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HIGH DOSES ETHANOL EFFECTS ON THE STRUCTURE OF SLEEP-WAKEFULNESS CYCLE IN RATS

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Summary

The effects of high doses of Ethanol on the some patterns of the structure of sleep-wakefulness cycle (SW-C) in rats were studied under conditions of chronic experiments. The analysis of obtained date gave evidence that amplitude of electrical activity of cortical areas after 15-30 min of administration of high dose (4,5g/kg) is suppressed to EEG-depression, muscle relaxation and spinal reflexes inhibition are observed as well. During EEG-depression the normal SW-C has not been generated. All phases are reduced in the successive SW-C due to EEG-depression. The disturbances of SW-C remained on another day. At dose 2,25 g/kg less EEG-effects and smaller disturbances of SW-C are observed.

Key Words: Ethanol, EEG-depression, sleep-wakefulness cycle.

Introduction

Sleep-wakefulness cycle (SW-C) with its composed phases and stages is one of the most important manifestations of brain integrative activity (Jouvet 1972; Moruzzi 1972; Oniani 1980; Hobson et al 1998). At the same time, the integrity of the cycle depends on the cause-consequence relationship of the phases, and the generation and regulation of the above-mentioned phases are due to activity of some brain structures (the limbic and thalamo-cortical systems, brain-stem) (Jouvet 1972; Moruzzi 1972; Oniani 1980) and their neurotransmitter mechanisms (Jouvet 1972). Investigation of effects of several psychotropic drugs should help one to look into the basic mechanisms of SW-C and to analyze the influence of the drugs on integrative activity of the brain.

Ethanol (E) belongs to psychotropic substances, with wide range of action. Recent investigations have shown that E can interaction with several of specific receptors such as GABA-ergic (Canches-Perez et al. 1999), opiate (Goodwin et al. 1999), NMDA (Hanaina et al. 1999), acetylcholinergic (Volpiselli 1987), serotoninergic (Maurel et al. 1999) etc., and it seems that variety of E effects depends on the activation of its binding site in the brain structures. At the same time it should be mentioned that neurophysiological data concerning E effects on the structure of the SW-C and disorders of sleep are sparse. Thus it was shown that after treatment by moderate doses of E until night sleep, the paradoxical phase of sleep (PS) was reduced and the duration of slow wave sleep (SWS) was increased (Yules et al. 1967; Zarcone et al. 1980; Burov and Viglinskaia 1981; Snyder 1984; Vein et al. 1985; Gillin et al. 1989). But the most of the data are based on clinical observations and they hardly help to afford an opportunity of studying neurophysiological mechanisms of disorders.

Thus the purpose of the present investigation was to study the effects of two high doses of E of the effects on the SW-C and to conduct neurophysiological analysis of the date received in experiments on animals.

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Methods

1. The object of the study and the procedure of electrodes implantation. The tests were conducted in mature albino rats (n=10), weighed 180-200g under conditions of chronic experiments. Throughout the studies animals were individually housed in the cage, under natural day-night condition, ambient room temperature (18-20^{o}C), food and water allotted in abundance. After adaptation period silver electrodes under hexenal anestezia were implanted in different cortical areas - sensorimotor and dorsal hippocampus projection, oculomotor and neck muscles in order to record electroencephalogram (EEG).

2. Recording of the SW-C. Polygraph recording of SW-C was started after postoperation rehabilitation. Daily records lasted 6-12 h. After establishment of the base line of structure of SW-C, animals were IP injected with different doses (4.5g/kg and 2,25g/kg) of 25% E solution. The EEG recording was conducted on 4-channel ink-writing electroencephalograph on the injection day and lasted several days till completely restoration of the SW-C. Three stages of the SW-C were identified according to the character of the electrocorticogram, electrooculogram and behavioral parameters of the animals: 1- wakefulness, 2- SWS, 3- PS.

Results

1. Changes in electrical activity of cortical areas at administration of narcotic and half-narcotic doses of E. At IP administration of narcotic dose of E (4,5g/kg) the corticogram was considerably changed. Fig.1 shows a record of the cortical areas until injection (A), 15 min. after injection (B) and 2 h later (C). As it is demonstrated, electrical activity of the cortex undergoes important changes. The amplitude was suppressed to EEG-depression. At the same time complete immobilization with muscle relaxation and spinal reflexes inhibition were observed.

