HYPOTHALAMIC SELF-STIMULATION IN MORPHINE-DEPENDENT RATS DURING THE ABSTINENCE SYNDROME

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UDC 616-008-02: [615.212.7:547.943].
099.085.246.9-092:616.831.41

Rats with lateral hypothalamic self-stimulation (SS) were given morphine injections twice a day for 15 days in doses rising from 20 to 120 mg/kg. Morphine facilitated SS starting with the 9th injection. Short-term (16-18 h) withdrawal of the narcotic from the rats or its discontinuation led to inhibition of SS. Complete suppression of SS was observed after injection of the morphine antagonist nalorphine in a dose of 5 mg/kg.

KEY WORDS: electrical self-stimulation, experimental morphinism, drug dependence, abstinence.

After repeated administration of morphine, facilitation of positive-reinforcing effects of central electrical stimulation can be observed [3, 7, 8]. The development of lasting facilitation of "reward" effects during the formation of morphine dependence can be regarded as an important element in the pathogenesis of narcotic addiction [1, 4, 5, 9]. Meanwhile the state of dependence is characterized not only by euphoria, arising after injection of the narcotic, but also by dysphoria and other manifestations specific for the state of abstinence [2]. The state of abstinence is characterized by various features which point to a deficiency of the "reward" system, but this has not been confirmed experimentally. It was accordingly decided to study the state of the positive-reinforcing system in morphine-dependent animals in a state of abstinence.

EXPERIMENTAL METHOD

Experiments were carried out on five noninbred male rats weighing 200-350 g. Nichrome monopolar electrodes were implanted bilaterally into the region of the lateral hypothalamus in accordance with coordinates of the stereotaxic atlas [6]. A self-stimulation (SS) response was formed in a Skinner's box with one pedal. The parameters of stimulation were: square pulses, frequency 100/sec, duration 1 msec, amplitude 0.8-2 V. Every time the animal pressed on the pedal, this caused self-stimulation of the brain with a series of 30-50 pulses. Altogether six "points" were tested with nine levels of intensity of electrical stimulation. All electrodes, as histological investigations showed, were located in the region of the **medial longitudinal forebrain** bundle.

After stabilization of the SS habit, morphine-dependence was produced. For this purpose, twice a day (at 9 a.m. and 6 p.m.) morphine solution was injected into the animals intraperitoneally for 15 days. During the first 10 injections the rats received a dose of 20 mg/kg per injection. In the second cycle of injections the dose was trebled, and in the third cycle the dose per injection was 120 mg/kg.

A state of abstinence was produced in three ways: 1) by short-term "withdrawal" (abstinence for 16-18 h after 8 and 18 injections); 2) complete discontinuation of the morphine after the 30th injection, and 3) intraperitoneal injection of the morphine antagonist nalorphine in a dose of 5 mg/kg at the height of action of the narcotic.

Besides the SS reaction, the rats' general behavior, the degree of catatonia, and the severity of the exophthalmos (effects characteristic of the action of large doses of morphine), and the effect on the pain reflex (squeezing the base of the tail by Dieffenbach's graduated forceps) were assessed. The intensity of catatonia was evaluated by the following scale: 0) absence of catatonia; 1) doubtful; 2) definite but not maximal catatonia; 3) maximal. The dimensions of the palpebral fissure were evaluated by a five-point scale: 0) eyes completely closed; 1) small palpebral fissure; 2) eyes half open; 3) normal opening; 4) wide opening; 5) exophthalmos.

Department of Pharmacology, Academician I. P. Pavlov First Leningrad Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 85, No. 3, pp. 304-307, March, 1978. Original article submitted June 29, 1977.

