skeletal muscles (Fig. 3). Unlike atenolol, propranolol caused a clear decrease in the blood supply to the heart. The change in the blood flow due to propranolol in the other vascular regions (including the kidneys and brain) was not statistically significant.

These data on the effect of propranolol on the regional hemodynamics in normotensive rats differ somewhat from results obtained in acute experiments on waking monkeys [4], but coincide almost completely with the results of experiments conducted on anesthetized normotensive and hypertensive rats during chronic administration of propranolol [5]. It was shown in the first investigation cited above that infusion of propranolol for 60 min leads to a decrease in the blood flow in the heart, kidneys, gastrointestinal tract, spleen, liver, and skeletal muscles proportional to the decrease in the cardiac output, but not in the brain. The second of the investigations cited, like the present experiments, showed that propranolol causes a greater decrease in the coronary and muscular blood flow than in the blood flow in other vascular regions. These differences in the effects of propranolol on the regional hemodynamics could be connected with differences in the experimental conditions (species of animals, effect of general anesthesia, etc.).

The results now obtained, showing a decrease in the coronary blood flow after administration of propranolol and in the renal blood flow in response to atenolol, accompanied by a negligible change in the corresponding fractions of the cardiac output are evidence that these effects of atenolol and propranolol are due to their influence on the vessels of the heart and kidneys. So far as the negligible effect of atenolol and propranolol, in the dose tested (0.5 mg/kg), on the blood supply to other vascular regions is concerned, this may be the result of a different functional role of β-adrenoreceptors in different vascular regions.

LITERATURE CITED

1. A. M. Barrett, Postgrad. Med. J., 33, Suppl. No. 3, 58 (1977).
2. B. J. Clar, in: Beta-Adrenoceptor Blocking Agents, Amsterdam (1976), pp. 45-78.
3. H. Flohr, H. W. Dahners, and W. Breull, Arzneimittel-Forsch., 25, 985 (1975).
4. A. S. Nies, G. H. Evans, and D. G. Shand, Am. Heart J., 85, 97 (1973).
5. K. Nishiyama, A. Nishiyama, M. A. Pfeiffer, et al., Blood Vessels, 15, 333 (1978).
6. A. M. Rudolph and M. A. Heimann, Circ. Res., 21, 163 (1967).

EFFECT OF LITHIUM HYDROXYBUTYRATE ON BRAIN SEROTONIN LEVEL IN INTACT RABBITS AND DURING HYPERACTIVITY OF CENTRAL SEROTONINERGIC SYSTEMS

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Lithium salts play an active role in central serotonin metabolism [17]. A decrease in the serotonin concentration has been demonstrated in the rat brain stem, midbrain, striatum, and hypothalamus during a course of lithium chloride [12] and carbonate [9]. Lithium prevents a rise in serotonin level caused by precursors of its synthesis, L-tryptophan and 5-hydroxytryptophan (5-HTP) [3], and increases the content of deaminated metabolic products of serotonin in the brain both of intact animals [15] and after electrical stimulation of the medial nucleus raphe in the midbrain [10].

The new original psychotropic agent lithium hydroxybutyrate [1] prevents amphetamine excitation [8] and 5-HTP- and nicotine-induced hyperkinesia [5], reduces electrical excitability of various subcortical structures

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TABLE 1. Effect of Lithium Hydroxybutyrate on Serotonin Concentration (μg/g wet weight of tissue) in Brain of Intact Rabbits and during Hyperactivity of Central Serotoninergic Systems (M ± m)

