ance of mediator activity in the CNS [4, 6, 12], and with retention of Na^+ in the neurons and their swelling. The inhibitory action of digoxin in a dose of 0.12 μg/g, on the other hand, may perhaps be explained by the activating effect of small doses of glycosides on the Na^+, K^+-pump [5].

The results of this investigation show the danger of use of cardiac glycosides (especially lipophilic) in patients with epilepsy, for they may provoke fits. Moreover, in this pathology the permeability of the BBB is increased, which facilitates possible central effects of glycosides.

LITERATURE CITED

1. R. G. Biniaurishvili, A. M. Vein, B. G. Gafurov, and A. R. Rakhimdzhanov, Epilepsy and the Functional State of the Brain [in Russian], Tashkent (1985).
2. E. V. Gubler, Computerized Methods of Analysis and Diagnosis of Pathological Processes [in Russian], Leningrad (1978), pp. 72-75.
3. T. Godfraind and L. D. Tona, Eur. J. Pharmacol., 60, No. 4, 329 (1979).
4. K. J. Collard and S. R. Williams, Biochem. Soc. Trans., 9, No. 1, 109 (1981).
5. T. J. Hougen, N. Spicer, and T. W. Smith, J. Clin. Invest., 68, No. 5, 1207 (1981).
6. T. Katsuragi and T. Furukawa, Arch. Int. Pharmocodyn., 238, No. 1, 4 (1979).
7. M. Kemali and V. Braitenberg, Atlas of the Frog's Brain, Berlin (1969), pp. 57-65.
8. R. H. Kennedy, T. Akera, and T. M. Brody, Eur. J. Pharmacol., 89, No. 3-4 (1983).
9. J. Kuhlmann, E. Erdmann, and N. Rietbrock, Naynyn-Schmiederbergs Arch. Pharmakol., 307, No. 1, 65 (1979).
10. F. S. La Bella, Trends Pharmacol. Sci., 3, No. 9, 354 (1982).
11. L. Matos, M. Istfanffy, R. M. Halmagyi, et al., Ergebn. Exp. Med., 37, 51 (1980).
12. Y. Nakazato, S. Ito, and A. Ohga, Eur. J. Pharmacol., 89, No. 1-2, 77 (1983).
13. A. C. Swann, Eur. J. Pharmacol., 119, No. 1-2, 67 (1985).

ROLE OF THE GABA-ERGIC SYSTEM IN THE MECHANISM OF THE STRESS-REGULATING ACTION OF FENIBUT

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UDC 615.214.22:547.466.3].015.4

KEY WORDS: GABA-ergic system; stress; fenibut*

An important stage in the mechanisms of emergency adaptation to extremal influence is "activation" of the adaptive function of the GABA-ergic inhibitory system of the brain [1, 2, 7, 12]. In the modern view, fenibut is a GABA-positive agent [10]. Meanwhile, it has been shown that fenibut, in relatively small doses (1-25 mg/kg) increases the resistance of animals to the action of various external factors, exerts a stress-regulating influence [3, 4], and protects the myocardium against stress-induced injury [5].

The aim of this investigation was to study the effect of fenibut on activity of GABA-system under normal and stress conditions. For this purpose concentrations of GABA and glutamic acid (GA) and activity of enzymes of GABA metabolism, namely glutamate decarboxylase (GDC) and GABA-transaminase (GABA-T) were studied in the rat thalamus and hypothalamus. The intensity of the stress reaction was determined by measuring the peripheral blood plasma levels of 17-hydroxycorticosteroids (17-HCS) and glucose — parameters closely linked with the intensity and duration of action of the stress factor [14].

EXPERIMENTAL METHOD

Experiments were carried out on 75 noninbred male albino rats weighing 120-170 g. The

*β-Phenyl-GABA.

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(Presented by Academician of the Academy of Medical Sciences of the USSR, A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 104, No. 11, pp. 588-590, November, k987. Original article submitted June 17, 1986.

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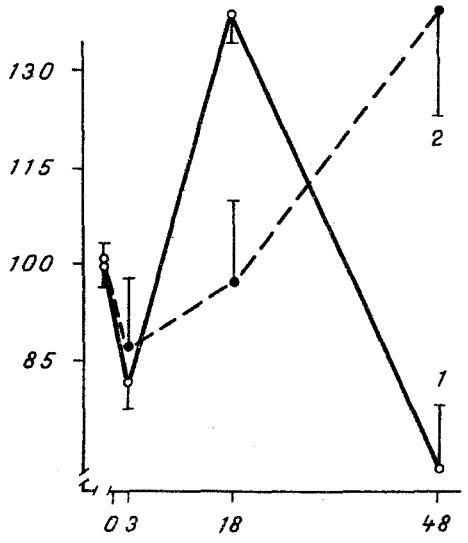

