EFFECT OF NEUROTROPIC DRUGS ON SLEEP DISTURBANCE CAUSED BY ELECTRICAL STIMULATION OF THE HYPOTHALAMUS IN CATS

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A state of stress induced in cats by electrical stimulation of the hypothalamus was shown to reduce the total duration of sleep at the expense of its paradoxical phase. Haloperidol (1, 2, or 3 mg/kg), diazepam (0.5 or 1 mg/kg), nitrazepam (1 or 6 mg/kg), Noxyron (glutethimide) (10, 30, and 60 mg/kg), and pentobarbital (5, 15, and 30 mg/kg) did not restore the structure of sleep when disturbed by stress, and lithium hydroxybutyrate (100 and 150 mg/kg), dimedrol (diphenhydramine) (1, 5, and 6 mg/kg), and imipramine (1, 3, and 6 mg/kg) increased the total duration of sleep on account of the slow-wave phase. Sodium hydroxybutyrate (100 mg/kg) restored the normal electrophysiological pattern of sleep, reduced the latent period, and increased the total duration and number of episodes of the paradoxical phase, and also reduced the number of awakenings.

KEY WORDS: sleep; stress; neurotropic drugs; sodium hydroxybutyrate.

According to reports in the literature, restorative processes corresponding to the consumption of the organism during waking take place during the slow-wave (SWS) and paradoxical phase (PPS) of sleep [6]. Since these phases of normal sleep are characterized by definite quantitative relations, which are disturbed by stress [2, 10], it must be assumed that pharmacological correction of these relations would be an important factor in ensuring the optimal course of restorative processes corresponding to the individual phases of sleep.

In this investigation the action of neurotropic drugs of different classes was studied on the electrophysiological structure of sleep, disturbed by hypothalamic stimulation, in order to seek drugs capable of abolishing the sequelae of stress.

EXPERIMENTAL METHOD

Experiments were carried out on 12 cats weighing 3.5-5 kg. To record the animal's sleep, electrodes were inserted under halothane anesthesia into the cortex, hippocampus, the region of the dorsal rectus muscle of the eye, and the dorsal group of cervical muscles. Stimulating electrodes were inserted into the hypothalamus at A 13.0, L 1.5, H −2.3 [11]. Not earlier than 2 weeks after the operation, the control sleep (between 12 and 15 h) of the cat was recorded consecutively for 7 days. The effect of drugs on the phases of ordinary sleep and the phases of sleep after stress was then studied. The drugs for testing were injected intraperitoneally 30 min before the electrophysiological recording began. The state of stress was induced in the cats by means of a series of electric stimulations of the hypothalamus by square pulses with a frequency of 100 Hz and duration 1 msec for periods of 20 sec with intervals of 3 min. The maximal strength of the current did not exceed 3.5 V. Before the experiment began the minimal voltage causing the cat to hiss was determined, and this voltage was then increased by 0.5-1 V, to produce repeated hissing, strong piloerection, dilatation of the pupil, salivation, and extension of the spine, and at the level of response obtained, a session of 25 stimulations was given. The animals were then transferred to the chambers for sleep, and after adaptation of the cats to the chambers for 30 min, continuous recording for 3 h began.

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TABLE 1. Effect of Neurotropic Drugs on Phases of Sleep under Ordinary Conditions and after Electrical Stimulation of Hypothalamus

Drug	Dose, mg/kg	Ordinary sleep			Sleep after stress		
		total duration of sleep, min	PPS, min	SWS, min	total duration of sleep, min	PPS, min	SWS, min
Control		128	41	87	104‡	16,7‡	87,2
Haloperidol	1	82‡	16,6†	65†	68	3,3	63
	2	74‡	14,4†	60†	90	15	75
	3	81‡	9,3‡	72‡	94	8	86
Diazepam	0,5	84,5†	16,5†	68†	56†	5,6†	50†
	1	59,4†	8,9†	50†	43†	3†	40†
Nitrazepam	1	15,3†	0,3‡	14,9‡	18‡	0,8‡	17,2‡
	6	16,2‡	0,5‡	15,7‡	9‡	0‡	9‡
Imipramine	1	160	16,8‡	143‡	104	7,8‡	6,2‡
	3	129	0‡*	129‡	91	0‡	91‡
	6	128	0‡*	128‡	138	0‡	138‡
Noxyron	10	101	15,7*	85,3	110	11	99
	30	130	16,9†	113†	79	1,2‡	77,8
	60	110	0‡	110‡	46,8	0‡	46,8‡
Dimedrol	1,5	98	7,8‡	90‡	131,3*	16,4	115*
	6	133	0,6‡	132,4‡	137*	0‡	137‡
Pentobarbital	5	95,4†	13,4*	82*	90	108,	79
	15	84,5†	13,4*	71†	83	0‡	83
	30	104,5†	0‡	104,5‡	111	0‡	111‡
Lithium hydroxybutyrate	100	157†	35,4*	122*	126*	22.2	104*
	150	160†	28,8†	131†	133*	20,8	112*
Sodium hydroxybutyrate	100	124	40,5	84	140‡	37,4†	103†
	150	127	36,8	90	144‡	10,1*	134*

