol in avitaminotic rats was doubled by thiamine injections [16]. On the other hand, the cholesterol content of the blood and tissues of B_1-deficient pigeons was found to be raised [1].

In this paper we present new data on the dependence of cholesterol biosynthesis in humans and experimental animals on the rate of simultaneously proceeding acetylation processes; the effect of thiamine on the connection between these processes is also examined.

METHODS AND RESULTS

Since isoniazid could affect cholesterol metabolism not only by diversion of acetyl residues, but also by interference with thiamine metabolism [6], we used a different drug, p-aminosalicylic acid (PAS), in our experiments. The use of this drug gave the following advantages: it is much less toxic than is isoniazid, for which reason it is used therapeutically in much higher dosage (12-15 g per diem), and 60-80% of the dose is eliminated in the urine as its acetyl derivative. Hence this drug provides a much more effective means of diverting acetyl groups than does isoniazid, the daily dosage of which does not exceed 1.5-2 g for humans. Apart from this, PAS has a much smaller effect on thiamine metabolism [7].

Working together with M. M. Korotkina, we found that the mean blood cholesterol content of patients suffering from pulmonary tuberculosis fell, after three days of administration of PAS at a rate of 12 g per diem, from 290 to 250 mg-%. That of experimental animals (20 rabbits) fell similarly from 95 to 78 mg-% after three days of administration of PAS (0.15 g per kg body weight). The fall in the blood cholesterol of rabbits was significant in 19 out of 20 animals (there was no change in one rabbit).

We found that when 20-40% glucose was injected together with thiamine (5-50 mg) into patients receiving PAS, the effect of the latter in lowering blood cholesterol was abolished, or, in some cases, even reversed. We performed a special series of experiments on animals, with the object of elucidating the relation between thiamine

TABLE 1. Blood Cholesterol of Rabbits (mg-%)

Rabbits given glucose		Rabbits given thiamine	
Before administration of PAS	After administration of PAS	Before administration of PAS	After administration of PAS
90	78	66	79
88	62	94	100
100	92	102	114
77	60	78	90
76	70	88	90
128	102	110	110
95	90	94	100
65	60	72	69
80	64	68	70
110	100	70	74
Mean 91	78	84	90

TABLE 2. Serum Cholesterol (determined by the method of V. A. Éngel'gardt and L. I. Smirnova) of Patients Suffering from Pulmonary Tuberculosis, Treated with Isoniazid

Name of Patient	Cholesterol content (mg-%)			
	Before treatment	On the 3rd day of treatment	On the 4th day of treatment, with thiamine injection	On the 6th day of treatment, without thiamine
K-i	161	130	148	140
S-o	168	126	144	130
B-o	139	96	130	120
K-sh	120	99	115	110
S-ch	134	119	150*	130
M-v	160	148	157*	136
Sh-a	134	111	136*	120
Ya-k	133	124	142*	121

* Cocarboxylase injections.

and cholesterol metabolism.

PAS was administered to two groups of ten rabbits each for 3 days, at a dosage rate of 0.2 g per kg body weight per diem. An intramuscular injection of 10 ml of 5%glucose was given at the same time to one group of rabbits, while the other group received a solution of 2 mg of thiamine chloride in 10 ml of physiological saline. Blood cholesterol was determined before, and after three days of administration of PAS (Table 1).

Glucose administered without thiamine did not affect the action of PAS on cholesterol metabolism: blood cholesterol fell in all cases. No such effect was observed when thiamine was given together with glucose, and in some cases there was even a rise in the blood cholesterol level. There can be no question of any antagonistic action between PAS and thiamine, since we had earlier observed a similar effect in patients receiving therapeutic doses of isoniazid. Because of the small number of such observations, we did not publish them earlier, without further experimental verification. The structures and mechanisms of action of PAS and isoniazid are quite different from each other. The only feature which they possess in common, in relation to cholesterol metabolism, is that they are both actively acetylated in the organism. Apart from this, isoniazid may inhibit phosphorylation of thiamine [6]. The data of Table 2 illustrate our observations on the serum cholesterol content of tuberculous patients on a daily dosage of 1.5 g isoniazid. On the 4th day they were given intramuscular injections of thiamine chloride (0.5 mg per kg body weight) or cocarboxylase (0.7 mg per kg body weight; the preparation was a mixture of thiamine phosphates,

containing 75% thiamine pyrophosphate).

