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EXPERIMENTAL STUDY OF THE ANTIAMNESIC ACTIVITY OF PIRACETAM IN ORCHIDECTOMIZED RATS

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The antiamnesic effects of piracetam, both experimental and clinical, are well documented. The mechanism of its action on integrative CNS functions is linked with its positive effect on neurometabolism and energy metabolism of the brain cells [12].

Meanwhile piracetam is known to be a hormonally active drug, stimulating function of the pituitary-gonads system [6], and exhibiting an estrogenizing effect [8] in infantile rats. Some effects of piracetam are mediated through function of the gonads: its action on mitochondrial respiration in the liver [7] and skeletal muscles [1] is exhibited in intact, but not in gonadectomized rats. Accordingly it was decided to assess the possible role of the gonads system in the realization of the antiamnesic effect of piracetam. There is no information on this subject in the published literature.

The aim of this investigation was to study the effect of gonadectomy on learning processes and on the structure of the lipid matrix of synaptosomal membranes of brain neurons in male rats and also to assess the effect of piracetam on the above-mentioned parameters in orchidectomized rats.

EXPERIMENTAL METHOD

The investigation was conducted on 118 noninbred orchidectomized albino rats weighing 130-150 g. Orchidectomy was performed under superficial ether anesthesia and the animals were used in the experiments 30 days after the operation. Ability of the animals to learn was tested in the conditioned passive avoidance reflex (CPAR), by the method giving maximal ability to learn in the control group [5]. Testing was carried out after 24 h and the percentage ability to learn in the group was determined from the number of trained animals. After testing the rats were killed and their blood serum testosterone level and microviscosity of the synaptosomal membranes of their cortical neurons determined. The serum testosterone level was tested by means of standard Sterone-T-I^{125} kits, produced by the Bulgarian Academy of Sciences. The microviscosity of the synaptosomal membranes of the neurons in cerebral cortical homogenates was determined by a method described previously [4].

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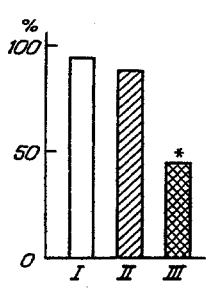

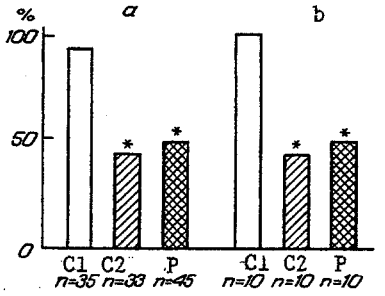

Fig. 1 Fig. 2

Fig. 1. Ability of rats to learn in the CPAR test 30 min after orchidectomy: *p < 0.05 compared with I. I) Intact animals (n = 20), II) animals undergoing mock operation (n = 20), III) orchidectomized animals (n = 20).

Fig. 2. Ability of orchidectomized rats to learn in CPAR test. a) After administration of piracetam for 10 days, b) after a single injection of piracetam; *p < 0.05 compared with C1. C1) Intact control, C2) orchidectomized control, P) orchidectomy + piracetam.

There were two series of experiments. In series I 20 rats were orchidectomized, 20 underwent a mock operation, and 20 rats were intact. The effect of gonadectomy on the above-mentioned parameters was studied.

In series II the antiamnesic effect of piracetam was studied in gonadectomized rats, using the same indicators. The following groups of animals were used in the experiments: I) control 1 (45 intact rats); II) control 2 (43 orchidectomized rats); III) 10 orchidectomized rats receiving a single dose of piracetam of 250 mg/kg, intraperitoneally, 1 h before learning the CPAR. Group IV comprised 45 orchidectomized rats receiving piracetam in the course of 10 days in a daily dose of 250 mg/kg, intraperitoneally (training was carried out 1 day after the end of piracetam administration).

Piracetam (water-soluble substance of the preparation was obtained from the Latvbiofarm Production Combine) was injected in 5% aqueous solution in a dose of 0.5 ml/100 g body weight. Control animals received the solvent (water for injections) in the same volume and by the same program.

EXPERIMENTAL RESULTS

The experiments showed that 1 month after orchidectomy ability to learn in the CPAR test was reduced by 50% in the rats compared with rats undergoing the mock operation and intact animals (Fig. 1); in the gonadectomized rats there was a significant increase (by 28%) in the microviscosity of synaptosomal membranes of the brain neurons, and an approximately tenfold lowering of the testosterone level (Table 1).

Since the behavioral and biochemical parameters in the mock-operated and intact rats were virtually indistinguishable (Fig. 1; Table 1), in the experiments of series II, only intact animals were used as the control.

After administration of the solvent for 10 days the 50% difference in the level of training of the orchidectomized and intact animals (learning ability in the groups amounted to 40% and 90% respectively) and the increased microviscosity of the membranes in the gonadectomized rats still remained. A single injection and a 10 day course of piracetam given to the orchidectomized rats did not change their learning ability statistically significantly (Fig. 2) and had no normalizing effect on the increased microviscosity of the synaptosomal membranes (Table 2). The testosterone level in all groups of orchidectomized rats was lower, on average by 10 times, than in the intact control (Table 2).

The experiments thus showed that orchidectomy, accompanied by a sharp fall in the testosterone level, leads to disturbance of the conditioned reflex activity of rats. Disturbance of the behavioral parameters is accompanied by changes in the structure of the lipid matrix of the synaptosomal membranes of the cerebral cortical neurons, expressed as an

TABLE 1. Microviscosity of Synaptosomal Membranes and Serum Testosterone Level in Rats 1 Month After Orchidectomy

Group of animals (n = 20)	Changes in microviscosity, conven. units	Testosterone content, ng/ml
Intact animals	1	2,77±0,73
Undergoing mock operation	1	2,75±0,76
Orchidectomized	1,28*,+	0,26±0,03*,+

Legend. *p < 0.05 relative to intact control, +) p < 0.05 compared with animals undergoing mock operation.

TABLE 2. Microviscosity of Synaptosomal Membranes and Serum Testosterone Level of Orchidectomized Rats After 10-Day Course of Piracetam

Groups	Dose, mg/kg	Changes in microviscosity	Testosterone content, ng/ml
Intact control (n = 35)	Physiol. saline	1	3,51±0,77
Orchidectomized control (n = 33)	p-p »	1,30*	0,35±0,06*
Orchidectomy + piracetam (n=45)	250	1,29*	0,33±0,03*

Legend. *p < 0.05 compared with intact group.

increase in their microviscosity. Piracetam does not impair the learning ability of orchidectomized rats in the CPAR test and has no normalizing effect on the structure of the lipid matrix of the synaptosomal membranes.

The results thus demonstrate that the antiamnesic effect of piracetam, like its action on the energy metabolism of the mitochondria of the liver and skeletal muscles, is realized solely through the presence of functioning gonads. One essential factor in the mechanism of action of piracetam may perhaps be its influence on biosynthesis of steroid hormones, whose involvement in the mechanism of integrative processes in the CNS is not disputed [2, 3]. Support for this view is given by data obtained previously on the activating effect of piracetam on the pituitary-gonads system [8], the increase in the blood testosterone and estradiol levels which we observed after a 10-day course of injections of-piracetam, despite their initially low level in rats [9], and the absence of any nootropic effect of piracetam and some of its analogs when administered together with aminoglutethimide , an inhibitor of steroid biosynthesis [11].

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