Dependence of the Anxiolytic Effect of Tranquilizers on the Level of Anxiety in a Conflict Situation

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Experiments on random-bred albino rats demonstrate that increasing current strength in a conflict situation abolishes the effects of minor tranquilizers while the effect of potent tranquilizers is preserved at a lower level. These differences are probably due to the differing ability of tranquilizers to compete with endogenous anxiogenic ligands.

Key Words: *tranquilizers; anxiolytic activity; agents of varying strength*

The spectrum of neurotic and borderline-neurotic states in continuing to broaden. An important role in their genesis is played by anxiety disorders brought on by frustrating factors. The severity of these pathological states varies depending on the seriousness of the adverse factors and the organism's resistance, calling for strictly individual evaluation and treatment. The main drugs used in the treatment of neurosislike and borderline states are tranquilizers, primarily of the benzodiazepine family, with variously expressed anxiolytic effect: daytime preparations (medazepam), potent (phenazepam, lorazepam), and moderately potent (diazepam) agents. Potent tranquilizers are effective against both neurotic and psychotic anxiety, whereas daytime anxiolytics are less effective even in patients with a neurotic level of anxiety [1]. These data attest to the different genesis of neurosislike disorders of varying severity and to peculiarities of the mechanisms of action of daytime and potent tranquilizers.

In light of this, the aim of the present study was to compare the effects of daytime (medazepam) and potent (phenazepam) tranquilizers under conditions of severe and moderate stress modeled by the delivery of electric current of various strength in a conflict situation test. We also compared the anxiolytic effect of the anticonvulsants sodium valproate and clonazepam, and of the antioxidant dibunol, the pharmacological activity of which includes an anxiolytic component.

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MATERIALS AND METHODS

The study was carried out on random-bred male albino rats weighing 180-220 g. The anxiolytic effect of phenazepam and medazepam was studied in a modeled approach-avoidance situation based on a conflict between drinking motivation and painful electrical stimulation [3,4,10]. The experiment was carried out for 3 days. On day 1 the animals were completely deprived of water. On the next day, i.e., after a 24-hour deprivation, the animals were conditioned during 5 min to take water from a dish in experimental chambers. On day 3 the animals were again placed in the experimental chambers but 10 sec after the first drink a direct current of either 0.5 mA (moderate stress) or 1 mA (severe stress) was delivered to the dishes. Thus, each attempt to drink was punished.

The rats were divided into two series for the study of the effects of weak and strong current. Each series comprised a control group and several experimental groups for each dose of the test preparation (or its combination with RO 15-1788, an antagonist of the benzodiazepine receptors). The groups for each dose as well as the control groups for weak and strong current consisted of 10-12 rats.

A reliably increased number of punished drinkings in an experimental group in comparison with the con-

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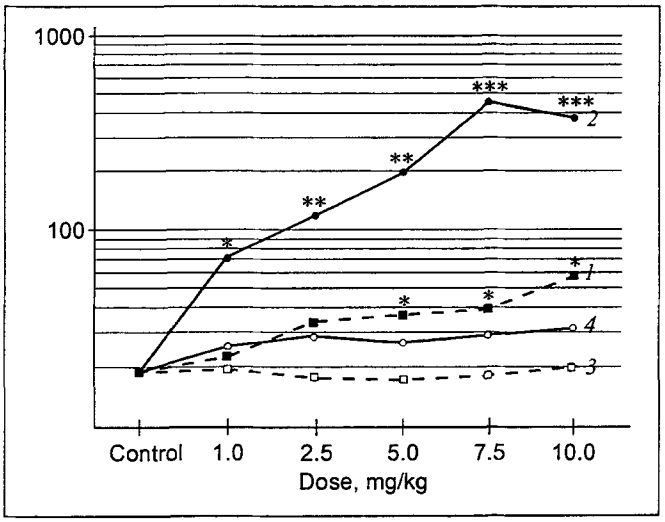

Fig. 1. Effect of phenazepam and medazepam on the number of punished drinkings in a conflict situation at a low strength of current (0.5 mA) applied to the dish and floor of the experimental chamber. Here and in Fig. 2: effects of medazepam (*1*) and phenazepam (*2*) alone and in combination with the benzodiazepine receptors antagonist RO 15-1788 (5 mg/kg, *3* and *4*, respectively). Here and in Figs. 2 and 3: the ordinate gives the number of punished responses (logarithmic scale). *$p<0.05$, **$p<0.01$, ***$p<0.001$ in comparison with the control.

trol served as a measure of the effect. The state of the animals was judged from behavioral parameters: motor activity (horizontal and vertical, visually evaluated) and the number of defecations.

