ANTIBODIES TO MORPHINE AND TO NEUROTRANSMITTERS IN THE BLOOD SERUM OF CHRONIC ALCOHOLICS

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The leading role of changes in functions of the catecholamine system of the body and, in particular, of the dopamine (DA) system, in the pathogenesis of chronic alcoholism has been established [1]. The system of endogenous opioid peptides performs an important modulating function in this connection [11]. According to the hypothesis of Davis and Walsh [12], endogenous morphine-like alkaloids, formed in the body from catecholamines under the influence of acetaldehyde, may also play a definite role in the pathogenesis of alcoholism. The presence of substances similar in structure to morphine in animal tissues has been confirmed by recent research [14, 15], and their endogenous origin has been proved [13].

One approach to the study of the possible role of endogenous morphine-like substances in the pathogenesis of alcoholism adopted in this investigation was to look for antibodies to morphine in the blood serum of chronic alcoholics, for antibodies are known to participate in regulation of the function of various biologically active substances in the body, such as neurotransmitters, hormones, and metabolic products [3, 6-8, 10].

Another aim of the investigation was to study the role of antibody formation to neurotransmitters (DA, noradrenalin — NA, serotonin — 5-HT) in the pathogenesis of chronic alcoholism, with the use of our own modification of the complement absorption test (CAT). Data in the literature indicating greater sensitivity during detection of autoantibodies of reactions based on complement fixation were taken into account [5].

EXPERIMENTAL METHOD

A group of chronic alcoholics in stage II (17 men, average age 37.6 ± 2.3 years, mean duration of the disease 12.1 ± 1.6 years) and a group of healthy subjects (21 men, average age 33.0 ± 2.8 years) were investigated. Antibodies to morphine and neurotransmitters in the blood serum were determined by the modification of CAT, carried out in the zone of 50% hemolysis of sensitized sheep's red blood cells, with colorimetric reading of the result of the test, expressed as the quantity of complement (in percent) bound in the presence of the corresponding antigen [4]. Neurotransmitter levels in the blood were determined by the method in [9].

EXPERIMENTAL RESULTS

The results of determination of antibodies to the neurotransmitters DA, NA, and 5-HT and to morphine in the blood serum of healthy subjects and chronic alcoholics are given in Table 1. In 14 alcoholics (82%) levels of antibodies to morphine were raised ($p < 0.1$), and in the other three there was a tendency toward their decrease (the possibility that the subjects tested may have taken preparations such as morphine, apomorphine, papaverine, and so on, capable of giving a false positive result, was ruled out). Comparison of average group values of antibody levels to neurotransmitters revealed no significant differences between the groups

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TABLE 1. Levels of Antibodies to Neurotransmitters and Morphine in Blood Serum of Healthy Subjects and Chronic Alcoholics ($\bar{X} \pm S\bar{x}$)

Group of subjects tested	Antibody level in 1 ml of serum, % of bound complement			
	DA	NA	5-HT	to morphine
Healthy (21)	3,29±0,57	3,99±0,73	3,00±0,68	2,41±0,52
Alcoholics:				
Whole group (17)	3,51±0,74	4,32±0,89	3,56±0,75	4,51±0,70**
Subgroup with elevated antibody level	6,11±0,80** (8)	8,11±0,83*** (7)	5,81±0,83** (9)	5,34±0,65*** (14)
Subgroup with depressed antibody level	1,19±0,38** (9)	1,66±0,42** (10)	1,01±0,34* (8)	0,63±0,35 (3)

Legend. *0.05 < p < 0.1, **p < 0.05, ***p < 0.01 compared with healthy subjects. Number of subjects tested shown in parentheses.

of healthy subjects and chronic alcoholics. In the whole group of alcoholics, however, it was possible to distinguish subgroups characterized by a rise or fall of the antibody levels to a particular neurotransmitter compared with the group of healthy subjects, and which differed significantly from each other. Evidence of a fall in the level of antibodies to histamine and 5-HT in chronic alcoholics compared with healthy subjects was given in [2]. If data in the literature indicating that antibodies to neurotransmitters block their biological effects are taken into account [3, 7, 8], it can reasonably be assumed that elevation of the level of these antibodies in some of the alcoholics may play a compensatory role and facilitate the more complete neutralization of the elevated neurotransmitter levels observed in alcoholism, especially in the presence of withdrawal symptoms [1]. Lowering of levels of antibodies to neurotransmitters and morphine in some alcoholics may reflect a general process of inhibition of immune responses, characteristic of chronic alcoholism. However, we could find no correlation between levels of antibodies to morphine and neurotransmitters, on the one hand, and the duration of the disease or the clinical manifestations at the time of investigation, on the other hand.

