ACTION OF LITHIUM HYDROXYBUTYRATE ON ELECTROENCEPHALOGRAPHIC EFFECTS OF AMPHETAMINE

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Lithium hydroxybutyrate possesses high therapeutic activity in cyclothymic schizophrenia [1, 5, 12]. Experiments on rabbits have revealed, on the one hand, a depriming action of the compound on the integral EEG, and on the other hand, specific facilitation of electrical excitability of the basal nuclei of the amygdala and dorsal hippocampus, with simultaneous inhibition of excitability in the motor cortex, posterior hypothalamus, caudate nucleus, and mesencephalic reticular formation [8]. Lithium salts inhibit amphetamine-induced hyperthermia, group toxicity, and activiation of locomotor activity by this psychostimulant [7]. They have been shown to have a beneficial effect in acute and chronic amphetamine poisoning [13].

The writers have compared the effect of lithium salts (hydroxybutyrate and chlorida) on global electrical activity of the cortex and certain deep brain structures during amphetamine excitation, used as a model of psychoses with symptons resembling those of schizophrenia and with maniaeal symptoms [16].

EXPERIMENTAL METHOD

Experiments were carried out on unrestrained rabbits with chronically implanted nichrome electrodes into the frontal and occipital regions of the cortex, basal ganglia of the amygdala, head of the caudate nucleus, dorsal hippocampus, posterior hypothalamus, and mesencephalic reticular formation, taking coordinates from [15]. Brain electrical activity was recorded on a 8-channel encephalograph of Orion type and evaluated by narrow-band analog filtration, using an analyzer and integrator from Estergrom. The power of the Δ-, Θ-, α-, β_1-, and β_2-rhythms constituting the integral EEG was determined for a 10-sec integration interval. The initial data were taken as zero. Lithium hydroxybutyrate, in an effective dose (10 mg/kg) was injected intravenously 30 min before systemic injection of amphetamine [8]. The dose of amphetamine was chosen individually. Animals in whose visual cortex rhythm binding to flashes increased up to 20 Hz or more, equivalent to 200-250% of the initial background, after injection of amphetamine were used in the experiments.

The action of lithium hydroxybutyrate was compared with that of sodium hydroxybutyrate in an equimolar dose (10 mg/kg) and with that of lithium chloride in an isoeffective (according to the EEG) dose (100 mg/kg).

EXPERIMENTAL RESULTS

In agreement with data in the literature [2-4, 10] after intravenous injection of amphetamine into rabbits improvement of the rhythm binding reaction of flashes was observed in most brain structures studied ($P < 0.05$; Fig. 1). The power of the high frequency β_1- and β_2-components of the EEG spectrum increased (by 13-25% relative to the initial background, $P < 0.05$; Fig. 2) in the reticular formation, posterior hypothalamus, visual cortex, amygdala, and caudate nucleus. Strengthening of α-activity in the amygdala, visual cortex, and posterior hypothalamus (by 15-25%, $P < 0.05$) was accompanied by its simultaneous inhibition in the caudate nucleus and motor cortex (by 15-40%, $P < 0.05$), The Δ- and Θ-rhythms in the EEG recorded from these formations showed no significant change. However, in the hippocampal EEG definite predominance of Δ-waves was found, evidence of inhibition of the functional activity of this structure, evidently on account of this overexcitation [2, 4, 9]. Amphetamine sharply

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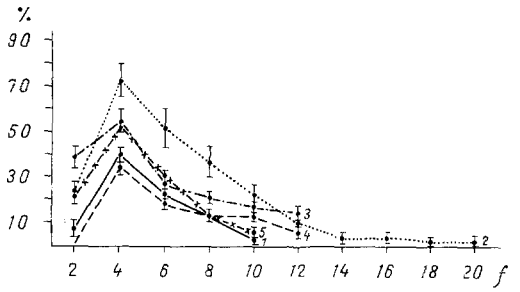

Fig. 1. Effect of lithium salts on rhythm binding to flashes after administration of amphetamine. Abscissa, frequency of photic stimulation (in Hz); ordinate, % of binding; 1) initial data; 2) 30 min after injection of amphetamine; 3) 1 h after injection of sodium hydroxybutyrate and amphetamine; 4) 1 h after injection of lithium hydroxybutyrate and amphetamine; 5) 1 h after injection of lithium chloride and amphetamin.

reduced the high initial power of all frequency bands of the EEG in the motor cortex (by 30-40%, $P < 0.05$).

The dose of lithium hydroxybutyrate used thus considerably potentiated the activating mechanisms of the brain and, at the same time, depressed activity of the caudocortical inhibitory systems. This is shown by the unmotivated restlessness of the animals observed after injection of amphetamine, the considerable increase in percentage of rhythm binding to flashes as a result of access of unfamiliar "noise" impulsation to the cortical neurons [2], and also the dominance of high frequencies in the EEG spectra.

