Effect of Systemic Administration of a New Piracetam Peptide Analog on Postresuscitation Recovery of the Central Nervous System

I. V. Nazarenko, A. A. Kamenskii, T. A. Gudasheva, and A. V. Volkov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 125, No. 1, pp. 34-37, January, 1998
Original article submitted October 25, 1996

Changes in the functions of the central nervous system were analyzed in albino rats resuscitated after a 12-min cardiac arrest. At the end of the first month after resuscitation, when the neurological status was completely restored, some emotional disturbances determining animal behavior were noted. Administration of GVS-111, a piracetam peptide analog, 30 min after the start of resuscitation increases survival rate, accelerates neurological recovery, and normalizes emotional reactivity in survivors.

Key Words: *clinical death; neurological status; emotional reactivity; nootropics; peptides*

Circulatory arrest and subsequent reperfusion are always accompanied by dysfunction of various organs, especially the brain [8]. This leads to more or less pronounced psychoneurological disturbances during the postresuscitation period [2]. Hence, correction and prevention of postresuscitation encephalopathies are an important medical problem. Of particular interest in this context are nootropics that improve cerebral circulation and metabolism and exert antihypoxic and antiamnestic activities [10]. GVS-111, a peptide piracetam analog synthesized on the basis of proline (Institute of Pharmacology, Russian Academy of Medical Sciences), is a new and very promising member of the nootropics family. Being similar to piracetam in pharmacological activity, this drug is effective in much lower concentrations [13].

The aim of the present study was to evaluate the effect of an early single injection of GVS-111 on the recovery of the central nervous system (CNS) after global circulatory arrest.

Institute of General Resuscitation, Russian Academy of Medical Sciences; M. V. Lomonosov Moscow State University; Institute of Pharmacology, Russian Academy of Medical Sciences, Moscow

MATERIALS AND METHODS

Experiments were carried out on 81 male random-bred rats weighing about 200 g. Circulation was stopped for 12 min by intrathoracal occlusion of the vascular band as described elsewhere [5]. The animals were resuscitated by external cardiac massage and jet ventilation [5]. GVS-111 aqueous solution (N-phenylacetyl-L-prolylglycine ethyl ester) was injected intraperitoneally in a dose of 0.3 mg/kg and in a volume of 1 ml/kg on the 30th min of resuscitation. Control animals received the same volume of physiological saline. Neurological status of experimental and control animals was assessed daily for 2 weeks as described previously.

Motor and exploratory activity was evaluated in the open field test. Animals were placed in a round area with a diameter of 80 cm and their horizontal and vertical motor activities, number of entries into central zone, grooming acts, and defecations were visually assessed. The animals were tested for 5 min. Three minutes after the start of testing illumination was switched from an incandescent lamp (150 W) to a red lamp (15 W) and 1 min latter the initial light intensity was restored.

Food-procuring behavior was conditioned for 4 days in a standard T-maze with 30-cm long arms.

0007-4888/98/0001-0026$20.00

The animals were placed into the maze for no longer than 3 min 5 times per day. Bread balls were used as the reinforcement. The following parameters were recorded: latency of leaving the start arm, time of reaction (period from leaving the start arm to obtaining the food reward), and error score (number of choices of empty arm).

The means and standard deviations of data files were calculated and compared using parametric (Student) and nonparametric (Mann-Whitney-Fisher) tests.

RESULTS

GVS-111 injected 30 min after the start of resuscitation significantly improved survival rate (to 90% *vs.* 47% in the control group) and accelerated recovery of neurological status during the postresuscitation period. The external neurological deficiency in 70% rats injected with GVS-111 disappeared on day 7, while in the control group this was observed only on day 9.

Animal behavior was tested 2 weeks after cardiac arrest and complete restoration of neurological status. The open field test showed a significantly higher number of entries to the central zone and rearings and a lower number of defecations in resuscitated rats compared with intact controls, while horizontal activity and the number of grooming acts were similar (Figs. 1 and 2). Injection of GVS-111 considerably suppressed horizontal and vertical components of motor activity of resuscitated animals under conditions of bright illumination (Fig. 1). Moreover, in rats injected with GVS-111 the number of entries to the central zone throughout the test was decreased, while the number of defecations was increased in comparison with the control group (Fig. 2).

