PSYCHOPATHOLOGICAL AND HORMONAL MAINFESTATIONS OF ALCOHOLIC INTOXICATION AND EMOTIONAL STRESS IN MONKEYS

S. K. Chirkova, A. M. Chirkov, I. S. Voit, G. V. Katsiya, and V. P. Poshivalov

UDC 616.89-008.441.13+613.863]-092.9-07: [616.89+616.154:[577.175.5+577.175.62

KEY WORDS: alcohol; emotional sress; catecholamines; cortisol; testosterone

Emotional stress (ES) is nowadays regarded as a factor in the development of pathological dependence on alcohol. This conclusion is based on the results of psychophysiological studies of the reducing effect of alcohol on negative emotions and also on data showing that animals with high inborn alcohol motivation have increased sensitivity to stress [4] and it indicates the need for a further study of the role of typological features of psychoemotional reactivity in the realization of the neurotoxic effect of alcohols [5]. Meanwhile, analysis of data in the literature reveals the great similarity of the neuroendocrine mechanisms of development of alcohol intoxidation (AI) and of ES [1, 4], evidence of the common biological basis of stress and AI, and at the same time it suggests that the mental and hormonal manifestations of stress are aggravated by preliminary intake of alcohol.

The aim of this investigation was to make a combined study of the behavioral and neurohormonal and neurohormonal components of AI and ES and also of the character of the stress reaction during combined exposure to alcohol and stress.

EXPERIMENTAL METHOD

Experiments were carried out on 25 sexually mature male baboons (*Papio hamadryas*) weighing 27-35 kg and 20 sexually mature male macaques (*Macaca rhesus*) weighing 8-12 kg. Alcohol was injected intravenously in the form of a 33% solution of ethanol, and by the intragastric route as a 40% solution. ES was induced by immobilization for 2 h, which acts as a powerful psychoemotional stimulus for monkeys [3]. The following series of experiments were undertaken: I) ethanol was given per os to five baboons in doses of 0.5 and 4 g/kg and to five macaques in doses of 0.5, 1, 3 g/kg; II) ethanol was injected intraveously into five baboons in a dose of 0.5 g/kg and five macaques in a dose of 1 g/kg; III) ethanol was injected intravenously into five macaques in increasing doses (0.2, 0.4, 0.8, 1, and 2 g/kg) with intervals of 2 weeks between the experiments; IV) 30 min before stress, a preliminary injection of ethanol was given in a dose of 0.5 g/kg to five baboons and in a dose of 1 g/kg to five macaques. In control epxeriments physiological saline was given to five intact male macaques and 10 baboons, and the animals were immobilized for 2 h.

The individual and intraspecific behavior of the monkeys, kept five to a case, was studied by an ethologic method, by recording the dynamic and frequency of 53 behavioral elements, and determining the structure of the hierarchy in each group of monkeys [8]. The ethologic parameters were recording in all series of experiments for 30 min before administration of alcohol or immobilization, for 4 h immediately after the procedure, for 30 min 6 h after the beginning of immobilization, and on the next 5 days for 30 min at 10 a.m., noon, and 4 p.m. Initial values of the ethologic parameters were determined during the previous 10 days in the monkeys of each group. The plasma cortisol and testosterone levels were determined by radioimmunoassay [6]. In all series of experiments the blood steroid level was studied at intervals: before immobilization and 2, 6, 24, 48, and 72 h thereafter. The functional state of the sympathicoadrenal system (SAS) was investigated by determining the 24-hourly excretion of catecholamines (CA) with the urine in monkeys adapted to life in metabolism cages (n = 15), on which the main series of experiments were additionally performed.

Laboratory of Psychopharmacology, Institute of Experimental Pathology and Therapy, Academy of Medical Sciences of the USSR, Sukhumi. Department of Pharmacology, Central Research Laboratory, I. P. Pavlov First Leningrad Medical Institute. (Presented by Alademician of the Academy of Medical Sciences of the USSR, B. A. Lapin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 103, No. 5, pp. 583-586, May, 1987. Original article submitted May 12, 1986.

0007-4888/78/0005-0663$12.50

CA were determined fluorometrically [7] with the MPF-4 spectrofluorometer (Hitachi, Japan). The 24-hourly urine was collected daily throughout the experiments and its background values were determined beforehand during the period of adaptation.