Lithium salts prevented the excitatory action of amphetamine on the CNS. The response of rhythm binding to flashes in the visual cortex remained within its previous limits.

The study of integral electrical activity by narrow-band analog filtration revealed significant differences in the action of the two lithium salts on the EEG changes induced by amphetamine. In the visual cortex, for instance, lithium chloride had a stronger depriming effect than lithium hydroxybutyrate on the power of the β_1-rhythm, increased by amphetamine. However, lithium hydroxybutyrate restored the electrocorticogram more nearly to its initial form. In addition, the hydroxybutyrate was more effective than lithium chloride in preventing changes in the EEG spectrum of the motor cortex induced by amphetamine.

Lithium chloride potentiated the effect of amphetamine on the frequency bands of the EEG from the caudate nucleus, whereas lithium hydroxybutyrate, on the other hand, proved to be an antagonist of amphetamine at the level of this structure. Electrogenesis of the basal nuclei of the amygdala did not differ significantly from its initial level after administration of lithium chloride and amphetamine, but it was significantly increased after injection of lithium hydroxybutyrate and amphetamine, the effect being stronger than that of amphetamine alone ($P < 0.05$). Lithium hydroxybutyrate modified the amphetamine type of hippocampal ECG, increasing the power of both high-frequency and low-frequency rhythms. Both lithium salts inhibited the action of amphetamine on β_1- and β_2-bands of EEG frequencies from the posterior hypothalamus and mesencephalic reticular formation and restores their EEG closely to its initial type.

Sodium hydroxybutyrate reversed the effect of amphetamine on cortical and subcortical electrogenesis. Compared with the control, sodium hydroxybutyrate nonspecifically dispersed the power of all ECG rhythms.

Lithium salts thus differ in their effect on the development of amphetamine excitation Lithium chloride completely prevents changes in the EEG induced by amphetamine in the reticular formation, posterior hypothalamus, and amygdala and, to a lesser degree in the motor and visual cortex, in agreement with the character of changes in electrical excitability of deep brain structures of the systemic injection of amphetamine into intact animals [6]. Potentiation of the effect of amphetamine on the EEG of the caudate nucleus by lithium chloride is evidently due to accumulation of dopamine in this structure [2, 6].