Experimental conditions	Cortex	Caudate nucleus	Dorsal hippocampus	Amygdala	Hypothalamus	Thalamus	Reticular formation
1. Control	0,14±0,086 (7)	0,60±0,043 (7)	0,22±0,018 (7)	0,51±0,046 (7)	0,77±0,049 (7)	0,32±0,018 (7)	0,47±0,026 (7)
2. Animals undergoing mock operation	0,13±0,07 (6)	0,62±0,046 (6)	0,21±0,018 (6)	0,52±0,086 (6)	0,75±0,043 (6)	0,32±0,08 (6)	0,49±0,020 (6)
3. Lithium hydroxybutyrate (10 mg/kg daily for 7 days)	0,17±0,018 (7)	0,41±0,016 (7) $P_{1-3}<0,001$	0,28±0,020 (7)	0,52±0,046 (7)	0,78±0,060 (7)	0,37±0,011 (7)	0,42±0,018 (7)
4. 5-HTP (50 mg/kg)	0,28±0,021 (8) $P_{1-4}<0,001$	1,65±0,08 (8) $P_{1-4}<0,001$	0,42±0,017 (8) $P_{1-4}<0,001$	0,98±0,076 (8) $P_{1-4}<0,001$	1,34±0,054 (8) $P_{1-4}<0,001$	0,65±0,026 (8) $P_{1-4}<0,001$	0,79±0,045 (8) $P_{1-4}<0,001$
5. Stimulation of dorsal nucleus raphe (10-20 Hz, 1 h)	0,28±0,018 (6) $P_{2-5}<0,001$	0,98±0,094 (6) $P_{2-5}<0,05$	0,37±0,016 (6) $P_{2-5}<0,05$	0,64±0,065 (6)	0,76±0,065 (6)	0,50±0,032 (6) $P_{2-5}<0,001$	0,52±0,032 (6)
6. Lithium hydroxybutyrate + 5-HTP	0,20±0,009 (6) $P_{1-6}<0,05$ $P_{1-6}<0,005$	0,75±0,067 (6) $P_{1-6}<0,05$ $P_{1-6}<0,005$	0,24±0,028 (6) $P_{4-6}<0,05$	0,49±0,121 (6) $P_{1-6}<0,05$ $P_{4-6}<0,005$	0,97±0,018 (6) $P_{1-6}<0,05$ $P_{4-6}<0,005$	0,37±0,018 (6) $P_{1-6}<0,005$	0,46±0,036 (6) $P_{4-6}<0,005$
7. Lithium hydroxybuturate + stimulation of nucleus raphe	0,16±0,009 (7) $P_{5-7}<0,005$	0,39±0,017 (7) $P_{2-7}<0,001$ $P_{5-7}<0,005$	0,19±0,018 (7) $P_{5-7}<0,005$	0,36±0,021 (7) $P_{2-7}<0,001$ $P_{5-7}<0,005$	0,55±0,049 (7) $P_{2-7}<0,001$ $P_{5-7}<0,005$	0,31±0,022 (7) $P_{5-7}<0,005$	0,42±0,028 (7) $P_{5-7}<0,005$

Legend. Number of experiments shown in parentheses.

of the rabbit brain [6], does not affect the brain noradrenalin content, but considerably increases the dopamine concentration in the caudate nucleus [7].

Arising from modern views on the possible role of serotonin in the pathogenesis of mental disorders and also in the mechanisms of the psychotropic activity of lithium salts, it was decided to study the effect of lithium hydroxybutyrate on the serotonin concentration in the brain of intact rabbits and during hyperactivation of central serotoninergic systems. This latter condition was achieved either by injecting the serotonin precursor 5-HTP or by stimulating the dorsal nucleus raphe in the midbrain.

EXPERIMENTAL METHOD

Experiments were carried out on 64 rabbits of both sexes weighing 2-2.5 kg. Lithium hydroxybutyrate was injected subcutaneously in a dose of 10 mg/kg [6] daily for 1 week. On the 8th day, 1 h after injection of the drug, the animals were decapitated. Distilled water was injected in control experiments.

Electrical stimulation of the dorsal nucleus raphe or intraperitoneal injection of 5-HTP (50 mg/kg) was carried out 30 min before decapitation. Stimulation was given through chronically implanted electrodes [14] by square pulses with a frequency of 10-20 Hz for 1 h [13]. Behavioral correlates of electrical stimulation were recorded in the animals. Animals undergoing mock operations served as the control for this series of experiments.

Weighed samples of the brain were quickly frozen. Serotonin was determined by the ninhydrin method [16] on a spectrofluorometer with sensitivity of 1×10^{-8} g/ml. In each series six to eight rabbits were used.

EXPERIMENTAL RESULTS

The serotonin concentration in the brain of the intact rabbits varied from 0.14 μg/g in the cortex to 0.77 μg/g in the hypothalamus (Table 1), in agreement with data in the literature [4]. Chronic administration of lithium hydroxybutyrate for 7 days did not change the serotonin concentration in the amygdala, dorsal hippocampus, posterior hypothalamus, cortex, or reticular formation. However, the compound selectively depressed the serotonin level in the caudate nucleus (by 32.7%; $P < 0.001$).

Considering that the strongest effect of lithium on the serotoninergic systems of the brain is observed during hyperactivity of these systems [10], the effect of lithium hydroxybutyrate on the serotonin concentration was investigated during 5-HTP loading and stimulation of the dorsal nucleus raphe.

Intraperitoneal injection of 5-HTP was accompanied by accumulation of serotonin in the brain, due to increased synthesis of the mediator. The greatest increase in its concentration under these conditions was found in the caudate nucleus (by 175%; $P < 0.001$), the least in the reticular formation (by 68%; $P < 0.001$).