*P < 0.05 compared with corresponding control.
†P < 0.01 compared with corresponding control.
‡P < 0.001 compared with corresponding control.

From the electrophysiological record the total duration of sleep and the duration of SWS and PPS in min were determined. The results were subjected to statistical analysis [3].

EXPERIMENTAL RESULTS

The experiments showed (Table 1) that imipramine, Noxyron, dimedrol, and sodium hydroxybutyrate had no significant effect on the total duration of sleep under ordinary conditions. Sleep was lengthened by lithium hydroxybutyrate but was shortened by haloperidol, diazepam, nitrazepam, and pentobarbital. SWS was increased by imipramine, Noxyron, dimedrol, pentobarbital (30 mg/kg), and lithium hydroxybutyrate, but reduced by haloperidol, diazepam, nitrazepam, and pentobarbital (5 and 15 mg/kg). Sodium hydroxybutyrate had no marked effect on the duration of SWS. All the drugs listed above, with the exception of sodium hydroxybutyrate, reduced PPS.

Stress developing in cats as the result of hypothalamic stimulation led to a decrease in the total duration of sleep on account of PPS; the duration of SWS was not significantly altered.

Haloperidol, imipramine, Noxyron, and pentobarbital had no marked effect on the total duration of sleep when reduced by stress; dimedrol, lithium hydroxybutyrate, and sodium hydroxybutyrate increased it, but diazepam and nitrazepam reduced it. After administration of haloperidol, diazepam, and lithium hydroxybutyrate the disturbances of PPS caused by stress were not significantly altered. Nitrazepam, imipramine, Noxyron, and dimedrol intensified the disturbances mentioned above, and only sodium hydroxybutyrate (100 mg/kg) increased the duration of PPS.

