EXPERIMENTAL STUDY OF THE GEROPSYCHOTROPIC PROPERTIES OF AN ANTIOXIDANT OF THE 3-HYDROXYPYRIDINE CLASS

T. A. Voronina, T. L. Garibova,
L. D. Smirnov, O. A. Kutepova,
and K. M. Dyumaev

UDC 615.272.4.014.425:547.823/.017:615.214/015.4:/612.821:612.67

KEY WORDS: aging, behavior, geropsychotropic properties, antioxidants, mnemic processes.

One of the many theories of aging is based on the hypothesis that a role in this process is played by free radicals [10, 13], and in this connection inhibitors of lipid peroxidation (LPO), which are substances stabilizing membranes when damaged by free radicals, are regarded as potential geroprotectors. Interesting members of this group are the derivatives of 3-hydroxypyridine (3-HP), whose psychotropic, membranotropic, and antioxidant properties [5, 8] suggest that they may not merely prolong life [6, 7], but may also improve viability.

Accordingly, in the present investigation the geropsychotropic action of a 3-HP derivative was studied: its effect on behavior, on emotional status, and on learning in animals during spontaneous aging.

EXPERIMENTAL METHODS

Experiments were carried out on male albino rats aged 3-5 and 16-18 months and weighing 160-210 and 550-620 g respectively. The 3-HP derivative, namely 2-ethyl-6-methyl-3-hydroxypyridine (2-Et-6-Me-3-HP) was given to the animals with their drinking water in a daily dose of 50 mg/kg for 2 months.

To estimate the neurologic deficit, methods generally used for this purpose were adopted: hanging from a horizontal bar, holding on to an inverted net, running along a horizontal bar, the revolving rod test [3]. The rats' orienting-investigative behavior was studued in an open field test and their spontaneous motor activity in an actometer (Ugo Basile, Italy). To study the rats' emotional status a scale of emotionality [4] was used; aggressiveness and nociceptive sensitivity were tested during application of painful electric shocks to a pair of rats

TABLE 2. Effect of 2-Et-6-Me-3-HP on Motor Activity of Rats (M ± m)

Experimental conditions	Age, months	Number of animals	Index of motor activity in open field test	Index of spontaneous motor activity
Intact rats	3	20	19,2±1,7	65,3±17,4
	16	17	5,9±1,3*	45,0±18,7
Control	5	10	4,5±1,9	20,8±11,5
	18	7	9,6±4,8	16,3±15,5
2-Et-6-Me-3-HP	5	10	9,4±4,7	22,3±18,1
	18	5	7,4±2,4	24,6±13,1

Legend. *P < 0.05 compared with animals aged 3 months.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 102, No. 9, pp. 307-310, September, 1986. Original article submitted October 23, 1985.

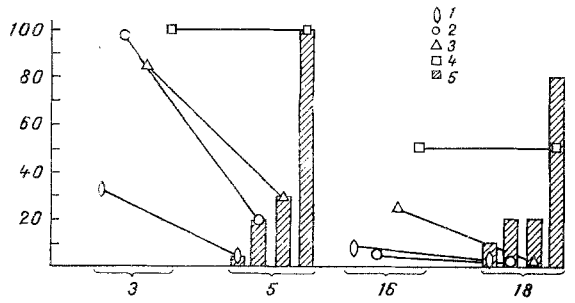

Fig. 1. Effect of 2-Et-6-Me-3-HP on motor behavior of rats of different ages. Abscissa, age of rats (in months); ordinate, number of animals performing test (in %). 1) Holding on to net; 2) suspension; 3) running along horizontal bar; 4) holding on to revolving rod; 5) effect of 2-Et-6-Me-3-HP on test performance.