The experimental data were processed using standard statistical software.

RESULTS

The experiments showed that the behavior of the controls depended on the experimental conditions (current delivered to the dish): the number of punished drinkings (Fig. 1) and motor activity (horizontal: 29.7±6.2; vertical: 18.4±5.9) were higher, whereas the number of defecations (2.1±0.8) was lower at 0.5 mA than at 1 mA (Fig. 2, motor activity and the number of defecations were 12.4±3.8, 6.1±2.7, and 4.3±0.9, respectively, $p<0.05$). This indicates that strengthening of the punishment increased anxiety in the experimental animals. Both test preparations, medazepam and phenazepam, exhibited an anticonflict activity under conditions of weak stress, which manifested itself in a reliably increased number of punished drinkings in comparison with the control, the effect of phenazepam being considerably more pronounced. The effects of the agents were dose-dependent. A decline of the animals' activity was observed for phenazepam in a dose of 10 mg/kg, presumably due to its sedative effect (Fig. 1). Under conditions of severe stress the daytime tranquilizer medazepam was inactive, while the effect of phenazepam was preserved, although at a lower level (Fig. 2). The benzodiazepine receptor antagonist RO 15-1788 (5 mg/kg) abolished the effects of both tranquilizers in the case of weak negative stimulation and the effect of phenazepam in the case of strong stimulation (Figs. 1 and 2). In both cases this points to the involvement of the benzodiazepine receptors. These variations in the action of medazepam and phenazepam are probably due to the variously expressed anxiolytic but not sedative effect characteristic for the spectrum of pharmacological activity of phenazepam, since sedatives (e.g., neuroleptics) are ineffective in a conflict situation.

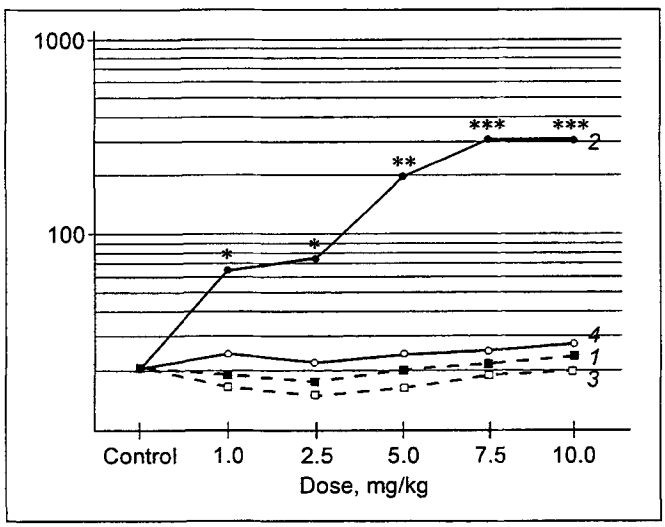

Fig. 2. Effect of phenazepam and medazepam on the number of punished drinkings in a conflict situation at a high strength of current (1.0 mA) applied to the dish and floor of the experimental chamber.