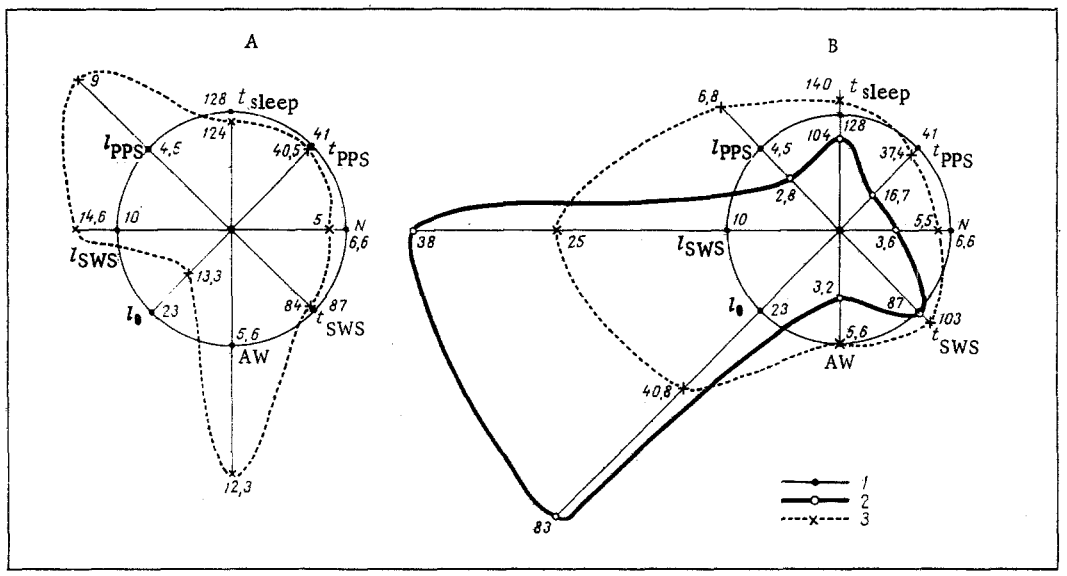

Fig. 1. Effect of sodium hydroxybutyrate on structure of ordinary sleep and of sleep disturbed by stress: 1) control sleep; 2) sleep after stress; 3) sleep after sodium hydroxybutyrate (100 mg/kg). A) Effect of sodium hydroxybutyrate on structure of ordinary sleep; B) effect of sodium hydroxybutyrate on disturbances of structure of sleep caused by stress. t_{sleep}) Total duration of sleep (in min) during 3 h of continuous recording; t_{PPS}) total duration of paradoxical sleep; N) number of episodes of paradoxical sleep; t_{SWS}) total duration of slow wave sleep; AW) mean duration of sleep without awakenings (total duration of sleep/number of awakenings); l_{SWS}) total duration of slow wave sleep before first episode of paradoxical; l_{PPS}) duration of first episodes of paradoxical sleep; l_0) time of appearance of first episode of paradoxical sleep after beginning of recording.

Imipramine, dimedrol, and lithium hydroxybutyrate can thus in all probability exert a positive action on sleep when disturbed by stress, for they lengthened it and, as these experiments showed, they reduce the number of awakenings. However, the increase in the duration of sleep observed after administration of these drugs takes place on account of SWS, and the disturbed equilibrium between the phases of sleep is not restored. Sodium hydroxybutyrate not only restores the quantitative ratio between the phases of sleep, but also improves many other indices of sleep (Fig. 1). It was shown previously that sodium hydroxybutyrate also increases PPS in disturbances of sleep caused by stress developing after introduction of a differential stimulus into the process of performance of a conditioned defensive reflex established previously [1]. The effect of sodium hydroxybutyrate on disturbances of PPS can tentatively be explained by the ability of the drug to increase the brain concentration of dopamine, the precursor of noradrenalin [7], for PPS in all probability is maintained chiefly by noradrenergic mechanisms [8]. This hypothesis is also based on information in the literature that the decrease in PPS after electrical stimulation of the hypothalamus [10] is evidently connected with a decrease in the noradrenalin level in the CNS under these conditions [5].

Sodium hydroxybutyrate thus may perhaps activate the noradrenergic mechanisms of the brain connected with the maintenance of PPS, by restoring the reserves of noradrenalin when exhausted by stress. Meanwhile, as Fig. 1B shows, sodium hydroxybutyrate not only increases PPS but also increases SWS and the mean duration of sleep without awakenings, possible evidence of the development of inhibitory processes in the brain systems maintaining wakefulness and activated by stress. This inhibition is probably connected with an increase in the brain level of the neuromediator of inhibition, namely GABA [9], for the possibility of conversion of sodium hydroxybutyrate into that amino acid cannot be ruled out [4].

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EFFECT OF GENERAL ANESTHETICS ON SURFACE ACTIVITY OF THE LUNG ALVEOLAR SURFACTANT

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The surface properties of the lung surfactant were studied with a modified Wilhelmy's apparatus after general anesthesia. Halothane and, to a lesser degree, pentobarbital, were shown to inhibit the surface activity of the surfactant. This phenomenon was observed only after prolonged (4-6 h) general anesthesia.

KEY WORDS: surface activity of the lung surfactant; general anesthetics.

After long operations under general anesthesia pulmonary complications often arise. In particular, the elasticity of the lung diminishes and atelectasis is observed [1, 3, 4, 7, 8]. These pulmonary disorders have been shown to be largely due to disturbance of the state of the surfactants which form the inner lining of the alveolar surface [10]. It has therefore naturally been suggested that under the influence of general anesthetics the properties of the surfactant are inhibited. It must be remembered that the possible mechanisms of disturbance of the surface activity of surfactants may be connected either with a direct disturbance of the surfactant activity by general anesthetics and with the "elution" of the surfactant from the alveoli as a result of unsuitable conditions of artificial ventilation of the lungs [13].

In this investigation the effect of general anesthetics on the surface activity of the surfactant was studied in rats breathing spontaneously.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred rats weighing 130-180 g. The animals were kept in an airtight chamber into which halothane was supplied in the proportion of 1-2 vol. % in a current of oxygen through a Ftorotek vaporizer. The halothane concentration at the outlet of the vaporizer was chosen so that the response of the rats to nociceptive stimulation (pricking with an injection needle) was suppressed. After halothane anesthesia for 2-6 h the heart–lung preparation of the rats was removed. A solution of surfactant was obtained by tracheal irrigation. For this purpose, 7-10 ml of physiological saline was injected from a syringe through the trachea into the lungs. After the lung had been filled, the washings were aspirated and the procedure repeated

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