Fig. 1

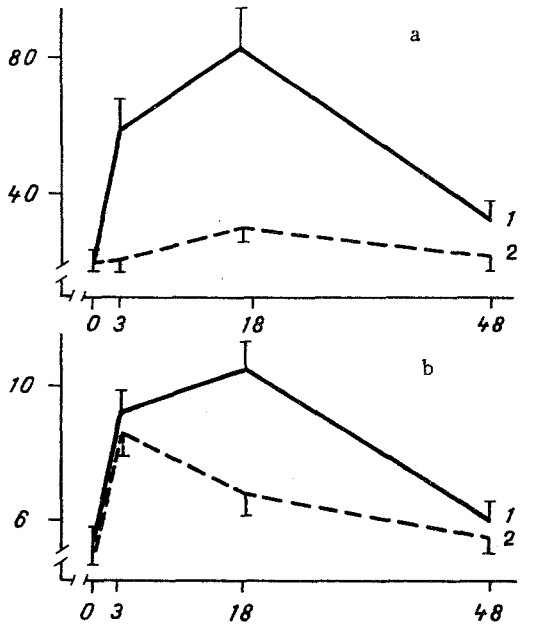

Fig. 2

Fig. 1. Time course of change in GABA and GA levels in thalamus and hypothalamus of rats during stress. Abscissa, duration of stress (in h); ordinate, change in GABA (1) and GA (2) concentration (in %).

Fig. 2. Effect of fenibut on 17-HCS and glucose levels in peripheral blood plasma of stressed rats. Abscissa, duration of stress (in h); ordinate: a) 17-MCS concentration (in μg %); b) glucose concentration (in mmoles/liter). 1) Stress; 2) stress + fenibut.

animals were used in the experiments after deprivation of food and water for 24 h. Stress was inducted by holding the rats by the dorsal cervical skin fold. The animals were decapitated 3, 18, and 48 h later. To rule out circadian variations in the parameters studied, the animals of all groups were killed at the same time (from 1 to 2 pm).

Fenibut was injected subcutaneously in the optimal stress-regulating dose of 1 mg/kg [4], a single injection being given 45-60 min before the beginning of exposure to stress for 3 or 18 h. When exposure to stress lasted 48 h, a second injection of fenibut was given 24 h after the first.

GABA and GA concentrations were determined in the thalamus and hypothalamus by one-way ascending chromatography in a thin layer of ion-exchange resin (Dowex 50 × 8), followed by densitometry [11]. In a separate series of experiments the GABA level was determined fluorometrically [15]. GDC activity was determined in the same structures by an adaptation of method [15] and GABA-T was determined by the method in [13]. Protein was determined quantitatively by Lowry's method [6]. Concentrations of 17-HCS and glucose in peripheral blood plasma were determined by fluorometric [9] and enzymic (using kits from Lachema, Czechoslovakia) methods, respectively.

The experimental data were subjected to statistical analysis by Student's t test (on the BZ-34 microcomputer).

EXPERIMENTAL RESULTS

The study of the effect of stress on GABA and GA levels in the rat thalamus and hypothalamus showed that the concentrations of both these neuroactive amino acids decrease during the first few hours, whereas the time course of their changes differed in character if exposure to stress was prolonged (Fig. 1). However, these changes in the GA concentration, by contrast with GABA, were not statistically significant. Meerson [7] showed previously that during exposure to emotional-painful stress for 8 h the GABA and GA concentration in the cerebral hemispheres fell sharply in response to activation of GDC and GABA-T. In Meerson's opinion this fact is evidence of enhanced function of the GABA-system. Meanwhile Andreev

TABLE 1. Effect of Fenibut on GABA Concentration and Activity of GDC and GABA-T in Thalamus and Hypothalamus of Intact and Stressed Rats (M ± m)

Experimental conditions		GABA concentration, μmoles/g wet weight of tissue	Activity of	
			GDC, μmoles GABA/h/g protein	GABA-T, μmoles NADH/h/g protein
Normal	(6)	3,63±0,24	122,5±4,24	7,64±0,19
Fenibut (after 18 h)	(4)	4,13±0,18	158,2±19,46	8,10±0,55
Control (stress 18 h)	(4)	5,04±0,13*	140,9±14,11	5,70±0,32*
Fenibut + stress 18 h	(4)	4,09±0,14**	163,3±22,70	6,95±0,53**

Legend. Number of experiments given in parentheses. *$p < 0.05$ compared with normal, **$p < 0.05$ compared with control.

et al. [1, 2] showed that exposure to emotional-painful stress for 1-3 h leads to a decrease in GABA-T activity, whereupon the GABA level rises correspondingly. It can be postulated that during the first hours of exposure to stress, GABA accumulation probably reflects neurotransmitter adaptation to stress. Meanwhile, prolonged exhausting stress leads to a disturbance of energy metabolism, and under these conditions the role of GABA as an energy substrate becomes more important and its concentration in brain tissue falls. This hypothesis is confirmed by the results of our own experiments (Table 1). We found that after exposure to stress for 18 h GABA-T activity falls significantly, whereas GDC activity remains virtually unchanged. Meanwhile, by the 18th hour of the stress reaction a potentially dangerous [16] hyperglucocorticoidemia develops (Fig. 2), with the result that stress injuries appear in target organs [4, 5, 16]. Consequently, it can be accepted that, starting from the 18th hour of stress, signs of insufficiency of the adaptive function of the GABA-system are observed.

