REFERENCES

1. V. P. Akopyan and L. S. Balyan, *Farmakol. Toksikol.* - № 1, 38-41 (1987).
2. V. V. Rozhanets, K. K. Chkhabra , N. D. Danchev, *et al., Byull. Eksp. Biol.*, **101**, № 1, 40-42, 1986.
3. Yu. A. Kholodov, The Brain in Electromagnetic Fields [in Russian], Moscow (1982).
4. V. V. Yasnetsov, I. N. Krylova, D. V. Pokatilov, *et al.*, Current Issues in Reflexotherapy and Traditional Medicine [in Russian], Moscow (1990), p. 50-51 .
5. R. Cumin, E.F.Bandle, E. Gamzu, and W. E. Haefely, *Psychopharmacology*, **78**, № 2, 104-111 (1982).
6. A. Lenegre, J. Avril, and R. D. Potsolt, Ibid. **96**, № 1, 35 (1988).
7. C. Masotto, J. A. Apud, and G. Racagni, *Pharmacol. Res. Commun.*, **17**, № 8, 749-772 (1985).
8. R. J. Miller and P. Cnatrecasas, *Adv. Biochem. Psychopharmacol.*, **20**, 135-147 (1979).
9. R. Simantov, S. H. Shyder, *Proc. Nat. Acad. Sci. USA*, **73**, 2515-2519 (1976).
10. G. Spignoli and G. Pepeu, *Pharmacol. Biochem. Behav.*, **27**, № 3, 491-495 (1987).

Evaluation of the Antipyretic Effect of Psychotropic Agents and Their Influence on the Fever-Lowering Effect of Acupuncture

M. V. Nezhentsev and S. I. Aleksandrov

UDC 615.214.017:615.212.3].07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 115, № 3, pp. 262–264, March, 1993
Original article submitted October 30, 1992

Key Words: *haloperidol; benactyzine; diazepam; amitriptyline; acupuncture*

At present, strenuous efforts are being directed toward the development of new therapeutic approaches as an alternative to the antipyretic and hypothermic drugs traditionally used to treat fever [6,9,10]. Despite the beneficial centuries-old application of acupuncture (AP) for fever reduction, no scientific explanation for this phenomenon has been found [3, 14]. In clinical observation, the antipyretic effect of AP in different hyperpyrexias turns out to be pronounced but short-lived [7,11,13]. It is thus desirable to seek new ways for prolonging and enhancing the antipyretic effect of AP by combining with pharmacological agents [1,4,5].

Department of Pharmacology , Pediatric Medical Institute, St.Petersburg.
(Presented by P. V. Sergeev, Member of the Russian Academy of Medical Sciences)

The aim of the present study was to investigate the effect of several psychotropic drugs on the antipyretic effect of AP.

MATERIALS AND METHODS

The experiments were carried out on 36 male Chinchilla rabbits weighing 2.5-3.5 kg. Pyrogenal (1 μg/kg) was injected intravenously for fever induction [8]. AP was performed at the shao-shan (P-11) and shan-yan (GI-1) point analogs 45 min after the start point for 30-45 sec [12]. The rectal temperature was measured with a TET-C-11 thermometer every 15 min for 6 h, inserting the probe 8 cm into the rectum.

Each set of experiments was performed on 9 animals. The control group consisted of animals on which AP was performed outside the points studied or in which AP was combined with physiological

0007–4888/93/0003–0277$12.50

saline injection. Haloperidol in doses of 0.1 and 1 mg/kg, diazepam in a dose of 2 mg/kg, benactyzine in doses of 0.1 and 1 mg/kg, or amitriptyline in doses of 5 and 10 mg/kg were injected intravenously 20 min before AP. As an additional control, for each set of the experiments animals were given the same doses of drugs and then AP outside the points.

The mean rectal temperature at every time point was determined. The difference of temperature between the control and experimental series, the maximal temperature change, and the duration of the antipyretic effect were estimated. The results of the experiments were subjected to statistical analysis by the Wilcoxson-Mann-Whitney nonparametric U test [2].