TABLE 1. Changes in Self-Stimulation Response during Action of Morphine and in Period of Abstinence

Period of experiment	Injections of morphine	Dose, mg/kg	Time after injection, h	Number of times rat pressed on pedal during 5 min (M ± m)
I. Control	—	—	—	280,8±16,1
II. Chronic injection of morphine	8-th	20	1	263,8±65,3
	8-th	20	16—18 Abstinence	17,8±9,4
	9-th	20	1	409,3±53,9
	18-th	60	1	510,3±82,0
	18-th	60	16—18 Abstinence	163,2±46,5
	19-th	60	1	464,6±52,6
	27-th	120	1	484,8±57,2
	27-th+ Plus nalorphine	5	0 5	0
	30-th	120	1	513,6±44,5
III. Discontinuation of morphine injections			24	88,8±42,1
			72	175,4±31,4
			100—120	109,4±28,3

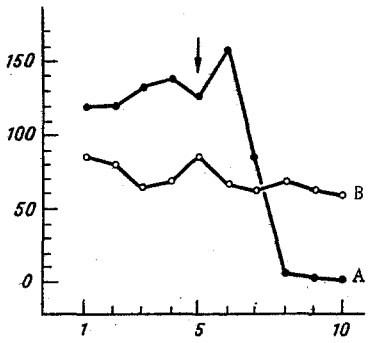

Fig. 1. Effect of nalorphine on SS response in morphine-dependent rats (rat A, 1.5 V). A) 1 h after 27th injection of morphine in a dose of 120 mg/kg before and after injection of nalorphine (5 mg/kg). Arrow marks time of injection; B) control (before beginning of course of morphine injections), same rat. Abscissa, time (in min); ordinate, number of presses on pedal per minute.

EXPERIMENTAL RESULTS

During chronic injection of morphine the gradual development of a stable facilitatory effect on "reward" in response to central stimulation was observed. The considerable increase in frequency of closure of the electrical circuit starting from the 9th injection is shown in Table 1 (for more details of the dynamics and special features of the SS facilitation curve, see [9]).

Despite the fact that on the whole no distinct changes in SS were observed in the rats of the experimental group 1 h after the 8th injection, "withdrawal" for 16-18 h led to sharp and statistically significant ($P < 0.001$) depression of the response (Table 1). "Withdrawal" of the same duration in the second cycle of morphine injections (after the 18th injection) also caused definite inhibition of SS ($P < 0.001$ compared with the effects of the 18th and 19th injections). The number of presses on the pedal fell to a level significantly lower ($P < 0.02$) than the initial level in the control period.

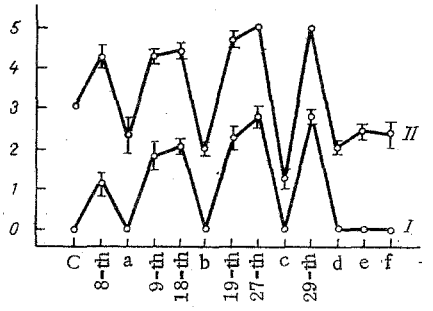

Fig. 2. Catatonia (I) and width of palpebral fissue (II) after injections of morphine and during abstinence. Abscissa: C) control; numbers with increments mark injections of morphine; letters denote periods of abstinence (a and b, 16-18 h after 8th and 18th injection respectively, c, after injection of nalorphine, 5 mg/kg, d, e, and f 24, 72, and 120 h respectively after discontinuation of morphine); ordinate, assessment of intensity of catatonia and width of palpebral fissure in points.

Complete discontinuation of morphine after the 30th injection also led to inhibition of the SS response (Table 1). This effect reached its highest intensity during the first day after discontinuation; on the third to fifth day SS still remained below the control level. Compared with the initial frequency of SS, depression of the response in the time intervals studied was significant (for the three time intervals indicated in Table 1, P was less than 0.001, 0.01, and 0.001 respectively).

The maximal degree of inhibition of SS was observed during abstinence provoked by injection of nalorphine (5 mg/kg). The effect of the drug was tested 30 min after injection and at the height of the activating effect of morphine. In all cases complete suppression of SS was observed, the response was not initiated even after 30 to 50 "timing" presses by the experimenter himself. The effect of nalorphine developed very quickly – during the 2 min after injection, as is illustrated in Fig. 1.

