Comparative Analysis of Brain Electric Activity after Intraventricular Administration of GABA and Glutamate: It There Any Correlation between Specific Neurochemical Modifications in the Brain and EEG Changes?

A. V. Yarkov, V. V. Gal'chenko, and G. I. Kovalev

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 124, No. 8, pp. 174-177, August, 1997
Original article submitted April 10, 1996

GABA, L-glutamate, and sodium hydroxybutyrate cause a decrease in the EEG power in the 7-12 Hz range. The latency of this decrease is 6-7 min after administration of GABA and 14-15 min after administration of L-glutamate. D-Glutamate induces no changes in this range. It is suggested that modifications of EEG observed after administration of L-glutamate reflect metabolic transformations of GABA.

Key Words: *GABA; D- and L-glutamate; sodium hydroxybutyrate; brain; intraventricular administration; EEG*

Previously, we showed that GABAergic systems are involved in formation and/or modulation of the total electric activity of the brain. The agonists of GABA-ergic receptors lower the EEG power in the 5-17 Hz range. This effects is not generalized; it is observed in narrow (1-2 Hz) bands. For the θ-rhythm the most stable changes occur in the 6-7 Hz range, for the α-rhythm in the 10-12 Hz range [6,7]. The effects of metabolic interactions between neurotransmitters on the integrative brain functions, specifically, on EEG, practically have not been investigated. In the present study we explore the possibility of correlation between specific neurochemical modifications in the brain and EEG after administration of GABA and L-glutamate. Being metabolically related (glutamate is the precursor of GABA), these compounds produce different biological effects [1,2]. We compared changes in EEG caused by GABA and L-glutamate with those caused by D-glutamate, a metabolically inactive glutamate isomer recognized by receptors [9]. In order to confirm our hypothesis that EEG changes are of metabolic nature, it was necessary to analyze EEG changes caused by compounds metabolically shunted to GABA, of example, GHBA. Conversion of these compounds into each other according to concentration gradient has been demonstrated *in vivo* [3,4].

Laboratory of Functional Neurochemistry, Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences, Pushchino; Laboratory of Medical Biophysics, Institute of Cell Biophysics, Russian Academy of Sciences, Pushchino; Laboratory of Radioisotope Methods, Institute of Pharmacology, Russian Academy of Medical Sciences, Moscow

MATERIALS AND METHODS

Experiments were performed on 16 conscious unrestrained male Wistar rats (300-350 g) with chronically implanted intraventricular cannula and electrodes in the cortex and profound structures. Implantation was carried out under anesthesia using a modified stereotaxic Meshchersky's apparatus and atlas of rat brain [10]. Electrical activity of the following structures was measured in the resting state:

0007-4888/97/0008-0776$18.00

the cortex (Isocortex), putamen, hypothalamus, and hippocampus. In this paper we analyze changes occurring in electrical activity of the cortex.

Cortical electrode was located above the cortex (P=8.3, L=-4.9 epidurally), and reference electrode was located above nasal cavities. The cannula had the following coordinates: P=0.4, L=3.2, H=3.7, α=20°. Test compound was injected intraventricularly using a 10-μl microsyringe.

GABA and L- and D-glutamate were administered in the lateral brain ventricle in doses 10^{-6} and 10^{-7} M per animal, respectively, injection volume being 6 μl. These doses were chosen on the basis of our previous results [8].

The effects of sodium hydroxybutyrate (800 mg/kg intraperitoneally), an analog of GABA readily crossing the blood-brain barrier, on EEG were examined in a separate series of experiments on 11 rats [4].

Control rats were administered the same volume of 0.1% NaCl via the same route.

The experiment was designed according to the recommendations [12]. EEG was recorded 1 min after administration of test compound and processed in a MicroVax computer using modified periodogram analysis. Consecutive 15-sec EEG segments were analyzed. The total amplitudes of rhythms in each studied subrange and ratios to the total amplitude of all analyzed frequencies in the given EEG range were calculated. Using original software, we performed averaging of individual frequency spectra, determined confidence intervals, and compared the averaged spectra, calculating the significance of differences between them (%) by Student's t test ($p<0.05$). All calculations were described in detail in our previous works [6-8].