EXPERIMENTAL RESULTS

Administration of alcohol by the intragastric route in a dose of 0.5 g/kg caused a relative increase in the frequency of the elements of preventive intraspecific aggression in all the experiments, while the normal pattern of behavior was preserved on the whole. Intravenous injection of alcohol in the same dose caused a significant increase in the aggressive responses and vocalization in baboons and, in a dose of 1 g/kg, in macaques, compared with the control. The animals showed a tendency toward motor excitation, against the background of a relative decrease in the frequency of elements of comfortable behavior (self-grooming, combing, shaking). During the first 6 h the baboons also exhibited periods of transient inhibition of motor acts.

With an increase in the dose of alcohol to 3 g/kg for macaques and 4 g/kg for baboons acute AI developed and was characterized by an extreme degree of psychoemotional inhibition, with no response to external stimuli or food, with vomiting, and inhibition of general motor activity. Against this background disturbances of voluntary motor acts and coordination, loss of balance and of supporting reflexes, the assumption of unnatural postures, and absence of indicators of intraspecific aggression and friendly behavior were observed. These changes developed 10-15 min after administration of alcohol and they continued for the next 6 h, and were most marked in dominant and low-ranking individuals. During the next 3 or 4 days the features of AI diminished and behavior gradually returned to normal.

Periodic tugging with the trunk and head and active attempts to get free were observed in the monkeys of all species, alternating with bursts of clonic and tetanic spasms of the limbs and trunk. After exposure to stress the animals developed a depression-like state, manifested as profound and prolonged (for 2-3 days) depression of psychoemotional and locomotor activity. The linear hierarchy was disturbed, customary means of communication were disturbed, and elements such as placing, grooming, and to and fro visiting, disappeared. Motor functions were inhibited, movements retarded, postures became rigid, and tremor developed.

Preliminary intravenous injection of alcohol in a dose of 0.5 g/kg into male baboons and in a dose of 1 g/kg into macaques 30 min before the beginning of immobilization for 2 h led to deeper inhibition of mental and motor functions than took place after exposure to ES alone. Changes in psychophysiological parameters under these conditions were on the whole similar to the character of the behavioral disturbances caused by large doses of alcohol.

The study of the functional state of SAS in response to various doses of alcohol showed progressive activation given. Besides the distinct dose-dependent effect of alcohol on noradrenalin excretion, there were also a sharp increase in dopamine excretion and a tendency for the adrenalin level to rise after injection of alcohol in doses of 1 and 2 g/kg (Fig. 1a). In acute AI, CA excretion was comparable with the level of their excretion in response to immobilization for 2 h, whereas during ES preceded by alcohol administration greater activation of SAS was observed (Fig. 1b). Analysis of changes in the functional state of SAS in the after-periods of AI, ES, and stress preceded by alcohol injection, and comparison of these data with the results of the ethologic tests, showed that normalization of CA excretion coincided in time with recovery of the parameters of individual and intraspecific behavior of the monkeys. Considering the important role of monoamines in the regulation of emotions and of adaptive forms of behavior [5, 8], and also data on changes in function of catecholaminergic brain systems in ES and AI [1, 4, 5], it can be postulated that the neurochemical basis of the appearance of reactive, depression-like behavior in monkeys during ES and the aggrevation of its psychopathological manifestations by the action of alcohol is excessive excitation of the central monoaminergic structures followed by depletion of the CA depots.

The study of hormonal function of the adrenal cortex showed that injection of alcohol in a dose of 0.5 g/kg did not cause an increase in adrenocortical activity in the male baboons. Meanwhile, with a combination of AI and ES, a significant rise of the blood cortisol level was observed. The curve showing changes in the cortisol concentration during ES preceded by alcohol administration was similar in character to the curve of changes in the hormone level during AI (Fig. 2a).