The phenomena of abstinence, however it was produced, were expressed also as changes in general behavior. Changes in general motor activity were observed (more often inhibition, sometimes obsessive hyperactivity), piloerection was well marked, tachypnea was observed, and defecation was more frequent. Movements of the jaws, stretching, sneezing, and movements of the "shaking of a wet dog" type were characteristic. The catatonia characteristic of the action of large doses of morphine typically disappeared (Fig. 2, I). The width of the palpebral fissure changed very clearly in response to the experimental procedures. The exophthalmos characteristic of the action of morphine did not simply disappear in the state of abstinence but, like the frequency of the presses during SS, it was replaced by a varied degree of closure of the palpebral fissure (Fig. 2, II). Not simply the disappearance of the analgesic action of the drug, but its increased sensitivity to pain also was typical. For instance, the animals showed signs of a pain reflex to stimulation previously below the threshold level for pain. Rats responded pathologically to being held by the hands, and the biting, so characteristic of the action of large doses of morphine, completely disappeared.

During the formation of morphine dependence, significant changes thus took place in the activity of the positive reinforcement system. The state of dependence was manifested, in particular, by the fact that the narcotic-deprived animal either did not stimulate the positive zones of the brain, or SS was below the control level. This may mean that the dysphoria of morphine deprivation may have as its neurophyschophysiological basis a deficit in the "reward" system; hyperactivation of the positive reinforcement system may equally be related to the artificial drug-induced production of a positive emotional state. This investigation thus shows that the SS phenomenon is a sensitive test for determining the animal's state during the formation of drug dependence.

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EFFECT OF TYPE E PROSTAGLANDINS ON CHANGES IN CEREBROVASCULAR RESISTANCE AND ARTERIAL PRESSURE PRODUCED BY TYRAMINE

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UDC 615.272.015.2:615.357:577.175.859].0.15.4:612.824

Investigation of the cerebrovascular resistance and arterial blood pressure by resistography showed that type E prostaglandins inhibit the pressor action of tyramine on the cerebral vessels and on the blood pressure. Indomethacin, which inhibits prostaglandin biosynthesis, delayed the development of tachyphylaxis to tyramine and restored its pressor effect. Iproniazid, a monoamine oxidase inhibitor, did not affect the rate of development of tyramine tachyphylaxis following administration of indomethacin but potentiated the pressor effect of tyramine. It is suggested that the effect of indomethacin on the pressor effect of tyramine is based on increased sensitivity of the vascular adrenoreceptors.

KEY WORDS: cerebral circulation; tyramine tachyphylaxis; prostaglandins; indomethacin; monoamine oxidase inhibition.

Tyramine – a biogenic amine which exerts its action through the liberation of endogenous noradrenalin (NA) from the tissue reserves [4] – has for a long time been investigated as a potential factor in the pathogenesis of migraine [1, 7]. Meanwhile the results of recent investigations point to the ability of prostaglandins (PG) of types E and F to participate in the processes responsible for the onset of the attack of migraine [12, 13].

Many investigations of the effect of PG on adrenergic transmission in the smooth-muscle structure of the vascular wall have now been published [3, 6], but there is only scanty information in the literature on interrelations between tyramine and PG [8-10], and hardly anything at all has been published on the study of these interrelations at the level of the cerebral circulation.

The object of this investigation was to study: a) the effect of tyramine on the cerebrovascular resistance and arterial blood pressure (BP) during the action of PG of type E; b) tyramine tachyphylaxis following inhibition of PG biosynthesis by indomethacin and during inhibition of monoamine oxidase (MAO) by iproniazid.

EXPERIMENTAL METHOD

Acute experiments were carried out on 42 cats anesthetized with pentobarbital (50 mg/kg). Changes in tone of the cerebral arteries in the internal maxillary system were recorded by resistography, with the aid of

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(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 85, No. 3, pp. 307-310, March, 1978. Original article submitted September 9, 1977.