Comparative Effects of Tranquilizers and Nootropes on the Elaboration and Functional Impairment of the Avoidance Response

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Experiments with rats show that pyracetam, phenazepam, and gidazepam accelerate the development of an avoidance response and diminish its functional impairment through unexpected exposure to electric current applied notwithstanding the relations established between stimuli, the response, and its sequelae. The drugs under study increase the reproducibility of avoidance responses in the rats after the indicated procedure, by preventing or diminishing the increase in intersignal reactions, i.e., exerted equivalent effects despite differences in the pharmacological spectra of the drugs. The results of this study show that the substances used affect emotional tension but do so by different mechanisms. Thus, the tranquilizers decrease emotional tension by acting on the emotional sphere directly, whereas pyracetam decreases it in an indirect way, by activating cognitive and mnestic processes.

Key Words: *tranquilizers; nootropic agents; avoidance response; functional impairment*

Tranquilizers and nootropes usually differ in their effects and applications. Transuilizers reduce anxiety and emotional tension (ET), cause sedation and myorelaxation, and, under certain circumstances, induce amnesia [2,4]. Nootropic agents, on the contrary, possess stimulatory properties and activate cognitive and mnestic processes [3,15]. These features of tranquilizers and nootropes dictate the selection of animal models. Anxiolytics are evaluated by traditional procedures of conflict situations and a number of other methods producing ET in animals [2,4, 9,12-14]. Nootropes are most often studied on models of conditioned responses and their disruption through various influences that cause deficiency of mnestic functions [3], such as unexpected exposure to electric current used notwithstanding the relations established between stimuli, the reaction, and its consequences [5,6,8]. This leads not only to disturbances of memory but also to increased ET. The latter circumstance suggests that tranquilizers and nootropes have a common target so that the same animal model can be used to study drugs of these two classes, which appears useful for understanding the mechanisms of action of both.

In the present study, we compared the effects of pyracetam, phenazepam, and gidazepam on the formation and impairment of avoidance responses (AR).

MATERIALS AND METHODS

Two series of tests using 112 random-bred male rats (body weight 180-200 g) were performed. In the first series, phenazepam (1 mg/kg) and gidazepam (2 mg/kg) were tested for their effects on the elaboration and functional impairment of AR. An AR was elaborated in rats for 4 days (25 stimulus presentations

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daily) in a shuttle box [5]. The conditioned stimulus was sound while the unconditioned stimulus was electric current switched on after 10 sec. On day 4 the AR was disrupted so that the animal's response did not result in switching off of the stimuli upon three runs, and the animal received electric current. After three responses, current was switched off immediately and sound after 2 sec. Thereafter, the AR level was recorded in 20 presentations under the conditions described above. Rats were injected with one of the drugs under study 30 min before each test.

The results were statistically analyzed by the nonparametric Wilcoxon and Kolmogorov—Smirnov tests.

RESULTS

Phenazepam exerted a beneficial effect in the 2nd and 3rd learning sessions (Fig. 1). The number of intersignal reaction (ISR) was higher than in the control group on day 2 of learning. Gidazepam accelerated the formation of an AR on day 1 of learning and increased the number of ISR on days 1, 2, and 3. In the presence of pyracetam, the AR and ISR exceeded their levels in the control animals in the 2nd and 3rd tests.

Disruption of the AR greatly impaired the elaborated habit in the control rats, with 1.6-fold and 2.1-fold decreases in the AR level in the second and first test series, respectively (Table 1), with a concurrent rise in the number of ISR (2 and 2.5 times, respectively) [10]. In the presence of pyracetam, phenazepam, or gidazepam, the AR was impaired less markedly, although disruption was not completely prevented. After the disruption, the AR level in the presence of any of those drugs was significantly higher than in the control. The drugs were also found to influence ET, as could be judged from changes in ISR. In the presence of phenazepam, there was virtually no increase in the number of ISR after disruption, whereas the presence of pyracetam resulted in a statistically significant increase in ISR ($p<0.05$), which, however, remained below their level in the control.

The nootropic agent and tranquilizers thus diminished the consequences of disruption, raising the level of AR reproduction and preventing or diminishing the increase in the number of ISR, i.e., they exerted equivalent effects despite differences in the spectra of their pharmacological activities.

