EFFECT OF PSYCHOTROPIC DRUGS ON SLEEP DISTURBANCES DURING ALCOHOL WITHDRAWAL IN RATS

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Clinical investigations reveal marked disturbances of sleep in alcoholism, which reach their climax in the withdrawal period [2]. Accordingly the search for and use of effective drugs for restoration of normal sleep may be one way of abolishing withdrawal symptoms.

In the present investigation the effect of certain drugs on sleep structure disturbances in the period of alcohol withdrawal was studied by means of an experimental model of chronic alcoholism in animals.

EXPERIMENTAL METHOD

Experiments were carried out on 40 noninbred male rats, kept individually but with free access to 15% ethanol solution and to water for 13 months, and consuming alcohol in a mean daily dose of 6.75 g/kg body weight (calculated as pure ethanol). Electrodes were implanted into the hippocampus (coordinates P 4.9, L 3.5, H 3.0) [5] and into the dorsal group of neck muscles of the animals, and 1 week after the operation a continuous electrophysiological recording was made of the animals' sleep from noon to 4 p.m. on 3 successive days, including the total duration of sleep (TDS), the duration and percentage of the slow (SPS) and fast (FPS) phases of sleep, the mean duration and number of episodes of FPS, its latent period, the time of onset of the first complete SPS-FPS cycle, and the mean duration of sleep without awakening during the latent period of FPS and during the whole of sleep (in minutes). The animals were then divided into five groups, access to alcohol was prohibited, and for 7 days sleep was recorded against the background of daily intraperitoneal injections of physiological saline (group 1), sodium hydroxybutyrate (group 2), phenazepam (group 3), apomorphine (group 4), and haloperidol (group 5), during the 30 min before recording began. The results were subjected to statistical analysis [9].

EXPERIMENTAL RESULTS

Alcohol withdrawal was accompanied by severe disturbances of the sleep structure in the animals receiving physiological saline: during the first 2 days TDS fell by 60 min at the expense of both phases compared with intact rats (Table 1). Inhibition of FPS was due to a decrease in the number of its episodes. On the 3rd and 4th days of alcohol deprivation normal sleep was restored, but by the 7th day it was again severely disturbed: the duration of SPS was reduced by half, and FPS accounted for 1% of TDS. The time of onset of the first complete SPS-FPS cycle was increased threefold, the latent period of FPS was increased by 1.7 times, and the mean duration of sleep without awakening during the latent period of FPS and the whole of sleep was reduced by half.

Sodium hydroxybutyrate (100 mg/kg) restored completely normal sleep during the period of alcohol withdrawal, starting from the 2nd day of injection: TDS, SPS, and FPS were virtually the same as in intact rats. Under these conditions sleep developed much faster than in the intact animals, and the rhythm between the phases of sleep, disturbed by alcohol deprivation, was restored. These facts indicate that this drug can prevent sleep disorders during the withdrawal period.

The effect of phenazepam may also be regarded as positive. In a dose of 1 mg/kg the drug increased TDS by comparison with animals in the abstinence period and in intact rats, mainly on account of SPS and an increase in the total duration of sleep without awakening during the latent period of FPS, and the total dura-

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TABLE 1. Effect of Drugs on Electrophysiological Indices of Sleep in Rats at Various Stages of Alcohol Withdrawal

Condition	Day of alcohol withdrawal															
	1st				2nd				3rd				4th			
	TDS, min	SPS, min	FPS, min	No. of episodes of SPS	TDS, min	SPS, min	FPS, min	No. of episodes of SPS	TDS, min	SPS, min	FPS, min	No. of episodes of SPS	TDS, min	SPS, min	FPS, min	No. of episodes of SPS
Intact rats	163	143	21	9	163	143	21	9	163	143	21	9	163	143	21	9
Abstinence (physiological saline)	102*	99*	3*	2*	113*	107*	6*	3*	139	125	14	7	76*	75*	1*	1*
Sodium hydroxybutyrate (100 mg/kg)	138	123*	15	8	168	143	25	12	170	143	27*	15*	167	141	26	12
Phenazepam (1 mg/kg)	175	161	14	6	192*	180*	12*	6*	174	154	20	8	144	130	14	5*
Apomorphine (0.1 mg/kg)	120*	108*	12*	5*	124*	112*	12	7	146	131	15	8	104*	95*	9*	5*
Haloperidol (1 mg/kg)	146	142	4*	2*	125*	125*	0*	0*	150	142	8*	3*	109*	104*	5*	3*

*$P < 0.05$ compared with control.

tion of sleep also was increased. Although the duration of FPS was longer in abstinent rats, it remained shorter than in intact animals. These facts indicate that phenazepam had a sedative and hypnotic effect, although the quantitative relations between the phases of sleep were not fully restored through its action.