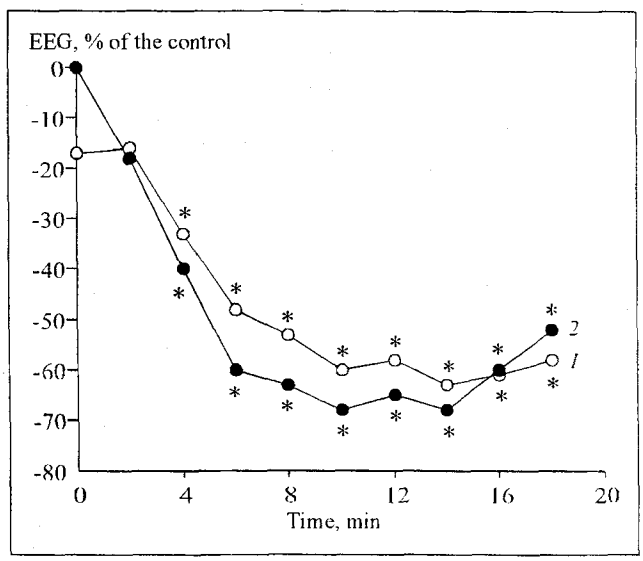

Fig. 1. Time course of frequency components of the EEG spectrum recorded from rat brain cortex after intraperitoneal administration of sodium hydroxybutyrate. *1*) 7 Hz; *2*) 12 Hz; *$p<0.05$ compared with the control.

RESULTS

Analysis of EEG spectrum in the 1-25 Hz range after administration of GABA revealed the most stable changes (a decrease in the rhythm power) in the

TABLE 1. Typical Effects of GABA (10^{-6} M) on Rat Brain Cortex

Time, min	Range, Hz										
	5	6	7	8	9	10	11.5	13	16	20	26
2	-2	8	-8	18	2	-8	-4	6	12	-6	-6
4	-5	2	-30*	3	-1	-5	-18	1	15	-7	-5
6	10	1	-7	13	0	-4	-9	4	4	-2	-1
8	1	8	-36*	3	-2	-37*	-19	9	19	0	2
10	15	26*	-27	2	-4	-35*	-30*	-2	14	0	34
12	13	23*	-20	9	-6	-39*	-29*	0	1	-13	0
14	4	4	-26	8	-3	-20	-24*	2	17*	-1	2
16	2	1	-16	0	-8	-22	-24*	1	9	-2	0
18	1	7	-12	14	0	-4	-1	5	20*	-2	1
20	13	36*	0	31*	-2	-18	-22*	1	19*	0	9
22	1	13	-16	1	-1	-4	-2	23*	29*	0	2
24	1	33*	-29*	15	2	-32*	-13	2	10	5	20
26	10	28	0	25	-1	-12	-25*	-4	0	0	-1

Note. The values are the means of determinations performed in 5 rats. Here and in Tables 2 and 3: changes are presented as the difference (%) between averaged spectra in experiment and control. Positive values indicate potentiating and negative values indicate suppression of rhythms of analyzed frequencies; *$p<0.05$ compared with the control.

TABLE 2. Typical Effects of L-Glutamate (10^{-7} M) on Rat Cortex

Time, min	Range, Hz								
	7	8	9	10	11.5	13	16	20	26
2	1	8	0	-2	0	-1	-1	-27*	-14
4	-6	18	1	-22	-22	-3	-1	-34*	-23*
6	-15	6	6	5	-16	2	6	-33*	-31*
8	-35*	10	0	-4	-7	2	12	-33*	-24*
10	-3	18	0	-4	-4	26*	24*	-37*	-25*
12	-21	32	5	0	5	6	20	-29	-28
14	-6	7	0	-29	-29*	-2	5	-20	-2
16	-6	12	-1	-7	-28*	1	11	-3	0
18	-39*	0	-6	-6	-23	6	10	-33*	-7
20	-38*	0	-2	-6	-10	-4	-1	-16	-9
22	-33*	4	-1	-36*	-20	0	0	-11	0
24	-16	1	-2	-37*	-33*	-14	-2	-37*	-8
26	-20	2	-10	-19	-31*	-1	0	-28	-4
28	-46*	8	-12	-12	-28	-15	-1	-51*	-44*

Note. Here and in Table 3: the values are the means of determinations performed in 3 rats.

TABLE 3. Typical Effects of D-Glutamate (10^{-7} M) on Rat Cortex

Time, min	Range, Hz								
	7	8	9	10	11.5	13	16	20	26
2	0	-2	-1	0	-3	0	4	13	12
4	0	16	0	-4	-5	0	-1	0	-1
6	1	-9	0	-1	0	9	4	-2	0
8	-3	0	1	14	6	0	0	0	-10
10	0	18	22*	0	18	17*	0	-3	-13
12	-5	-2	0	0	1	-4	-21*	-35*	-53*
14	-16	0	0	1	0	-5	-19	-36*	-51*
16	-8	-1	1	0	1	0	-28*	-44*	-64*
18	-2	-20*	2	0	-4	-19*	-31*	-53*	-66*
20	-1	0	-1	-23*	-7	-23*	-34*	-47*	-64*
22	1	1	17	2	2	-2	-25*	-40*	-60*
24	-10	1	-8	1	-3	-18*	-25*	-35*	-52*
26	-1	-6	-2	0	-1	0	-6	-33*	-49*
28	1	1	2	5	1	-9	-26*	-44*	-52*

narrow frequency ranges: 7, 10, and 12 Hz starting from the 6th minute after administration (Table 1).

