COMBINED ACTION OF LITHIUM SALTS AND SEROTONIN ON THE CAUDATE NUCLEUS

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Besides dopamine, acetylcholine, and γ-aminobutyric acid, the caudate nucleus also contains a high concentration of serotonin, but no serotonin-containing neurons have been discovered. The principal serotoninergic terminals to the caudate nucleus (CN) run in the composition of the medial lemniscus from the dorsal nucleus raphe, stimulation of which induces liberation of the transmitter in CN [11-13]. CN is highly sensitive to many psychotropic drugs, including lithium salts. According to our data, systematic administration of serotonin and its direct injection into the nucleus depress excitability of the head of CN during high-frequency stimulation considerably. Accumulation of dopamine and a fall in the serotonin concentration in CN are observed whereas their levels in other parts of the brain are relatively stable. The compound inhibits the rise of the serotonin concentration in CN after loading with 5-hydroxytryptophan (5-HTP) and reverses the serotonin-positive action of electrical stimulation of the dorsal mesencephalic nucleus raphe [4, 6, 7].

In the investigation described below the character of interaction between lithium hydroxybutyrate and serotonin was investigated at the CN level.

EXPERIMENTAL METHOD

Experiments were carried out on 25 Chinchilla rabbits weighing 2.7-3.5 kg with nichrome electrodes chronically implanted into the dorsal mesencephalic nucleus raphe and into the dorsal segment of the head of CN [15]. In some experiments, a chemical electrode was inserted into CN. The animals were kept under ordinary conditions of alternation of light and darkness and on a standard diet.

The electroencephalogram (EEG) was recorded on an eight-channel "Orion" encephalograph (Finland) with band frequency analyzers and energy integrators for the δ-, ϑ-, α-, β_1-, β_2-, and γ-bands, by the method described previously [5]. The electrographic manifestation of increased activity of the head of the caudate nucleus is a low-frequency δ-rhythm [8].

Intracaudate injections of lithium hydroxybutyrate (5 μg), lithium chloride (50 μg), and serotonin creatine-sulfate (from Gee Lawson Chemicals) (5 μg) were given by means of a special microinjector, in 5 μl of bidistilled water (pH 7.0). Lithium salts were injected 10 min before serotonin. The EEG was analyzed 10-15 min after microinjection of serotonin. In experiments to study changes in electrogenesis in the caudate nucleus during systemic administration of lithium hydroxybutyrate and electrical stimulation of the dorsal nucleus raphe, the compound was injected intravenously in a single dose of 10 mg/kg, 5-10 min before, or in daily injections for 1 week (the last injection 5-10 min before) stimulation of the nucleus raphe. The latter was stimulated electrically by square pulses with a frequency of 10-20 Hz and voltage 3-6 V for 50 min. Electrical activity of the caudate nucleus was analyzed 5-10 min after the end of stimulation.

The character of interaction of lithium salts and serotonin was assessed by Webb's equation [9]:

$$Iab = Ia + Ib - (Ia \cdot Ib),$$

where $I = 1 - (K_c/K_e)$; I denotes the intensity of the effect when each drug is used separately and in combination; K_c and K_e denote absolute values of the index in the control and experiment respectively. During addition of the agent $Iab = Ia + Ib - (Ia \cdot Ib)$, during antagonism $Iab < Ia + Ib - (Ia \cdot Ib)$, and during potentiation $Iab > Ia + Ib - (Ia \cdot Ib)$.

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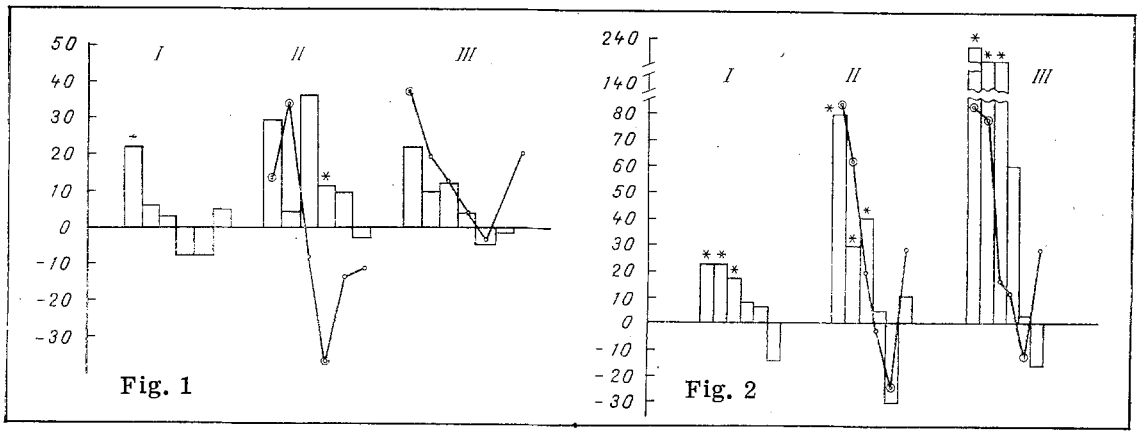

Fig. 1. Effect of combined action of lithium salts and serotonin on electrogenesis in CN (in %). I) Serotonin; II) serotonin + lithium hydroxybutyrate, line with circles – lithium hydroxybutyrate per se; III) serotonin + lithium chloride, line with circles – lithium chloride per se. Columns from left to right: δ-, ϑ-, α-, β_1-, β_2- and γ-rhythms. $P < 0.05$ compared with initial background.

