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EFFECTIVENESS OF LITHIUM HYDROXYBUTYRATE IN RESERPINE DEPRESSION

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In view of data in the literature on the therapeutic value of lithium salts in depression [3, 14, 15] and of the specific features of the psychotropic profile of lithium hydroxybutyrate [2, 4, 7, 8] it was decided to investigate the effectiveness of this compound on a model of reserpine depression.

EXPERIMENTAL METHOD

Experiments were carried out on 35 rabbits weighing 2.5-3.0 kg with electrodes implanted permanently by the technique described previously [8]. Electrodes were inserted into the frontal and occipital regions of the cortex, the basal nuclei of the amygdala, head of the caudate nucleus, dorsal hippocampus, and posterior hypothalamus. Brain electrical activity was recorded on an 8-channel Orion electroencephalograph and analyzed by the method of narrow-band analog filtration, using an analyzer and integrator from Estergom. The powers of the δ-, θ-, α-, β_1-, β_2-, and γ-rhythms, components of the whole electroencephalogram (EEG), were determined in a 10-sec integration interval. In each experiment no fewer than three EEG cuts were integrated for each brain structure, so that the total time of EEG analysis was 5 min or more. The initial data were rated at zero.

Rhythm binding to flashes of different frequencies, applied by an FS-02 photostimulator, served as the indicator of the functional state of the visual cortex.

Conditioned reflex experiments were carried out on rats weighing 180-200 g. A conditioned avoidance reaction (CAR) was formed in the animals in a special chamber with electric floor and a vertical rod. The conditioned stimulus was acoustic (a bell ringing for 5 sec). The time between conditioned and unconditioned (electric shocks through the floor, 50-80 V, 5 sec) stimuli was not more than 0.5 sec, and between individual tests it was 20 sec. The conditioned reflex was considered to have been formed if eight out of ten responses were positive.

Lithium hydroxybutyrate (10 mg/kg) or distilled water (1 ml/kg, control) was injected subcutaneously daily at the same time for 1 week. On the 8th day reserpine (in the form of rausedil) was injected subcutaneously into the animals in a dose of 0.125 mg/kg. An additional control series was set up to estimate the effects of reserpine: rabbits and rats were injected

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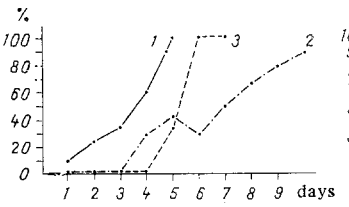

Fig. 1

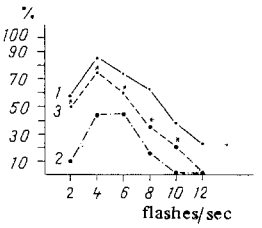

Fig. 2

Fig. 1. Effect of lithium hydroxybutyrate on CAR formation after administration of reserpine. 1) Control, 2) reserpine, 3) lithium hydroxybutyrate + reserpine. Abscissa, time of investigation (in days); ordinate, percent of avoidance conditioning in group of ten animals.

Fig. 2. Effect of lithium hydroxybutyrate on rhythm binding to flashes and effect of reserpine on it. 1) Initial data, 2) reserpine, 3) lithium hydroxybutyrate + reserpine. Abscissa, frequency of photic stimulation (flashes/sec); ordinate, percent of binding. Points indicate $P < 0.05$ relative to initial data, asterisks — $P < 0.05$ relative to reserpine only. Here and in Fig. 3, results of four tests, after 1, 3, 5, and 7 days, are pooled.

with water in a volume of 0.05 ml/kg instead of reserpine. During the following week (without stopping the lithium hydroxybutyrate injections) the EEG was analyzed and a CAR formed. The EEGs were analyzed 1, 3, 5, and 7 days after injection of rausedil. The rectal temperature and respiration rates were determined concurrently. CAR formation began 1 h after injection of reserpine and the reflex was consolidated every subsequent day with an interval of 24 h between experiments. The results were subjected to statistical analysis by parametric and nonparametric states.

