LITERATURE CITED

1. V. V. Zakusov, Pharmacology of Central Synapses [in Russian], Moscow (1973), p. 16.
2. G. Kh. Bunyatyan, V. G. Egiyan and G. A. Turshyan, Problems in Brain Biochemistry [in Russian], Vol. 1, Erevan (1964), p. 27.
3. G. Kh. Bunyatyan, Zh. Vses. Khim. Obshch. D. I. Mendeleeva, 21, 130 (1976).
4. S. A. Mirzoyan and V. P. Akopyan, Byull. Eksp. Biol. Med., No. 1, 45 (1978).
5. S. A. Mirzoyan and A. P. Tatevosyan, Dokl. Akad. Nauk Arm. SSR, 16, No. 3, 177 (1978).
6. C. Hebb, Annu. Rev. Physiol., 32, 765 (1970).
7. S. Tewari and C. F. Baxter, J. Neurochem., 16, 171 (1969).
8. L. W. Lee, C. L. Liao, and M. Yatsu, J. Neurochem., 23, 721 (1974).

CHANGES IN DEFENSIVE AND FEEDING BEHAVIOR OF RABBITS FOLLOWING REPEATED INJECTIONS OF HASHISH INTO DIFFERENT PARTS OF THE BRAIN

S. Yu. Berdyaev and V. N. Pokryshkin

UDC 615.212.7:547.914].015.4:612.833

KEY WORDS: hashish, hypothalamus; central grey matter of the midbrain defensive and feeding behavior.

The central mechanisms of development of addiction to hashish are still largely unexplained. Most investigations have been devoted to the discovery of brain structures concerned in the realization of a particular momentary action of hashish or of its chief active principle tetrahydrocannabinol (THC). Corresponding investigations have been made of the hallucinogenic [9], behavioral [1, 5], analgesic [13], hypothermic [15], and other effects of hashish [6, 10, 12].

Addiction to hashish is one form of pathological motivation which determines the individual's need for the narcotic, and during chronic administration it assumes the property of reinforcement; the introduction of the substance into the body abolishes the pathological motivation which has arisen. It is well known that the hypothalamic region contains centers for defensive behavior — the ventromedial nucleus [7, 8], and feeding behavior — the lateral hypothalamus [8]. Meanwhile, besides the hypothalamus, the central gray matter of the midbrain also plays an important role in the reception of nociceptive stimulation and in the realization of aggressive-defensive responses [4, 7].

It was accordingly decided in the investigation described below to study physiological responses arising during stimulation of motivation zones of the brain; the ventromedial nucleus and lateral zone of the hypothalamus and the central gray matter of the midbrain, during prolonged injection of hashish into these structures.

To differentiate the effect of hashish on the emotional-defensive response during central stimulation from its action on segmental defensive reflexes, the effect of the drug on the threshold of onset of a response to painful stimulation of the skin also was studied.

EXPERIMENTAL METHOD

Microcannulas were inserted into the parts of the brain to be studied in 12 waking rabbits weighing 3 kg by the "wandering" electrode method [2]. The design of the microcannula provided for electrical stimulation of the brain structures and injection of substances into them by means of a microinjector with an accuracy of 0.5 μl. The location of the micro-

Laboratory of Pharmacology of Narcotics, Professor V. P. Serbskii Central Research Institute of Forensic Psychiatry, Ministry of Health of the USSR, Moscow. (Presented by Academician of the Academy of Medicinal Sciences of the USSR G. V. Morozov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 9, pp. 300-303, September, 1980. Original article submitted December 26, 1979.