Unlike the response of the pituitary-adrenocortical system to alcohl and stress, more marked inhibition of the testicular endocrine function was observed in the monkeys. It will

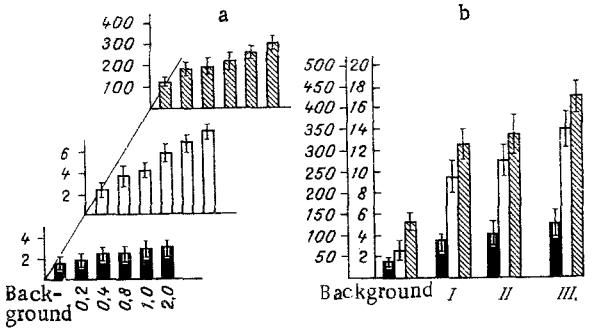

Fig. 1

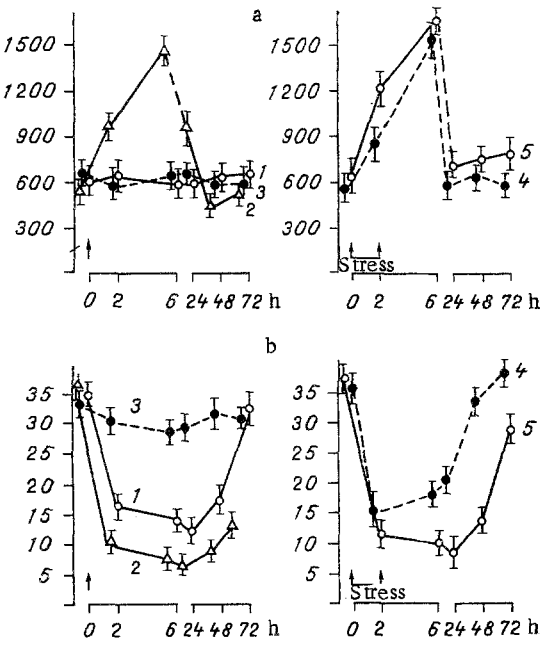

Fig. 2

Fig. 1. Effect of alcohol and stress-inducing stimuli on CA excretion with the urine in mature male macaques. Abscissa (a), doses of ethanol (in g/kg); ordinate (a, b), CA excretion (in μg/24 h). a) Change in excretion of adrenalin (A), noradrenalin (NA), and dopamine (DA) under the influence of alcohol in doses of 0.2, 0.4, 0.8, 1, and 2 g/kg; b) changes in CA excretion following injection of ethanol in a dose of 3 g/kg (I), in response to immobilization for 2 h (II), and in response to stress preceded by injection of alcohol in a dose of 1 g/kg (III).

Fig. 2. Changes in blood cortisol (a) and testosterone (b) levels in mature male baboons after injection of alcohol and exposure to stress. Abscissa, time of taking bold (in h, after beginning of exposure; 0) before injection of alcohol or beginning of immobilization); ordinate, concentration of steroid hormones (in mmoles/liter). Injection of alcohol in doses of: 1) 0.5 g/kg; 2) 4 g/kg; 3) injection of physiological saline (control); 4) immobilization for 2 h; 5) immobilization for 2 h preceded by injection of alcohol in a dose of 0.5 g/kg. Arrow, injection of alcohol; two arrows, immobilization for 2 h.

be clear from Fig. 2b that, in response to a small dose of alcohol, the blood testosterone level fell considerably, and it regained its initial values only on the 3rd day. The inhibitory effect of alcohol on testosterone secretion was exhibited to an even greater degree when the dose of ethanol was increased. During stress preceded by alcohol administration a tendency was found for greater depression of testicular hormonal activity than in response to stress in the control experiments.

The results of this investigation thus demonstrate great similarity between the neuroendocrine mechanisms of AI and ES — states which lead as a whole to a behavioral deficit due to reduction of the animals' mental and motor activity. Intensification of the psychopathological manifestations of ES and overactivation of SAS, observed under the influence of small doses of ethanol, are evidently mediated through the inhibitory action of alcohol on the production of testosterone, which has an inhibitory action on CA release [2].

LITERATURE CITED

1. I. P. Anokhina, Neurochemical Mechanisms of Mental Diseases [in Russian], Moscow (1975).
2. L. K. Bakhova, "Effect of dihydrotestosterone and androstakazol on some aspects of catecholamine metabolism," Author's Abstract of Dissertation for the Degree of Candidate of Biological Sciences, Khar'kov (1975).
3. T. D. Bol'shakova, A. M. Chirkov, and V. G. Startsev, Izv. Akad. Nauk SSSR, Ser. Biol., No. 6, 822 (1985).
4. Yu. V. Burov and N. N. Vedernikova, The Neurochemistry and Pharmacology of Alcoholism [in Russian], Moscow (1985).

