CORRELATION BETWEEN THE PRINCIPAL HISTOCOMPATIBILITY SYSTEM IN MICE AND MEN WITH PREDISPOSITION TO THE DEVELOPMENT OF NARCOTIC DEPENDENCE

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Analysis of antigens of the principal histocompatibility system of human tissues (HLA) can serve as objective criterion of genetic predisposition of the individual to various diseases. There is evidence of association between the HLA system and mental disturbances, notably schizophrenia and manic-depressive psychosis [5, 9]. Determination of marker antigens characteristic of a particular pathology enables the risk of development of that disease in a concrete individual to be estimated and it is also of diagnostic and prognostic importance in clinical practice [6].

The object of this investigation was to study the role of the principal histocompatibility system in regulating the sensitivity of experimental animals and man to chronic administration of narcotics.

EXPERIMENTAL METHOD

Experiments were carried out on mice of congenitally resistant strains based on A/Sn and C3H/Sn: A/Sn, A.Sw and C3H.OH, C3H.Sw, obtained from the Laboratory of Expermental Biological Models, Academy of Medical Sciences of the USSR. Males weighing 20-25 g, which were kept on an ordinary laboratory diet, were used. Physical dependence on morphine was reproduced by a scheme including administration of morphine hydrochloride in increasing doses for 4 days. Toward the end of narcotic administration the total dose of morphine was 1300 mg/kg body weight. The quantitative index of the severity of physical dependence was the number of stereotyped jumps provoked by injection of nalorphine (100 mg/kg), a morphine antagonist, into the narcotized mice.

For the clinical part of the investigation patients of Russian nationality with a diagnosis of multiple drug dependence of stage II-III, receiving a course of treatment in hospital or at a drug addiction dispensary in Moscow were chosen. HLA antigens were types by Terasaki's lymphocytotoxic test on trays. A suspension of lymphocytes (2000 cells/mm^3) isolated from heparinized blood in a Ficoll–Verografin density gradient was used in the test. Altogether 48 antisera (from Behringwerke, West Germany) and antigens of loci A, B, and C were used. The reaction was assessed on a 3-point scale. Data obtained in the Institute of General Genetics, Academy of Sciences of the USSR, during typing of 126 healthy subjects of Russian nationality [7], were used as the control. The coefficient of relative risk was calculated by the formula

$$X = \frac{AD}{BC},$$

where A is the number of patients carrying the antigen; B the number of patients in whom the antigen under evaluation is absent; C the number of healthy subjects carrying the antigen; D the number of healthy subjects in whom this antigen is absent.

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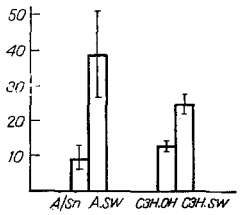

Fig. 1. Intensity of withdrawal syndrome in mice of different strains. Ordinate, jumping activity (number of jumps in 15 min).

TABLE 1. Particular Features of Distillation of HLA Antigens in Patients with Multiple Drug Dependence

HLA antigen	Frequency of occurrence of antigens		Coefficient of relative risk
	patients (~=59)	healthy subjects (~=126)	
AI	0,25	0,30	0,79
A2	0,49	0,48	1,03
A3	0,14	0,17	0,74
A9	0,22	0,21	1,04
A10	0,29	0,22	1,42
A11	0,20	0,18	1,14
A28	0,05	0,08	0,62
B5	0,37	0,12	4,00*
B7	0,20	0,24	0,82
B8	0,10	0,12	0,84
B12	0,12	0,17	0,67
B13	0,15	0,14	1,08
B14	0,12	0,04	3,26
BW15	0,12	0,11	1,00
BW17	0,14	0,05	3,14
B27	0,09	0,06	1,37
BW35	0,20	0,19	1,09
B40	0,12	0,15	0,76
CW/4	0,42	0,20	2,97*

*Difference statistically significant by chi-square test.

EXPERIMENTAL RESULTS

Jumping activity of morphinized animals provoked by antagonists, which we used to assess the severity of an experimental withdrawal syndrome is known to be directly proportional to the dose of the narcotic administered, and other conditions being the same, to the sensitivity of the animals to morphine [1]. Mice of congenitally resistant strains differ from one another only with respect to the H-2 system or adjacent regions of the chromosome and are homozygous for all other genes. Accordingly, differences obtained in the experiments on congenitally resistant strains must be attributed to variations in the structure of the H-2 system. Data illustrating differences in the jumping activity of mice of congenitally resistant strains during simulation of the withdrawal syndrome are given in Fig. 1. It was shown previously in the writers' laboratory that the H-2 system participates in monitoring the sensitivity of animals to the analgesic action of morphine [2, 3, 10]. The results of the present investigation show that the principal histocompatibility system of mice also determines the response of the animals to chronic administration of the narcotic.

The experimental results provided a basis for the hypothesis that a particular haplotype of the HLA system may facilitate the development of dependence on narcotics. In that case, marker HLA antigens, found more frequently than in a control population of healthy subjects, could be distinguished in the group of patients with narcotic dependence. Typing patients with multiple drug dependence for HLA antigens led to the discovery of some special features of their distribution (Table 1). Whereas the occurrence of antigens of the A locus was similar to that in the control group, among antigens of the B and C loci,

HLA-B5, HLA-B14, HLA-BW17, and HLA-CW4 antigens were discovered more frequently. Statistically significant differences, by the chi-square test, were observed only for HLA-B5 and HLA-CW4 antigens. The coefficient of relative risk of the disease for carriers of these antigens was 4.00 and 2.97, respectively.

The increased frequency of discovery of HLA-B5 antigen was noted previously in certain diseases of varied etiology [15]. Association of HLA-B5 antigen with Buerger's disease — a disease of the peripheral vessels — is found most frequently in heavy smokers and has been interpreted as manifestation of a genetic link between this antigen and pathological addiction to tobacco smoking [11]. The most interesting finding in connection with the present investigation is a considerable increase in the frequency of the HLA-85 antigen in schizophrenics and children with infantile psychosis [12]. In the USSR, this last disease is classified as childhood schizophrenia. Considering the well-known features of personality and character of narcotic addicts, it can be postulated that the purpose of the present investigation was to discover genetic markers of increased predisposition to narcotics in subjects with a psychopathically changed personality. However, on the basis of the experimental data described above, a direct link between the HLA system and a tendency toward the development of drug addictions seems more probable. It is important to emphasize that the associations discovered between antigens of the principal histocompatibility system of the tissues and various types of drug addiction will contribute to the more precise classification of nosological forms of this disease and will help to confirm or reject their genetic connection with other mental diseases.

The enormous general biological importance of the HLA system is due to its regulation of the level of antibody formation. The connection between the HLA phenotype and susceptibility to most diseases having a disturbance of the function of the immune system in their pathogenesis is explained by its participation in the regulation of the immune response of the body. To explain the connection between nonimmune diseases and the principal histocompatibility system, it has been postulated recently that certain HLA antigens may have structural similarity with receptors of endogenous ligands — hormones, neurotransmitters, and so on [13, 14]. Disturbance of neurotransmitter function may be the cause of an inherited predisposition to a development of certain pathological processes. In the present writers' opinion, similar mechanisms lie at the basis of association of the HLA-B5 antigen with a hereditary predisposition to narcotic addiction. On the basis of the results described above we consider that HLA-B5 and HLA-CW4 antigens can be used as genetic markers for the detection of increased sensitivity to narcotics.

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