EFFECT OF LITHIUM HYDROXYBUTYRATE ON SEROTONIN AND 5-HYDROXYINDOLEACETIC ACID LEVELS IN THE RABBIT BRAIN

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Serotoninergic mechanisms participate in the realization of the central effects of lithium [6-10]. Lithium hydroxybutyrate, which has a normothymic type of action [3], prevents the accumulation of serotonin in the rabbit brain caused by injection of 5-hydroxytryptophan (5-HTP) or stimulation of the dorsal nucleus raphe [4]. However, judging by the results of the writers' previous electroencephalographic investigations [3, 4], the lithium preparation differs in its effect on the serotoninergic system of the caudate nucleus if administered once only or over a long period of time. After a single injection, antagonism is observed with the action of serotonin on the caudatogram, whereas after administration of the drug for 8 days, synergism is observed.

The effect of lithium hydroxybutyrate was studied on the level of serotonin and its principal metabolite — 5-hydroxyindoleacetic acid (5-HIAA) in the brain of intact rabbits receiving serotonin in a single dose or over a long period of time (8, 15, and 29 days).

EXPERIMENTAL METHOD

Experiments were carried out on mature male rabbits weighing 2.5-2.8 kg in March and April. Lithium hydroxybutyrate, in a dose of 10 mg/kg daily, was injected intravenously (single dose) or intramuscularly (chronic experiments) in the form of a 0.1% aqueous solution. The control animals received injections of the corresponding volume of solvent. The animals were decapitated 1 h after the last injection of the drug and weighed samples of individual brain structures were quickly frozen at −10°C. The concentrations of serotonin and 5-HIAA were determined fluorometrically [1]. The numerical results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

The concentrations of serotonin and 5-HIAA in the brain of animals of the control group showed no significant change in the course of two months. The highest serotonin concentration was found in the hypothalamus and striatum, the highest 5-HIAA concentration in the midbrain and hypothalamus (Tables 1 and 2), in agreement with data in the literature [2].

The serotonin and 5-HIAA levels 1 h after injection of lithium hydroxybutyrate were statistically significantly lowered only in the striatum, evidence of inhibition of serotoninergic processes in that structure and, in particular, of inhibition of serotonin biosynthesis. The concentrations of serotonin and its metabolites was unchanged in the other brain formations.

After injection of lithium hydroxybutyrate daily for 8 days significant ($P < 0.05$) accumulation of serotonin was observed in the cortex (by 50%), striatum (by 54%), amygdala (by 45%), hypothalamus (by 16%), thalamus (by 38%), and midbrain (by 40%), with a simultaneous fall in the 5-HIAA concentration in all these formations (except the striatum and the thalamus), evidence of inhibition predominantly of serotonin metabolism.

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TABLE 1. Effect of Lithium Hydroxybutyrate on Serotonin Concentration (in μg/g Wet Weight of Tissue) in Rabbit Brain (M ± m)

Experimental conditions	Cortex	Striatum	Dorsal hippocampus	Amygdala	Hypothalamus	Thalamus	Midbrain
Control	0,31±0,02 (7)	0,79±0,04 (7)	0,44±0,3 (8)	0,52±0,04 (8)	0,81±0,03 (8)	0,44±0,03 (8)	0,61±0,04 (7)
Lithium hydroxybutyrate single intravenous injection	0,35±0,03 (5)	0,67±0,03** (5)	0,44±0,02 (5)	0,52±0,02 (5)	0,82±0,03 (5)	0,49±0,03 (5)	0,64±0,02 (5)
intramuscularly:							
7 days	0,47±0,04*	1,22±0,11*	0,53±0,06*	0,75±0,06*	0,94±0,05**	0,61±0,05*	0,86±0,08*
15 »	0,43±0,02* (5)	0,01±0,03* (5)	0,55±0,01* (5)	0,49±0,04 (5)	1,07±0,12** (5)	0,56±0,03* (5)	0,77±0,01* (5)
29 »	0,28±0,02 (7)	0,56±0,03* (7)	0,36±0,02** (7)	0,46±0,04 (7)	0,63±0,05* (7)	0,36±0,03** (7)	0,53±0,02** (7)

Legend. Here and in Table 2 number of animals given in parentheses; *P < 0.01, **P < 0.05.

TABLE 2. Effect of Lithium Hydroxybutyrate on 5-HIAA Concentration (in μg/g Wet Weight of Tissue) in Rabbit Brain (M ± m)