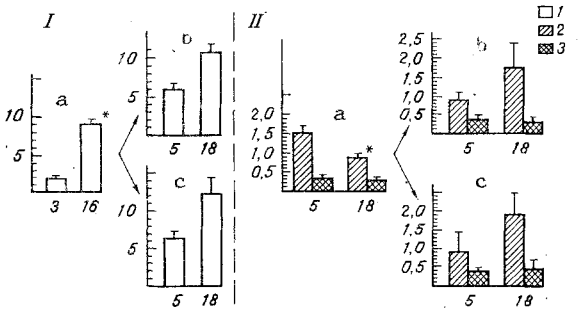

Fig. 2. Effect of 2-Et-6-Me-3-HP on time course of changes in emotional status and thresholds of aggressiveness and sensitivity to pain of rats of different ages. Abscissa, age of rats (in months); ordinate: I) index of emotionality (in points); II) thresholds of pain sensitivity and aggressiveness (in mA). a) Intact rats; b) control; c) 2-Et-6-Me-3-HP. 1) Emotional status; 2) threshold of aggressiveness; 3) threshold of sensitivity to pain. *P < 0.05 compared with corresponding control.

on an electrode floor [3]; ability to learn and to preserve a reflex were estimated in the conditioned passive avoidance reflex test (CPAR) [4].

EXPERIMENTAL RESULTS

When the parameters of the neurologic deficit were assessed it was shown that rats aged 16 months differed from the younger animals (3 months) in having reduced functional capacity, connected with a disturbance of coordination and muscle tone. Administration of 2-Et-6-Me-3-HP for 2 months did not disturb the motor functions of young animals. Meanwhile administration of the antioxidant for 2 months to rats aged 16 months led to an improvement of all the behavioral parameters studied compared with the control: animals of the same age group (Fig. 1). Assessment of motor skills in the open field test showed that rats aged 16 months also differed from the younger animals in having reduced orienting-investigative activity; at the same time, no changes were observed in their spontaneous motor activity. Administration of 2-Et-6-Me-3-HP for 2 months to rats aged 16 months had no appreciable effect on these parameters (Table 1).

Age disturbances in the rats were thus manifested in tests connected mainly with complex motor functions and requiring control, coordination, and muscular effort, and it was these disturbances which were corrected by 2-Et-6-Me-3-HP. Similar results were obtained in a study of the effect of the nootropic drug encephabol on the motor functions of old rats [12].

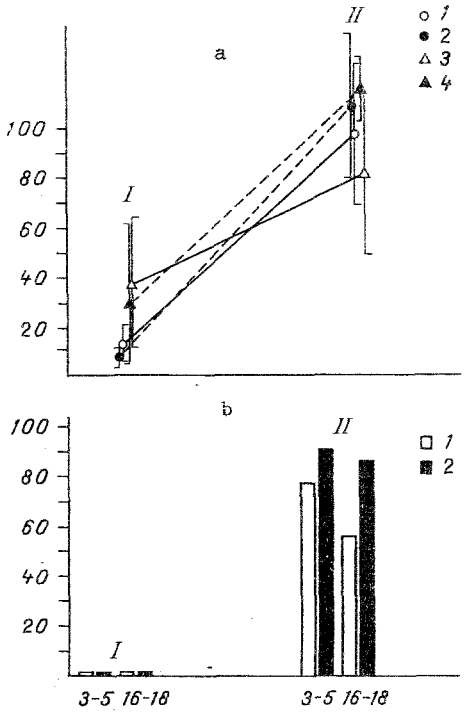

Fig. 3. Effect of 2-Et-6-Me-3-HP on reproduction of CPAR by rats of different ages. a) Latent period (in sec) of visiting dark compartment before learning (I) and during recall of memory trace 12 days layer (II): 1) control (3-5 months), 2) 2-Et-6-Me-3-HP (3-5 months), 3) control (16-18 months), 4) 2-Et-6-Me-3-HP (16-18 months); b) number of animals (in %) not visiting dark compartment, before learning (I) and during recall of memory trace 12 days layer (II); 1) control, 2) 2-Et-6-Me-3-HP. Abscissa, age (in months).

The study of the animals' emotional status showed that rats aged 16 months differed significantly from young rats, by demonstrating greater emotional reactivity in response to psychogenic stress stimuli. The 16-month-old rats also had a lower threshold of aggressiveness than the young animals, but their threshold of sensitivity to pain was idential. Prolonged administration of the antioxidant did not affect the emotional status of the young or old animals and did not change the thresholds of aggressiveness of the animals or of their sensitivity to pain (Fig. 2).

Age changes in the animals' ability to learn were studied by the CPAR method, based on the formation of a spatial orienting skill of choice between light and dark compartments as a result of a single presentation of a painful training stimulus (electric shock) in the dark compartment. It was found that rats aged 16 months, after training and reproduction of CPAR on the 12th day after training differed from the younger animals in showing appreciable extinction of the memory trace, as shown by shortening of the latent period of visting the dark compartment and a decrease in the number of animals remembering the situation (Fig. 3).

