Chemistry of Natural Compounds, Vol. 34, No. 2, 1998

FEATURES OF THE SYNTHESIS OF PROTEINS IN THE DIGESTIVE ORGANS OF ANIMALS UNDER THE ACTION OF SOME TOXIC CHEMICALS*

O. Kh. Saitmuratova, É. A. Tursunov, M. A. Nishanbaeva, and O. U. Muradov

UDC 612.591.04

The influence on protein synthesis of toxic chemicals in the digestive organs on single and repeated administration has been studied. It has been shown that the actions of Harvade F25, α-sum, and T-86 on protein synthesis are different. Toxic chemicals change the levels not only of ribosomal but also of nuclear protein synthesis.

We have investigated the action of the pesticide Harvade F25, the insecticide α-sum, and the growth factor T-86 on the total biosynthesis of protein in digestive organs (stomach, liver, and duodenum) after their single and repeated introduction into the animal organism.

According to the work of Érgasheva [1], on the basis of its (intragastric) toxicity parameters Harvade F25 belongs to the group of moderately hazardous substances, while with respect to its inhalation action it is a highly dangerous compound. From the mechanism of its toxic action, Harvade F25 belongs to the chemical substances exhibiting a hematotoxic and hepatotoxic action.

An investigation of the rate of protein synthesis in the digestive organs with a single administration of the preparations (after 2 h) has shown (Table 1) that under the action of Harvade F25 the biosynthesis of protein falls by 50% in comparison with the norm in the stomach, by 25% in the liver and by 19% in the duodenum.

Under the action of α-sum, protein biosynthesis fell by 19% in the stomach, by 59% in the liver, and by 14% in the duodenum, as compared with a control. T-86 stimulated these processes by 60-70% in the stomach and liver and by more than 100% in the duodenum. We then investigated the action of Harvade F25 on protein biosynthesis after single and repeated administration.

The falls in protein synthesis in these organs 24 h after a single administration amounted to 38, 35, and 29%, respectively. On the administration of Harvade F25 daily for 30 days, the synthesis of protein in the stomach, liver, and duodenum began to recover and the suppression of protein synthesis was only 12-20% (Table 1).

On this basis it may be stated that Harvade F25 is eliminated from the organism with time and may therefore be considered a nontoxic substance. In the early periods a destructive change takes place in the internal organs, and this, in its turn, affects protein biosynthesis. On repeated administration of the substance, the change bears a compensatory nature, as a result of which protein synthesis normalizes. This circumstance is apparently explained by an adaptation of the organism to Harvade F25.

The experimental results obtained showed that Harvade F25 is an inhibitor of protein synthesis, while T-86 stimulates this process. As yet, it is difficult to say precisely what proteins they affect the synthesis of, and, therefore, in continuing our experiments we investigated the influence of Harvade F25 and T-86 on nuclear protein synthesis.

*The materials of this paper were presented at the Second International Symposium on the Chemistry of Natural Compounds (SCNC, Eskişehir, Turkey, October 22-24, 1996).

Tashkent Pediatric Medical Institute. A. S. Sadykov Institute of Bioorganic Chemistry, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (3712) 162 70 71. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 205-208, March-April, 1998. Original article submitted November 10, 1997.

0009-3130/98/3402-0163$20.00

TABLE 1

Organs*	Protein synthesis, %	Radioactivity (pulses/min) per 100 mg of crude tissue, %		
		Single administration		Multiple administration (30 days)
	2 h	2 h	24 h	
Stomach				
Control	100			
Harvade F25	50	50	62	88
α-Sum	81			
T-86	171			
Liver				
Control	100			
Harvade F25	75	75	65	82
α-Sum	41			
T-86	165			
Duodenum				
Control	100			
Harvade F25	81	81	71	80
α-Sum	86			
T-86	205			

*Concentrations of the preparations administered (single introduction); Harvade F25) 7.5; α-sum) 75; T-86) 3.75 g/kg.

The rate and kinetics of biosynthesis of proteins in nuclei have nonlinear natures (Fig. 1). The nonuniform biosynthesis of protein in liver nuclei permits the assumption that the active formation of protein takes place in the interval from 15 to 45 min from the beginning of the reaction. Under the action of Harvade F25 for 60 min, the synthesis of protein fell, although only slightly, and even an increase in the dose did not affect protein synthesis. At the same time, an identical dose of T-86 increased the rate of protein synthesis in the nuclei almost twofold in comparison with the control (see Fig. 1). It follows from this that the stimulation of protein synthesis in the cytoplasm and in the cell nucleus in the presence of T-86 is probably a result of an increase in the activity of certain enzymes participating in this process. Under the action of Harvade F25, conversely, the activity of the factors participating in protein synthesis falls.

The action of the substances under trial on the kinetics of the protein-synthesizing activity of nuclei can be followed better in an analysis of differential graphs of the changes in the dynamics of the inclusion of [^{35}S]-methionine in the nuclear synthesis of protein in comparison with a control (Fig. 2).

When the nuclei were examined under the microscope it was found that the action of T-86 led to a small increase in the volume of the nuclei and a rise in the number of nucleoli and informosomes partially located under the karyolemma. A euchromatization of the nuclei was observed which showed a rise in the functional activity of the nuclear structures (Fig. 3).