5. A. V. Val'dman and V. P. Poshivalov, Pharmacological Regulation of Intraspecific Behavior [in Russian], Leningrad (1984).
6. N. P. Goncharov, S. Chekan, A. V. Antonichev, et al., Vopr. Med. Khin., No. 1, 92 (1979).
7. E. Sh. Matlina, Z. M. Kiseleva, and I. Z. Sofieva, Methods of Investigation of Some Hormones and Mediators [in Russian], Moscow (1965), pp. 25-32.
8. V. P. Poshivalov, Experimental Psychopharmacology of Aggressive Behavior [in Russian], Leningrad (1986).

EMITIC AND ANTIEMETIC PROPERTIES OF SOME REGULATORY PEPTIDES

V. V. Yasnetsov, Yu. V. Drozd, and V. S. Shashkov

UDC 612.327.7.014.46:577.175

KEY WORDS: peptides; vomiting; μ- and δ-opioid receptors; chemoreceptive trigger zone; vomiting center

Information on the emitic action of certain regulatory peptides (RP), mainly of enkephalins and β-endorphin, can be found in the literature. For instance, in 1977 it was shown [9] that Met-enkephalin (ME), when injected into the stomach, induces vomiting in cats. The emetic effects of enkephalins and β-endorphin in cats and dogs were later observed by other workers [1, 5, 8]. However, no special investigation of the vomiting action of the various RP has yet been undertaken. In addition, the possible antiemetic effects of endogenous peptides have virtually not been studied. The existence of these latter properties of the peptides would provide a basis for their prospective use in the prevention and treatment of vomiting, which is a characteristic symptom of many pathological processes and, in particular, of motion sickness and radiation sickness.

The aim of the present investigation was accordingly to compare the emetic and antiemetic properties of certain RP: enkephalins, endorphins, β-lipotropin, ACTH, and substance P (SP).

EXPERIMENTAL METHOD

Experiments were carried out on 30 unanesthetized, unrestrained cats weighing 2.2-4.5 kg. Under general anesthesia (pentobarbital sodium, 30-40 mg/kg, intraperitoneally) cannulas were introduced into the fourth ventricle of the brain at coordinates P = 11, L = 0, H = −4.6, from the atlas [13], 3-5 days before the beginning of the experiment. The position of the cannula in the fourth ventricle was verified later with the aid of Evans' blue dye at autopsy on the animals. In the course of the experiment the ECG and respiration were recorded on an RM-150 polygraph (Nikon Kohden, Japan), and later the heart rate (HR) and respiration rate (RR) per minute were calculated from these parameters.

Morphine (an agonist of μ-opioid receptors), ME and Leu-enkephalin (LE), D-Ala -D-Leu - enkephalin (DDLE) — an agonist predominantly of δ-opioid receptors, and β-, γ-, and des-Tyr-γ-endorphins, obtained from Professor M. I. Titov, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, porcine β-lipotropin and $ACTH_{1-39}$, provided by Corresponding Member of the Academy of Medical Sciences of the USSR, Yu. A. Nankov, of the Institute of Experimental Endocrinology and Hormone Chemistry, Academy of Medical Sciences of the USSR), and also SP (provided by Professor K. Hecht, East Germany), were dissolved in doses of 10-500 μg in sterile isotonic sodium chloride solution, and injected into the fourth ventricle from a microsyringe (Hamilton, Great Britain) in a volume of 50-100 μl. Opioid receptors were blocked by means of naloxone (Endo Laboratories, USA), a specific antagonist of opiates and opioids, and ICI 154, 129, a selective antagonist of δ-opioid receptors (provided by Dr. Med. Sci. O. S. Medvedev), were used.

Institute for Medico-biological Problems, Ministry of Health of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 103, No. 5, pp. 586-588, May, 1987. Original article submitted July 3, 1986.

 0007-4888/87/0005-0666$12.50