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CORRECTION OF PSYCHODEPRESSANT EFFECTS OF BENZODIAZEPINE TRANQUILIZERS BY ADMINISTRATION OF PSYCHOENERGIZERS

Yu. G. Bobkov and I. S. Morozov

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The benzodiazepine tranquilizers are being increasingly used in clinical practice, including for the correction of neurotic states in clinically healthy subjects. Besides their marked antineurotic action, these substances may induce psychodepressant effects, which restrict their use in the working population. Together with the search for new benzodiazepines free from the undesirable effects mentioned above, in order to widen the indications for the use of existing preparations the search can be made for substances correcting this psychodepressant action. Such a corrector must satisfy the following demands: it must abolish the psychodepressant action of the tranquilizer but must not introduce modifications into the optimal character of the therapeutic activity of the tranquilizer as established previously, and it must likewise not reduce the tranquilizing effect of the correcting agent. Correcting properties of substances belonging to the amphetamine group have been demonstrated previously in relation to the psychodepressant effects of diazepam and phenazepam [4, 10]. However, the use of amphetamine in clinical practice is undesirable because of the possibility of development of addiction to it. The use of sydnocarb as corrector of the psychodepressant effects of phenazepam is highly effective under experimental conditions [2]. However, indications for the use of this combination are even more restricted than those for phenazepam alone [1]. The writers previously demonstrated the high and optimal corrective activity of substances with primarily dopaminomimetic properties [4, 6].

It was accordingly decided to investigate the corrective properties of other classes of compounds which possess elements of a psychostimulant action. Particular interest was shown in the effect of so-called psychoenergizers on the central effects of benzodiazepine tranquilizers. The effect of acephen, mefexamide, euclidane (nicametate citrate), and actebral (cyprodenate) on the psychodepressant action of diazepam and phenazepam was studied in the investigation described below.

EXPERIMENTAL METHOD

Experiments were carried out on 54 noninbred male albino rats. The active avoidance method [11] was used to assess the psychotropic effects of the various substances. Experiments were carried out in a situation and by a program which were fully described previously [7]. The characteristics of the experimental program were: the time of discontinuing the painful electrical stimulation after a single pressure on the pedal was 20 sec, the following frequency of the stimuli was once every 5 sec, and their duration 1 sec. An alternating current with frequency of 50 Hz and with the current strength stabilized at 1 mA irrespective of the resistance of the object was used for stimulation. In the course of the experiment the character of operant activity was recorded graphically and the number of shocks avoided was counted automatically. During subsequent processing of the data histograms of distribution of intervals between pressures on the pedal of different duration were constructed for each animal. Twenty classes were distinguished, each 1 sec in duration. The histograms were used to describe the optimality of the character of operant activity, and the number of avoided electric shocks reflected its resultativeness [9]. Stress-protective activity of the combination of drugs tested was assessed by the same method. Operant activity was tested after the animals had been securely immobilized for 1 h. Experiments were carried out on previously trained animals which missed not more than 60 shocks during an experi-

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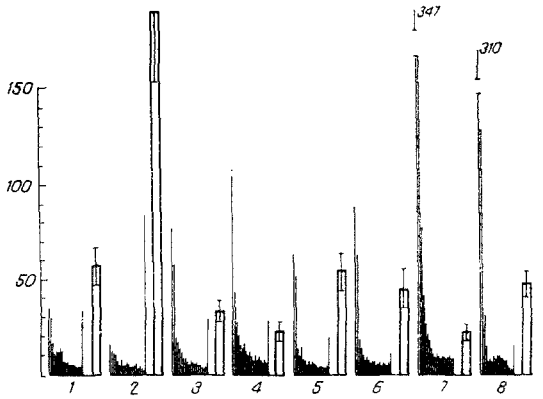

Fig. 1. Action of euclidane and sydnocarb on psychodepressant effects of phenazepam in rats as shown by operant activity test under active electric shock avoidance conditions. On left – interval histograms, columns on right – number of missed shocks. 1) Initial operant activity, 2) after injection of phenazepam, 1 mg/kg, 3, 4) after injection of euclidane in doses of 25 and 50 mg/kg respectively, 5, 6) after injection of phenazepam (1 mg/kg) and euclidane in doses of 25 and 50 mg/kg respectively, 7) after injection of sydnocarb, 15 mg/kg, 8) after injection of sydnocarb (15 mg/kg) and phenazepam (1 mg/kg).