The following conclusions can be drawn from what has been said above:

1. On a single administration to animals, the toxic chemicals Harvade F25, α-sum, and T-86 affect the total synthesis of protein in the digestive organs. Under the action of Harvade F25 and α-sum, protein synthesis in the stomach, liver, and duodenum is slightly suppressed, while T-86 stimulates this process fairly considerably.

2. On the repeated administration of Harvade F25 and α-sum to animals the biosynthesis of protein recovers after 30 days and approaches the norm.

3. Harvade F25, α-sum, and T-86 apparently act on enzymes and change the level not only of the ribosomal synthesis of protein but also of the nuclear synthesis of protein in the liver.

EXPERIMENTAL

We used new commercial preparations: Harvade F25, which is used as a defoliant, α-sum — an insecticide, and T-86 — a plant growth factor.

Acute experiments were performed on white random-bred male rats weighing 160-180 g, which were given the preparations intragastrically in a dose of 1/10 to 1/2 of the LD_{50}. The LD_{50} of Harvade F25 for rats is 7.5 g/kg, that of α-sum 75 mg/kg, and that of T-86 3.75 g/kg. The toxic chemicals were dissolved in physiological solution before administration to the animals. Under the conditions of a chronic experiment the preparation was administered daily for 30 days in a dose of 1/10 LD_{50}. [^{35}S]Methionine with a specific activity of 1 μCurie/mmole (100,000 pulses/min) was administered intraperitoneally an

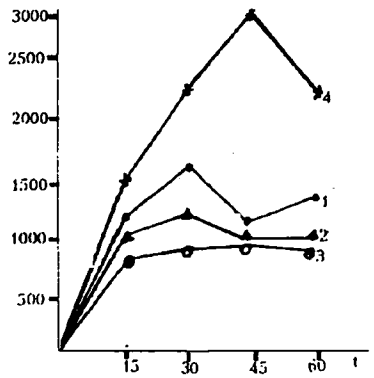

Fig. 1. Kinetics of the biosynthesis of nuclear proteins of the livers of control and experimental animals 2 h after the administration of the substances: *1*) control; *2*) Harvade F25, 1/2; *3*) Harvade F25, 1/10 LD_{50}; *4*) T-86, 1/2 LD_{50}.

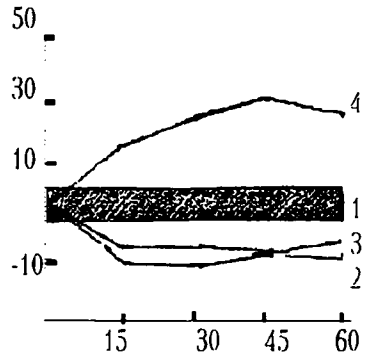

Fig. 2. Kinetics of the changes in the differential radioactivity values (relative to a control) under the influence of Harvade F25 and T-86 on the protein-synthesizing activity of the nuclei of rat livers 2 h after the administration of the substances: *1*) control; *2*) Harvade F25, 1/2 LD_{50}; *3*) Harvade F25, 1/10 LD_{50}; *4*) T-86, 1/2 LD_{50}.

hour before sacrifice. At 2, 24, and 30 days after the administration of the preparation, the animals were decapitated and the rate of protein synthesis in the individual organs was determined from the inclusion of the [^{35}S]-methionine. The control animals were treated with physiological solution in parallel.

The ribosomal synthesis of protein was studied in homogenates of the mucous membrane of the stomach and the duodenum and also in the liver tissues. The animals were decapitated 2, 24, and 30 days after the administration of the substances. All the manipulations with the organs were performed in a cold room at 2-4°C. After decapitation the organs were dissected out and were rinsed with cold physiological solution. The tissue samples weighed 50-100 mg. Hydrolysis was carried out with formic acid, 1 ml of which was added to each sample over 2 h at 80°C in a thermostat. The hydrolysates of organs were transferred by pipette to nitrocellulose filters, washed free from unbound radioactive amino acids with 5% TCAA until no unbound radioactivity remained, and, finally, were washed with ethyl alcohol and dried in the air. Radioactivity was measured in ZhS-8 scintillation liquid on a β-counter. The levels of protein synthesis in the organs were determined from the inclusion of the [^{35}S]-methionine in the proteins isolated from the tissues. They were calculated as pulses/min per 100 mg of crude tissue (%).

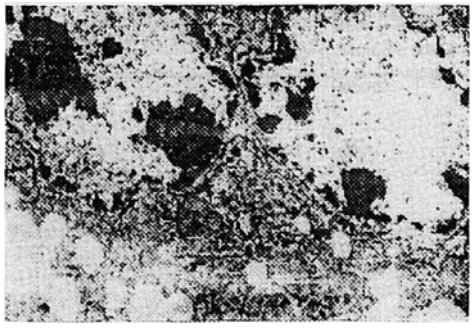

Fig. 3. Euchromatization of rat liver nuclei under the action of the preparation T-86. Magnification ×6000.

The nuclear synthesis of protein in rat livers was determined on isolated nuclei from the inclusion of [^{35}]-methionine as described in [2]. Smears were prepared from the isolated nuclei, and they were stained with nuclear dyes and examined under a MBI-15 microscope. The results obtained were treated by the method of variational statistics [3].

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