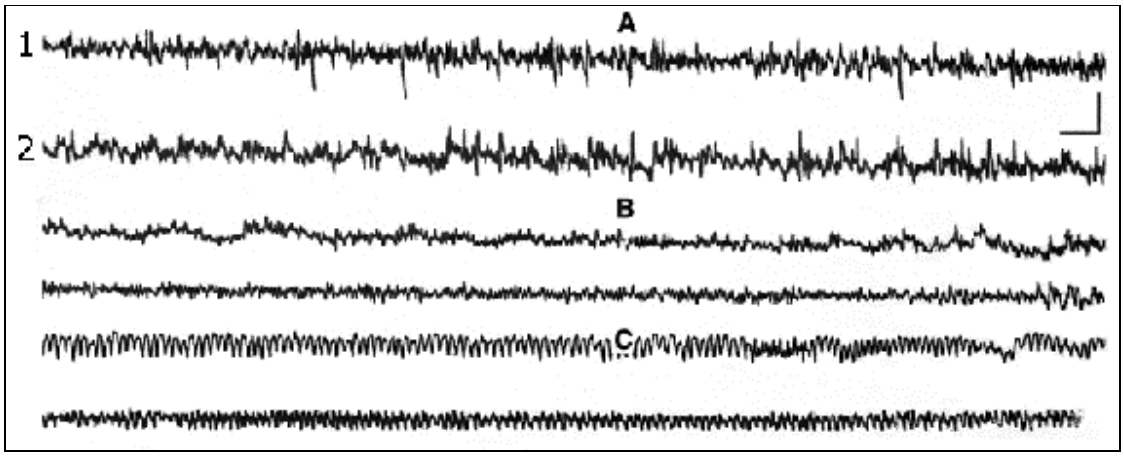

Figure 1. Electroencephalograph changes of different areas of new cortex at narcotic dose of ethanol.
1. SM-cortex, 2. occipital area (hippocampal projection). A - background, B - after 15 min of ethanol administration, C - after 2 hours of injection. Calibration - 1 sec, 100μV.

Two hours later motor reflexes were partially restored. Synchronized low amplitude rhythm (in ratio 4/sec) was registered. It is very important to note that during such activity the SW-C had not been revealed. The motor activity was restored after 3-4 hours while the SW-C was not.

Half-narcotic dose (2.25 g/kg) of E evoked less EEG-effect and its duration was significantly shorter.

2. Changes of ratio of phases in the SW-C at narcotic and half-narcotic doses of E. Administration of narcotic dose of E evoked significant changes in the SW-C. As mentioned above during EEG-depress in the SW-C had not been generated.

Percentage ratio of various phases in the successive SW-C after E administration is shown in Fig.2. A single injection of E (4,5 g/kg) caused significant decrease of all phases of the SW-C. Wakefulness decreased from 40% to 29%, SWS reduced from 53% to 29%, PS was suppressed from 7% to 2%. EEG-depression occupied 39% of the total experimental time. As it was mentioned above, polygraph recording of the cycle was continued on the second day of E treatment. The total duration of wakefulness was longer as compared to the background; the total length of SWS and PS consequently was suppressed.

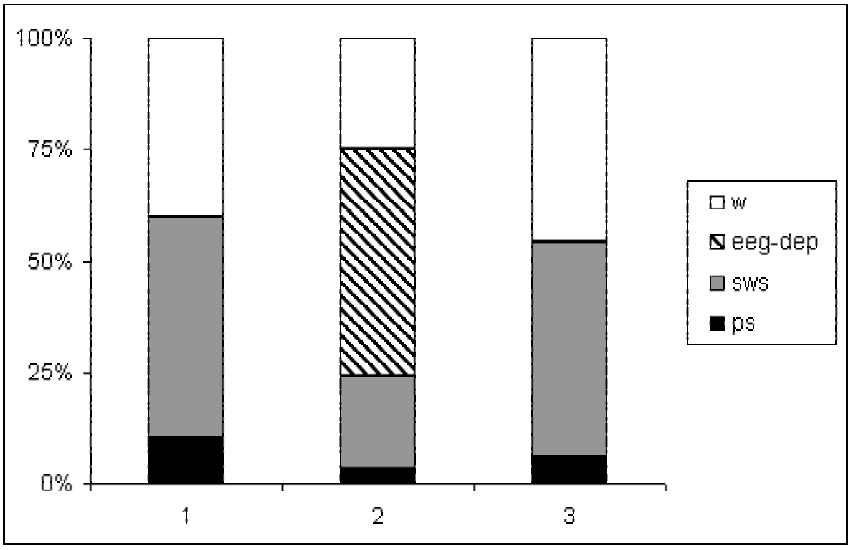

Figure 2. Changes of ratio of phases in the SW-C at narcotic and moderate doses of ethanol.
B - background, A1 - at narcotic doses (4.5 g/kg), A2 - at moderate dose (2.25 g/kg).