Lithium hydroxybutyrate prevented the increase in the serotonin level induced by injection of its precursor. The results are in good agreement with data in the literature on the effect of other lithium salts on elevation of the serotonin level [3].

Considering the imperfect nature of the technique of creating hyperactivity of serotoninergic systems of the brain through injecting 5-HTP [4], it was decided to use electrical stimulation of the dorsal nucleus raphe in the midbrain [13]. Depending on the parameters of stimulation applied, this technique enables the serotonin turnover to be considerably quickened, with an increase or a decrease in its concentration, but always with a fall in the 5-hydroxyindoleacetic acid level in the forebrain [11].

Electrical stimulation caused no special abnormalities in the animals' behavior. However, general inhibition of motor activity predominated, as reflected in inhibition of investigative behavior, postural "freezing," and increased tension. The serotonin concentration was raised in the cortex, caudate nucleus, and thalamus and to a lesser degree in the hippocampus, a result which corresponds to projections of the dorsal nuclei raphe to the forebrain [11].

Lithium hydroxybutyrate not only prevented accumulation of the mediator due to electrical stimulation of the nucleus raphe, but also depressed its level relative to the control values (by 10-30%; $P < 0.05$); in the caudate nucleus its level was almost halved ($P < 0.001$).

Lithium hydroxybutyrate thus reduces the serotonin concentration only in the caudate nucleus, inhibits an increase in its concentration in all deep brain formations of rabbits during 5-HTP loading, and reverses the serotonin-positive action of electrical stimulation of the dorsal nucleus raphe.

The fall in the serotonin level observed in the caudate nucleus during chronic administration of lithium hydroxybutyrate and its preventive effect against accumulation of serotonin in several brain structures can evidently be attributed to the more rapid breakdown of the mediator either through activation by lithium or monoamine oxidase [2] or through intensification of its reuptake [10]. However, the probable inhibition of serotonin synthesis by lithium hydroxybutyrate likewise cannot be ignored [9]. Evidently chronic administration of lithium affects small stages of serotonin turnover, not only individual stages of this process.

The selective reduction in the serotonin content in the caudate nucleus revealed by these experiments is noteworthy. The striatum is one of the most sensitive structures to the action of lithium [6]. It is in the caudate nucleus that serotonin increases the dopamine concentration [7] without any significant effect on its concentration elsewhere in the brain. Dopamine and serotonin behave in the striatum as functional antagonists. It may be that the specific cytotropic action of lithium hydroxybutyrate is due to some extent to its interference in the complex relationships between these systems at the level of the caudate nucleus.

LITERATURE CITED

1. A. P. Arendaruk, A. P. Skoldinov, V. V. Zakusov, et al., Inventor's Certificate No. 552094 (USSR).
2. I. P. Kiseleva, Vopr. Med. Khim., No. 5, 502 (1972).
3. G. F. Oksenkrug, in: Serotoninergic Processes in the Action of Psychotropic Drugs [in Russian], Leningrad (1970), p. 68.
4. N. K. Popova, E. V. Naumenko, and V. G. Kolpakova, Serotonin and Behavior [in Russian], Novosibirsk (1978).
5. A. S. Saratikov, L. P. Alekseeva, V. P. Agarkova, et al., in: Neuromediators and Mechanisms of Action of Neurotropic and Cardiovascular Drugs [in Russian], Moscow (1979), p. 19.
6. A. S. Saratikov, L. P. Alekseeva, V. P. Agarkova, et al., Farmakol. Toksikol., No. 4, 353 (1980).
7. A. S. Saratikov, L. P. Alekseeva, V. P. Agarkova, et al.., Byull. Éksp. Biol. Med., No. 10, 442 (1980).
8. A. S. Saratikov, T. A. Zamoshchina, L. P. Alekseeva, et al., Byull. Éksp. Biol. Med., No. 7, 46 (1982).
9. P. Ahlywalia and R. L. Singhal, Br. J. Pharmacol., 71, 601 (1980).
10. K. J. Collard, Br. J. Pharmacol., 62, 137 (1978).
11. A. Ho, H. Loh, F. Craves, et al., Eur. J. Pharmacol., 10, 72 (1970).
12. W. Kostowski, E. Gialcalone, S. Garattini, et al., Eur. J. Pharmacol., 7, 170 (1969).
13. C. Sawyer, S. Everett, and J. Green, J. Comp. Neurol., 10, 801 (1954).
14. J. Schildcraut, Am. J. Psychiat., 122, 509 (1965).
15. S. Snyder, J. Axelrod, and M. Zweig, Biochem. Pharmacol., 14, 831 (1965).
16. A. Swann, G. Heinger, et al., Life Sci., 28, 347 (1981).