In the healthy group positive correlation was found between levels of antibodies to DA and to NA ($r = 0.64$, $p < 0.01$) and to 5-HT ($r = 0.80$, $p < 0.001$). In the group of patients with chronic alcoholism, significant positive correlation (although weaker) was found only between levels of antibodies to DA and 5-HT ($r = 0.61$, $p < 0.05$), possible evidence of definite disturbances in the character of autoimmune responses, ensuring hemostasis, in alcoholism. Comparison of blood levels of the neurotransmitters DA and 5-HT with levels of antibodies to them in the healthy subjects revealed positive (although not significant) correlation, which may be indirect evidence in support of the compensatory, neutralizing role of antitransmitter autoantibodies. The opposite tendency was found in the chronic alcoholic group. This fact may be confirmation of the view that weakening of the process of formation of appropriate autoantibodies is one cause of the raised blood neurotransmitter level in alcoholics.

Similar experiments were carried out on rats to which a 15% solution of ethanol was administered. In the group of rats compulsorily fed with alcohol for 4 months (eight animals) a tendency was noted for the level of antibodies to DA to be raised and the levels of antibodies to NA and 5-HT to be lowered compared with control animals. In the group of rats compulsorily fed with alcohol for 7 months (eight animals) a tendency was noted for levels of antibodies to morphine and DA to rise and of antibodies to NA and 5-HT to fall. In the group of rats compulsorily fed with alcohol for 8 months (10 animals) levels of antibodies to the neurotransmitters and morphine were lowered on average by half, evidence of inhibition of immune responses as a whole. Examination of the parameters for individual animals in the groups showed changes in either an upward or a downward direction in the corresponding antibody levels. On the whole the results of these experiments on animals agree with data obtained during clinical studies.

In conclusion, it must be pointed out that these data showing the presence of antibodies to morphine in human serum are of great interest, for they are indirect confirmation that endogenous substances similar in structure to morphine are present in the human body. Elevation of the level of antibodies to morphine in the majority of the chronic alcoholics tested is evidence that these substances play a definite role in the pathogenesis of the disease.

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EFFECT OF PHENTOLAMINE ON CORONARY VASCULAR RESISTANCE AND HEART RATE

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Several mechanisms of the cardiostimulating and vasodilator effects of phentolamine have been discussed in the literature. In particular, it has been suggested that the preparation possesses β-adrenomimetic activity. The β-adrenomimetic mechanism of the cardiostimulating [1, 4, 6] and vasodilator [6] actions of phentolamine has been confirmed by a number of investigations. However, some workers [1] found no effect of β-adrenoreceptor blockade on the vasodilator effect of phentolamine. The mechanisms of the effect of phentolamine on coronary vascular resistance have not so far been studied.

The aim of this investigation was to study the action of phentolamine on coronary vascular resistance and on the heart rate and also the effect of β_1-adrenoreceptor blockade on the effects of phentolamine.

EXPERIMENTAL METHOD

Experiments were carried out on 23 isolated hearts of cats anesthetized with pentobarbital (30-40 mg/kg), perfused with donor's blood under constant pressure (80-100 mm Hg). The inflow of blood into the coronary arteries was recorded by means of an electromagnetic flowmetric transducer (type MF-46 flowmeter, from Nihan Kohden Kogyo, Japan). The pressure in the right atrium and left ventricle and the perfusion pressure were recorded by means of electromanometric transducers (EMT-746, Siemens-Elema, Sweden). The parameters were recorded on a Mingograf-82 apparatus (Siemens-Elema). Coronary blood flowing out into the left compartment of the heart was drained through a catheter into the apex of the left ventricle, ensuring

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