The results of these investigations are in agreement with data in the literature on the inducing effect of TCD on the microsomal system of the liver DOP, in the dose studied (50 mg/kg), had a similar action. The combined effect of these two compounds is synergic.

The hepatotropic action of the above-mentioned substances was not confined to activation of cytochrome P-450-dependent enzymes, but was manifested as disorganization of energy and protein metabolism and of hepatocyte organelles.

The results are evidence of the hepatotoxic action of small doses of chlorinated diphenyls and of esters of orthophthaleic acid.

## LITERATURE CITED


1. L. B. Zavodnik, P. I. Lutsenko, and M. I. Bushma, Farmakol. Toksikol., No. 3, 95 (1989).
2. N. A. Zaitsev, Med. Ref. Zh., 7, No. 2, 44 (1989).
3. A. S. Loginov, E. A. Bendikov, P. N. Lyubchenko, et al., "A new method of estimating the state of the liver function in patients with internal diseases and during dispensarization of certain groups of the population," Technical Recommendations [in Russian], Moscow (1990).
4. T. F. McMahon et al., Xenobiotica, **20**, No. 5, 501 (1990).
5. M. Rousseau, Preventique, **26**, 47 (1989).
6. P. N. Shaw and J. B. Houston, Toxicol. Appl. Pharmacol., **84**, 232 (1986).
7. A. R. Siddika et al., Biochem. Soc. Trans., **17**, No. 6, 1073 (1989).
8. Srivastava Sadha et al., Indian J. Exp Biol., **27**, No. 10, 885 (1989).
9. P. A. Stehr-Green et al., Arch. Environ. Hlth., **43**, No. 6, 420 (1988).


# FEBRIFUGAL ACTIVITY OF ACUPUNCTURE AND ITS POTENTIATION BY PROPRANOLOL


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KEY WORDS: acupuncture; propranolol; fever


With the increasingly widespread use of acupuncture in clinical medicine, the elucidation of its anatomical and physiological basis assumes great importance [6, 11, 13]. There have now been many investigations into the neurophysiological and neurochemical mechanisms of acupuncture analgesia [5, 8, 10, 12]. Many workers have noted the involvement of adrenergic structures in its realization [4, 14, 15]. Yasnetsov [9] reports potentiation of the analgesic effect of acupuncture by propranolol in a dose of 1.5 mg/kg. In studies by other workers [1] propranolol weakened acupuncture analgesia. On the whole, the problem of the oriented action of drugs on various aspects of the therapeutic action of acupuncture has received comparatively little study. There are only isolated reports of the effect of benactyzine on the antipyretic effect of acupuncture, which depends on the dose of the cholinolytic [7].

The aim of the investigation described below was to study the relationship between the febrifugal effect of acupuncture and the $\beta$-adrenoblocker propranolol (anaprilin).


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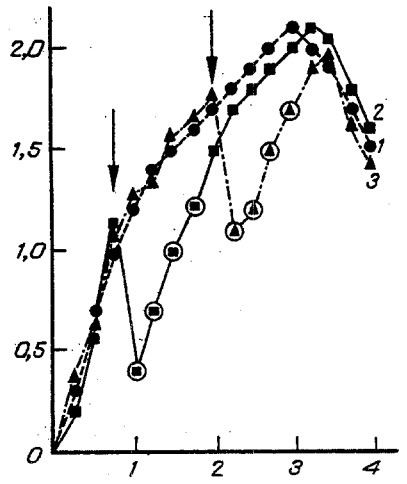


