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Antimutagenic Properties of Ubiquinone-10

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The effect of biotechnologically obtained ubiquinone-10 on the level of photrin- and dioxydin-induced chromosomal aberrations is studied for different doses of the preparations by assessing chromosomal aberrations in bone marrow cells of C57Bl/6 mice. It is shown that ubiquinone-10 does not exhibit its own mutagenic effect and does not potentiate the effect of the test mutagens.

Key Words: *ubiquinone-10; antimutagenic agent; chromosomal aberrations*

Many man-made chemical compounds have mutagenic properties and, acting upon the genetic structures, lower the level of fitness in the human population and adversely affect the health of some individuals [1,2,4,13]. These negative effects may be prevented with antimutagenic compounds inhibiting or reducing the genotoxic effects of xenobiotics. In some cases a search for mutagens may be goal-specific. For example, if damage to the genome is due to the prooxidant properties of a particular agent, its negative effects can obviously hope to be corrected with antiradical and antioxidative compounds [7,11]. This assumption has often been experimentally corroborated in studies of the effect of synthetic and natural antioxidants on mutagenesis caused by diverse inducers in different test systems [1,6,11]. In view of the foregoing, ubiquinone-10 (UB-10), a natural metabolite widely distributed in the human organism, which exhibits antioxidant properties, but which has not been tested for possible antimutagenic activity, has attracted attention.

In the present study we explored the influence of biotechnologically obtained UB-10 on the cytogenetic effects of the mutagens dioxydin (DO) and photrin (PT) *in vivo*.

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MATERIALS AND METHODS

The study was carried out by assessing chromosomal aberrations in bone marrow cells of male C57Bl/6 mice (the breeding stations Svetlye Gory and Kryukovo of the Russian Academy of Medical Sciences) aged 1.5-2 months and kept under standard conditions in the vivarium. Pharmacological preparations of DO in doses of 10, 100, and 300 mg/kg and of PT in doses of 7 and 14 mg/kg were used as inducers of mutagenesis. We performed a single intraperitoneal injection of each compound in a volume of 0.2 ml of physiological saline; the animals were sacrificed 24 h after the injection. The inducers of mutagenesis were chosen in accordance with earlier obtained data [5] indicating that free-radical processes play the leading role in the cytogenetic effects of the above-mentioned compounds. UB-10 (State Research Institute Sintezbelok) was injected in olive oil (0.2 ml) intraperitoneally and *per os* 1 h after injection of the mutagens. Cytogenetic preparations of bone marrow cells were obtained and microscopi-

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TABLE 1. Effect of UB-10 Injected *Per Os* on Mutagenic Effects of PT in Mice ($M \pm m$)

Preparation, dose	Number of cells	Chromosomal aberrations per 100 cells				Percentage of damaged metaphases	Reliability
		single fragments	paired fragments	exchanges	genes		
PT, 7 mg/kg	500	9.6	1.0	0.2	4.0	13.6±1.5	
UB-10:							
20 mg/kg	500	11.4	1.0	0	2.2	11.6±1.4	⩾0.05
2 mg/kg	400	11.8	1.3	0	1.3	11.8±1.6	⩾0.05
0.2 mg/kg	500	10.6	1.2	0	1.0	12.8±1.5	⩾0.05
PT, 14 mg/kg	500	31.4	2.8	0.6	4.4	29.0±2.0	⩽0.05
UB-10:							
20 mg/kg	500	24.8	1.0	0	2.2	19.8±1.8	⩽0.05
2 mg/kg	500	26.2	2.0	0	2.0	22.0±1.9	⩽0.05
0.2 mg/kg	500	28.2	2.2	0.2	2.6	25.2±1.9	⩾0.05

cally analyzed as described previously [10]. Five animals were used in each experimental variant.

RESULTS

The results of studies of the influence of UB-10 injected *per os* on the mutagenic effects of PT are presented in Table 1. It was established that in a dose of 7 mg/kg the mutagen alone caused chromosomal injury in 13.6±1.5% and in a dose of 14 mg/kg in 29.0±2.0% of cells, which virtually coincided with earlier findings obtained in cytogenetic studies of the preparation [11]. UB-10 in doses of 0.2, 2, and 20 mg/kg did not exert any marked effect upon the level of bone marrow cells damaged by PT in a dose of 7 mg/kg. However, when the mutagen was used in a dose of 14 mg/kg, we observed a statistically reliable reduction of its cytogenetic effect under the influence of UB-10 in doses of 2 and 20 mg/kg. In the first case the level of damaged metaphases dropped 2% and in the second case 32%.