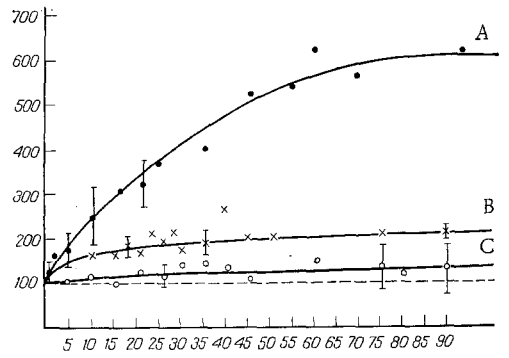

Fig. 1

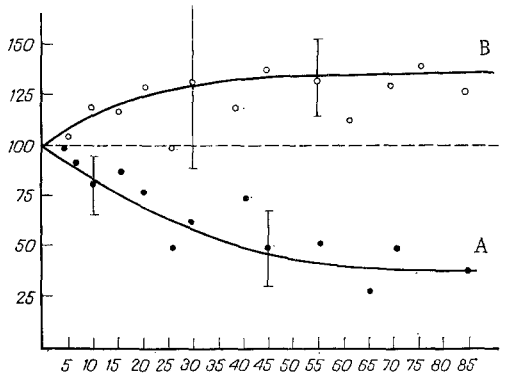

Fig. 2

Fig. 1. Effect of injection of 30 μg extract of hashish (A, B) and of the solvent (C) into ventromedial hypothalamic nucleus on threshold of appearance of defensive reflex to electrical stimulation (B). Abscissa, time (in min) after injection of drug; ordinate, ratio of threshold after injection of drug (V_t) to original threshold (V_o), in %.

Fig. 2. Effect of injection of 30 μg extract of hashish (A) and of solvent (B) into lateral hypothalamus on threshold of onset of feeding response. Legend as to Fig. 1.

cannula tip was determined by the projection method [14] using coordinates from a stereotaxic atlas [3]. A petroleum extract of hashish containing 19.6% THC, 5.6% cannabinol, and 2.3% cannabidiol, was dissolved in physiological saline with the addition of 1% Tween-80 and injected in a volume of 1-3 μl in doses of 30, 60, and 90 μg daily for 30 days immediately after the animal had been weighed. Only the solvent was injected in control experiments. Before and after the intracerebral injection the rectal temperature was measured by a TPZ-1 electrothermometer, photic stimulation was applied by a "Kaiser" photostimulator, acoustic stimulation by a ZG-8 apparatus, and electrodermal stimulation by the ÉSL-2 apparatus by means of bipolar steel needle electrodes sutured to the skin of the hind limb, daily for the first 5 days, and thereafter every 3 days. During stimulation of the above-mentioned central formations, monopolar square pulses were applied with a frequency of 50-100 Hz, during 1 msec, and amplitude of 2-10 V; the duration of the volley of pulses was 1-2 sec. The results were subjected to statistical analysis by Student's t-test.

EXPERIMENTAL RESULTS

During a gradual increase in the intensity of electrodermal stimulation, a local flexor reflex, vegetative manifestations (vigilance, tachypnea and tachycardia, untidiness of the fur, dilatation of the pupils) and a passive avoidance reflex (sudden withdrawal of the paw, leaping forward, attempts to run away), with elements of aggressive behavior (striking with the hind limbs, and so on) developed in succession. In response to central electrical stimulation vigilance, an analogous orienting reaction to any afferent stimulus, vegetative manifestations, and a passive avoidance reflex developed successively in the case of stimulation of the ventromedial hypothalamic nucleus and the central gray matter, or a typical food response appeared in a satiated rabbit to stimulation of the lateral hypothalamus. Since the flexor reflex and vegetative manifestations are nonspecific for a nociceptive response and can arise as a result of reception of a stimulus not necessarily nociceptive in character, the intensity of stimulation required to cause the beginning of a passive avoidance response was taken as the threshold of the emotional-defensive reaction, and the intensity of stimulation required to initiate a goal-directed search for food, its discovery and consumption, by a satiated animal was taken as a threshold of the feeding response.