RESULTS

Pyrogenal led to a marked rise in the temperature of the rabbits, detected 15 min after injection. The fever peaked after 3 h of the experiment. The rectal temperature then dropped gradually.

AP had a pronounced antipyretic effect. The statistically significant difference in temperature between the experimental and control rabbits was maintained during 60 min after AP (see Table 1).

The neuroleptic haloperidol, whose pharmacodynamics involves the blockade of the dopamine receptors, had a pronounced dose-dependent effect on the fever course and on the antipyretic effect of AP. Its injection (1 mg/kg) resulted in a dramatic drop of the temperature below the initial level. The antipyretic activity of haloperidol was so strong that AP exhibited no detectable effect on it. A lower dose of the drug (0.5 mg/kg) produced a reliable drop of temperature. AP on this background resulted in a more pronounced drop of temperature in the experimental animals just 15 min after AP. The combined application of haloperidol (0.5 mg/kg) and AP led to a more pronounced and prolonged temperature drop in the animals as compared to AP alone (Table 1).

Our investigations showed that AP is contraindicated in combination with tranquillizers, whose pharmacodynamics involves blocking of the benzodiazepin receptors . One representative of this group, diazepam, when injected intravenously did not affect pyrogenal-induced fever. Combined application of diazepam and AP revealed a short-term antipyretic effect, which was less marked in comparison with that of AP alone ($p<0.05$; Table 1).

A representative of another group of tranquillizers, benactyzine, which acts by blocking the central M-cholinoreceptors, in a dose 0.1 mg/kg induced a long-term (2.5 h) drop of temperature in rabbits. When combined with AP, it resulted in an even more pronounced drop of temperature, the maximal decrease observed being 2,07±0.17°C, whereas benactyzine alone (0.1 mg/kg) caused a drop of 1.46±0.11 and AP alone 0.79±0.08°C. However, the antipyretic activity of benactyzine was not enhanced by increasing the dose. The effect of a combined application of 1 mg/kg tranquillizer and AP did not differ reliably from the effect of benactyzine alone in the same dose (see Table 1), apparently due to some common elements in the mechanism of their action.

TABLE 1. Influence of Pharmacological Agents on the Antipyretic Effect of AP in Rabbits with Pyrogenal Induced Fever Compared to Control Animals ($M \pm m$)

Administration and dose, mg/kg	Number of experiments	Drop of temperature, °C		Duration of antipyretic effect, min
		maximal	mean	
AP	36	0.79±0.08(60)	0.61±0.06	60±5
Haloperidol, 1	9	2.29±0.11(75)	1.77±0.11	195±10
Haloperidol,1 + AP	9	2.48±0.12(75)	1.87±0.12	195±10
Haloperidol, 0.5	9	0.67±0.09(45)	0.56±0.08	90±5
Haloperidol, 0.5 + AP	9	1.24±0.11*(75)	0.84±0.10	165±10*
Diazepam, 2	9	0	0	0
Diazepam, 2+AP	9	0,49±0.06*(60)	0.45±0.06*	45±5*
Benactyzine, 0.1	9	1.46±0.11(75)	0.89±0.10	210±10
Benactyzine, 0.1 + AP	9	2.07±0.17*(75)	1.16±0.12	210±10
Benactyzine, 1	9	1.73±0.14(60)	1.12±0.11	210±10
Benactyzine, 1 + AP	9	1.82±0.17(60)	1.25±0.12	210±10
Amitriptyline, 5	9	0	0	0
Amitriptyline, 5 + AP	9	0.94±0.09*(60)	0.83±0.08*	60±5*
Amitriptyline, 10	9	0	0	0
Amitriptyline, 10 + AP	9	1.08±0.11*	0.72±0.09*	105±5*

Note. Asterisk means significant differences ($p<0.05$) in comparison with drug treatment alone; figures in parentheses denote time after pyrogenal injection (min).

