DEVELOPMENT OF TOLERANCE TO THE ACTIVATING ACTION OF MORPHINE, AMPHETAMINE, AND ALCOHOL ON THE POSITIVE REINFORCEMENT SYSTEM IN RATS

Yu. V. Burov and S. A. Borisenko

UDC 615.212.7+615.31:547.262].015.5

KEY WORDS: morphine; amphetamine; alcohol.

Cases of polynarcomania – the taking of a combination of drugs causing euphoria, and, if need be, the replacement of one such drug by another [8], known in clinical practice suggest that the effects of these drugs are realized by common, including neurochemical, brain mechanisms. This is confirmed, in particular, by data in the literature [1, 5, 9, 12] showing that changes in the neuromediator systems of the brain arising under the influence of the different drugs causing narcomania are qualitatively similar in direction. Besides euphoria, an indispensable element in the chain of formation of narcomanic dependence is the development in the course of this effect of tolerance to the narcotic used. The writers showed previously [2-4] that substances giving rise to toxicomania lead to activation of the positive reinforcement system in rats, whereas substances unable to induce toxicomania are without this effect.

The object of the present investigation was to study the development of tolerance, and also of crossed tolerance to the activating effect of morphine, amphetamine, and alcohol on the positive reinforcement system in rats.

EXPERIMENTAL METHODS

Experiments were carried out on 11 male rats weighing 250-350 g, into which electrodes were implanted in accordance with coordinates from De Groot's brain atlas [10], into the medial forebrain bundle at the level of the lateral hypothalamus: A = 4.4 mm, L = 1.5 mm, H = 8.5 mm. The operation was performed under pentobarbital anesthesia (40-50 mg/kg, intraperitoneally). Seven days after the operation the rats were trained in self-stimulation until the threshold of the response and number of self-stimulations in a period of 10 min, using currents of different strengths, were stable. The brain was stimulated by sinusoidal pulses with a duration of 0.02 sec and a frequency of 50 Hz. After training of the animals to a stable level of self-stimulation skill, the initial degree of activation of the response was determined by measuring the lowering of the threshold and the increase in the number of self-stimulations under the influence of equivalent doses of amphetamine (0.5 mg/kg), morphine (3 mg/kg), and ethanol (0.5 g/kg of the 15% solution), which were injected intraperitoneally, 30 min before the experiment began. Animals in which a facilitatory effect on self-stimulation was observed as early as after the first injections of the drugs were used in the experiments. The above-mentioned doses of the drugs, as was shown previously [2, 4], are the minimal equivalent doses in which these drugs exhibit a distinct, quantitatively practically equal, activating effect on self-stimulation in the same animal. Immediately after subsequent single testing injections of each drug, one of them was injected once daily in the same dose until the development of tolerance to it, i.e., until it ceased to have any facilitating effect on self-stimulation. Against the background of tolerance to the main drug, subsequent testing was carried out with two other drugs in the initial doses, and also with the main drug in twice the initial dose. Fisher's method [7] was used for the statistical analysis of the results.

EXPERIMENTAL RESULTS

The original values for the threshold of the self-stimulation response in different animals varied from 20 to 140 μA. The intensity of self-stimulation was inversely proportional to the original values of the response threshold and amounted to 220-560 presses on the pedal in 10 min. Amphetamine in a dose of 0.5

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 89, No. 6, pp. 698-700, June, 1980. Original article submitted October 10, 1979.

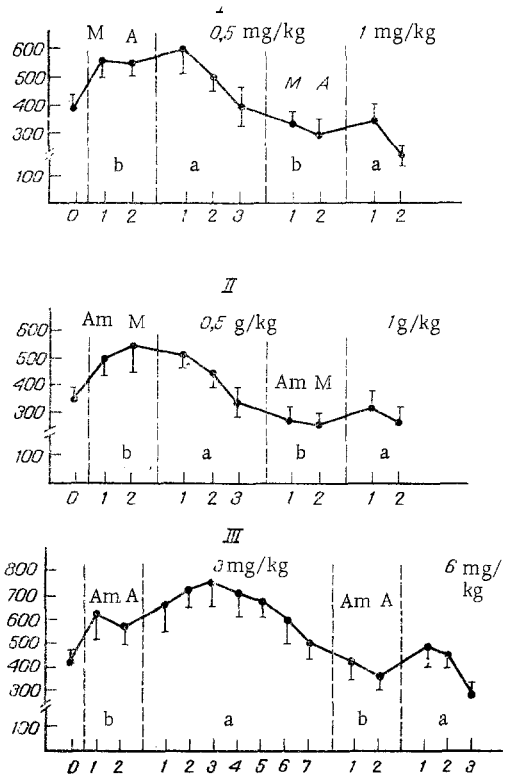

Fig. 1. Development of tolerance to the activating action of amphetamine (I), alcohol (II), and morphine (III) on the structure of positive reinforcement. Abscissa, day of injection of principal (a) or testing (b) drugs; ordinate, number of self-stimulations in 10 min. Am) Amphetamine; A) alcohol; M) morphine. Averaged values given for number of self-stimulations obtained against the background of each drug in all animals used in the experiments.

