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Abstract

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Features of the Action of Mercamine and Inhibitors of Radical-Chain Processes in Reactions Modeling Lipid Oxidation

Proceeding from the important role of free-radical states and processes in the mechanism of radiation injury, one of us proposed the use of nontoxic inhibitors of radical-chain reactions as possible means for the prophylaxis and therapy of radiation sickness (^1).

Since, among the various biochemical shifts characteristic of radiation injury, a certain role is played by oxidative processes developing in lipids after irradiation (^2,3), we carried out a comparative assessment of the action of several known protective agents (mercamine) and typical inhibitors of radical-chain reactions (hydroquinone) on the oxidation process of methyl oleate, which we selected as a model system.*

The inhibition of oxidative processes by additions of chemical substances may be achieved either as a result of the replacement of the active radicals that carry the chains by inactive radicals formed from the molecules of the added substances, or owing to the destruction of peroxide compounds, which are the primary products of oxidation and, in a number of cases, branching agents (^5).

From the standpoint of the use of inhibitors for the prophylaxis and therapy of radiation sickness, it is expedient to distinguish three types of chemical substances, differing in their mechanism of action: 1) inhibitors of radical-chain processes, interacting with radicals of the type $R^{\bullet}$ according to the scheme $R^{\bullet} + \mathrm{HIn} \rightarrow RH + In^{\bullet}$; 2) inhibitors interacting with radicals of the type $RO_2^{\bullet}$ according to the scheme $RO_2^{\bullet} + \mathrm{HIn} \rightarrow ROOH + In^{\bullet}$, where HIn is the inhibitor, $In^{\bullet}$ is a low-activity radical; 3) substances that destroy peroxide compounds.

It is assumed that inhibition of oxidation reactions by hydroquinone proceeds according to the reactions (^6).

$$\mathrm{HO{-\!\!-}OH} + RO_2^{\bullet} \rightarrow \mathrm{HO{-\!\!-}O^{\bullet}} + ROOH$$

semichinone radical;

$$\mathrm{HO{-\!\!-}O^{\bullet}} + RO_2^{\bullet} \rightarrow \mathrm{O{=\!\!=}O} + ROOH.$$

Figure 1. Kinetic curves of the accumulation of peroxides (1-3) and oxides (4-6): 1, 4 —for uninhibited methyl oleate; 2, 5 —with addition of $1.04 \cdot 10^{-2}$ mmol/ml mercamine; 3, 6 —with addition of $1.46 \cdot 10^{-3}$ mmol/ml hydroquinone.

Figure 1: Figure 1. Kinetic curves of the accumulation of peroxides (1-3) and oxides (4-6): 1, 4 —for uninhibited methyl oleate; 2, 5 —with addition of $1.04 \cdot 10^{-2}$ mmol/ml mercamine; 3, 6 —with addition of $1.46 \cdot 10^{-3}$ mmol/ml hydroquinone.

Our data on the irradiation of inhibited methyl oleate in the presence and in the absence of oxygen also indicate that hydroquinone is consumed mainly as a result of interaction with radicals of the RO_2 type.

Hydroquinone added before the beginning of the reaction delays the formation of the primary products of methyl oleate oxidation: peroxides and oxides—and increases the induction period (Fig. 1). Hydroquinone added to an already re-

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* The method for obtaining methyl oleate and for determining the functional groups formed during oxidation is given in work (^4).

the reacting system also retards the formation of peroxides, but does not inhibit the process of their decomposition. As a result, there is some decrease in the content of peroxide compounds (Fig. 2), which indicates the existence of a chain pathway for the decomposition of methyl oleate peroxides.

The rate constant for peroxide decomposition proved to be equal to the decomposition constant calculated for the oxidized mixture when access of air was stopped ([5]). (For a peroxide concentration of $6.7 \cdot 10^{-4}$ mole/g, $K_{T=80^\circ\mathrm{C}} = 1.1 \cdot 10^2$ g/mole $\cdot$ h.) It was of interest to examine the effect on the oxidation of methyl oleate of such a widely used prophylactic agent as mercamine,

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which is a good reducing agent. Consequently, it may be assumed that it will react with the peroxide compounds formed during the oxidation of methyl oleate. In our experiments mercamine was introduced into an already reacting mixture at the stage of oxidation when the amount of peroxides had reached a significant value ($6 \cdot 10^{-4}$ mole/g). In this case, a rapid decrease in the peroxide content was indeed observed (Fig. 2).

Apparently, by interacting with peroxides, mercamine is converted into sulfone derivatives, since the molar amount of decomposed peroxides exceeds the amount of introduced mercamine by a factor of 2-3. The amount of oxides remains unchanged. Introduction of mercamine before the start of the reaction retards the oxidation of methyl oleate in the same way as hydroquinone (Fig.

1).

It is interesting to note that mercamine retards not only the appearance of peroxides, but also that of oxides, with which it does not enter into direct interaction.