Similar effects were observed in the 7, 10, and 12 Hz ranges 12-14 min and in the 20-26 Hz range 1 min after administration of L-glutamate (Table 2).

D-Glutamate caused a greater decrease in the spectrum power than L-glutamate only in the high-frequency range 10 min after administration (Table 3).

After administration of sodium hydroxybutyrate (800 mg/kg), an increase in the power of the low-frequency component [7] coincided with a decrease in the 5-12 Hz range (Fig. 1). GABA and L-glutamate caused a similar narrow-band decrease in the 7-12 Hz range. This effect was not observed after administration of D-glutamate. The latencies of GABA- and L-glutamate induced changes in the α-range were 6-7 and 14-15 min, respectively. L-Glutamate reduced the rhythm power in the high-frequency range (20-26 Hz) 1-2 min after administration, while D-glutamate produced a stronger effect in this range

after 10-11 min. Systemic administration of sodium hydroxybutyrate enhanced the low-frequency component and suppressed the power of α-rhythm, which was typical of GABA. It can be hypothesized that similar changes in the 7-12 Hz range caused by GABA and L-glutamate, compounds producing physiologically different effects, reflect the glutamate—GABA transitions [4]. Presumably, these effects are formed during interaction of GABA with the receptors: first, exogenous GABA, and then *de novo* synthesized GABA from exogenous L-glutamate. This hypothesis is supported by the absence of changes in the 7-12 Hz range after administration of D-glutamate (D-glutamate exhibits receptor but not metabolic activity [9]) and 8 min longer latency of changes in this range after administration of L-glutamate in comparison with GABA. This latency is consistent with the time required for such transformations [11]. On the other hand, administration of both D- and L-glutamate modifies the high-frequency range, the latency of the L-glutamate effect being 1-2 min. Thus, it is reasonable to suggest that changes in the high-frequency range are characteristic of glutamate. So far, the causes of the longer latency for the effect of D-glutamate remain unclear; specific interactions of D-glutamate receptors may be one of them. Sodium hydroxybutyrate-induced decrease in spectrum power in the α-range is similar to changes observed in this range after administration of GABA. This may reflect the GHBA—GABA transition according to the concentration gradient. Our results agree with sedative and electrophysiological effects observed after administration of glutamine, a precursor of glutamate [11]. Thus, our findings indicate that specific metabolic transformations in the brain correlate with EEG modifications caused by GABA and glutamate.

REFERENCES

1. S. A. Dambinova, *Itogi Nauki Tekhniki, Ser. Fiziologiya Cheloveka Zhivotnykh* [in Russian], Vol. 36, Moscow (1989), pp. 32-52.
2. I. V. Komissarov, *Mechanisms of Chemical Sensitivity of Synaptic Membranes* [in Russian], Kiev (1986).
3. R. U. Ostrovskaya, "Neuropharmacology of GABA shunt," Author's Synopsis of Doct. Med. Sci. Dissertation [in Russian], Moscow (1977).
4. K. S. Raevskii and V. Georgiev, *Transmitter Amino Acids: Neuropharmacological and Neurochemical Aspects* [in Russian], Moscow - Sofia (1986).
5. V. Yu. Urbakh, *Biometric Methods* [in Russian], Moscow (1964).
6. A. V. Yarkov, V. V. Vorob'ev, A. A. Gal'chenko, and G. I. Kovalev, *Fiziol. Zh. SSSR*, **75**, No. 10, 1677-1685 (1989).
7. A. V. Yarkov, V. V. Vorob'ev, and G. I. Kovalev, *Ibid.*, **77**, No. 11, 12-20 (1991).
8. A. V. Yarkov, G. I. Kovalev, and A. A. Gal'chenko, *Zh. Eksp. Klin. Farmakol.*, **57**, No. 4, 6-11 (1994).
9. H. McLennan, T. P. Hiks, and J. G. Hall, in: *Amino Acid Neurotransmitters*, F. V. DeFeudis and P. Mandel (Eds.), New York (1981).
10. L. J. Pellegrino, A. S. Pellegrino, and A. J. Cushman, *A Stereotaxic Atlas of the Rat Brain*, New York (1979).
11. D. Rotiroti, F. Naccari, G. B. De Sarro, *et al.*, *Res. Commun. Psychol. Psychiat. Behav.*, **6**, No. 3, 241-250 (1981).
12. A. Routtenberg, *Behav. Biol.*, **7**, No. 5, 601-641 (1972).