EFFECTS OF NEUROTROPIC DRUGS ON HYPOTHALAMIC SELF-STIMULATION

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Amphetamine, cocaine, caffeine, morphine, and imipramine were shown to lower the threshold of the self-stimulation response at the hypothalamic level. Meprobamate, diazepam, and chlordiazepoxide have no effect on the threshold of self-stimulation but increase the number of self-stimulations in response to threshold, optimal, and above-optimal strengths of current. Benactyzine, DLK-25, and phenobarbital lower the threshold of self-stimulation and increase the number of self-stimulations to currents of all parameters. It is concluded that the drugs of the first group have a direct activating action on the system of positive emotions. Tranquilizers activate this system indirectly, through their depriming action on the system of negative emotions. Benactyzine, DLK-25, and phenobarbital activate the system of positive emotions and depress the system of negative emotions.

KEY WORDS: self-stimulation; lateral hypothalamus; neurotropic drugs.

Emotional changes under the influence of different classes of pyschotropic drugs differ qualitatively, because these substances act on different brain structures belonging to different functional systems and integrating positive and negative emotions. The writers showed previously that neuroleptics, tranquilizers, and antidepressants act chiefly at points within the system of structures which integrate negative emotions [1, 4, 5].

The object of this investigation was to study the effect of different classes of psychotropic drugs on brain structures forming positive emotions at the hypothalamic level.

EXPERIMENTAL METHOD

In experiments on 32 male albino rats weighing 250-350 g, monopolar Nichrome electrodes 250 μ in diameter were inserted bilaterally into the medial forebrain bundle at the level of the lateral hypothalamus, following the coordinates of De Groot's brain atlas [8]: 1.5 mm caudally to the bregma, 1.5 mm from the median suture, and 8.5 mm from the surface of the skull. The operation was performed under pentobarbital anesthesia (40 mg/kg, intraperitoneally). Seven days after the operation the rats were taught to press on a pedal in order to obtain brain stimulation, produced by sinusoidal pulses 0.02 sec in duration and with a frequency of 50 Hz. Each pressure on the pedal was accompanied by brain stimulation for 0.5 sec. After determination of the subthreshold and threshold levels, the strength of the current was increased gradually to 10 μA. The number of pressures on the pedal in 5 min was determined for four values of the current: a) subthreshold strength – the maximal current for which the frequency of pressing on the pedal did not exceed 100; b) threshold – the minimal current at which the frequency of pressing exceeded 200 but not 300; c) optimal – the current at which the animal gave the largest number of presses; d) a strength of current 10-20 μA above optimal. Amphetamine, cocaine, caffeine, benactyzine, diazepam, meprobamate, chlordiazepoxide, impramine, phenobarbital, morphine, and DLK-25 were injected intraperitoneally 30-50 min before the experiments in doses used most frequently to study the effect of these substances on behavioral responses. Control indices of the self-stimulation response and changes in their values under the influence

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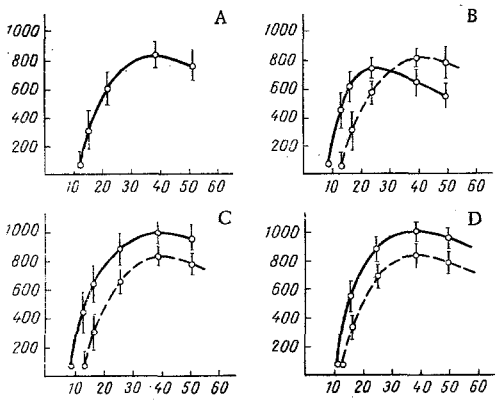

Fig. 1. Frequency of self-stimulation as a function of current strength: A) general character of relationship, B) effect of amphetamine (1 mg/kg), C) effect of benactyzine (3 mg/kg), effect of diazepam (1 mg/kg). Broken line) control, continuous line) effect of drugs. Abscissa, strength of current (in μA); ordinate, number of self-stimulations. Data obtained in experiments on six rats with similar values of the threshold and frequency of self-stimulation are shown.

of the drugs were determined. Graphs showing the relationship between the frequency of self-stimulation and the strength of the current were plotted, and curves smoothed by the method of least squares were constructed on their basis. Mean values were calculated and the significance of their differences determined with the aid of Fisher's criterion [6].

EXPERIMENTAL RESULTS AND DISCUSSION

The rats trained in self-stimulation gave up to 100 presses on the pedal in the course of 5 min, even if pressing on the pedal was not accompanied by brain stimulation. The frequency of pressing on the pedal in response to a current of subthreshold strength thus was practically the same as that in the trained rats without electrical stimulation. An increase in the current strength above threshold (5-15 μA) led to an increase in the frequency of self-stimulation, to reach the maximum (900-1200 presses in 5 min) at 30-40 μA. With an increase in the strength of the current above optimal, the number of self-stimulations decreased appreciably. Despite the active attempts of the rats to obtain brain stimulation in these experiments, elements (movement of the head and body backward, stretching out the head, jumping away from the pedal) indicating unpleasant or, possibly, painful sensations appeared. If the strength of the current was increased still more, these phenomena were aggravated and the rats refused to press on the pedal but ran into the opposite corner of the chamber. To restore self-stimulation, the strength of the current had to be reduced. The curve of number of self-stimulations versus current strength was shaped like a parabola with a single maximum (Fig. 1A).