The hypocholesterolemic action of isoniazid was abolished in all the eight patients examined by a single injection of thiamine, and even more markedly by thiamine phosphates. This effect of thiamine was no longer apparent on the day following its injection.

Thus these observations, made at different times, and with different drugs, which had the common property of being readily acetylated in the organism, made it evident that the mechanism of their action on cholesterol metabolism was basically the same in both cases. In this respect, the data derived from patients and from animal experiments were in complete consonance. Both PAS and isoniazid caused a definite drop in the level of blood cholesterol. This effect was not abolished by glucose, and, in individual cases, administration of thiamine during treatment with the chemotherapeutic preparations even raised the blood cholesterol level above the initial value.

We have found [8,9,10] that the free serum thiamine levels of patients suffering from hypertension and atherosclerosis were very high, as were also their transketolase and thiamine dehydrogenase activities. All this affords evidence of a general activation of thiamine metabolism, which is geared to a higher level of activity. We do not believe that this association between activation of thiamine metabolism and pronounced hypercholesterolemia encountered in the majority of individuals suffering from hypertensive disease can be purely fortuitous. It seems that thiamine is actively concerned in the generation of active acetyl, and that it promotes a preponderance of anabolic over catabolic processes of lipid metabolism. Not enough is as yet known about other pathways of lipid metabolism involving thiamine, and additional research on this question is required. In view of the results here presented we think it may be of practical importance to reconsider the question of the use of thiamine in the treatment of hypertensive disease.

SUMMARY

The effects of PAS and isoniazid on blood cholesterol are ascribed to diversion of active acetyl residues from cholesterol synthesis to acetylation reactions. Thiamine is thought to function as an activator of processes of lipid anabolism. The need for caution in the use of thiamine in treatment of hypertensive disease and atherosclerosis is indicated.

LITERATURE CITED

1. O. N. Abbakumova, Collection of Scientific Papers from the Department of Biochemistry of the 1st Leningrad Medical Institute (1958) p. 28.
2. Yu. S. Kagan, Farmakol. i Toksikol., 6 (1949) p. 16.
3. G. I. Loibman, Ukr. Biokhim. Zhurn., 24, 1 (1952) p. 19.
4. I. A. Myasnikova, Trudy Voenno-morsk. Akad. L., 8 (1947) p. 140.
5. Yu. M. Ostrovskii, D. Z. Kagan, and A. A. Yaroshevich, Byull. Éksper. Biol. i Med., 45, 5 (1958) p. 34.
6. Yu. M. Ostrovskii, Zdravookhr. Belorussii, 5 (1955) p. 49.
7. Yu. M. Ostrovskii, Vopr. Med. Khimii, 2 (1957) p. 109.
8. Yu. M. Ostrovskii, Vopr. Pitaniya, 1 (1957) p. 32.
9. Yu. M. Ostrovskii, Transactions 2nd Scientific Meeting, Grodno Medical Institute (1960) p. 46.
10. Yu. M. Ostrovskii, Byull. Éksper. Biol. i Med., 50, 7 (1960) p. 66.
11. Yu. M. Ostrovskii, Ukr. Biokhim. Zhurn. 31 (1959) p. 617.
12. J. W. Cornforth, Rev. Pure Appl. Chem., 4 (1954) p. 275.
13. D. Kritchevsky, Cholesterol (New York, 1958).
14. T. Matsukawa and H. Kawasaki, J. Pharmacol. Soc. Japan, 74 (1954), p. 893.
15. L. J. Reed, J. Am. Chem. Soc., 75 (1953) p. 1267.
16. J. N. Williams, Fed. Proc., 18 (1959) p. 351.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
