EFFECT OF VALPROIC ACID ON SLEEP STRUCTURE AND ETHANOL CONSUMPTION IN RATS DIFFERING IN TYPES OF INDIVIDUAL REACTIVITY, BEFORE AND AFTER STRESS

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The GABA-ergic system plays an important role in the regulation of adaptive responses to stress and also in the mechanisms of action of drugs effective in the treatment of anxiety states [10]. Considering that GABA is an endogenous inhibitory mediator it is argued that, by raising the GABA level in the brain, valproic acid preparations will at the same time depress the excitability of the motor areas of the brain and their predisposition to seizures, and thereby improve the mental state and mood of such patients. Valproic acid has been used mainly in various forms of epilepsy and the effect of the drug on sleep has not been adequately studied.

The aim of this investigation was to examine the effect of the GABA-ergic drug valproic acid, which induces GABA accumulation in the brain, on sleep in normal individuals and after deprivation of paradoxical sleep (PS). In view of the connection between sleep disturbances and alcohol motivation, it was also interesting to study the effect of valproic acid on ethanol consumption after PS deprivation. Since individual sensitivity in responses to stress factors and to drugs is of great importance, the experiments were conducted on animals with different types of individual reactivity.

EXPERIMENTAL METHOD

Chronic experiments were carried out on 52 noninbred male albino rats weighing 200-250 g. The animals were divided beforehand into two groups: those with high (HA) and low (LA) activity, by recording motor activity during unavoidable swimming during unsuccessful attempts to get out of the water with the aid of freely revolving rings [3, 7]. Nichrome electrodes 0.2 mm in diameter were then inserted into the dorsal hippocampus, sensomotor cortex, and dorsal cervical muscles of the animals at coordinates A4, L2, H3.5 and A1, L2, H1, and fixed on to the skull with quick-hardening "Noracryl" plastic [1]. The waking – sleep cycle of the animals was recorded 5-7 days after the operation and adaptation to the experimental room, on a 17-channel "Nihon Kohden" electroencephalograph (Japan) from noon to 4 p.m. The animals were then subjected to PS deprivation for 24 h in a chamber with a safe area and an electrode floor, to which a current of 0.5 nA was applied. The electroencephalogram (EEG) was recorded before and after PS deprivation. The rats were then kept for 10 days in individual cages, equipped with two measuring bowls, allowing them free choice between 15% ethanol solution and water.

There were two series of experiments. In series 1 valproic acid (Convulex, from "Garot," Austria) was administered before recording the waking–sleep cycle began and immediately after recording of the EEG, before the animals were transferred into the deprivation chamber. In the second series valproic acid was given once, after PS deprivation and before the beginning of postdeprivation electroencephalographic recording of the waking–sleep cycle. Valproic acid (VA; 200 and 400 and mg/kg) was given to the animals perorally 30-40 min before the EEG was recorded. Control animals were given the same volume of physiological saline perorally.

The results were subjected to statistical analysis with estimation of the significance of differences between mean values of the total duration of sleep (TDS), the duration of slow sleep (DSS), the duration of paradoxical sleep (DPS), the latent period (LP) of the first episode of PS, the number of episodes of PS, and also ethanol consumption for HA and LA animals, using Student's test [5].

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TABLE 1. Effect of Valproic Acid on Sleep Structure of Animals Differing in Individual Reactivity ($M \pm m$)

	Dose, mg/kg	HA animals					LA animals				
		TDS, min	DSS, min	DPS, min	LP of first episode of PS	number of episodes of PS	TDS, min	DSS, min	DPS, min	LP of first episode of PS	number of episodes of PS
Before deprivation of PS											
Control		130,6±8,8	101,6±10	29,0±2,5	23,6±5,6	16,7±1,8	128±8,9	105,3±8,6	22,7±3,8	30,0±6,1	21,2±0,6
Convulex	200	139,2±6,7	105,5±5,9	33,7±4,1	30,5±6,2	19,3±1,7	138,1±6,2	112,8±7,1	25,3±5,1	37,7±5,3	24,1±1,4
	400	164,6±8,3*	123,3±6,6*	41,3±3,9*	45,1±7,6*	26,1±2,8*	167,9±7,2*	133,3±10*	34,6±3,6*	53,0±4,8*	31,8±4,1*
After deprivation of PS											
Control		163,9±4,9	103±1,6	60,9±5,4	18,5±2,5	27,8±2,8	156,2±3,7	100,7±7,1	55,5±8,3	20,8±3,9	34,4±2,6
Convulex	200	160,4±5,5	97,2±8,1	63,2±3,9	19,2±4,3	26,3±3,1	149,3±7,1	102,8±3,9	46,5±5,9	19,5±1,1	35,2±2,1
	400	167,1±6,5	105±6,5	62,1±4,6	23,2±3,7	31,5±1,7	154±5,6	95,5±6,2	58,5±6,7	26,8±2,5	32,1±2,2

Legend. Asterisk indicates significant differences compared with control at $p < 0.05$.

