GENETIC CONTROL OF SENSITIVITY TO EXPERIMENTAL ADJUVANT ARTHRITIS IN INBRED MICE

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Much information has now been obtained on the connection between tissue incompatiblity antigens and predisposition to diseases [5-7]. Autoimmune diseases are an example of this. Genetic differences in the immune response are controlled by Ir-genes, which play an important role in the control of sensitivity to diseases, and in particular, to autoimmune processes. This has been demonstrated on models of experimental allergic encephalomyelitis in certain strains of rats [3], guinea pigs [8], and mice [1]. At the same time, it has been shown [4] that the large histocompatibility complex does not control sensitivity to experimental allergic encephalomyelitis in mice. Contradictory results also have been obtained in studies of sensitivity of mice to other experimental autoimmune processes. The investigations cited above have aroused interest in the search for the connection between H-2 antigens and experimental adjuvant arthritis.

The aim of this investigation was to study genetic control of sensitivity to experimental adjuvant arthritis in mice of inbred, congenitally resistant lines.

EXPERIMENTAL METHOD

Inbred strains of mice, and congenitally resistant, recombinant, and hybrid mice used in the investigation were obtained from the Department of Genetics, Research Laboratory of Experimental Biological Models, Academy of Medical Sciences of the USSR. Mice aged 2 months, weighing initially 18-20 g, were used in the experiments. The animals were kept on the standard animal house diet, with 10 animals to a cage.

Adjuvant arthritis was induced by the model suggested by Brackertz et al. [2]. Freund's complete adjuvant (FCA; from Calbiochem, USA) was injected subcutaneously in a dose of 0.05 ml into the hind footpads of the mice. The sensitivity of the mice to adjuvant arthritis was estimated by measuring edema of the limb joints.

On the 35th day of development of arthritis the animals were killed and the weight of the joints of the hind limbs determined. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

The first stage of the investigation was the study of sensitivity of inbred mice to experimental adjuvant arthritis.

Interlinear differences in the development of experimental adjuvant arthritis were discovered in mice of the different genotypes. B6 and B10 mice were most sensitive to arthritis. The weight of the joints in the affected B6 mice was statistically significantly greater than in mice of other strains. The smallest increase in the weight of the joints was found in CBA mice. Thus these strains of mice were opposite as regards induction of experimental adjuvant arthritis, i.e., the B6 strain was sensitive but the CBA strain was resistant. It must be noted that arthritis did not develop in CBA (M523) mice, a strain isogenic with CBA, i.e., the mutation in H-2K did not change sensitivity to adjuvant arthritis. An intermediate position as regards the degree of development of arthritis in response to injection of FCA was occupied

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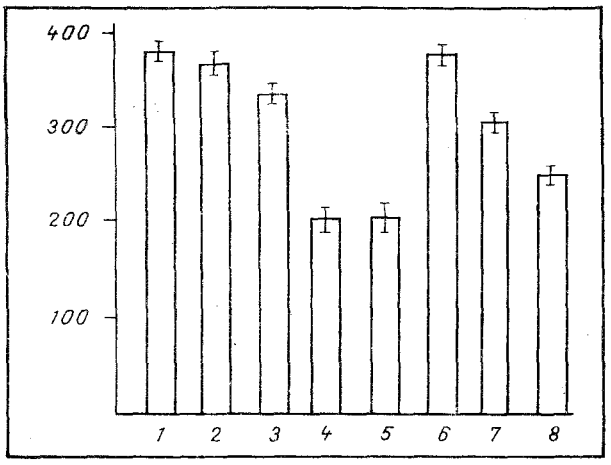

Fig. 1. Experimental adjuvant arthritis in hybrid mice. Abscissa: 1) B6; 2) B6 × CBA)F_1; 3) F_2 (sensitive); 4) F_2 (resistant); 5) CBA; 6) F_1 × B6; 7) F_1 × CBA (sensitive); 8) F_1 × CBA (resistant); ordinate, weight of joints (in mg).

by mice of strains A, C, SWR, and I. Interlinear differences in sensitivity to induction of adjuvant arthritis are evidence of their genetic nature.