Resuscitated animals showed considerably higher number of positive reactions and lower latencies in the T-maze test on all days of training in comparison with intact rats (Fig. 3), while their time of reaction did not differ from the control values. In resuscitated rats GVS-11 had no effect on the latency and number of positive responses, but markedly reduced the time of reaction on days 1, 3, and 4 of training. The number of errors was the same in both experimental groups (Fig. 3).

These experiments demonstrate some changes in emotional status in rats survived 12-min cardiac arrest at the end of the first postresuscitation month which determine some peculiarities in their behavior.

The data obtained in the open field test (increased number of entries to the central zone and rearing, and a reduced number of defecations) point to reduced anxiety and weakened passive-defensive reactions in resuscitated animals, which results in activation of exploratory behavior. Reduced latency in the T-maze also indicates lower fear in resusci-

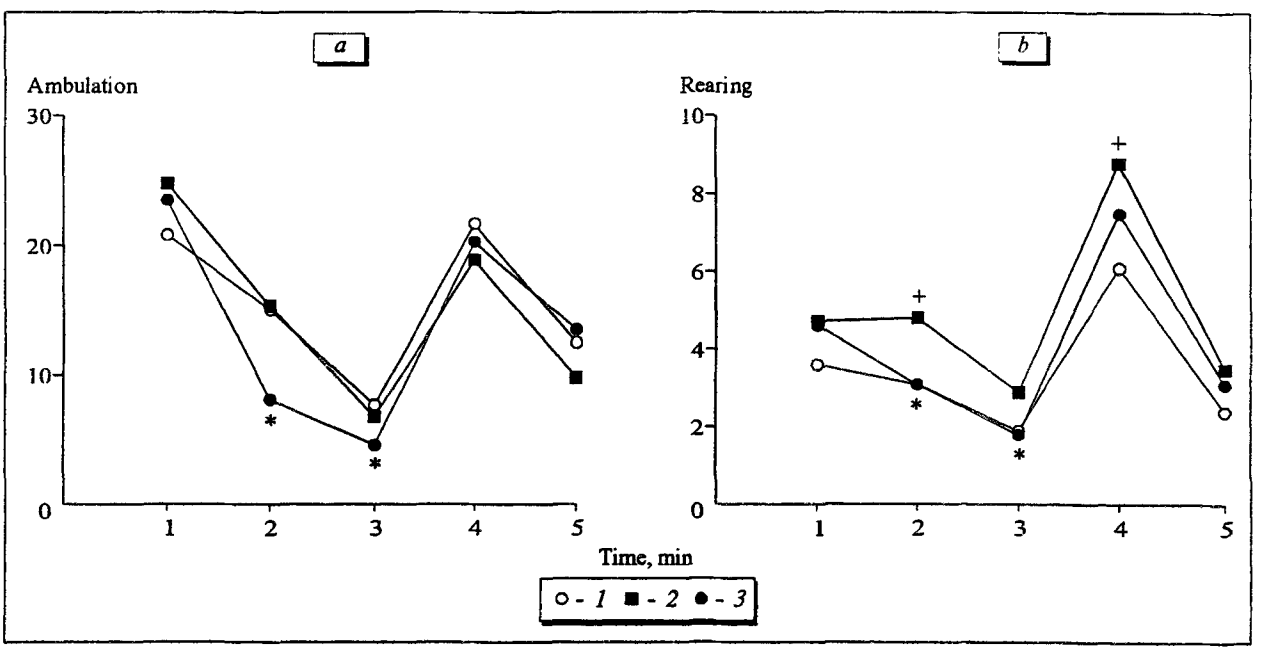

Fig. 1. Effect of the piracetam peptide analog GVS-111 on the open field behavior of albino rats survived 12-min cardiac arrest.

a) horizontal component of motor activity; *b*) vertical component of motor activity. Here and on Fig. 2 and 3: *1*) intact rats (n=20); *2*) resuscitated rats (n=17); *3*) resuscitated rats injected with GVS-111 (n=15).

p<0.05: *compared with the control rats; +compared with intact rats.

