EFFECT OF LITHIUM HYDROXYBUTYRATE ON CORTICAL AND SUBCORTICAL EXCITABILITY IN RABBITS

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Microinjections of lithium hydroxybutyrate (10 μg/μl) had a depriming action on spontaneous cortical and subcortical electrical activity. The compound reduced the excitability of the motor cortex, hippocampus, caudate nucleus, thalamus, posterior hypothalamus, and mesencephalic reticular formation; the excitability of the amygdala was increased. In its depriming effect, lithium hydroxybutyrate surpassed lithium chloride.

KEY WORDS: Lithium hydroxybutyrate; lithium chloride; sodium hydroxybutyrate; electrical excitability of the brain.

With a view to combining the antimaniacal properties of lithium and the tranquilizing action of gamma-hydroxybutyric acid (GHBA), an original compound (lithium hydroxybutyrate) has been synthesized in the Institute of Pharmacology, Academy of Sciences of the USSR. The compound has low toxicity, inhibits conditioned reflexes, depresses spontaneous motor activity, prevents amphetamine excitation, and induces and EEG synchronization reaction. Clinical trials have shown the high therapeutic activity of lithium hydroxybutyrate, as reflected in alleviation of the symptoms of maniacal and depressive phases of circular psychosis [2, 5]. Previous investigations showed that systemic administration of lithium hydroxybutyrate in a dose of 10 mg/kg has a depriming effect on spontaneous electrical activity of the brain and various subcortical structures, which spreads from the cortex to the subcortex. The inhibitory action of the compound also has been demonstrated on electrical excitability of the motor cortex, mesencephalic reticular formation, posterior hypothalamus, medial thalamic nuclei, and caudate nucleus. Meanwhile the compound activated the hippocampus and amygdala.

Considering the complexity of the intracentral relations of these various brain formations, in order to elucidate the direct effect of lithium hydroxybutyrate on them it was decided to use the method of direct injection of the compound into the cortex and into certain subcortical brain structures.

METHODS

Experiments were carried out on 50 rabbits of both sexes weighing 2.8-3.2 kg. Microinjections of a 0.1% solution of lithium hydroxybutyrate into the motor cortex and subcortical structures were given by means of "chemotrodes" [3]. The compound (10 μg in 1 μl) was injected below the stimulating electrode by means of a special microinjector in the course of 10 min. In control experiments a solution of sodium hydroxybutyrate or bidistilled water was injected. The EEG was recorded for 2 h after injection of the preparation. The results were assessed from changes in the convulsive threshold in response to electrical stimulation of the hippocampus, caudate nucleus, and amygdala, changes in the threshold and duration of the activation reaction to stimulation of the mesencephalic reticular formation, and the threshold and amplitude of the recruiting reaction obtained from the medial thalamic method. The functional state of the posterior hypothalamus was judged from the change in the threshold and components of the behavioral response. Stimulation was applied by the ÉST-10 electronic stimulator. Statistical analysis of the data was carried out by the direct differences method [6].

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RESULTS

Microinjections of lithium and sodium hydroxybutyrate into the hypothalamus, medial thalamus, mesencephalic reticular formation, sensomotor cortex, and hippocampus caused changes in spontaneous electrical activity in the same direction: the appearance of high-amplitude slow potentials up to 100-150 μV and with a frequency of up to 2-3 Hz. After injection of lithium hydroxybutyrate into the caudate nucleus, a synchronization reaction and the appearance of sleep spindles were observed; the electrogenesis of the caudate nucleus was unchanged in control experiments. Recovery of the EEG took place towards the end of the first hour of observation. Neither compound had a significant effect on spontaneous electrical activity of the amygdala.

Microinjections of lithium hydroxybutyrate into the caudate nucleus and sensomotor cortex, like intravenous injection (10 mg/kg), raised the threshold of paroxysmal discharges by 30% and 20% respectively compared with the control (bidistilled water ($P < 0.05$). By contrast with the results of systemic administration, the convulsive threshold of the hippocampus was increased by 15-20% as a result of direct injection of the compound into the structure ($P < 0.05$). The duration of the after-discharges was not significantly changed.

How can the different character of the effect of lithium hydroxybutyrate on electrical excitability of the hippocampus during systemic administration and after direct injection into the structure concerned be explained? The opinion is held that the limbic system has its own activating system — the posterior part of the hypothalamus [9, 11]. Moreover, an important role in the realization of many central effects of lithium ions is ascribed to the latter [10]. The increase in hippocampal activity after intravenous injection of lithium hydroxybutyrate may perhaps be the result of the stronger depriming effect on the region of the posterior hypothalamus. After direct injection of the compound in the hippocampus, the inhibitory action of lithium ions [7] and also, possibly, activation of the numerous GABA-ergic neurons in this formation were manifested [1, 8].

Lithium hydroxybutyrate raised the threshold of the recruiting reaction to stimulation of the median thalamus by 15-20% ($P < 0.05$), without affecting its amplitude. The compound also raised the threshold of the orienting—investigative reaction evoked by electrical stimulation of the posterior hypothalamus by 30-35% ($P < 0.01$), without causing any change in its component and duration. After injection of lithium hydroxybutyrate directly into the mesencephalic reticular formation a more marked depriming effect was observed than after intravenous injection on the activation reaction: elevation of the threshold by 25% and shortening of the reaction by 72% ($P < 0.05$).

Unlike the other structures, the excitability of the amygdala was increased by microinjection (and also by systemic administration) of lithium hydroxybutyrate: The threshold of the after-discharges was lowered by 12-15% ($P < 0.05$) and their duration was increased by 8-10% ($P < 0.05$) compared with the control experiments, in which bidistilled water was injected. Similar results were obtained previously as a result of direct injection of lithium chloride into the amygdala [7]. They were evidently due to the specific effect of lithium salt on the electrical excitability of this structure. The property of the anionic component could possibly have some role to play, for GABA can activate the amygdala [8].

In control experiments microinjections of bidistilled water into the various structures studied caused no change either in their bioelectrical activity or in their electrical excitability. Injection of an equimolar dose of sodium hydroxybutyrate either did not affect their excitability or caused changes similar to but weaker than the effect of lithium hydroxybutyrate.

Lithium hydroxybutyrate thus has a direct depriming action on the various brain structures studied except the amygdala, the excitability of which was increased.

The changes in bioelectrical activity under the influence of microinjections of 10 μg lithium hydroxybutyrate, described above, are similar to the action of microinjections of 100 μg lithium chloride [7]. The two compounds have similar effects on activity of the hippocampus, caudate nucleus, posterior hypothalamus, mesencephalic reticular formation, median thalamus, and amygdala. However, in the degree and duration of its action, lithium hydroxybutyrate is much more active. Moreover, unlike in the experiments with lithium chloride, lithium hydroxybutyrate had a direct inhibitory effect on the motor complex, which was evidently associated with the action of the GHBA anion, because sodium hydroxybutyrate has a

similar effect [4]. With lithium hydroxybutyrate, potentiation of GBHA of the depriming effect of lithium ions on the CNS is evidently facilitated.

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