Table 2 shows the results of studies of the influence of UB-10 injected *per os* on the cytogenetic effects of DO. DO in doses of 100 and 300 mg/kg damaged 5.6±1.0 and 20.4±1.8% of studied cells, respectively, while in a dose of 10 mg/kg it did not exert any marked effect upon the level of spontaneous mutations, which was consistent with the earlier-published data [8].

In a dose of 0.2 mg/kg UB-10 did not have any impact on the cytogenetic effect of DO in any of the experimental variants. In doses of 2 and 20 mg/kg UB-10 statistically reliably reduced the mutagenic effect of DO in a dose of 300 mg/kg (by 33 and 49%, respectively). When the dose of

TABLE 2. Effect of UB-10 Injected *Per Os* on Mutagenic Effects of DO in Mice ($M \pm m$)

Preparation, dose	Number of cells	Chromosomal aberrations per 100 cells					Percentage of damaged metaphases	Reliability
		single fragments	paired fragments	exchanges	genes	*M.A.*		
DO, 10 mg/kg	500	1.8	0	0	0.4	–	2.2±0.7	
UB-10:								
20 mg/kg	500	2.2	0.2	0	0.2	–	2.2±0.7	⩾0.05
2 mg/kg	500	1.8	0.2	0	0.2	–	2.0±0.6	⩾0.05
0.2 mg/kg	500	1.2	0	0	0.4	–	1.6±0.6	⩾0.05
DO, 100 mg/kg	500	4.0	0.4	0	1.2	–	5.6±1.0	
UB-10:								
20 mg/kg	500	2.4	0	0	1.2	–	2.4±0.7	⩽0.05
2 mg/kg	500	4.2	0	0	0.8	–	3.8±0.9	⩾0.05
0.2 mg/kg	500	3.4	0	0	0.6	–	4.0±0.9	⩽0.05
DO, 300 mg/kg	500	13.8	0.8	0.4	1.8	9.2	20.4±1.8	
UB-10:								
20 mg/kg	500	6.6	0.2	0	0.6	3.2	10.4±1.4	⩽0.05
2 mg/kg	500	14.0	0.2	0.2	1.4	4.6	13.6±1.5	⩽0.05
0.2 mg/kg	500	14.6	0.6	0.2	0.6	6.8	18.2±1.7	⩾0.05

Note. Here and in Table 4: *M.A.* denotes cells with multiple chromosomal aberrations (more than 5 aberrations per cell).

TABLE 3. Effect of Peritoneally Injected UB-10 on Mutagenic Effects of PT in Mice ($M \pm m$)

Preparation, dose	Number of cells	Chromosomal aberrations per 100 cells				Percentage of damaged metaphases	Reliability
		single fragments	paired fragments	exchanges	genes		
PT, 7 mg/kg	500	9.6	1.0	0.2	4.0	13.6±1.5	
UB-10:							
20 mg/kg	500	8.4	1.4	0	0.6	10.2±1.4	≥0.0
2 mg/kg	500	8.4	0.4	0	0.4	8.0±1.2	≤0.05
0.2 mg/kg	300	4.0	0.3	0.6	0.7	5.0±1.3	≤0.05
PT, 14 mg/kg	500	31.4	2.8	0.6	4.4	29.0±2.0	
UB-10, 20 mg/kg	500	22.6	2.4	0	1.4	21.8±1.8	≤0.05

mutagen was 100 mg/kg, UB-10 in a dose of 20 mg/kg virtually abolished the effect of DO. The results obtained in this case (2.4±0.7%) did not differ from the control values (1.5±0.5%).

The results obtained when UB-10 was combined with DO in a dose of 10 mg/kg did not differ from the control. In studies of the influence of intraperitoneally injected UB-10 on the cytogenetic effects of PT (Table 3) it was demonstrated that at 20 mg/kg UB-10 statistically significantly (by 25%) reduced the effect of the mutagen in a dose of 14 mg/kg.

However, we noted no protective effect of UB-10 in the same dose for the use of PT in a dose of 7 mg/kg. In this experimental variant a statistically significant reduction of the effect of the mutagen was observed when UB-10 was used in doses of 2 and 0.2 mg/kg (by 37 and 63%, respectively).