After injection of 30 μg hashish into the above-mentioned brain structures significant changes took place in the animal's behavior during the first 15-20 min. The rabbits remained motionless on the spot, made no attempt to examine surrounding objects actively, and did not respond to external acoustic or photic stimuli. During this period the rectal temperature fell by $1.5 \pm 0.1°C$ ($P < 0.05$) and the corneal reflex was considerably depressed. The effects of microinjections of hashish described above were observed after intravenous injection of the drug (10 mg/kg) also, but in that case they developed later and were weaker, with the exception of depression of the corneal reflex.

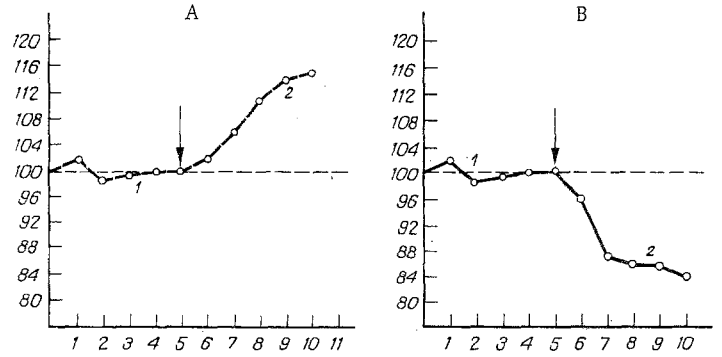

Fig. 3. Changes in body weight of animals before (1) and during (2) daily injection of 30 μg hashish extract into lateral region (A) and ventromedial nucleus (B) of hypothalamus. Abscissa, time (in days) before and after beginning of injection of hashish indicated by arrow); ordinate, ratio of body weight after injection of hashish (P_t) to initial body weight (P_o), in %.

Injection of 30 μg hashish extract into the ventromedial nucleus or central gray matter caused a sharp rise in the thresholds of appearance of defensive responses (Fig. 1A). The effect increased steadily and after 1.5-2 h the threshold was raised on average by 1 order of magnitude ($P < 0.01$); the threshold of appearance of the response to painful electrical stimulation of the skin (Fig. 1B) was increased by 1.5-2 times ($P < 0.05$). The increase in threshold in the control experiments was not significant (Fig. 1C).

Microinjections of hashish into the lateral hypothalamus led to significant enhancement of the feeding response to stimulation of that structure. The level of food consumption increased immediately after the injection and remained high for 10-30 min. Thresholds of manifestation of feeding behavior were significantly ($P < 0.05$) lowered (Fig. 2A). In some cases the increased food consumption was produced by injection of hashish without electrical stimulation of the lateral hypothalamus. The solvent had no such effect (Fig. 2B).

During daily injections of hashish (30 μg) into this region of the brain there was a distinct increase in the animal's body weight (Fig. 3A), but after repeated injections of hashish into the ventromedial nucleus, the body weight decreased (Fig. 3B). The same picture continued for 7-10 days and was unchanged by an increase in the dose of hashish.

After repeated daily injections of hashish extract ever-increasing doses of the drug (60-90 μg) were needed to obtain the initial responses to central and peripheral stimulation by the 3rd-15th days, evidence of the development of tolerance primarily to the analgesic effect (1st-3rd days), but later to the behavioral (10th day) and hypothermic (15th day) effects of the narcotic.

No clear picture of the development of a withdrawal syndrome could be discovered after discontinuation of hashish (90 μg). However, increased irritability of the animals, an inadequate response to stimuli (photic, acoustic), and an appreciable intensification of motor activity were observed in the animals 2-3 days after deprivation of the drug.

Repeated injections of hashish extract directly into emotiogenic zones of the brain thus led initially to considerable changes in the animal's behavior, but this was followed by the formation of tolerance to the action of the drug. The change in behavioral reactions under the influence of this drug depended on the modality of the motivating excitation that developed following electrical stimulation of one or other central structure; hashish suppressed negatively motivated excitation connected with pain and fear and facilitated positively motivated responses, due to the taking of food.