Amphetamine (1 mg/kg) lowered the threshold of self-stimulation and led to an increase in the number of self-stimulations in response to a current of threshold strength and to a decrease in response to optimal or higher strengths of current (Fig. 1B). Qualitative changes in the threshold and frequency of self-stimulation similar to those produced by amphetamine also were caused by cocaine (10 mg/kg), caffeine (30 mg/kg), morphine (3 and 6 mg/kg), imipramine (3 mg/kg), and benactyzine (1 mg/kg). In a dose of 3 mg/kg benactyzine lowered the response threshold and increased the number of presses on the pedal, whatever the strength of the current (Fig. 1C). DLK-25 (0.1 mg/kg) and phenobarbital (5 and 10 mg/kg) had a similar action. Diazepam (0.5 and 1 mg/kg) had no effect on the threshold of self-stimulation but caused an increase in the number of self-stimulations in response to currents of threshold, optimal, or above optimal strengths (Fig. 1D). Meprobamate (10 and 20 mg/kg), chlordiazepoxide (3 mg/kg), and phenobarbital (20 mg/kg) had a similar action. Caffeine (15 mg/kg) caused an increase in the number of presses only to a current of threshold strength. Morphine (10 mg/kg) and DLK-25 (0.5 mg/kg) caused an increase in the threshold of the response but a decrease in the frequency of self-stimulation. The results are summarized in Table 1.

TABLE 1. Effect of Neurotropic Drugs on Indices of Self-Stimulation Response at the Hypothalamic Level

Drug	Dose (in mg/kg)	Changes in indices of self-stimulation response (in % of initial value)			
		threshold of response	number of self-stimulations		
			with current of threshold strength	with current of optimal strength	with current of above-optimal strength
Amphetamine	1	(—) 25	(—) 31	(—) 12	(—) 15
Cocaine	10	(—) 24	(—) 20	(—) 14	(—) 16
Caffeine	30	(—) 16	(—) 10	(—) 10	(—) 12
Benactyzine	1	(—) 15	(—) 29	—5	(—) 13
	3	(—) 23	(—) 31	(—) 24	(—) 21
Diazepam	0,5	No effect	(—) 40	(—) 12	(—) 26
	1	» »	(—) 31	(—) 14	(—) 24
Meprobamate	10	» »	(—) 30	(—) 21	(—) 16
	20	» »	(—) 25	(—) 17	(—) 20
Chlordi-azepoxide	3	» »	(—) 35	(—) 24	(—) 26
Imipramine	3	(—) 13	(—) 25	(—) 10	(—) 15
Phenobarbital	5	(—) 10	(—) 12	(—) 14	— 6
	10	(—) 14	(—) 17	(—) 12	(—) 25
	20	No effect	(—) 28	(—) 10	(—) 22
Morphine	3	(—) 18	(—) 35	(—) 11	(—) 18
	6	(—) 20	(—) 15	(—) 13	(—) 16
	10	(—) 20	(—) 57	(—) 30	— 8
DLK-25	0,05	No effect	—8	—6	— 7
	0,1	(—) 12	(—) 14	(—) 11	(—) 12
	0,5	(—) 10	(—) 54	(—) 26	(—) 13

Legend: (+), (-) Statistically significant ($P < 0.05$) increase or decrease, +, - increase or decrease not statistically significant ($P > 0.05$)

Structures for positive emotions in the hypothalamus are known to be situated immediately next to structures for negative emotions [9, 10, 12]. Accordingly, it is possible for structures for positive and negative emotions to be excited simultaneously through the same electrode. Intracerebral negative stimulation applied at the moment of self-stimulation is known to reduce the number of self-stimulations [7, 11]. The increase in the number of presses on the pedal obtained in the present experiments in the interval between subthreshold and optimal values of the current strength can thus be interpreted as the result of excitation of the positive reinforcement system. The subsequent decrease in the number of presses with an increase in the current strength was due to enlargement of the focus of excitation and to activation of the negative reinforcement system of the hypothalamus. A negative emotional state formed in animals in response to hypothalamic stimulation has been shown to be blocked by tranquilizers [2, 3]. The ability of tranquilizers – benactyzine, diazepam, meprobamate, chlordiazepoxide – to facilitate self-stimulation may therefore be the consequence of their blocking effect on the hypothalamic system for negative emotions. The effect of drugs which lower the threshold of self-stimulation and increase the number of self-stimulations in response to a current of threshold strength, but which reduce the intensity of the response to currents of optimal or above-optimal strength, can be interpreted as the consequence of their direct activating effect on the positive reinforcement system. Neurotropic drugs which, besides lowering the threshold, facilitate self-stimulation to a current of above-optimal strength evidently have a direct activating effect on the positive reinforcement system and also a depriming effect on the structures of the negative reinforcement systems.

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