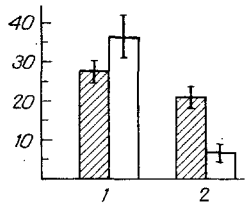

Fig. 1

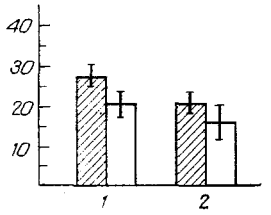

Fig. 2

Fig. 1. Effect of valproic acid administered before and after recording EEG before PS deprivation, on ethanol consumption. unshaded columns — ethanol consumption after Convulex (400 + 400 mg/kg); 1) HA animals, 2) LA animals. *$p < 0.05$ compared with control.

Fig. 2. Effect of valproic acid administered after PS deprivation on ethanol consumption. Unshaded columns — ethanol consumption after Convulex (400 mg/kg). Remainder of legend as to Fig. 1.

EXPERIMENTAL RESULTS

The results of the experiments of series 1 showed that when the EEG of the waking—sleep cycle was recorded before PS deprivation valproic acid had a sedative action on the normal sleep of both HA and LA rats, which depended on the dose of the drug (Table 1). Like other sedatives, VA caused an increase in DSS and LP of the first episode of PS. Unlike them, however, it increased VPS and the number of its episodes. In the postdeprivation period, under the influence of VA, no significant differences in the sleep parameters compared with the control were observed after deprivation of PS. Comparison of the ethanol consumption of the control and experimental animals after deprivation of PS showed that the ethanol consumption of both HA and LA animals was very slightly reduced, but the differences were not significant (Fig. 1). In the experiments of series 2, in which VA was given after deprivation of PS and before the postdeprivation recording of the waking—sleep cycle, no further changes were observed in the sleep structure of the kind observed after deprivation of PS in the control animals. Only an increase in LP of the first episode of PS was noted in animals of both types (Table 1). Comparison of the ethanol consumption of the control and experimental animals, allowed free choice between 15% ethanol solution and water, after deprivation of PS under the influence of BA showed that the HA rats consumed rather more (but not significantly more) ethanol than animals of the control group. By contrast, the ethanol consumption of the LA rats under the influence of VA fell significantly below the control level (Fig. 2).

The results thus indicate that VA has a sedative effect. Several different views are currently held on the mechanism of action of VA. On the one hand it has been shown to be an inhibitor of α-ketoglutarate.GABA transaminase, an enzyme responsible for inactivating GABA. By inhibiting the activity of this enzyme, VA induces accumulation of the mediator in the

brain [8]. In view of data showing a connection between PS and GABA metabolism [6], it can be tentatively suggested that this is one of the main factors involved in the effect of VA on the sleep structure. At the same time, the change in the sleep structure under the influence of VA resembles effects of gamma-hydroxybutyric acid (GHBA) [2]. In view of evidence [9] that GHBA accumulates under the influence of VA it can be tentatively suggested that under certain conditions the effect of VA on sleep may be mediated by GHBA. Analysis of differences observed in the action of VA on ethanol consumption of HA and LA animals showed that it can be postulated that the inhibitory functions and activity of the GABA-ergic system in HA animals are initially expressed more strongly than in LA rats [4]. Since we know that one cause of the development of an alcohol motivation in LA animals is the activating action of ethanol on functions of the CNS, it can be argued that VA, by potentiating the inhibitory functions of the GABA-ergic system, also depresses ethanol consumption. The absence of effect of VA in HA animals may probably be due to the fact that in animals of this type, unlike LA rats, the inhibitory processes of GABA are initially quite well marked and do not require correction.

The experimental results are evidence that the GABA-ergic system, together with other mediator systems, is involved in the regulation of sleep processes and also in the formation of primary motivation for ethanol under conditions of stress induced by sleep disturbances. In view of the positive action of VA on the sleep structure, the possibility cannot be ruled out that it may be an effective sedative. Taking into account data showing changes in the alcohol motivation of LA animals under the influence of VA, it can be tentatively suggested that the drug will also be effective in the treatment of some forms of alcoholism.

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