Fenibut, in a dose of 1 mg/kg had virtually no effect on the GABA and GA levels in the thalamus and hypothalamus of intact animals 3, 18, and 48 h after injection, and did not change the 17-HCS and glucose concentrations in the peripheral blood. However, 1 h after its injection GDC activity in the brain structures tested was increased by 1.6 times and GABA-T activity by 1.5 times 1 h after its injection. Thus, fenibut, unlike short-term exposure to stress, activates enzymes of GABA metabolism and corrects the energy metabolism of the brain, without causing any changes in the GABA concentration during 18-h exposure to stress and prevents its subsequent fall. Under these circumstances fenibut restores the rate of GABA degradation, thereby accelerating its turnover. As a result of this, fenibut evidently prevents activation of the hypothalamo-hypophyseo-adrenal system, as was shown by the absence of hyperglucocorticoidemia and the decrease in the intensity of hyperglycemia (Fig. 2). These findings suggest that the role of GABA as a neurotransmitter in emergency adaptation is significant only in the case of short-term exposure to stress. During long-term stress the ability of the GABA-system to restrain potentially dangerous excitation of the stress-regulating system is lost. Meanwhile preliminary activation of the GABA shunt increases resistance of the GABA system as a whole and increases the duration of its function in mechanisms of urgent adaptation. It can be tentatively suggested that limitation of stress-induced damage to target organs by fenibut [4, 5] is due to this mechanism of its action. The ability of fenibut, observed by clinicians [8], to improve the emotional state, intellectual activity, and memory, and also to increase working capacity under conditions of increased strain, fatigue, and the action of acute asthenizing and other external factors, is linked with optimization of the adaptive and energy-yielding functions of the GABA-system of the brain.

LITERATURE CITED

1. B. V. Andreev, Yu. D. Ignatov, Z. S. Nikitina, and I. A. Sytinskii, Zh. Vussh. Nerv. Deyat., No. 3, 511 (1982).
2. B. V. Andreev, G. É. Galust'yan, Yu. D. Ignatov, et al., Ukr. Biokhim. Zh., No. 6, 652 (1983).

3. N. A. Bogachev, Pharmacology and Clinical Use of Neuroactive Amino Acids and Their Analog [in Russian], Volgograd (1985), pp. 93-98.
4. G. V. Kovalev, A. A. Spasov, and N. A. Bogachev, New Data on Eleutherococcus and Other Adaptogens [in Russian], Vladivostok (1981), pp. 51-56.
5. G. V. Kovalev, K. G. Gurbanov, and I. N. Tyurenkov, Farmakol. Toksikol., No. 3, 41 (1983).
6. G. A. Kochetov, Textbook of Practical Enzymology [in Russian], Moscow (1980), pp. 224-26.
7. F. Z. Meerson, Pathogenesis and Prevention of Stress-Induced and Ischemic Heart Lesions [in Russian], (1984).
8. L. S. Mekhilane and V. É. Vasar, Mechanism of Action and Clinical Aspects of Gamma-Aminobutyric Acid Derivatives [in Russian], Tartu (1984), pp. 112-123.
9. Yu. M. Pankov and I. Ya. Usvatova, Methods of Clinical Biochemistry of Hormones and Mediators [in Russian], Moscow (1973), pp. 66-70.
10. K. S. Raevskii, Farmakol. Toksikol., No. 5, 517 (1981).
11. A. A. Spasov and O. V. Ostrovskii, Pharmacology and Clinical Use of Neuroactive Amino Acids and Their Analogs [in Russian], Volgograd (1985), pp. 34-38.
12. S. Kh. Khaidarliu, Functional Biochemistry of Adaptation [in Russian], Kishinev (1984).
13. T. De Boer and J. Bruinvels, J. Neurochem., 28, 471 (1977).
14. M. B. Hennessy, J. P. Heybach, J. Vernikos, and S. Levine, Physiol. Behav., 22, 821 (1979).
15. I. P. Lowe, E. Robins, and G. S. Eyreman, J. Neurochem., 3, 8 (1958).
16. G. Sayers, Physiol. Rev., 30, 241 (1950).