EXPERIMENTAL RESULTS

Reserpine in a dose of 0.125 mg/kg inhibits the CNS of rabbits and rats: the animals' motor activity was depressed and their behavior was characterized by general inhibition and by weak responses to chance stimuli. Similar results were obtained previously after injection of larger doses of the drug into animals [1, 3, 12]. In the dose now used, reserpine also had a very significant effect on CAR production in rats, for even by the 10th day of daily training 100% success was not achieved (Fig. 1). Synchronization of the EEG, a marked increase in amplitude and slowing of the rhythm in all leads, and impairment of rhythm binding to flashes in the visual cortex also served as indicators of the depressant action of reserpine on the CNS (Fig. 2). Marked vagotonia was observed in the rabbits: the rectal temperature fell from 37.3 ± 0.62 to 35.4 ± 0.51°C ($P < 0.05$) and the respiration rate slowed from 135 ± 12.4 to 96 ± 9.8 cycles/min ($P < 0.05$), and slight hyperemia of the mucous membranes was observed.

It was shown by means of band analyzers and energy integrators of EEG rhythms (Fig. 3) that reserpine considerably increased the power of δ- and α-waves in the caudocortical system, the energies of all low-frequency components increased in the EEG of the posterior hypothalamus and amygdala, and high frequencies on the EEG of the thalamus were sharply depressed. In the hippocampus there was a tendency for the energy to increase over the whole range of the spectrum, but more especially that of the α-waves.

Considering the functional role of individual EEG rhythms in the activity of the posterior hypothalamus and medial thalamus [5, 10], it must be accepted that reserpine depresses activating mammillothalamic mechanisms but potentiates the synchronizing influences of the thalamus on the cortex. Predominance of averaged and low frequencies on the EEG of the caudate nucleus is evidence of activation of the inhibitory mechanisms of that structure [11].

The dorsal hippocampus and basal–lateral amygdala behave as part of a general inhibitory system in the activity of brain systems [6]. The EEG correlates of involvement of the hippocampus in the organization of goal-directed behavior is evidently the θ-rhythm. Desynchronized fast activity is an indicator of excitation of the structure [6]. In the light of these

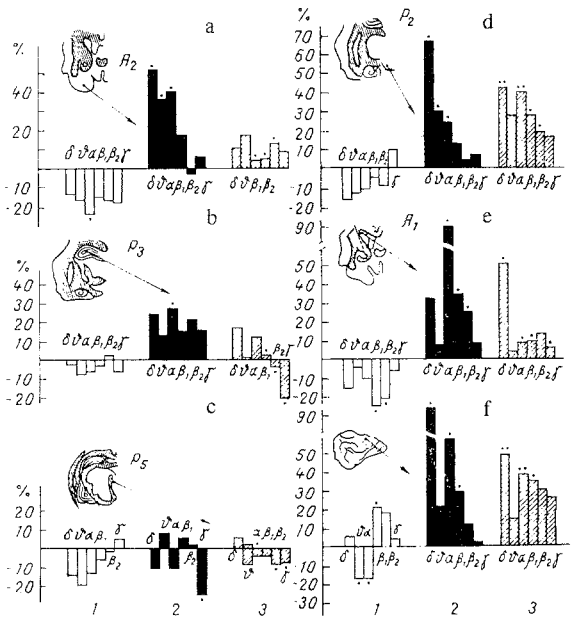

Fig. 3. Effect of reserpine (2), and of lithium hydroxybutyrate + reserpine (3) on frequency components of EEG in amygdala (a), hippocampus (b), thalamus (c), posterior hypothalamus (d), caudate nucleus (e), and sensomotor cortex (f). Abscissa, EEG rhythms; ordinate, weighted values of EEG rhythms (in % of initial data). 1) Control. Black dots indicate $P < 0.05$ relative to initial data; empty circles — $P < 0.05$ relative to reserpine injection only.

findings it is evident that during reserpinization the functional tone of the dorsal hippocampus is enhanced. Other workers have mentioned the possible excitatory action of reserpine on the hippocampus [1, 12].