We previously showed that the formation of oxides in methyl oleate proceeds independently and in parallel with the formation of peroxides ([4]). The retardation of oxide formation upon addition of hydroquinone indicates that the oxide compounds of methyl oleate are formed by a free-radical mechanism. In this connection, the fact that the process of formation of oxide compounds is inhibited by additions of mercamine can be explained, for example, by assuming that mercamine is at the same time a weak inhibitor of the "radical" type. However, this question requires further study. In its action, additions of mercamine are equivalent to additions of weak inhibitors. At the same time, mercamine, like many other antioxidants ([7]),

acting by the mechanism of peroxide destruction, is a strong synergist for inhibitors that interact with radicals. We studied the combined action of a mixture of hydroquinone and mercamine on the process of methyl oleate oxidation.

Synergism can be characterized by the magnitude of the difference ($\Delta\tau_{syn}$) between the induction period produced by the mixture of inhibitors ($\tau_{mixture}$) and the sum of the induction periods produced by each of the inhibitors separately (in this case, $\tau_{hydroquinone}$ and $\tau_{mercamine}$).

We established that $\Delta\tau_{syn}$ depends to a much greater extent on the amount of mercamine introduced than on the amount of hydroquinone. Thus, for example, at a constant mercamine concentration equal to $5 \cdot 10^{-3}$ mmol/ml, and different hydroquinone concentrations ($1.37 \cdot 10^{-3}$ and $0.7 \cdot 10^{-3}$ mmol/ml), identical values of $\Delta\tau_{syn}$, equal to 6 h (at 80°C), were obtained. At the same time, when the mercamine concentration was decreased to $2.5 \cdot 10^{-3}$ mmol/ml (hydroquinone concentration $1.37 \cdot 10^{-3}$ mmol/ml), the value of $\Delta\tau_{syn}$ decreased to 3 h.

The result obtained can be explained if it is assumed that the mechanism of this effect consists in the reduction of the oxidized form of hydroquinone (for example, the semiquinone radical). As a result, there is, as it were, an increase in the amount of the radical-type inhibitor participating in the reaction, one stronger than mercamine itself. Therefore the value of $\Delta\tau_{syn}$ will be the greater, the greater the difference in the inhibiting strength of these two antioxidants. Taking into account the ability of mercamine to destroy peroxides and to reduce the oxidized forms of inhibitors, its protective properties can be explained by the fact that mercamine protects tissue inhibitors from destruction by radiation and preserves the specificity of their action.

Fig. 2. Kinetic curves for the accumulation of peroxides. 1 –for uninhibited methyl oleate, 2 –with addition to the system of hydroquinone (0.06 mmol/ml), 3 –with addition to the system of mercamine (0.3 mmol/ml).

As already indicated, introduction of mercamine and hydroquinone before oxidation of methyl oleate causes practically the same effect. This occurs only because the process of peroxide formation in methyl oleate is a chain process.

In the case of radical processes, the introduction of such inhibitors as hydroquinone or diphenylamine, which interact mainly with radicals of the $RO_2^{\bullet}$ type, may prove ineffective, since elimination of the free valence is coupled with the formation of an identical amount of peroxides.

Therefore, for the purposes of preventing radiation sickness and delaying the development of free-radical states and processes arising after irradiation, it is very important to have at one' s disposal inhibitors capable of destroying radicals of the $R^{\bullet}$ type. When such substances are introduced, the free valence formed in the biostructure under the action of irradiation is destroyed, but no new substances harmful to the organism, such as peroxides, arise, and the natural tissue inhibitors are preserved. In experiments on the therapy of acute radiation sickness under conditions in which the natural tissue inhibitors have already been destroyed to a certain degree, while oxidative radicals and peroxide compounds are present, the use of substances of the mercamine type will already be insufficient.

In therapy, the main role will apparently belong to inhibitors of the radical type. Since, in the organs of irradiated animals, the content of peroxide compounds proves to be higher, it is advisable, in developing combined therapy, to use, together with radical inhibitors, substances that destroy peroxides.

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REFERENCES

1 N. M. Emanuel, Reports at the symposium devoted to the primary mechanisms of the biological action of ionizing radiation, May 30–June 1, 1960. **2** B. N. Tarusov, *Fundamentals of the Biological Action of Radioactive Radiation*, Moscow, 1954. **3** A. Sheval' e, K. Byurg, in: *Problems of Radiobiology*, ed. by G. M. Frank, IL, 1956, p. 11. **4** E. B. Burlakova, B. G. Dzantiev, A. K. Zeifroy, G. B. Sergeev, N. M. Emanuel, *Izv. Vyssh. Uchebn. Zaved., Khim. i Khim. Tekhnol.*, **3**, no. 2, 265 (1960). **5** N. N. Semenov, *On Certain Problems of Chemical Kinetics and Reactivity*, Publishing House of the Academy of Sciences of the USSR, 1955. **6** E. T. Denisov, N. M. Emanuel, *Uspekhi Khimii*, **27**, no. 4, 365 (1958). **7** G. W. Kennerly, W. L. Patterson, *Ind. and Eng. Chem.*, **48**, 1917 (1956).

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