Fig. 2. Effect of combined action of stimulation of dorsal nucleus raphe and lithium hydroxybutyrate on electrogenesis in caudate nucleus (in %). I) Stimulation of dorsal nucleus raphe; II) stimulation with sodium hydroxybutyrate (single dose), line with circles – lithium hydroxybutyrate per se; III) stimulation with lithium hydroxybutyrate (7 days), line with circles – lithium hydroxybutyrate per se. Remainder of legend as to Fig. 1.

EXPERIMENTAL RESULTS

Injection of serotonin directly into the caudate nucleus was accompanied by increased power in the δ-band (by 22%, $P < 0.05$) and by inhibition (not significant) of the β_1-frequency band in the EEG recorded from CN (Fig. 1). Electrical stimulation of the dorsal nucleus raphe caused more marked changes in electrogenesis in CN: besides an increase in power of the δ-rhythm (by 22%, $P < 0.05$) the number of ϑ- and α-waves also increased by 21 and 16% respectively ($P < 0.05$, Fig. 2).

Microinjections of lithium hydroxybutyrate per os into CN increased the energies of the ϑ-band (by 35%, $P < 0.05$), but depressed the power of the β-rhythm (by 36%, $P < 0.05$; Fig. 1). More marked changes were found in the spectrum of the caudate EEG after systemic administration of a single dose: The power of the δ- and ϑ-components was increased by 130% and 65% respectively ($P < 0.05$), whereas that of the β_2-rhythm was reduced (by 25%, $P < 0.05$). However, after administration of lithium hydroxybutyrate for 7 days, its action on CN weakened (Fig. 2). Injection of lithium chloride into CN was accompanied by a significant increase in energy of δ-activity only (by 35%, $P < 0.05$, Fig. 1).

Integral analysis of the electroencephalogram recorded from CN thus indicates that serotonin, lithium salts, and stimulation of the nuclei raphe have concordant effects on the power characteristics of the frequency bands of the electrocaudatogram: an increase in the abundance of low frequencies and a decrease in that of high. However, lithium hydroxybutyrate (5 μg) had a stronger action on the caudate nucleus than lithium chloride (50 μg), and it was evidently this which was responsible for the greater shifts in electrical excitability of CN under the influence of hydroxybutyrate [4]. Prolonged electrical stimulation of the nuclei raphe similarly was more effective than microinjections of 5 μg serotonin. The writers showed previously that stimulation of the dorsal nucleus raphe leads to accumulation of large quantities of mediator in the structure [7].

Electrical stimulation of the nuclei raphe, against the background of intravenous injection of lithium hydroxybutyrate, in a single dose of 10 mg/kg or daily for 7 days, was accompanied by an increase in power of all the low-frequency bands and depression of the β_2-rhythm.

Combined injections of 5 μg of lithium hydroxybutyrate and 5 μg serotonin into CN caused an increase in power of both low-frequency (δ and α) and high-frequency (β_1) components of the spectrum of the electrocaudatogram (Fig. 1), but statistically significant changes were discovered only for energies of the β_1-band. No significant changes were found in the EEG of CN as a result of combined microinjections of 50 μg lithium chloride and serotonin, only a tendency toward strengthening of low-frequency rhythms.

TABLE 1. Character of Interaction of Lithium Salts and Serotonin in Caudate Nucleus (by Webb's method)

Preparations	EEG rhythms					
	δ	ϑ	α	β_1	β_2	γ
Serotonin + lithium hydroxybutyrate	—	—	+	—	—	—
Serotonin + lithium chloride	—	—	+	—	—	—
Stimulation of nucleus raphe + lithium hydroxybutyrate (single injection)	—	—	+	—	—	+
Stimulation of nucleus raphe + lithium hydroxybutyrate (7 days)	+	+	+	+	—	+

Consequently, under the combined influence of lithium salts and serotonin (or during stimulation of the nuclei raphe) on the frequency characteristics of the EEG recorded from CN a tendency remained for the power of the low-frequency bands to increase and that of the high-frequency bands to decrease. The exception was a series of experiments with combined injection of serotonin and lithium hydroxybutyrate into CN, when, although the pattern described above was preserved with respect to low frequencies, strengthening of the β_1-wave ($P < 0.05$) and the β_2-wave ($0.1 > P > 0.05$) was observed.

Taking into account the data described above on the functional importance of individual rhythms of the electrocaudatogram, it can be tentatively suggested that the action of lithium salts and serotonin, whether separately or combined, on the caudate nucleus leads to manifestation of its inhibitory properties. Stimulation of the nuclei raphe or injection of serotonin into CN, by limiting activity of dopamine neurons [10, 14], evidently disinhibit the activity of cholinergic neurons in CN and potentiate its functional activity [3].

Analysis of the experimental data by Webb's method demonstrates the existence of antagonistic relations between the effects of serotonin and lithium salts on parameters of the electrocaudatogram when only a single dose of lithium was injected (Table 1). Injection of lithium hydroxybutyrate and serotonin into CN was accompanied actually by weakening of functional activity of the nucleus (Fig. 1). The γ-hydroxybutyrate ion evidently makes a definite contribution to the serotonin-negative action of lithium hydroxybutyrate. Meanwhile, by Webb's method it was possible to detect synergism between the effect of long-term injection of hydroxybutyrate and stimulation of the nuclei raphe on the frequency components of the electrocaudatogram. A single dose of lithium hydroxybutyrate, interacting with the serotoninergic structures of CN, evidently prevents their reaction with serotonin. In the case of long-term administration of the compound hypersensitivity of the serotonin receptors can perhaps develop.

Lithium hydroxybutyrate thus exerts a serotonin-like action on the power characteristics of the frequency bands of the electrocaudatogram. However, if given in a single dose, lithium hydroxybutyrate is an antagonist of serotonin at the caudate nucleus level, whereas if given over a long period of time, on the contrary, it potentiates the effect of serotonin.

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