The tricyclic antidepressant amitriptylin also exhibited a dose-dependent effect on the antipyretic activity of AP. In a dose of 5 mg/kg it caused a slight and short-term enhancement of the antipyretic effect of AP without altering the dynamics of the pyrogenal-induced fever. When the effects of AP alone and of AP in combination with the indicated dose of amitriptyline were compared, a significant difference in temperature was observed only for one time point (90 min after the start), the temperature being 0.38±0.07°C lower in combined administration versus AP alone ($p<0.05$). Raising the dose of amitriptyline to 10 mg/kg also had no effect on the fever dynamics. The antipyretic effect of AP was prolonged by combination with 10 mg/kg versus 5 mg/kg amitriptyline, but the intensity of the effect was unchanged. When comparing the effects of AP and its combination with 10 mg/kg amitriptyline, it should be noted that the injection prior to AP results in a marked prolongation and some enhancement of the effect (Table 1).

Thus, AP possesses a marked but transient antipyretic effect. Haloperidol in doses of 0.5 and 1 mg/kg and benactyzine in doses of 0.1 and 1 mg/kg reduce fever in experimental animals, while diazepam in a dose of 2 mg/kg and amitriptyline in doses of 0.5 and 10 mg/kg have no effect on the dynamics of pyrogenal-induced fever. Haloperidol in a dose of 0.5 mg/kg, benactyzine in a dose of 0.1 mg/kg, and amitriptyline in doses of 5 and 10 mg/kg enhance the antipyretic effect of AP, while no enhancement occurs when haloperidol and benactyzine are injected in a dose of 1 mg/kg; diazepam in a dose of 2 mg/kg reduces both the intensity and duration of the antipyretic effect of AP.

REFERENCES

1. S. I. Aleksandrov and S. V. Kunkov, *Problems of Theoretical and Practical Medicine* [in Russian] , Ufa (1992), pp.17-18.
2. E. V. Gubler, *Computing Methods for Analysis and Identification of Pathological Processes* [in Russian], Moscow (1978).
3. M. V. Nezhentsev and S. I. Aleksandrov, *Byull. Eksp. Biol.*, **113**, № 3, 288-290 (1992)
4. M. V. Nezhentsev and S. I. Aleksandrov, *Eksp. Klin. Farmakol.* № 1, 58-61 (1992)
5. M. V. Nezhentsev and S. I. Aleksandrov, *Acupuncture and Traditional Medicine* [in Russian], Vladivostok (1992), pp. 5-6.
6. M. K. Oskolkova, D. A. Podgallo, I. P. Bryazgunov, *et al.*, *Pediatriya*, № 3, 53-56 (1980).
7. A. A. Umanskaya, E. S. Ketiladze, F. I. Ershov, *et al.*, *Nonspecific Remedies and Methods for the Prevention of Flu and other Acute Respiratory Disorders* [in Russian], Leningrad (1986), pp. 109-117.
8. E. Hac and I. Gagalo, *Pol. J. Pharmacol.*, **39**. № 3, 219-227 (1987).
9. M. Qiu, C. Sheng, N. Li, et al., *Research on Acupuncture, Moxibustion, and Acupuncture Anesthesia*, Beijing (1986), pp.820-828.
10. L. Pengtao, *Chin. Acupunct. Moxibust.* **10**, № 4, 29-31 (1990).
11. K. Sciensinski, *Scientifur.*, **13**, № 2, 116-121 (1989).
12. H. Tenk, *Praktikum der chinesischen Akupunktur und Punktmassage fur die Kinderheilkunde*, Vienna (1988).
13. Y.Wang, C. Tian, Z. Li, *Selections from Article Abstracts on Acupuncture and Moxibustion*, Beijing (1987), pp. 220-221.
14. C. C. Wu, Y. H. Houng, *Bull. Tapei Med. Coll*, **7**, 1-10 (1977).