These data may be explained as follows. On the one hand, the effects of benzodiazepine tranquilizers are shown to be mediated through the benzodiazepine receptors [7], and their efficacy under both clinical [9] and experimental [5] conditions correlates with their ability to interact with the receptor complex. On the other hand, there are known to be anxiogenic ligands in the organism [6] which interact with the benzodiazepine receptors similarly to exogenous ligands. Stress increases the content of these endogenous ligands [6] and/or modulates the efficiency of binding with receptors. This effect can be assumed to depend on the degree of stress, an assumption which was indirectly confirmed by the observed decrease in punished responses and the changes in behavior of animals exposed to the stronger current in our study, as well as by previously reported modulation of benzodiazepine receptor functioning in response to stress [6,11]. Thus, under conditions of weak stress characterized by a low content of endogenous ligand and/or its weak interaction with the receptors, both the potent and minor tranquilizers are beneficial, since they are able to expel the anxiogenic ligand from the

ligand-receptor complex. When the stress factor is exacerbated, the content of anxiogenic ligand rises and/or its interaction with the receptor becomes stronger to the extent that daytime tranquilizers with low receptor affinity cannot expel it, whereas potent anxiolytics, with high receptor binding, do drive out the endogenous ligand and continue to produce an anticonflict effect, albeit less pronounced one.

It is known that benzodiazepines with predominantly anticonvulsant properties also exhibit tranquilizer activity. This prompted us to study the anticonflict effect of these preparations (in our study we chose clonazepam) under conditions of negative stimulation of varying intensity. Moreover, since diazepines act in close concert with the GABA-ergic system [7], we may anticipate that the above effects will also prove characteristic for substances with intrinsic GABA-positive activity. We therefore studied the anxiolytic activity of sodium valproate, which, apart from elevating the GABA content in the brain, exhibits a direct GABA-positive effect, augmenting postsynaptic inhibition [8]. We also used the conflict test to study the anxiolytic effect of the antioxidant dibunol, which can be abolished by the GABA-blocker bicuculline [2].

All these substances were found to increase the number of punished drinkings in a conflict situation when a current of 0.5 mA was delivered to the water dishes. When the current was increased to 1 mA, the effect was noted only for clonazepam (Fig. 3). Thus, the above assumption is also valid for these agents: dibunol and valproate are effective in moderate anxiety but not under conditions of intense stress, whereas the effect of the potent anticonvulsant clonazepam is preserved. Similar relationships were revealed in the clinical study of the anxiolytic effect of valproate. This preparation was found to be effective in reducing neurotic anxiety, i.e., minor disorders, but had practically no effect on the more severe anxiety disorders which are characteristic for epilepsy.

Thus, the findings allow us to conclude that daytime tranquilizers offer no benefit in severe anxiety disorders due to the stress-enhanced interaction of endogenous anxiogenic ligands with the receptors. The fact that potent anxiolytics retain their antianxiety activity in these cases presumably has to do with their ability to expel the endogenous ligands from the ligand-receptor complex even under conditions of severe stress.

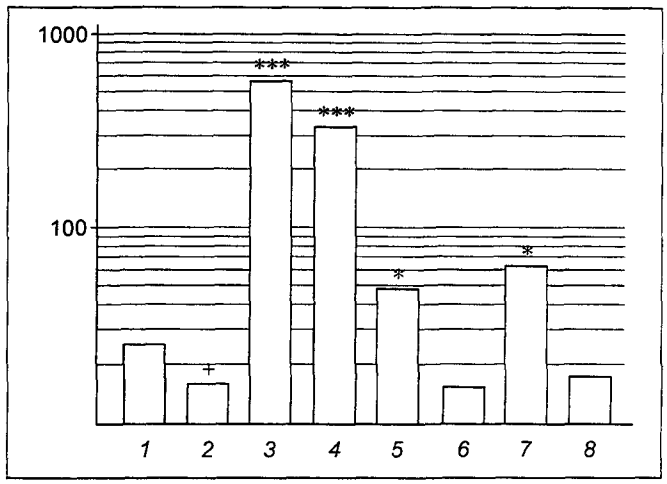

Fig. 3. Effect of stress intensity on the anticonflict (anxiolytic) effect of clonazepam, dibunol, and sodium valproate. *1* and *2*) control group, 0.5 and 1 mA, respectively; *3* and *4*) clonazepam (5 mg/kg, 0.5 and 1 mA, respectively; *5* and *6*) dibunol (400 mg/kg), 0.5 and 1 mA, respectively; *7* and *8*) valproate (400 mg/kg), 0.5 and 1 mA, respectively. $^{+}p<0.05$ in comparison with the number of punished responses in the control group.

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