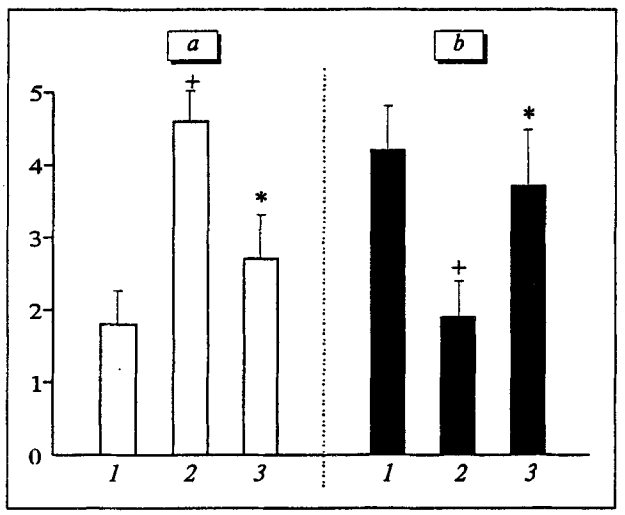

Fig. 2. Effect of the piracetam peptide analog GVS-111 on the open field behavior of albino rats survived 12-min cardiac arrest. *a*) number of entries to the central zone; *b*) number of defecations

tated rats. No differences in food motivation between resuscitated and control rats were noted. Under these conditions, food-procuring behavior predominates due to suppression of defensive behavior [7], which promotes acquisition of the corresponding skill, in particular increases the number of positive responses. These findings are consistent with previous reports on enhanced exploratory activity and improved learning in Skinner test in animals survived 10-min cardiac arrest [4], which was attributed to behavioral activation due to overexcitation.

Single administration of GVS-111 on the 30th min of resuscitation accelerated the recovery of neurological status and diminished behavioral deviations in rats survived cardiac arrest. GVS-111 normalized reduced emotional reactivity and exploratory activity in resuscitated animals. The indices of anxiety in the open field in rats injected with GVS-111 did not differ from those in intact animals. The rats survived cardiac arrest did not differ from intact rats in horizontal activity. In GVS-111-treated rats horizontal and vertical activities were suppressed, i.e., GVS-111 promoted habituation to experimental conditions. Similar process may improve the performance of food-procuring runs in T-maze test, which manifests itself as a much shorter time reaction than in the control group starting from the first day of conditioning. Similar accelerating effect of GVS-111 on adaptation to new conditions was shown on intact rats [9]. The observed changes in behavioral parameters of animals survived cardiac arrest are probably related to a variety of pathological processes in the CNS induced by ischemia-reperfusion [1,8,11,12,14]. Hence, there are various targets for pharmacological influences aimed at restoration of CNS functioning after clinical death. The preparation used in our experiments may affect various mechanisms of pathogenetic process in the brain during the postresuscitation period. This assumption is confirmed by the ability of GVS-111 to improve the resistance to low-pressure hypoxia (elevation to an altitude to 11000 m) and its antioxidant activity under conditions of immobilization and emotional stress [15].