A characteristic feature of the EEG of the amygdala is the bursting, spindle-like activity in the α-band, associated with the highest degree of activation of that structure [16] or with emotional excitation [6]. Dominance of low frequencies was observed in the slow sleep phase [16]. Consequently, under the influence of reserpine inhibitory mechanisms of the basal—lateral amygdala were strengthened.

After injection of reserpine the activating system of the brain was thus depressed and activity of synchronizing and inhibitory formations was enhanced.

Lithium hydroxybutyrate significantly weakened the action of reserpine on the CNS. The rhythm binding response to flashes returned close to its initial level. EEG of the amygdala, thalamus, and hippocampus returned to normal. The energies of low-frequency and middle ranges of waves in the caudocortical system were reduced. However, in the posterior hypothalamus, together with inhibition of the power of the δ-band, an increase was observed in the energies of the α-, β_1-, and β_2-rhythms. Consequently, lithium hydroxybutyrate on the one hand blocks excessive activation of inhibitory structures by reserpine at the level of the basal—lateral amygdala, cortex, hippocampus, and caudate nucleus, and on the other hand it enhances the functional capacity of the activating systems. The result of this intracentral reorganization must evidently be the prevention by lithium hydroxybutyrate of inhibition of animals receiving reserpine, normalization of their autonomic parameters (rectal temperature 36.4 ± 0.85°C, respiration rate 120 ± 8.71 cycles/min), and improvement of avoidance conditioning in rats, observed in these experiments. For instance, whereas for 5 days combined administration of reserpine and lithium hydroxybutyrate to the animals (especially on the 4th day) was accompanied by some potentiation of the pharmacologic effects of reserpine, which can evidently be explained by the inhibitory effect of lithium hydroxybutyrate itself on CAR [2], a conditioned reflex was found in all animals as early as on the 6th day. The compound thus considerably accelerates CAR formation when inhibited by reserpine. Lithium carbonate has a similar effect [3].

The results indicate that lithium hydroxybutyrate has a marked antireserpine action, evidence that it possesses antidepressant properties.

Reserpine disturbs catecholamine and serotonin deposition in synapses of the CNS, as a result of which behavioral depression and EEG synchronization develop, with the appearance of high-amplitude waves [1, 12]. In the present experiments reserpine considerably strengthened activity of the brain inhibitory systems and inhibited activity of the activating systems. First and foremost weakening of the activating systems evidently led to the development of slow-wave activity in the cortex and subcortex [10, 12]. The opposite picture of intercentral relations on the EEG was observed after injection of amphetamine into rabbits in a dose of 0.8-1.2 mg/kg [8]; unlike reserpine, amphetamine potentiates central catecholamine transmission. The psychostimulant considerably raised the functional tone of the mesencephalic reticular formation, posterior hypothalamus, and cortex while at the same time weakening activity of inhibitory structures: the caudate nucleus and hippocampus.

Lithium hydroxybutyrate is effective both in amphetamine excitation and in depression induced by reserpine: the compound restores more or less normal functioning of most brain structures in animals. The probable explanation is the property of lithium salts of restoring normal function of the adrenergic synapse either at the presynaptic level [13] or by stabilizing the receptor [17]. Potentiation of the effect of amphetamine, observed on the EEG of the amygdala under the influence of lithium hydroxybutyrate, but weakening of the effect of reserpine, may perhaps be attributed to the ability of amphetamine and lithium hydroxybutyrate to modify excitability of the amygdala and functioning of the dopaminergic synapses in the same direction [4, 5, 7-9], whereas reserpine has opposite properties [5, 9, 12].

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