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EFFECT OF LITHIUM HYDROXYBUTYRATE ON THE CORTICAL AND SUBCORTICAL CATECHOLAMINE LEVEL IN THE RABBIT BRAIN

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Lithium hydroxybutyrate, synthesized and studied experimentally at the Institute of Pharmacology, Academy of Medical Sciences of the USSR, successfully combines the antimaniacal properties of the lithium ion and the tranquilizing effect of γ-hydroxybutyric acid (GHBA), a natural metabolite of brain tissue [1, 3]. Investigation of the electroencephalogram (EEG) revealed a predominantly depriming effect of lithium hydroxybutyrate on spontaneous bioelectricalactivity and electrical excitability of the cortex and of some deep brain formations in rabbits [9]. As a result of synergism between Li^+ and the anionic component, the compound is superior to lithium chloride in its activity, as reflected in several EEG indices [7].

Considering the possible role of central monoamines in the mechanism of the psychotropic action of lithium salts [4, 15, 16], the effect of lithium hydroxybutyrate was investigated and compared with that of sodium hydroxybutyrate and lithium chloride on the catecholamine content in individual structures of the rabbit brain.

EXPERIMENTAL METHOD

Experiments were carried out on 35 rabbits of both sexes weighing 1.5-2 kg. Aqueous solutions of the compounds were injected intravenously: lithium hydroxybutyrate 10 mg/kg, lithium chloride 10 mg/kg (the isoeffective dose according to EEG indices), and sodium hydroxybutyrate 10 mg/kg (the equimolar dose). Control animals received injections of the same volume of physiological saline. The animals were decapitated 1 h after injection of the compound. A weighed sample of the corresponding part of the brain (200 mg for the hypothalamus and caudate nucleus, 400-600 mg for other structures) was frozen without delay. The catechol-

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TABLE 1. Effect of Lithium Salts on Catecholamine Content (in μg/g) in Structures of Rabbit Brain (M ± m)

Brain region	Preparation	Adrenalin		Noradrenalin		Dopamine	
		control	experiment	control	experiment	control	experiment
Caudate nucleus	LH	0,08±0,02	0,12±0,02	0,45±0,11	0,39±0,06	3,39±0,4	8,02±1,18‡
	LC		0,08±0,01		0,39±0,04		4,47±0,31*
	SH		0,07±0,01		0,35±0,04		3,06±0,37
Motor cortex	LH	0,05±0,01	0,06±0,01	0,28±0,05	0,22±0,03	1,43±0,18	1,71±0,15
	LC		0,05±0,001		0,22±0,003		1,73±0,29
	SH		0,05±0,01		0,22±0,02		1,57±0,21
Hippocampus	LH	0,05±0,001	0,06±0,001	0,29±0,03	0,28±0,03	1,80±0,19	2,10±0,27
	LC		0,04±0,001		0,24±0,09		1,24±0,12*
	SH		0,04±0,01		0,22±0,02		1,34±0,12
Amygdala	LH	0,12±0,01	0,13±0,02	0,61±0,01	0,51±0,05	4,37±0,80	4,63±0,57
	LC		0,14±0,02		0,64±0,05		4,68±0,29
	SH		0,11±0,01		0,62±0,05		3,79±0,33
Hypothalamus	LH	0,12±0,01	0,11±0,02	0,83±0,01	0,77±0,10	4,54±0,51	4,95±0,31
	LC		0,14±0,02		1,01±0,17		4,61±0,43
	SH		0,13±0,02		0,88±0,16		4,32±0,59
Thalamus	LH	0,05±0,01	0,05±0,01	0,28±0,02	0,24±0,04	1,59±0,24	1,27±0,19
	LC		0,04±0,01		0,21±0,03		1,07±0,21*
	SH		0,06±0,02		0,021±0,03		0,95±0,09*
Mesencephalic reticular formation	LH	0,04±0,002	0,05±0,001	0,24±0,002	0,24±0,002	1,33±0,23	1,29±0,15
	LC		0,04±0,001		0,18±0,03		0,94±0,05†
	SH		0,04±0,001		0,17±0,01		0,84±0,06†

*P < 0.05;
†P < 0.01.
‡P < 0.001.

Note. LH) Lithium hydroxybutyrate, LC) lithium chloride, SH) sodium hydroxybutyrate. Mean results of eight or nine determinations are shown.

amine content was determined by a spectrofluorometric method, which provided for removal of dopamine-like compounds [5, 6].

EXPERIMENTAL RESULTS

Lithium hydroxybutyrate and chloride in EEG-effective doses did not change the noradrenalin and adrenalin content in parts of the brain tested 1 h after injection (Table 1). The increase in the noradrenalin concentration in the thalamic region described by the writers previously [7] under the influence of lithium chloride was not confirmed.

Some workers consider that lithium ions may act directly on noradrenergic brain structures without any change in mediator level [13, 15, 16]. According to our own observations [10], lithium hydroxybutyrate and chloride inhibit the excitatory action of amphetamine, which liberates catecholamines from synaptic vesicles of nerve endings, on the CNS. Evidently, lithium salts have a normalizing action on noradrenergic mediation: On the one hand, they prevent activation of motor activity in mice by amphetamine, and, on the other, they inhibit the development of reserpine-induced hypothermia and ptosis.

The elective accumulation of dopamine in the caudate nucleus under the influence of lithium hydroxybutyrate and chloride (Table 1) is most interesting. This effect is evidently due mainly to Li^+, for lithium chloride, in the isoeffective (with regard to EEG) dose (11.5 mg/kg Li^+) caused an increase in the dopamine concentration in the caudate nucleus of up to 8.02 μg/g tissue, whereas the increase produced by lithium hydroxybutyrate (0.6 mg/kg Li^+) was only up to 4.47 μg/g tissue. Some central effects of GHBA are known to be accompanied also by the accumulation of dopamine in the corpus striatum [11, 14], but doses of GHBA of 0.5-1.5 g/kg are required for this purpose (in the present experiments the dose of sodium hydroxybutyrate was only 0.01 g/kg).

The fall in electrical excitability of the caudate nucleus of rabbits, described previously [8, 9], and potentiation of amphetamine stereotypy in rats produced by lithium salts [10] are evidently due to the accumulation of dopamine, which is the principal mediator in the nigro-striatal pathways [2], in the caudate nucleus. Dopamine inhibits activity of most neurons of the corpus striatum and mediates the restraining control of the nigro-striatal system on activity of the neostriatum. The antidepressive properties of lithium salts evidently also are realized through this mechanism, for endogenous depression may be the result of blockade of dopamine receptors or exhaustion of dopamine in the presynaptic endings of the nigro-striatal pathways [17].

How can it be explained that lithium hydroxybutyrate and chloride, in the doses we used, are isoeffective as regards depressing electrical excitability of the caudate nucleus, although the dopaminergic properties of lithium hydroxybutyrate are much weaker? The distinguishing feature of the central action of this substance, depending on the presence of the hydroxybutyrate anion in its molecule, is the depriming action of the compound on the motor cortex [9]. As a result of this property lithium hydroxybutyrate evidently depresses descending, activating corticofugal influences on the striatum [12], which ultimately potentiates the specific neurotropic activity of the compound.

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