The second stage of the investigation was a study of the sensitivity of first and second generation hybrids to experimental arthritis. To establish the character of inheritance of sensitivity to experimental arthritis, a hybridologic analysis was undertaken on (B6 × CBA)F_1 and F_2 mice. It will be clear from Fig. 1 that the weight of the joints in F_1 hybrids with arthritis was approximately the same (359 ± 5.7 mg) as that of sensitive B6 mice. Inheritance of sensitivity to arthritis in mice is thus of the dominant type. Analysis of the sensitivity of second generation (F_2) hybrids to induction of arthritis showed that 80% of the animals were sensitive to arthritis and 20% were resistant. Consequently, during induction of arthritis in F_2 hybrids segregation takes place for sensitivity to arthritis in the progeny, i.e., 39 of 49 mice developed severe arthritis. This segregation corresponds to that expected in monohybrid crossing ($\chi = 0.67$; $0.5 > P > 0.25$).

Hybrid mice from back crossing (B6 × CBA)F_1 × B6 (weight of the joints 382 ± 3.52 mg) also were highly sensitive to induction of arthritis. In the case of analytic crossing of (B6 × CBA)F_1 × CBA mice two classes were distinguished: resistant (weight of joints 252 ± 3.5 mg) and sensitive (weight of joints 324 ± 3.4 mg), at a level close to the F_1 sensitivity.

The next stage of the investigation was to determine the connection between genes responsible for development of adjuvant arthritis and the H-2 histocompatibility complex. Induction of arthritis in mice of congenitally resistant strains and recombinants for the H-2 haplotype showed that B10 (H-2^b) mice were most sensitive to induction of arthritis. Similar results were obtained by induction of arthritis in B10.M (H-2^f) mice. Meanwhile, arthritis virtually did not develop at all in BR (H-2^k) mice (weight of joints 261 ± 5.3 mg).

Interesting results were obtained by induction of arthritis in B10.A (2R) and B10.A (5R) mice. B10.A (5H) (H-2^{i5}) mice were sensitive to induction of arthritis (weight of joints 327 ± 7.4 mg), whereas B10.A (2R) (H-2^{h2}) mice virtually did not develop arthritis (weight of joints 256 ± 3.5 mg). This suggests that sensitivity to adjuvant arthritis is located in the K region or on the left of the S region of the H-2 complex.

Analysis of the results shows that more severe arthritis develops in mice with the H-2^b haplotype and the parameters were higher than those of mice with the H-2^k haplotype. However, in CC57W and CC57BR mice (H-2^b in both cases) arthritis developed less severely than in C57BL/6 and C57BL/10 mice, possibly due to the presence of a modifier gene in those strains. On induction of arthritis in congenitally resistant strains of mice it was found that animals identical to one another with respect to all genes except those of the H-2 complex develop arthritis to different degrees. Consequently, some of the genes responsible for the development of arthritis may perhaps be located in the H-2 complex, whereas other genes lie outside that complex. Further genetic analysis, with the use of congenitally resistant strains with recommended H-2 haplotypes will enable the region in H-2 responsible for the development of arthritis to be localized more exactly. Thus, sensitivity to adjuvant arthritis in mice is under

genetic control and is inherited as a dominant trait. The gene (or genes) is linked with the H-2 complex, and according to the preliminary data, is located on the left of the S region.

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MUTAGENIC AND ANTIMUTAGENIC PROPERTIES OF BEMITIL

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Proof of the role of induced mutations in the spread of hereditary diseases and in the development of malignant neoplasms has stimulated research aimed at the discovery of chemical mutagens and the search for compounds with modifying, antimutagenic properties [1, 2]. Such compounds can be used in conjunction with drugs which have a genotoxic effect, but which have not been withdrawn from practice because of their medical importance [7]. It is evident that the search for modifiers should take place among substances capable not only of preventing or reducing harmful effects, but at the same time, reinforcing the therapeutic effect. Such compounds include certain psychotropic agents, tranquilizers, and actoprotectors, widely used in combination pharmacotherapy.

The aim of this investigation was to study the effect of a new actoprotector, bemitil, a derivative of 2-mercaptobenzimidazole, on the level of spontaneous mutations and of mutations induced by alkylating agents.

EXPERIMENTAL METHOD

The investigation was conducted in accordance with the technical recommendations of the Ministry of Health of the USSR on mutagenicity testing [4]. The action of bemitil in a concentration of 10 mg/ml on the spontaneous mutation level in *Drosophila melanogaster* was studied

TABLE 1. Effect of Bemitil on Level of Recessive Sex-Linked Lethal Mutation in *D. melanogaster* (M ± m)

Experimental conditions	Total number of chromosomes investigated	Frequency of mutations, %
Control	753	0,4±0,2
Bemitil (10 mg/ml)	685	0,4±0,2

Legend. Here and in Tables 2-4: *P > 0.05 compared with control.

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