Experimental conditions	Cortex	Striatum	Dorsal hippocampus	Amygdala	Hypothalamus	Thalamus	Midbrain
Control	0,31±0,01 (8)	0,65±0,04 (7)	0,41±0,02 (8)	0,56±0,01 (8)	0,79±0,04 (7)	0,63±0,05 (7)	1,02±0,06 (7)
Lithium hydroxybutyrate: single intravenous injection	0,27±0,02 (5)	0,55±0,02** (5)	0,37±0,01 (5)	0,53±0,02 (5)	0,80±0,03 (5)	0,62±0,03 (5)	0,98±0,03 (5)
intramuscularly daily for							
7 days	0,25±0,02* (6)	0,75±0,06 (6)	0,37±0,03 (6)	0,48±0,04 (6)	0,67±0,04 (6)	0,59±0,02 (6)	0,78±0,08** (6)
15 »	0,43±0,01* (5)	0,88±0,3* (5)	0,54±0,02* (5)	0,61±0,02** (5)	0,92±0,03** (5)	0,70±0,03 (5)	0,98±0,03 (5)
29 »	0,23±0,02* (7)	0,39±0,01* (7)	0,41±0,02 (7)	0,50±0,02 (7)	0,61±0,04* (7)	0,63±0,05 (6)	0,83±0,05 (6)

Administration of lithium hydroxybutyrate for 15 days was accompanied by an increase in the serotonin concentration in the cortex, striatum, hippocampus, hypothalamus, thalamus, and midbrain, although the increase was smaller than after administration for 8 days. Meanwhile the 5-HIAA level rose considerably in all brain formations studied except the midbrain in which its concentration did not differ significantly from the control. Evidently in the course of injections of lithium hydroxybutyrate for a period of 2 weeks intensification of serotonin synthesis and breakdown is observed in the above-mentioned structures (except the midbrain), evidence of the more rapid turnover of the mediator.

After injections of lithium hydroxybutyrate for 4 weeks the serotonin level fell below the control value in the striatum, hippocampus, thalamus, and hypothalamus (by 19-28%). The 5-HIAA concentration also fell (by 13-40%) in the cortex, striatum, hypothalamus, and midbrain, indicating a depressant effect of the compound on serotoninergic processes in the brain.

A single injection and prolonged administration of lithium hydroxybutyrate are thus accompanied by dissimilar changes in serotonin metabolism in the brain. Whereas after a single dose of the compound inhibition of serotoninergic processes was observed only in the striatum, after injections over a period of 8 days accumulation of serotonin and inhibition of its metabolism in structures of the forebrain were noted. During administration of the compound for 15 days, a more rapid turnover of serotonin was observed in most formations tested. After administration of lithium hydroxybutyrate for 4 weeks serotoninergic processes were inhibited not only in the striatum (just as after a single dose), but also in the cortex, hippocampus, amygdala, thalamus, hypothalamus, and midbrain.

It will be easy to see that changes in serotonin metabolism in the striatum after injection of lithium hydroxybutyrate precde changes in synthesis and breakdown of serotonin

in other brain formations. The writers' previous electrophysiological investigations showed that the caudate nucleus is more sensitive to this compound [3, 4]. As we know, the caudate nucleus has powerful serotoninergic projections from the dorsal nucleus raphe [9]. A high concentration of the mediator and a considerable density of serotonin receptors are found in that structure, although no marked correlation could be found between these characteristics [2, 6]. Negative feedback is present between functional activity of the serotoninergic terminals and the nucleus raphe, and is realized through presynaptic serotonin autoreceptors [5].

By inducing primary inhibition of serotonin metabolism in the caudate nucleus, lithium hydroxybutyrate, in the case of more prolonged administration (8 days), evidently activates this feedback: synthesis of mediator is stimulated in serotoninergic neurons of the nuclei raphe, its transport toward the forebrain is intensified, and it accumulates in structures receiving an innervation from the dorsal nucleus raphe. Activity of the serotoninergic synapses of these formations is compensatorily intensified, and this is accompanied by increased breakdown of the mediator. This tendency was observed first in the caudate nucleus, but 15 days later in other parts of the brain also. This hypothesis is in agreement with weakening of the EEG changes evoked by stimulation of the dorsal nucleus raphe and by potentiation of these effects after administration of lithium hydroxybutyrate for 8 days, which we observed previously after a single injection of that compound. Activation of serotonin synthesis and breakdown in the terminals during a 15-day course of lithium hydroxybutyrate, evidently due to increased affinity in the mediator for the enzyme [8], caused inhibition of serotonin synthesis in neurons of the nucleus raphe and its transport toward the forebrain. As a result, by the 29th day the serotonin and 5-HIAA levels had started to fall in all the brain formations studied.

Prolonged administration of lithium hydroxybutyrate thus causes adaptive changes in the serotoninergic system, which is inhibited initially in the caudate nucleus, possibly through a selective reduction of synaptosomal trypophan uptake in that structure by the compound [13] or through reduced affinity of the receptors for serotonin [7, 12]. The possibility cannot be ruled out that this last effect itself can modify synaptosomal tryptophan uptake.

This phasic nature of serotonin metabolism during long-term administration of lithium hydroxybutyrate may evidently be accompanied by fluctuations of postsynaptic serotoninergic activity. In fact, single doses of lithium salts inhibit serotoninergic transmission, but long courses of lithium salts (5-10 days) may increase behavioral hypersensitivity to serotonin after administration of reserpine [14] or 5-HTP [10, 11] and after stimulation of the nucleus raphe [3].

When patients are treated with lithium hydroxybutyrate, the phasic nature of the action of the compound on serotoninergic processes, revealed by this investigation, must be taken into account.

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