EFFECT OF ANTIBACTERIAL CHEMOTHERAPEUTIC PREPARATIONS OF THE SYNTHESIS OF p-AMINOHIPPURIC ACID IN RAT LIVER SLICES

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The most interesting aspect of the action of bactericidal chemotherapeutic preparations is that of their effect on reactions of synthesis, particularly of proteins.

For this reason we thought it would be of interest to study the effect of chemotherapeutic preparation on the formation of peptide bonds.

For this purpose we applied the model reaction of synthesis of p-aminohippuric acid (PAHA) by rat liver slices from p-aminobenzoic acid (PABA) and glycine [2].

The experimental methods used were described in our previous paper [1]. We compared the amount of PAHA synthesized by liver slices from the same animal, after incubation for 5 hours, with and without addition of the chemotherapeutic substance.

We examined the effects of the antibiotics streptomycin, penicillin, chloromycetin, and biomycin, and of the antituberculosis drugs Tubazid, Ftivazid, and Tibon.*

In those cases in which the amount of antibacterial drug added exceeded its solubility in the medium we added it in the form of a fine suspension.

EXPERIMENTAL RESULTS

The results given by our experiments are presented in Tables 1, 2, and 3.

It appears from the data of Table 1 that Tubazid, Ftivazid, and Tibon do not significantly affect the synthesis of PAHA by liver slices.

The data of Table 2 show that penicillin in high concentrations (100 – 10,000 units per ml) inhibits synthesis of PAHA. At concentrations such as are achieved in the organism for therapeutic purposes we could find no interference with biosynthesis. Streptomycin sulfate depresses synthesis at a concentration of 4000 units per ml, while streptomycin–calcium chloride complex either has no action, or stimulates synthesis, even at very high concentrations.

Table 3 shows that chloramphenicol, syntomycin, dextromycetin, and chlortetracyclin suppress synthesis of PAHA by rat liver slices, at concentrations of 1000 μg/ml. Total inhibition of biosynthesis of PAHA is achieved by concentrations of 10,000 μg/ml of chloromycetin and syntomycin.

DISCUSSION OF RESULTS

Our experiments show that the antituberculosis chemotherapeutic drugs Tibon, Ftivazid, and Tubazid, as well as streptomycin, do not inhibit the reaction of biosynthesis of PAHA, even when taken in very high

* Transliteration of Russian – Publisher's note.

TABLE 1

Effect of Chemotherapeutic Antibacterial Drugs on Synthesis of PAHA by Rat Liver Slices

Serial No.	Name of drug	Weight of liver tissue (g)	Synthesis of PAHA, as % of control, in presence of the drug (μg/ml)					
			10 000	5 000	1 000	100	10	1
1	Tubazid	0.2	—	—	97	—	82	—
2	Ftivazid	0.2	—	—	90	—	100	—
3	Tibon	0.2	84	88	—	86	—	—

TABLE 2

Effect of Penicillin and Streptomycin on Synthesis of PAHA by Rat Liver Slices

Serial No.	Antibiotic	Weight of liver tissue (g)	Synthesis PAHA as % control in presence of antibiotic (units per ml)											
			10 000	5 000	4 000	1 000	500	400	100	50	40	5	4	1	0.1
1	Penicillin (sodium salt)	0.2	0	—	—	34	—	—	76	—	—	—	—	113	95
2	Crystalline penicillin (K salt)	0 2	2	—	—	—	—	—	76	—	—	—	—	—	—
3	Ditto	0.2	15	—	—	50	—	—	79	—	—	—	—	94	94
4	Streptomycin sulfate	0.2	—	—	64	—	—	—	—	—	93	—	89	—	—
5	Streptomycin-calcium chloride complex	0.2	—	109	—	—	119	119	—	145	—	102	—	—	-
6	Ditto	0.2	—	109	—	—	137	—	—	123	—	109	—	—	—

TABLE 3

Effect of Antibiotics on Synthesis of PAHA by Rat Liver Slices

Serial No.	Name of antibiotic	Weight of liver tissue (g)	Synthesis PAHA, as % of control, in presence of the antibiotic (μg/ml)				
			10 000	1 000	100	10	1
1	Sintomitsin	0.2	28	45	87	93	93
2	»	0.2	13	61	100	—	—
3	»	0.2	0	78	100	—	—
4	Chloramphenicol	0.2	3	19	105	—	—
5	»	0.2	5	66	93	—	—
6	»	0.2	—	67	—	—	—
7	Dextramycetin	0.2	0	42	48	122	—
8	»	0.2	—	55	114	—	—
9	Chlortetracyclin	0.2	—	50	89	89	—
10	»	0.2	—	50	83	—	—

concentrations. The slight inhibition observed at very high concentrations of streptomycin was probably due to the presence of impurities in the antibiotic preparation; a purer preparation of streptomycin, viz., its calcium chloride complex, not only did not inhibit synthesis, but even had a stimulating effect.