In order to assertion the cause of disturbance of the normal of the SW-C under E administration, a detailed analysis of the cyclograms was carried out. An analysis of the calculation of data had shown that average duration of phases in the cycle as compared to the background was changed. This was connected to duration of wakefulness and SWS, the average length of PS was not changed (Fig.3), but the frequency of PS significantly decreased (Fig.6, A1). The latency of SWS increased (Fig.4) and the frequency of arousal also enhanced (Fig.5, A1) and thus the structure of the SW-C became fragmentary.

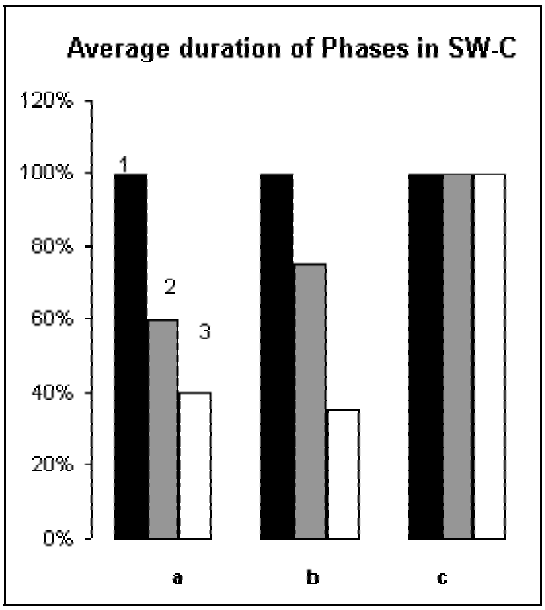

Figure 3. Changes of average duration of phases in SW-C and latency of SWS.
I. A - wakefulness, B - slow wave sleep, C - paradoxical sleep; 1 - background, 2 - after narcotic dose administration, 3 - at moderate dose.

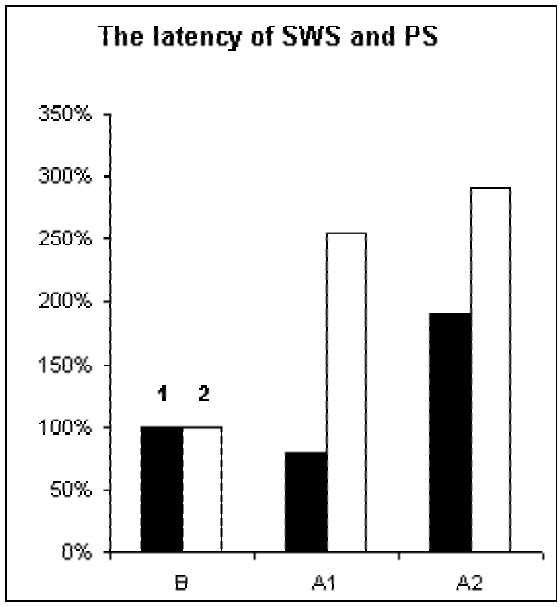

Figure 4. Changes of latency of SWS and PS during of ethanol administration.
B - background, A1 - after narcotic dose administration, A2 - at moderate dose. 1 - SWS, 2 - PS

Half-narcotic dose of E at minor influence on the EEG-activity evoked less disturbance of the structure of the SW-C. The cycle developed with all its phases. But the total duration of SWS as well as PS was shorter and the total length of wakefulness was rather longer as compared to the background (Fig. 3, A2). At the same time average duration wakefulness and SWS was shorter, the frequency of PS was lower as compared to the base-line, but higher than during at E narcotic dose administration (Fig.6, A2) the latency of SWS before PS manifestation was enhanced (Fig.3, A2). The frequency of awakenings was higher (Fig.5, A2) and so the structure of SW-C was fragmented. Therefore the disturbance of the SW-C at the treatment with narcotic dose of E was development due to EEG-depression.