Apomorphine (0.1 mg/kg) abolished some of the withdrawal symptoms affecting the structure of sleep. Although the phases of sleep did not return to the normal physiological state, a tendency was observed for these indices to increase compared with those in the abstinent animals. However, these effects of apomorphine were seen only during the first 1.5-2 h of recording, probably because of the rapid breakdown of the drug in the body.

Haloperidol (1 mg/kg) did not restore normal sleep during alcohol withdrawal. For instance, by the 7th day of its administration TDS and SPS were still one-third below their values in intact rats. The drug not only did not restore FPS, but it also had an additional inhibitory action on it, demonstrating its inability to restore normal sleep during the withdrawal period.

There is evidence in the literature that sleep disorders are maximal during the period of abstinence [10]. At the same time, it has been shown that abstinence is accompanied by marked changes in neuromediator processes in the CNS [1], which play an important role in the regulation of sleep [7]. Alcohol withdrawal has been shown to lead to activation of catecholaminergic metabolic processes. For instance, in patients with alcoholism in the predelirious state the plasma dopamine level is 3 or 4 times higher than normal [3], from which it can be concluded that an increase in activity of the dopaminergic system is responsible for the formation of withdrawal states. Accordingly administration of drugs depressing dopamine activity, in the present writers' opinion, may be a very promising method of alleviating withdrawal symptoms and, in particular, of restoring normal sleep, and the results of the present investigation are evidence that sleep can be corrected during the alcohol withdrawal period by the use of certain drugs.

The beneficial effect of sodium hydroxybutyrate and phenazepam on sleep disorders, the writers consider, is due to their action on the GABA-ergic system which, in turn, has an inhibitory action on dopaminergic neurons of the nigrostriatal system, responsible for dopamine conservation in these neurons. The dopaminergic system is thus blocked, and the accumulating dopamine virtually does not function [11]. Sodium hydroxybutyrate and phenazepam evidently increase activity of the GABA-ergic system and thereby obstruct the development of certain manifestations of withdrawal states [4].

The tendency toward normalization of sleep under the influence of apomorphine can probably be explained on the grounds that the drug, in small doses, is a direct agonist of presynaptic dopamine receptors [6]. It inhibits the synthesis and secretion of dopamine, as a result of which activity of the dopaminergic system, increased during the period of abstinence, is lowered. However, the action of apomorphine is extremely brief, and for that reason its effect in the present experiments lasted only during the first 1.5-2 h after its injection.

Haloperidol did not restore normal sleep during the period of alcohol deprivation. The reason was probably the fact that haloperidol has the opposite effect to sodium hydroxybutyrate on the dopaminergic system. Haloperidol reduces the GABA concentration in neurons. Lowering the GABA level in these neurons

leads to a corresponding decrease in their inhibitory effect on dopaminergic nigrostriatal neurons and, consequently, to activation of the dopamine turnover [8].

Consequently, it can be concluded from the results of this investigation that the most effective drugs for abolishing the sleep disorders in the alcohol withdrawal period are sodium hydroxybutyrate, which restores physiologically normal sleep, and phenazepam, which has a powerful sedative and hypnotic effect. Administration of apomorphine leads to a tendency toward the normalization of sleep although normal levels of sleep indices are not achieved. Haloperidol is probably unsuitable for correcting sleep disorders during the period of alcohol withdrawal.

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NIPECOTIC ACID, A COMPETITIVE INHIBITOR OF ^{3}H-GABA NET UPTAKE BY RAT BRAIN SYNAPTOSOMES

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Nipecotic acid (piperidine-3-carboxylic acid) is known as an active inhibitor of the ^{3}H-GABA uptake system, with a high degree of affinity [1, 7]. It has been shown that nipecotic acid and GABA use the same carrier, and that the former has a higher degree of affinity for it than GABA [6]. It is generally considered that inhibition of GABA uptake by nipecotic acid takes place by a noncompetitive mechanism [5]. Recently the idea has been developed that homoexchange of GABA takes place at the level of the presynaptic terminal, and that it may play a role in the accumulation of the labeled exogenous amino acid [8, 9], and new techniques have been developed [10] for isolating the so-called pure or net uptake of GABA. These developments have provided a basis for the comparative study of the kinetics of inhibition by nipecotic acid of the "apparent" and net uptake of ^{3}H-GABA by synaptosomes isolated from the rat cerebral cortex, and the investigation described below was devoted to this problem.

EXPERIMENTAL METHOD

Synaptosomes were isolated from the rat cerebral cortex by Hajos' method [4]. Half of the material obtained was not subjected to further treatment, and the other half was used to prepare "depolarized" synaptosomes. For this purpose the synaptosomes were suspended in medium with an increased K^+ concentration

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