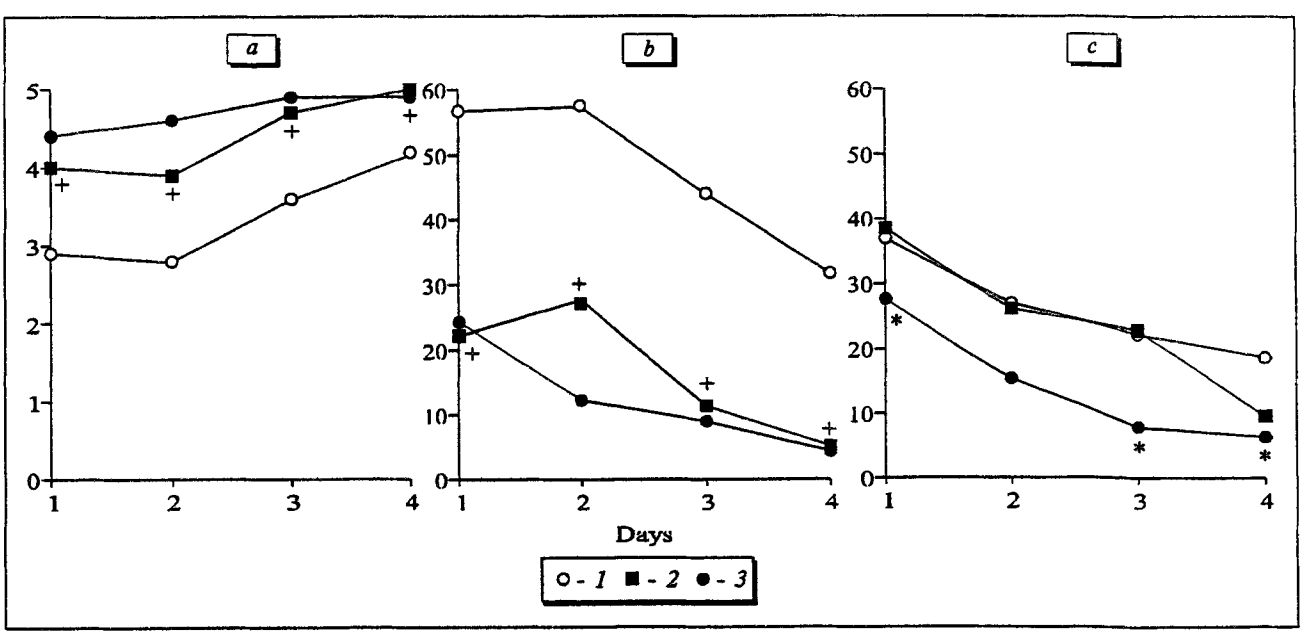

Fig. 3. Effect of the piracetam peptide analog GVS-111 on T-maze performance of albino rats survived 12-min cardiac arrest *a*) number of accomplished reactions; *b*) latency of leaving the start arm; c) time of reaction, sec.

Thus, an early single injection of the piracetam peptide analog GVS-111 promotes the recovery of CNS after a 12-min cardiac arrest. This preparation provides a promising basis for the development of new drugs.

REFERENCES

1. M. Sh. Avrushchenko, *Byull. Eksp. Biol. Med.*, **114**, No. 8, 176-79 (1992).
2. G. V. Alekseeva, *Anest. Reanimatol.*, No. 3, 70-71 (1980)
3. T. A. Gudasheva, G. G. Rozanov, R. U. Ostrovskaya, *et al., Khim.Farm. Zh.*, **29**, No. 1, 15-18 (1995).
4. A. M. Gurvich, E. A. Mutuskina, and Yu. V. Zarzhetskii, *Anest. Reanimatiol.*, No. 5, 6-9 (1994).
5. V. G. Korpachev, S. P. Lysenkov, and L. Z. Tel', *Pat. Fiziol.*, No. 3, 78-80 (1982).
6. V. G. Korpachev, S. P. Lysenkov, and L. Z. Tel', in: *Clinical Picture, Pathogenesis, and Management of Emergent States* [in Russian], Novosibirsk (1982), pp. 8-13.
7. A. S. Maklakova, I. V. Nazarenko, V. A. Dubynin, et al., *Zh. Vyssh. Nervn. Deyat.*, **45**, No. 6, 1143-1150 (1995).
8. V. A. Negovskii, A. M. Gyrvich, and E. S. Zolotokrylina, *Postresuscitation Disease* [in Russain], Moscow (1987).
9. R. U. Ostrovskaya and T. A. Gudasheva, *Byull. Eksp. Biol. Med.*, **111**, No. 5, 644-647 (1991).
10. R. U. Ostrovskaya, T. A. Gudasheva, S. S. Trofimov, *et al., in: Pharmacology of Nootropics* {in Russian], Moscow (1989), pp. 26-35.
11. D. W. Choi, *J. Neurobiol.*, **23**, 1261-1276 (1992).
12. H. Hara, T. Sukamoto, and K. Kogure, *Prog. Neurobiol.*, **40**, 645-670 (1993).
13. R. U. Ostrovskaya, T. A. Gudasheva, S. S. Trofimov, *et al., Biological Basis of Individual Sensitivity of Psychtropic Drugs.* Eds. S. B. Seredenin *et al.*, Edinburgh (1995), pp. 79-91.
14. P. Safar, *Ann. Emerg. Med.*, **22**, Pt. 2, 324-327 (1993).
15. S. B. Seredenin, T. A. Voronina, T. A. Gudasheva, *et al., U.S. Patent* No. 5,439,930, August 8, 1995, New York (1995).