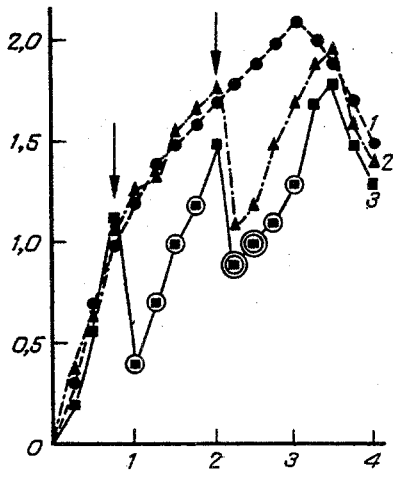


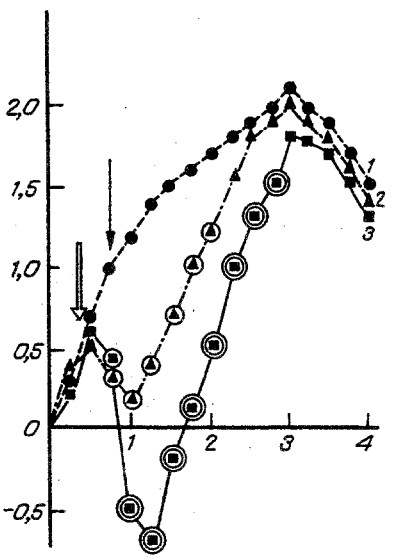


Fig. 1 Fig. 2 Fig. 3

Fig. 1. Effect of single application of acupuncture on pyrogenal-induced fever in rabbits. Abscissa, time after injection of pyrogenal (in h); ordinate, change of temperature (in °C). 1) Control; 2) acupuncture in initial phase of development of fever, 3) acupuncture against the background of developed fever. Arrow indicates time of acupuncture. Values differing significantly from control at the $p < 0.05$ level are circled.

Fig. 2. Effect of repeated acupuncture on pyrogenal-induced fever in rabbits. Abscissa, time after injection of pyrogenal (in h); ordinate, change of temperature (in °C). 1) Control, 2) single application of acupuncture, 3) repeated acupuncture. Arrow indicates time of acupuncture. Values differing significantly at the $p < 0.05$ level from 1 and 2 are circled once, those differing from 1 are circled twice.

Fig. 3. Effect of propranolol on antipyretic effect of acupuncture in rabbits with pyrogenal-induced fever. Abscissa, time after injection of pyrogenal (in h); ordinate, change of temperature (in °C). 1) Control, 2) propranolol, 3) propranolol + acupuncture. Double arrow denotes time of injection of propranolol, single arrow indicates acupuncture. Values differing significantly at the $p < 0.05$ level from 1 are circled once, those differing from 1 and 2 are circled twice.

## EXPERIMENTAL METHOD

Experiments were carried out on conscious, unanesthetized, lightly restrained male Chinchilla rabbits weighing 2800-3200 g, kept without food for 12 h in order to abolish any individual differences in metabolism before the investigation. Fever was induced in all series of experiments by injection of pyrogenal in a dose of 2 $\mu$g/kg into the marginal vein of the ear [2]. In the experiments of series I, acupuncture was carried out on the animals at the Shao-Shan (Lu-II) and Shan-Yan (LI-I) points simultaneously on both limbs for 30-45 sec, in the initial phase of development of fever (45 min after the beginning of its induction). In series II, acupuncture was carried out in the same way as in the experiments of series I in the phase of maximal intensity of fever (at the 120th minute of the experiment). In series III, acupuncture was given at the same points twice, at the 45th and 120th minutes after injection of pyrogenal. In series IV, the rabbits were given an intravenous injection of propranolol (inderal, Yugoslavia) in a dose of 1-2 mg/kg 20 min before acupuncture, which was carried out in the same way as in the experiments of series I. In the control series the animals received acupuncture away from the biologically active points and/or they received an injection of propranolol in the corresponding dose. Each series of experiments was conducted on nine rabbits. The temperature was recorded by means of a TET-Ts-II thermometer every 15 min, the transducer being introduced into the rectum for a distance of 3 cm. The results of measurement

of the rectal temperature were plotted for the test period in the form of graphs, where the initial temperature was taken as the zero line. The results were subjected to nonparametric statistical analysis by the Wilcoxon–Mann–Whitney U test [3].

## EXPERIMENTAL RESULTS

Injection of pyrogenal into intact rabbits caused a febrile reaction which reached its maximum by the end of the 3rd hour after injection of the substance. Acupuncture applied at the test points during the beginning of the rise of temperature and at the time of its full development led to an equally strong antipyretic action irrespective of the phase of fever (Fig. 1).

The data describing pyrogenal-induced fever obtained during this investigation were virtually identical with those given previously by other workers [2]. The character of the temperature changes in the groups of animals, on whom acupuncture was carried out against the background of marked fever and in the initial phase of its development was identical. The febrifugal activity of acupuncture was exhibited for 60 min, when the mean fall of rectal temperature was $0.61 \pm 0.06$°C and $0.59 \pm 0.07$°C respectively. Maximal development of the febrile response was shifted a little compared with the control parameters, for the greatest changes of temperature were obtained in the 4th hour of the experiment. Later, the temperature of the experimental animals gradually fell in the same way as in the control group, and no significant differences were present between the parameters ($p > 0.05$, Fig. 1).