mg/kg, morphine in a dose of 3 mg/kg, and ethanol in a dose of 0.5 g/kg lowered the threshold of self-stimulation by 5-40 μA ($P < 0.05$) and increased the number of self-stimulations in response to a current of threshold strength by 120-310 ($P < 0.05$) compared with the initial values. Under these circumstances, a more marked lowering of the response threshold, determined from absolute values of intensity of the stimulating current, was observed in animals with comparatively higher initial values of the self-stimulation threshold. The duration of the period of development was individual in character in different animals, and amounted on average to 3 days for amphetamine, 3.2 days for ethanol, and 7.3 days for morphine (Fig. 1). Administration of the other two substances in the initial doses, when tolerance had developed to the primary drug, did not lead to activation of self-stimulation, but in most cases the tendency toward weakening of self-stimulation which was observed persisted after injection of the test substances. If the dose of the principal drug was doubled, as a rule, facilitation of self-stimulation was observed, once only in the case of amphetamine (1 mg/kg) and ethanol (1 g/kg), or for longer (2-4 days in different animals after injection of morphine in a dose of 6 mg/kg), and this was followed by weakening of self-stimulation to the level which existed against the background of tolerance. The duration of facilitation of self-stimulation after administration of twice the dose of the drug correlated directly with the duration of the period of development of tolerance to it. In one case, after administration of amphetamine, and in two cases after administration of ethanol, doubling the dose led to a more forced weakening of self-stimulation.

It can be concluded from these results that repeated administration of amphetamine, ethanol, and morphine in minimal doses effective for the facilitation of self-stimulation leads to initial activation of the positive reinforcement system, followed by weakening of the reactivity of this system to administration of the drugs, and

ultimately to the development of tolerance to them. The fact that against the background of tolerance developing to the principal drug, testing drugs in equivalent doses have no activating effect on the positive reinforcement system, i.e., that crossed tolerance is found, may be accepted as evidence that the effect of these drugs are realized through common neurophysiological and neurochemical mechanisms.

The role of activating component in the positive reinforcement systems of the hypothalamus is known to be played mainly by adrenergic structures [6, 14]. It has been shown that alcohol, amphetamine, and morphine act in a similar direction on adrenergic structures, increasing the release of adrenergic mediators, causing changes in reassimilation processes, and leading to a reduction and exhaustion of their reserves [1, 11-13]. Hence, it can be concluded that the effects of these drugs on the positive reinforcement system are realized at the hypothalamic level with the aid of adrenergic mechanisms. This fact, in our view, also explains the development of crossed tolerance to alcohol, amphetamine, and morphine which was obtained in the present experiments. The unequal periods of development of tolerance to these drugs may be explained by their action on different stages of adrenergic mediation processes.

LITERATURE CITED

1. I. P. Anokhina, in: Abstracts of Proceedings of the 2nd All-Union Conference on the Clinical Picture, Prevention, and Treatment of Alcoholism and Drug Additions [in Russian], Moscow (1978), pp. 69-72.
2. Yu. V. Burov and S. A. Borisenko, Byull. Éksp. Biol. Med., No. 1, 43 (1976).
3. S. A. Borisenko, Byull. Éksp. Biol. Med., No. 4, 429 (1977).
4. Yu. V. Burov and S. A. Borisenko, Farmakol. Toksikol., No. 3, 291 (1979).
5. E. Gellhorn and G. N. Loofbourrow, Emotions and Emotional Disorders [Russian translation], Moscow (1966).
6. N. A. Patkina, in: Proceedings of an All-Union Conference on Problems in Higher Nervous Activity [in Russian], Moscow (1974), pp. 89-90.
7. N. A. Plokhinskii, Biometrics [in Russian], Moscow (1970).
8. I. N. Pyatnitskaya, Clinical Aspects of the Study of Narcotics [in Russian], Leningrad (1975).
9. F. Svec, Pharmacodynamics of Drugs [in Russian], Bratislava (1963).
10. J. De Groot, The Rat Forebrain in Stereotaxic Coordinates, Amsterdam (1959).
11. B. E. Leonard, Biochem. Pharmacol., 21, 1289 (1972).
12. E. Maynert and G. Klingman, J. Pharmacol. Exp. Ther., 135, 285 (1962).
13. L. McGumne, Acta Physiol. Scand., 58, Suppl. 204, 1 (1963).
14. L. Stein, in: Psychopharmacology. A Review of Progress, Washington (1968), pp. 105-123.