ET is known to interfere with problem solving, and a decrease in ET facilitates this process [2,4]. Problem solving, in its turn, influences ET. Emotion is a function of some need and of the difference between existing and required information [10]. This implies that ET may be decreased by increasing the

TABLE 1. Effects of Pyracetam, Phenazepam, and Gidazepam on the Avoidance Response (AR) and Intersignal Reactions in Blocks of Five Presentations Before and After Disruption of the Response

Drug (No. of rats)	Before disruption	After disruption			
	21-25	1-5	6-10	11-15	16-20
Avoidance response					
1st series					
Phenazepam (31)	99.4±0.6**	72.9±3.4***	86.5±3.0	95.5±1.8	99.4±0.6
Saline (19)	99.0±1.0***	46.3±5.3	84.2±3.3	84.2±4.2	99.0±1.0
Gidazepam (38)	96.3±1.3***	67.4±3.8***	83.2±3.3	93.2±2.5	95.3±2.8
2nd series					
Pyracetam (12)	96.5±2.4*	80.0±5.2*	96.5±2.4*	96.5±2.4	100±0
Saline (12)	92.5±2.5*	60.5±4.7	65.7±4.3	72.5±4.1	92.5±2.7
Intersignal reactions					
1st series					
Phenazepam (31)	23.2±7.1	24.5±3.2	38.1±4.2*	25.8±4.5	9.0±3.1
Saline (19)	14.7±4.8*	36.8±7.2	54.7±6.5	37.9±6.1	6.3±3.4
Gidazepam (38)	27.4±7.4	33.7±9.6	39.5±7.9*	31.3±6.3	21.6±7.6*
2nd series					
Pyracetam (12)	20.5±8.1*	35.8±6.0	28.0±7.2	28.0±7.2	20.5±8.1
Saline (12)	18.3±7.9**	37.2±6.3	43.6±9.8	35.8±6.0	12.0±4.2

Note. *$p<0.05$, **$p<0.01$, ***$p<0.001$ for means before and after disruption; *$p<0.05$, **$p<0.01$, ***$p<0.001$ for means in the test and control animals.