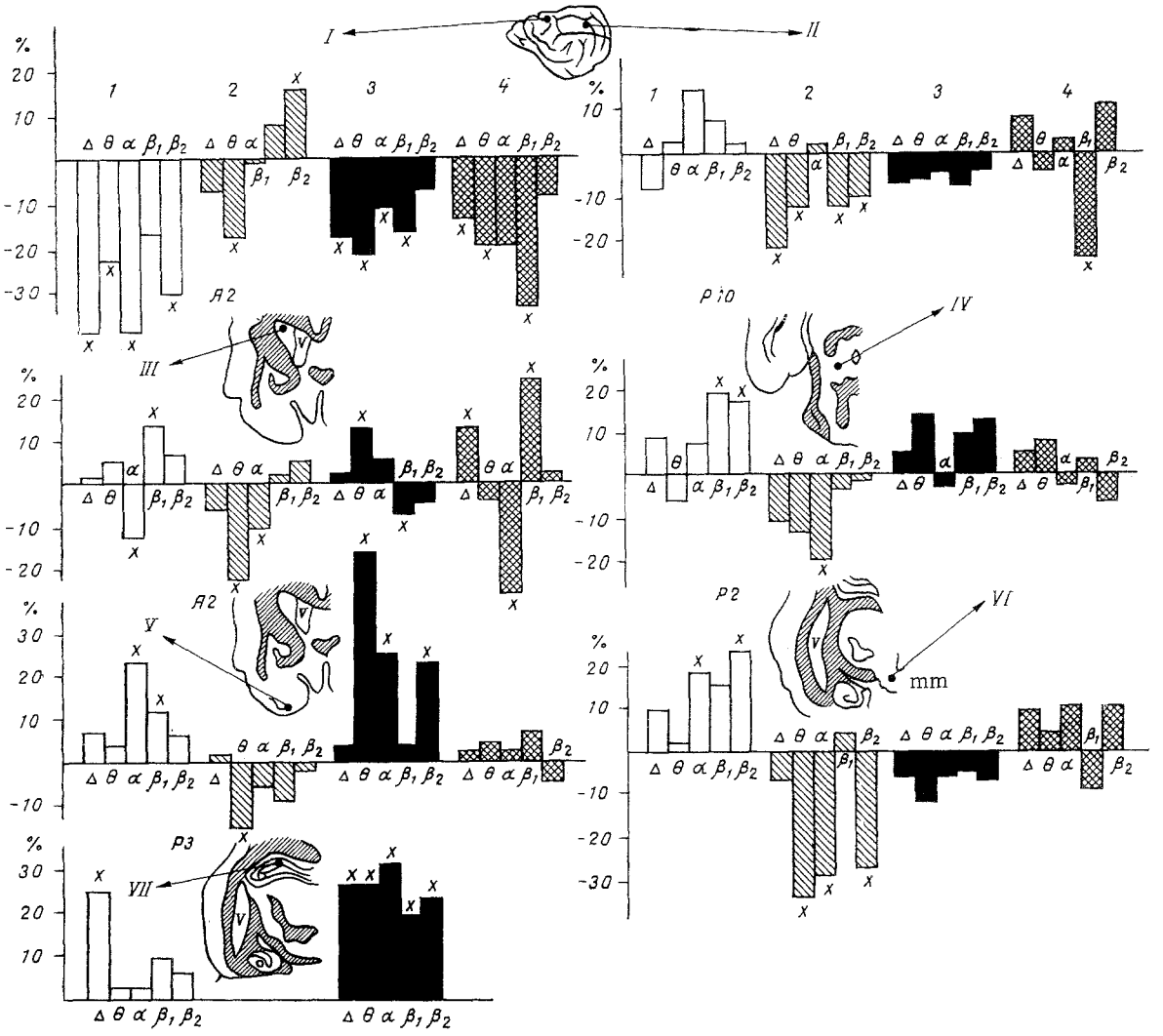

Fig. 2. Effect of amphetamine (1), sodium hydroxybutyrate + amphetamine (2), lithium hydroxybutyrate + amphetamine (3), and lithium chloride + amphetamine (4) on frequency components of ECG recorded from motor (I) and visual (II) areas of the cortex, caudate nucleus (III), mesencephalic reticular formation (IV), amygdala (V), posterior hypothalamus (VI), and hippocampus (VII). Abscissa, ECG rhythms; ordinate, relative contribution of EEG rhythms (in % of initial values). X) Values differing significantly from initial ($P < 0.05$).

Lithium hydroxybutyrate not only has an antiamphetamine action in the region of the posterior hypothalamus, reticular formation, and motor and visual cortex, and to a lesser degree also in the region of the caudate nucleus, but it is a synergist of amphetamine at the level of the hippocampus and amygdale. In the hippocampus the compound as it were "pulls up" the power of all the rhythms of its EEG to the power of the Δ-rhythm, established by amphetamine, thus restoring the physiological activity of the structure and enabling the body to respond to signals with little chance of reinforecement [9]. The power characteristics of the principal rhythms of the "amphetamine" amygdalar ECG are considerably potentiated by lithium hydroxybutyrate in the region of the Θ-rhythm and high-frequency β_2-rhythm. The appearance of the latter in the EEG of the amygdale is characteristic of the strongest degree of activation of that structure [9]. These features distinguishing the action of lithium hydroxybutyrate on "amphetamine" EEGs of the hippocampus and amygdala may perhaps depend on its ability to depress the excitability of these brain formations [8].

Dominance of θ-activity in the EEG of the caudate nucleus, amygdala, hippocampus, and reticular formation in response to combined administration of amphetamine and lithium hydroxybutyrate deserves attention, for it may be evidence of liquidation of brain activity and the reduction of its functional state to the optimal level of response [2, 4].

Not withstanding the undoubted similarity to sodium hydroxybutyrate and lithium chloride [6], lithium hydroxybutyrate thus possesses definite specificty of action on the electroencephalographic effects of amphetamine, and this may perhaps be due to the special character of its pharmacokientics [11]. In the light of modern views on the role of the frontal cortex, amygdala, hippocampus [9], and caudate nucleus [14] in the genesis of affective disorders, the experimental data described above are in good agreement with recommendations that lithium hydroxybutyrate be used mainly in cyclic psychoses with a schizophrenia-like symptomatology [1].

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DISTURBANCE OF ^{3}H-GABA TRANSPORT IN SYNAPTOSOMES BY TETANUS TOXIN

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Depression of central inhibition by tetanus toxin (TT) is due to presynaptic blockade of amino-acidergic synapses [1, 3, 11, 12]. It has been shown that slices of brain structures poisoned *in vivo* and nerve endings isolated from them liberate less γ-aminobutyric acid (GABA) on depolarization than in the control [10, 15]. Disturbance of GABA secretion has also been obtained through the direct action of TT on isolated nerve endings (synaptosomes) [5, 6].

In the present investigation the dependence of the action of TT on synaptosomes on the transmembrane ionic gradients was analyzed.

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