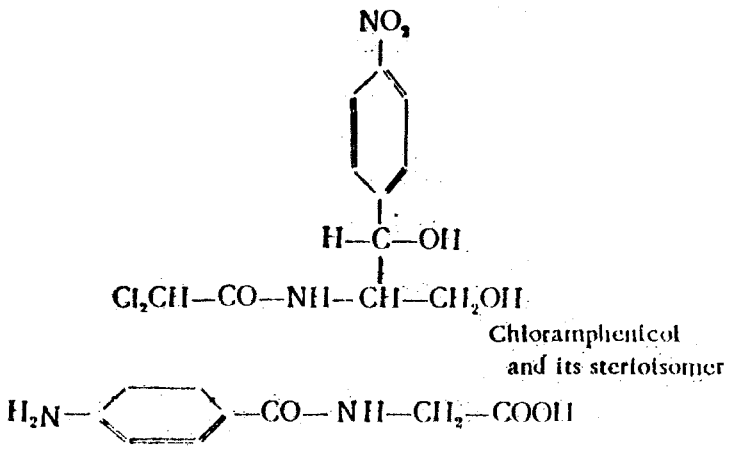
It thus appears that neither the specific action of antituberculosis drugs, nor the toxic effects which they may exert, can be related to their effect on the biosynthesis of hippuric acid and its derivatives.

The widely used antibiotics penicillin, chloramphenicol (levomycetin), syntomycin, and chlortetracyclin, at concentrations such as are achieved in the organism therapeutically, do not inhibit the reaction of biosynthesis of p-aminohippuric acid. Very high concentrations of antibiotics (1000 and 10,000 μg/ml).

It is clear that the mechanism of action of these chemotherapeutic preparations cannot be related to this reaction.

The effect of high concentrations of chloramphenicol, of its d- and dl-forms, and of penicillin and chlortetracyclin on the biosynthesis of PAHA is of theoretical significance insofar as the effect is one of inhibition of a reaction by substances analogous in structure to the products of the inhibited biosynthetic reaction (presence of amide bonds).

As an illustration of the structural similarities we give the formulae of chloramphenicol and PAHA.



Chloramphenicol and its stereoisomer

p-Aminohippuric acid

It should, however, be borne in mind that at such high concentrations these agents may also interfere with other biochemical processes, and this may secondarily affect the process under examination.

The antituberculosis chemotherapeutic preparations Tubazid, Ftivazid, and Tibon, as well as streptomycin, do not interfere with the biosynthesis of p-aminohippuric acid by liver slices.

Penicillin, chloramphenicol, syntomycin, dextramycetin, and chlortetracyclin have no effect on the biosynthetic reaction at concentrations corresponding to therapeutic levels, but at higher concentrations they suppress synthesis, down to total inhibition.

The inhibition of the biosynthetic reaction by chloramphenicol, its stereoisomers, penicillin, and chlortetracyclin may be related to the similarity of molecular structure of the inhibitors and reaction product.

SUMMARY

The effect of chemotherapeutic preparations on the synthesis of peptide bonds was studied.

The reaction of synthesis of para-aminohippuric acid (PAHA) in sections of a rat's liver from para-aminobenzoic acid (PABA) and glycine was used. This method was described by P. P. Cohen and R. W. Gilwery. It was established that antituberculous chemotherapeutic preparation Tubazid, Ftivazid, Tibon, and streptomycin do not disturb biosynthesis of para-aminohippuric acid by liver slices. Penicillin, chloramphenicol,

syntomycin, dextromycetin and chlortetracyclin in low concentrations, which correspond to therapeutic, have no effect on the above reactions of biosynthesis. In high concentrations these drugs suppress this reaction up to complete inhibition. Depression of reaction of biosynthesis of PAHA by chloramphenicol and its stereoisomers, penicillin, and chlortetracyclin may be explained by similarity of the chemical structure of the depressing substances with the products of this reaction.

LITERATURE CITED

[1] G. N. Pershin and L. I. Shcherbakova, Synthesis of PAHA by slices of rat liver containing malignant tumor tissue. (In print).*

[2] P. P. Cohen and R. W. Gilwery, J. Biol. Chem., v. 166, p. 261.

* In Russian.