After injection of 2-Et-6-Me-3-HP extinction of the memory trace was more prolonged but less well preserved, as shown by better performance of the conditioned reflex than in the control by both young and old animals. It must be emphasized that the improvement of mnemic functions under the influence of the antioxidant was more marked in old than in young animals (Fig. 3).

It was thus shown that 2-Et-6-Me-3-HP can exert a corrective action on age disturbances of CNS functions by improving memory processes, learning of motor skills, and movement coordination functions. Substances with a nootropic type of action, such as the a-pyrrolidone

derivative pyracetam, and encephabol [11, 12], have a similar effect on age disturbances of behavior and memory in old animals.

Analysis of the spectrum of psychotroic activity of 3-HP derivatives, determined previously [5] leads to the conclusion that these substances can increase the resistance of an organism to the action of traumatic, extremal factors of varied genesis (stress, hypoxia, convulsions, painful stimulation, and so on). These properties, and also the fact discovered in the present investigation concerning the corrective effect of the 3-HP derivative on age disturbances of CNS functions, suggest that the general level of adaptation of the organism and maintenance of its homeostasis are enhanced by 3-HP derivatives. These results are in good agreement with the theory of adaptive regulation [9], according to which the lifespan is determined by relations between two processes: aging and what Frol'kis calls the "vitauct" aimed at increasing viability of the organism.

The molecular biochemical mechanisms of the central action of 3-HP derivatives have not yet been explained and do not fit in with traditional views regarding the participation of neurotransmitter systems and receptor binding in the realization of psychotropic effects. According to the synaptic membrane hypothesis of memory [1, 14] the mechanism of memory formation is connected with stabilization of conformational changes in macromolecules of the membrane proteins of the synapse.

Without ruling out the possibility that the action of 3-HP derivatives on memory may be realized through other mechanisms, we postulate that in this case there is a direct membrane-modulating effect.

We know that 3-HP derivatives inhibit LPO of the membrane and modify its phospholipid composition, permeability, and the function of membrane-bound enzymes and receptors [2, 8]. According to our hypothesis, this combination of membrane-modulating effects of 2-Et-6-Me-3-HP is responsible for the appearance of stable structural changes in lipid-protein complexes of the neuron membrane and, in particular, of conformational changes in protein macromolecules.

LITERATURE CITED

1. Yu. S. Borodkin, Mechanisms of Memory Control [in Russian], Leningrad (1979), pp. 14-24.
2. E. B. Burlakova, Ch. V. Kairane, E. M. Molochkina, et al., Vopr. Med. Khimii, No. 1, 66 (1984).
3. T. A. Voronina, Yu. I. Vikhlyaev, L. N. Nerobkova, et al., Phenazepam [in Russian], Kiev (1982), pp. 145-151.
4. T. L. Garibova, V. V. Rozhanets, I. Kh. Rakhmankulova, et al., Med.-Biol. Inform. (Bulgaria), No. 4, 8 (1985).
5. K. M. Dyumaev, T. A. Voronina, and L. D. Smirnov, Vest. Akad. Med. Nauk SSSR, No. 11, 3 (1984).
6. L. K. Obukhova, Usp. Khimii, No. 10, 1914 (1975).
7. L. D. Smirnov and L. K. Obukhova, Abstracts of Proceedigs of the 3rd All-Union Symposium on Phenolic Compounds [in Russian], Tbilisi (1976), p. 154.
8. L. D. Smirnov and K. M. Dyumaev, Khim.-farm. Zh., No. 4, 412 (1982).
9. V. V. Frol'kis, Physiological Mechanisms of Aging [in Russian], Leningrad (1982), pp. 187-197.
10. N. M. Émanuél', Gerontology and Geriatrics: Annual Review [in Russian], Kiev (1976), pp. 103-110.
11. R. T. Bartus, R. L. Dean, III, B. Beer, and A. S. Lippa, Science, 217, 408 (1982).
12. H. Coper, Encephabol Preparation in Medical Practice, Moscow (1982), pp. 29-36.
13. D. Harman, J. Gerontol., 23, 476 (1968).
14. H. Matthies, Life Sci., 15, 2017 (1974).