mental session lasting 60 min. Groups of trained animals were formed, with nine rats in each group. The following program was undertaken on each group: initial operant activity was recorded after administration of physiological saline, activity was recorded after injection of the corrector in two doses, parameters of activity were again recorded after injection of the test tranquilizers, and again after combined administration of the potential correctors in two doses with the tranquilizers. Activity also was recorded after immobilization (before and after injection of the various compounds). Experiments on each group were carried out not more often than once every 3-4 days. The order of performance of the steps in the experimental program was random for each group. In the course of the program the character of activity after injection of physiological saline (control) for each group was recorded several times in order to assess the possible effect of learning. The action of the two potential correctors and of their combinations with the benzodiazepines was investigated on the animals of one group. The results, described below, were obtained during 429 experimental sessions. During experiments in which the corrective activity of the various preparations was assessed during ordinary operant activity, diazepam and phenazepam were injected in doses of 5 and 1 mg/kg respectively. In the doses specified these drugs had a marked tranquilizing effect, with manifestations of a hypnotic or sedative action. During evaluation of stress-protective activity of the test combinations phenazepam was given in a dose of 0.5 and diazepam in a dose of 2 mg/kg. These doses are optimal for exhibition of the stress-protective action of diazepam and phenazepam in this particular test [5]. Acephen, mefexamide, euclidane, and actebral were injected in doses of 25 and 50 mg/kg. As the drug for comparison, sydnocarb in a dose of 15 mg/kg was used. All compounds were injected intraperitoneally 60 min before the experiment began.

EXPERIMENTAL RESULTS

After injection of the test benzodiazepines, under conditions uncomplicated by any emotiogenic procedure, characteristic changes were observed in operant activity (Fig. 1). The number of "warning" pressures on the pedal was substantially reduced (intervals between pressures on the pedal under 20 sec). There was a particularly marked decrease in the number of short (1-2 sec) intervals. The number of "avoiding" pressures (intervals 20 sec or longer in duration) was increased. The number of missed shocks was considerably increased. These changes after injection of phenazepam in a dose of 1 mg/kg and of diazepam in a dose of 5 mg/kg were approximately equal in intensity (Fig. 1). Combined administration of diazepam and acephen caused a substantial decrease in the intensity of the psychodepressant effects of diazepam. The number of intervals 1-2 sec in duration and the total number of pressures on the pedal increased, whereas the number of missed shocks and

TABLE 1. Effect of Acephen, Euclidane, and Sydnocarb on Stress-Protective Effect of Diazepam and Phenazepam (M ± m)

Pharmacological conditions	Number of intervals 1-2 sec in duration	Number of intervals 20 sec in duration	Number of missed shocks
Control without immobilization	68±7	31±3	53±10
Control with immobilization	20±3	51±4	148±21
Diazepam (2)	62±5	24±5	93±11
Phenazepam (0.5)	65±5	29±6	97±10
Acephen (25) + diazepam (2)	72±5	26±4	82±9
Acephen (50) + diazepam (2)	78±6	24±4	75±6
Euclidane (25) + diazepam (2)	68±4	29±2	83±4
Euclidane (50) + diazepam (2)	72±6	24±3	77±6
Acephen (25) + phenazepam (0.5)	77±6	31±5	86±9
Acephen (50) + phenazepam (0.5)	80±7	22±1	71±9
Euclidane (25) + phenazepam (0.5)	71±6	24±6	80±6
Euclidane (50) + phenazepam (0.5)	77±4*	25±9	74±7
Sydnocarb (15) + phenazepam (0.5)	160±13*	15±4	62±7

Legend. *P < 0.05 compared with initial data without immobilization; dose of drug (in mg/kg) shown in parentheses.

the number of intervals 20 sec in duration decreased, the former to its initial level. This effect of acephen was more marked when it was given in a dose of 50 mg/kg. In the doses studied, acephen also reduced the intensity of the psychodepressant effects of phenazepam.