When injected intraperitoneally, UB-10 (20 mg/kg) statistically significantly (by 23%) reduced the cytogenetic effect of DO in a dose of 300 mg/kg (Table 4). Meanwhile, when the mutagen was used in a dose of 100 mg/kg, a statistically reliable protective effect of UB-10 was observed only at 0.2 mg/kg. In this case the preparation completely abrogated the cytogenetic effect of DO: the value obtained (1.8±0.7%) did not differ from the result characteristic of the level of spontaneous mutations in C57Bl/6 mice.

We may conclude that synthetic UB-10 has an antimutagenic activity vis-a-vis the cytogenetic effects of PT and DO.

There is evidence that the antimutagenic effect is directly proportional to the degree of damage exerted by the mutagen [8]. Indeed, UB-10 injected *per os* had no detectable effect on the cytogenetic impact of PT in a dose of 7 mg/kg; however, a protective effect of the test compound in doses of 2-20 mg/kg was observed when PT was used in a dose of 14 mg/kg. On the other hand, in the case where DO was the mutagen, the picture was different. For example, when the damaging factor was used in a dose of 300 mg/kg, UB-10 injected by different routes did not reduce the effect of the mutagen by more than 49%, whereas the cytogenetic effect of DO in a dose of 100 mg/kg was completely abrogated.

Another specificity of UB-10 was an evident dependence of its antimutagenic effect on both the mode of injection and the type of mutagen. For example, the intraperitoneal route was more effective because under these conditions its modifying effect on the mutagenic activity of PT manifested

TABLE 4. Effect of Intraperitoneally Injected UB-10 on Mutagenic Effects of DO in Mice ($M \pm m$)

Preparation, dose	Number of cells	Chromosomal aberrations per 100 cells					Percentage of damaged metaphases	Reliability
		single fragments	paired fragments	exchanges	genes	*M.A.*		
DO, 100 mg/kg	500	4.0	0.4	0	1.2	–	5.6±1.0	
UB-10:								
20 mg/kg	500	3.8	0.8	0	0.0	–	4.0±0.9	≥0.05
2 mg/kg	500	2.4	0.6	0	0.2	–	3.2±0.8	≥0.05
0.2 mg/kg	400	2.0	0	0	0.3	–	1.8±0.7	≤0.05
DO, 300 mg/kg	500	13.8	0.8	0.4	1.8	9.2	20.4±1.8	
UB-10, 20 mg/kg	500	14.0	1.6	0	0.4	4.6	15.6±1.6	≤0.05

itself at lower doses than in the case of its injection *per os*. On the other hand, when DO (300 mg/kg) was used, UB-10 was more effective *per os*. The results obtained using 100 mg/kg DO demonstrated that in a dose of 20 mg/kg UB-10 was more effective when injected *per os*, while in a dose of 0.2 mg/kg the intraperitoneal route was more effective.

The study of antimutagenic activity as a function of dose is very important, especially with respect to substances with antioxidative activity, since a dose-dependent switch from protective to mutagenic and mutagen-potentiating effects is typical of these substances [11]. UB-10, according to our findings, has the advantage of not exhibiting such an inversion of its effect. We did not note any mutagen-potentiating effects of UB-10 in the test doses in any instance, either against the background of marked cytogenetic effects of the test mutagens or for their use in doses exerting no marked effects (DO, 10 mg/kg). A study of UB-10 in doses from 0.2 mg/kg to 0.5 LD_{50} in a series of tests recommended for evaluating the mutagenic activity of new drugs [10] did not reveal it to have its own mutagenic activity. The differences between the antimutagenic doses of UB-10 which were found in this study in different experimental variants probably resulted from differences in the bioaccessibility of the test compound for different modes of injection, as well as from pharmacokinetic and other specificities of the test mutagens.

The described peculiarities of the antimutagenic effect of UB-10 corroborate the opinion [3,11] that the pharmacological development of a corrector of mutagenic effects must be geared specifically to the individual damaging factor.

Our findings indicate that UB-10 has antimutagenic properties, exhibiting obvious advantages (with respect to the possible inversion of the protective effect) vis-a-vis other antimutagenic agents. Further study of this compound as a pharmacological means of protecting genetic structures thus seems to hold promise.

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