The results suggest that the ventromedial nucleus and lateral zone of the hypothalamus, and also the central gray matter of the midbrain play an important role in the central action of hashish. These structures evidently play an active part in the mechanisms of formation of tolerance to the effects of hashish and in processes of appearance of pathological motivation to it. A fact which may perhaps confirm this conclusion is that at the height of the be-

havioral effect of THC it accumulates rapidly to a high level in the thalamohypothalamic region [11].

LITERATURE CITED

1. I. P. Anokhina, T. T. Bondarenko, G. D. Zabrodin et al., Zh. Nevropatol. Psikhiat., No. 2, 264 (1975).
2. V. I. Badikov, "Comparative characteristics of electrical indices of the cerebral cortex during positive and negative emotional states," Candidate's Dissertation, Moscow (1972).
3. J. Bures, M. Petran, and I. Zachar, Electrophysiological Methods of Investigation [Russian translation], Moscow (1962).
4. A. V. Val'dman, Neuropharmacology of Narcotic Analgesics [in Russian], Leningrad (1972).
5. I. I. Vanshtein, in: Physiological Features of Positive and Negative Emotional States [in Russian], Moscow (1972), p. 13.
6. V. E. Vetsner, "Clinical-physiological investigation of hashish poisoning," Candidate's Dissertation, Moscow (1969).
7. J. Szentagothai et al., Hypothalamic Regulation of the Anterior Pituitary [Russian translation], Budapest (1965).
8. K. V. Sudakov, Biological Motivations [in Russian], Moscow (1971), p. 64.
9. Z. Amit et al., Neuropharmacology, 16, 121 (1977).
10. E. H. Boyd, E. S. Boyd, and L. E. Brown, Neuropharmacology, 14, 533 (1975).
11. W. M. McIssak, R. T. Harris, and B. T. Ho, Acta Pharm. Suec., 8, 703 (1971).
12. R. J. Pandina and R. E. Musty, Pharmacology, 13, 297 (1975).
13. J. M. Parker and T. C. Dubas, Int. J. Clin. Pharm., 7, 75 (1973).
14. F. C. Quzman et al., Bol. Inst. Estud. Med. Biol. Mex., 16, 29 (1958).
15. W. T. Schmeling and M. J. Hosko, Arch. Int. Pharmacodyn., 227, 302 (1977).

EFFECT OF ETHMOZINE AND ITS DIETHYLAMINO ANALOG ON THE SLOW INWARD AND OUTWARD CURRENTS OF FROG ATRIAL FIBERS

L. V. Rozenshtraukh and V. N. Chikharev

UDC 615.22.015.4:612.172.4

KEY WORDS: ethmozine; diethylamino analog of ethmozine; slow inward current; outward current.

The new antiarrhythmic drug ethmozine and its diethylamino analog (DAA-ethmozine) abolish arrhythmias arising experimentally 24 h after occlusion of the coronary artery [1, 2, 4, 7, 9]. These drugs inhibit the fast inward sodium current and reduce the rate of rise of the leading edge of the transmembrane action potential [3, 5, 8]. DAA-ethmozine differs from ethmozine in causing longer inhibition of the fast inward sodium current and in the longer duration of its antiarrhythmic action in the late stage of experimental myocardial infarction [3]. The antiarrhythmic action of ethmozine and of DAA-ethmozine in the late stage of myocardial infarction can thus be linked with the effect of these drugs on the fast inward sodium current. However, this hypothesis has not yet been adequately verified, for the action of these drugs on other ionic currents of heart muscle cells has not been studied.

The object of this investigation was to study the action of ethmozine and DAA-ethmozine on the slow inward and outward currents of myocardial cells.

EXPERIMENTAL METHOD

The voltage clamp method under double sucrose gap conditions was used to record the ionic currents. Experiments were carried out on isolated atrial trabeculae of *Rana ridibunda*

Laboratory of Electrophysiology of the Heart, All-Union Cardiological Scientific Center, 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. 90, No. 9, pp. 303-305, September, 1980. Original article submitted October 10, 1979.

0007-4888/80/9009-1218$07.50