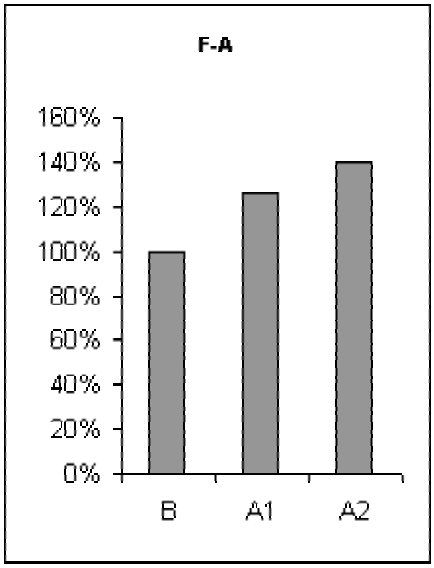

Figure 5. The frequency of awakenings at ethanol administration.

B - background, A1 - at narcotic dose, A2 - at moderate dose.

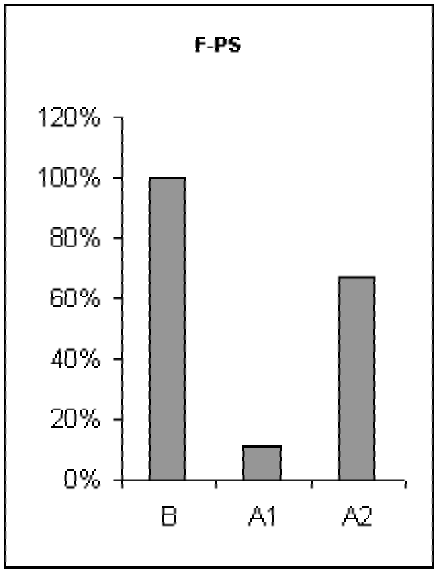

Figure 6. The frequency of paradoxical sleep onset at ethanol administration.

B - background, A1 - after narcotic dose administration, A2 - at moderate dose.

Discussion

It is expedient to analyze the obtained data using two conceptions: Normal SW-C with its compound phases and stages express the readiness of the brain to maintain homeostasis of the brain integrity (Moruzzi 1972; Oniani 1980). The cycle itself could used as a model to study the effects of various pharmacological and non-pharmacological manipulations because its phases are cause-consequently connected to each other and actually any action, which could disturb this connection, may reflect changes in normal integrative activity of the brain (Oniani 1980).

On the other hand according to Borbely (Borbely 1982; Tobler et al. 1992) hypothesis (The Two-Processes Model of Sleep Regulation) sleep and wakefulness are regulated by two partially independent processes: a circadian factor (process C) which controls the daily circadian changes in arousal and a homeostatic factor (Process S). The last can be conceptualized as a sleep promoting substance, which is dissipated during sleep. Process S is linked to SWS deprivation and decrease gradually with sleep duration.

At the same time there are two hypotheses in the available literature concerning alcoholism: Tension Reduction Hypothesis and Endorphin Compensation Hypothesis (Volpiselli 1987). According to the first, alcohol consumption is connected with withdrawal of tension, fears and stress. According to the second hypothesis, alcohol stimulates endorphin activity (Volpiselli 1987). Alcohol and opiate exert similar subjective effects. An important reason individuals give for using both and opiates to obtain a "high feeling" (Blum et al. 1977; Volpiselli 1987). It has been demonstrated that alcohol drinking is influenced by endorphin activity. The suppression of endorphin levels may reflect a direct effect of alcohol on the endogenous production of endorphins. In general, when the endorphinergic activity is low, alcohol drinking increases and when endorphinergic activity is high then alcohol drinking is reduced. Therefore it may concluded that E injection evokes increase of endogenous production of endorphins. At the same time it has been shown that at a single administration of opiates in general and according to above-mentioned Endorphin Compensation Hypothesis, the dopaminergic, noradrenergic and serotoninergic systems are activated and the rate of ACH release is changed (Zarcone et al. 1980).

Recent data prove that ACH and some other neurotransmitter systems are stimulated or may be blocked by E. E effects are shown on different specific receptors such as GABA, NMDA, opiate, cholinergic, serotoninergic and ect (Zarcone et al. 1980; Canches-Perez et al. 1999; Goodwin et al. 1999; Maurel et al. 1999) and the effects have dose-dependent character. As it is known most of these neurotransmitters are involved in the regulation and release of phases of SW-C (Jouvet 1972). On the other hand it should be noted that there is plenty of these receptors in the limbic brain, which is the most important system for regulation and manifestation of emotional reactions (Oniani 1980) and the SW-C as well (Oniani 1980). And in case of using E in high doses reciprocal relationship between the structures functioning in different regimes and controlling mechanisms of their neurotransmitters are disturbed, which finally is reflected in EEG-depression and complete disorders in SW-C.

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