After injection of acephen alone, changes in operant activity characteristic of drugs with activity of stimulating type was observed: an increase in the number of short intervals and in the total number of pressures on the pedal, a decrease in the number of missed shocks and of intervals 20 sec in duration. This action was seen more clearly when acephen was given in a dose of 50 mg/kg.

Mefexamide, within the dose range tested, also reduced the psychodepressant effects of diazepam and phenazepam. Injection of mefexamide alone (proportionally to the dose) had the characteristic effect of acephen on operant activity. Compared with acephen, mefexamide in a dose of 50 mg/kg caused a less marked increase in the number of short (1-2 sec) intervals and a greater increase in the total number of pressures on the pedal. Euclidane, when given together with diazepam and phenazepam (Fig. 1), also optimized operant activity when disturbed as a result of administration of the tranquilizers. However, after injection of euclidane in doses of 25 and 50 mg/kg together with tranquilizers, the number of short intervals increased considerably compared with the control. The use of euclidane alone led to an increase in the number of short intervals compared with the original level by 3 times or more. The total number of pressures on the pedal increased only a little, whereas the number of missed shocks was considerably less than in the background period (Fig. 1). Actebral, within the dose range tested, had virtually no effect on the intensity of the psychodepressant effects of diazepam and phenazepam, according to the test used. After injection of sydnocarb there was a marked (by 16-17 times) increase in the number of short intervals, an increase in the number of pressures on the pedal, and a statistically significant decrease in the number of missed shocks. In the dose tested, sydnocarb also corrected the psychodepressant effects of the tranquilizers. However, the character of operant activity after injection of sydnocarb together with the test tranquilizers differed significantly from its initial character, chiefly with respect to the number of short intervals (Fig. 1).

Immobilization of the animals for 1 h led to significant changes in the character and resultativeness of the operant activity (Table 1). There was a considerable (threefold) increase in the number of missed shocks and also in the number of intervals 20 sec in duration ("avoiding" pressures). The number of short intervals between pressures on the pedal was reduced compared with their number in the animals under ordinary conditions by more than two-thirds. Diazepam and phenazepam (Table 1) in small doses (2 and 0.5 mg/kg respectively)

normalized operant activity when disturbed because of the action of emotiogenic factors. Injection of the psychoenergizers in doses of 25 and 50 mg/kg preserved the normalizing action of these tranquilizers on the character of the animals' operant activity after immobilization. The basic parameters of operant activity under these circumstances did not differ significantly from their corresponding values for groups of animals not immobilized. The exceptions were results obtained with animals receiving mefexamide (50 mg/kg) and diazepam (2 mg/kg) and also euclidane (50 mg/kg) and phenazepam (0.5 mg/kg) after immobilization. In those cases the character of operant activity differed from the initial form in the larger number of short (1-2 sec) intervals between pressures on the pedal, which was observed also when mefexamide or euclidane was given alone. Similar changes in the character of this type of operant activity were observed as a result of combined administration of diazepam with sydnocarb [4]. Sydnocarb, if injected together with phenazepam, had a similar action under these conditions (Table 1).

The results thus indicate that acephen, mefexamide, and euclidane, if administered together with diazepam and phenazepam, are able to correct the psychodepressant effects of these tranquilizers, namely lowering of the quality and changes in the character of a complex form of behavior studied, more optimally than sydnocarb. The stress-protective properties of the tranquilizers themselves are unaffected. Actebral, within the dose range tested, proved to be ineffective as a corrector of the psychodepressant effects of diazepam and phenazepam.

The mechanism of the corrective effect of substances with a psychostimulant type of action tested previously (amphetamine, metamphetamine, and sydnocarb) is associated with their activating effect on central dopaminergic and noradrenergic mediator systems [4, 6, 10]. The psychoenergizers have no effect on catecholamine metabolism and have neither adrenomimetic nor adrenosensitizing properties. The mechanism of their psychostimulant action is probably connected with changes in metabolism of central neurons, for with the exception of actebral, these compounds definitely increased physical endurance and resistance to various extremal factors [2].

The use of substances increasing the supply of energy for activity of nerve cells may thus be another possible pharmacological method of correcting the psychodepressant effects of tranquilizers of the benzodiazepine series.

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