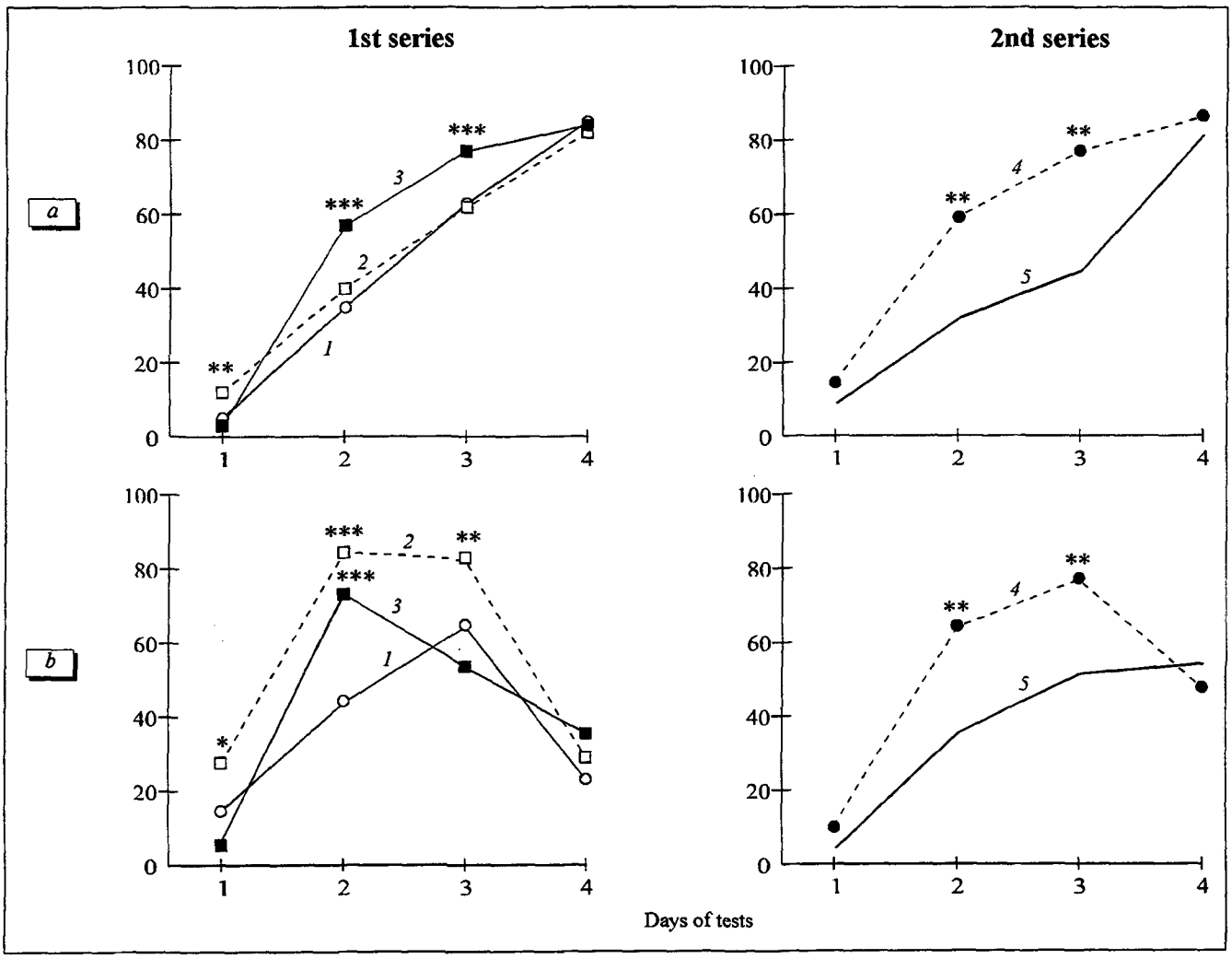

Fig. 1. Effects of pyracetam, phenazepam, and gidazepam on the establishment of avoidance responses (*a*) and intersignal reactions (*b*). Ordinate: mean values for the reactions shown in percent of the number of presentations. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ relative to the control. *1* and *5*) control rats in the 1st (*1*) and 2nd (*2*) test series, respectively; *2*) gidazepam; *3*) phenazepam; *4*) pyracetam.

amount of information on how a given problem can be solved (i.e., how a given need can be met) by raising the intellectual and mnestic potentials, optimizing the analytical/synthetic activity, and activating integrative capacities of the central nervous system, which is a prerogative of nootropes, in particular pyracetam. This drug enabled the rats to analyze more rapidly and more accurately the information contained in the results of the first attempt after disruption to get rid of electric current, so that the previously elaborated AR again became effective.

It follows, then, that substances classed among tranquilizers or nootropes influence ET but do so in different ways, with transquilizers acting on the emotional sphere directly and nootropes decreasing ET indirectly.

In view of the differences just mentioned, it is of interest that the tranquilizers prevented the growth of ISR (Table 1), whereas, as shown earlier [6], pyracetam and other nootropic agents only diminished it. Emotions and enhancement of motor activity reflect both adaptive processes associated with the mobilization of physical capabilities of the organism in situations threatening its integrity and the search for a new solution under changed conditions where the old solution is no longer effective [1,7,10,11]. In the presence of pyracetam, deviations from the experimental conditions led to an increase in the number of ISR, though to a lesser extent than in control animals (Table 1). Pyracetam prevented excessive development of the adaptation processes mentioned above without inhibiting them. In our view, this may be attributed to the fact that nootropic agents, unlike tranquilizers, influence ET indirectly, through activation of cognitive and mnestic processes.

In summary, tranquilizers and nootropes influence ET but do so by different mechanisms. Tranquilizers alleviate ET by acting on the emotional

sphere directly, whereas nootropes exert their activity in an indirect way, through activation of cognitive and mnestic processes.

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REFERENCES

1. P. K. Anokhin, *Biology and Neurophysiology of the Conditioned Reflex* [in Russian], Moscow (1968).
2. T. A. Voronina, in: *Gidazepam*, Ed. S. A. Andronati [in Russian], Kiev (1992), pp. 63-75.
3. T. A. Voronina, in: *Pharmacology of Nootropic Agents (Experimental and Clinical Studies)* [in Russian], Moscow (1989), pp. 8-19.
4. T. A. Voronina, Yu. I. Vikhlyaev, L. N. Nerobkova, *et al.*, in: *Phenazepam* [in Russian], Kiev (1982), pp. 145-151.
5. A. N. Inozemtsev and L. L. Pragina, *Zh. Vyssh. Nervn. Deyat.*, **39**, No. 4, 764-766 (1989).
6. A. N. Inozemtsev, L. L. Pragina, F. A. Firova, *et al.*, *Eksper. Klin. Farmakol.*, **58**, No. 3, 15-16 (1995).
7. V. B. Kennon, *Physiology of Emotions* [in Russian], Leningrad (1927).
8. L. L. Pragina, T. A. Voronina, A. N. Inozemtsev, *et al.*, *Farmakol. Toksikol.*, **53**, No. 3, 8-10 (1990).
9. S. B. Seredenin, Yu. A. Blednov, A. D. Durnev, *et al.*, in: *Gidazepam*, Ed. S. A. Andronati [in Russian], Kiev (1992), pp. 92-103.
10. P. V. Simonov, *The Emotional Brain* [in Russian], Moscow (1981).
11. K. V. Sudakov, *Biological Motivations* [in Russian], Moscow (1971).
12. J. E. Barret, in: *Animal Models in Psychopharmacology. Advances in Pharmacological Sciences*, Basel-Boston-Berlin (1991), pp. 37-53.
13. S. File, *Neuropsychobiology*, **13**, 55-62 (1985).
14. P. C. Moser, M. D. Tricklebank, D. N. Middlemiss, *et al.*, *Br. J. Pharmacol.*, **99**, 343-349 (1990).
15. *Nootropil. Basic Scientific and Clinical Data*, Brussels (1977).