Repeated application of acupuncture 75 min after the first procedure (45 and 120 min after injection of pyrogenal) led to a more marked fall of temperature compared with a single application of acupuncture (Fig. 2).

The febrifugal activity of repeated acupuncture 75 min after the first procedure was exhibited for 60 min, the mean fall of temperature being $0.87 \pm 0.06$°C, which is $0.28 \pm 0.06$°C more than in animals receiving a single acupuncture ($p < 0.05$). Later a tendency was observed for the temperature curves characterizing the experimental and control groups of animals to be equalized, or even to be completely congruent (Fig. 2). Consequently, a second session of acupuncture 75 min after the first led to some potentiation of the febrifugal effect, but not to its prolongation.

Injection of propranolol into the animals caused a significant fall of temperature, which was greatest at the 60th minute of the experiment ($p < 0.05$; Fig. 3).

Comparison of the curves reflecting the febrile response to acupuncture at the points chosen for study combined with the action of propranolol, and injection of the $\beta$-adrenoblocker alone, shows that the combination of acupuncture and the drug led to synergism of the antipyretic action of the potentiation type, which continued for 2 h ($p < 0.05$) and which exceeded the combined febrifugal effect of two consecutive sessions of acupuncture (Fig. 3).

The fact that potentiation of the antipyretic effect took place during $\beta$-adrenoreceptor blockade suggests that the mechanism of the febrifugal activity of acupuncture includes a noradrenalin-negative component.

It can accordingly be concluded from these investigations that repeated acupuncture, while not prolonging the antipyretic effect, nevertheless causes some degree of its potentiation. The results also showed that the combined use of acupuncture and propranolol is a rational procedure for lowering fever in infectious diseases. Under these circumstances, potentiation of the febrifugal action of acupuncture under the conditions of $\beta$-adrenoreceptor blockade points to a possible role of the noradrenalin system in the mechanism of realization of the antipyretic action of acupuncture.

## LITERATURE CITED


1. E. O. Bragin, N. N. Batueva, and R. A. Durinyan, Byull. Éksp. Biol. Med., No. 10, 9 (1983).
2. P. N. Veselkin, I. S. Repin, and B. N. Smirnov, Models of Diseases [in Russian], Moscow (1973), pp. 46-59.
3. E. V. Gubler, Computational Methods of Analysis and Diagnosis of Pathological Processes [in Russian], Leningrad (1978), pp. 68-91.
4. Yu. D. Ignatov, A. T. Kachan, and Yu. N. Vasil'ev, Acupuncture Analgesia [in Russian], Leningrad (1990), pp. 31-159.
5. L. V. Kalyuzhnyi and O. V. Fedoseeva, Byull. Éksp. Biol. Med., No. 7, 3 (1990).
6. M. A. Kornev, P. V. Pugach, and S. I. Aleksandrov, Arkh. Anat., No. 1, 85 (1991).
7. S. V. Kunkov, Current Problems in Theoretical and Practical Medicine [in Russian], Minsk (1991), p. 113.
8. O. S. Raevskaya and G. G. Grishanin, Byull. Éksp. Biol. Med., No. 10, 339 (1990).
9. V. V. Yasnetsov, Farmakol. Toksikol., No. 2, 44 (1982).

10. Chakrabarti and M. K. Poddar, Biogen. Amines, **6**, No. 5, 417 (1989).
11. W. K. K. Ho and H. L. Wen, Neuropharmacology, **28**, No. 9, 961 (1989).
12. A. Starr, G. Abraham, Y. Zhu, et al., Arch. Neurol., **46**, No. 9, 1010 (1989).
13. Q. Wang, L. Mao, and J. Han, Brain Res., **513**, No. 1, 60 (1990).
14. D. Z. Wu, Clin. Neurol. Neurosurg., **92**, No. 1, 13 (1990).
15. S. F. Xu, Acupunct. Electrother. Res., **14**, No. 2, 103 (1989).

# EXPERIMENTAL STUDY OF THE ANTIAMNESIC ACTIVITY OF PIRACETAM IN ORCHIDECTOMIZED RATS

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**KEY WORDS:** piracetam; orchidectomy; testosterone; amnesia; microviscosity of membranes

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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