CROSS TOLERANCE DURING COMBINED TREATMENT WITH BENZODIAZEPINES AND OTHER DRUGS

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One feature which distinguishes the prolonged administration of drugs of the benzodiazepine series to man and animals is the rapid development of tolerance as reflected in the muscle relaxing effect [1, 3]. The absence of correlation between the blood levels of benzodiazepine or its biotransformation products and the development of tolerance based on the muscle relaxing effect in mice [3, 6] indicates that the mechanism of habituation for this type of action is unconnected with pharmacokinetic factors. By analogy with addiction to morphine, it can be suggested that tolerance to benzodiazepines is based on disturbance of interaction between the drug and its receptor.

To obtain a broader view of the mechanism of tolerance to benzodiazepines, in the investigation described below the ability of various psychotropic drugs and hypothetical endogenous ligands of benzodiazepine receptors to replace benzodiazepines during repeated administration of the drugs was studied.

EXPERIMENTAL METHOD

Male mice weighing 18-24 g were used. The muscle-relaxing effect of the drugs was assessed by determining disturbance of movement coordination by means of the revolving rod test [2]. In the experiments of series I the substitute drugs were injected after prolonged administration of phenazepam in the course of development of tolerance to that drug. In the experiments of series II phenazepam was given against the background of prolonged administration of various substitute drugs. In series III administration of phenazepam alternated with that of the substitute drug; phenazepam on one day, the substitute for one day, and so on.

All drugs were used in equieffective doses, at which a well-marked muscle relaxing effect was observed in 100% of animals. The drug was injected intraperitoneally once a day. The drugs used were: tranquilizers of the benzodiazepine series – phenazepam (40 mg/kg), lorazepam (50 mg/kg), diazepam (40 mg/kg), grandaxine* (400 mg/kg); tranquilizers from other classes of chemical compounds: lonetil (400 mg/kg), meprobamate (200 mg/kg), and atarax* (100 mg/kg); neuroleptics – chlorpromazine (8 mg/kg), trifluoperazine (4 mg/kg); the sedative phenobarbital (100 mg/kg); ethanol (4 mg/kg); GABA-positive drugs – calcium valproate (480 mg/kg), muscimol (3 mg/kg); presumptive endogenous ligands of benzodiazepine receptors: nicotinamide (2200 mg/kg), inosine (1000 mg/kg).

EXPERIMENTAL RESULTS

Phenazepam, in a single dose of 40 mg/kg, caused marked disturbances of a muscle relaxing nature (disturbance of movement coordination, inhibition of the pulling reflex) in 100% of animals. In response to a second injection of phenazepam the effect persisted in 20% of animals, after a third injection in only 5%, and after the fourth and subsequent injections of the drug the muscle-relaxing effect disappeared completely. Against the background of developing tolerance to phenazepam (on the 6th day) administration of lorazepam or diazepam showed complete substitution of phenazepam and preservation of tolerance, and when grandaxine was given a muscle-relaxing effect occurred in only 20% of animals. By contrast to drugs of the benzodiazepine series, chlorpromazine, trifluoperazine, ethanol, phenobarbital, tranquilizers of nonbenzodiazepine structure

*Translator's note: Grandaxine = tofisopam; atarax = hydroxyzine.

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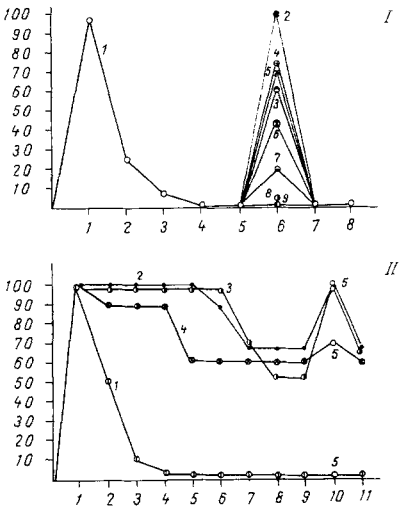

Fig. 1

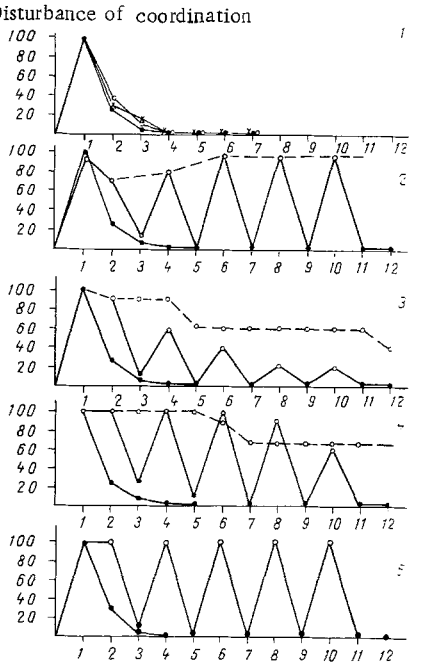

Fig. 2

Fig. 1. Cross tolerance during administration of benzodiazepine and depriming agents. Abscissa: frequency of stimulation (in Hz), ordinate: effect (in %). I) Effect of depriming substances on tolerance to phenazepam: 1) phenazepam, 2) meprobamate, atarax, chlorpromazine, trifluoperazine, phenobarbital, ethanol, or muscimol, 3) calcium valproate, 4) inosine, 5) lonetil, 6) nicotinamide, 7) grandaxine, 8) lorazepam, 9) diazepam; II) effect of phenazepam on tolerance to depriming agents: 1) diazepam, 2) meprobamate, 3) phenobarbital, 4) nicotinamide, 5) phenazepam.

Fig. 2. Development of tolerance to phenazepam when administered alternately with other psychotropic drugs. Abscissa, days of injection; ordinate, effect: disturbance of coordination (in %). Filled circles indicate phenazepam. 1) Diazepam (empty circles) or lorazepam (crosses); 2) calcium valproate (empty circles); 3) nicotinamide (empty circles); 4) meprobamate (empty circles); 5) chlorpromazine (empty circles).

(meprobamate, atarax), or the GABA-ergic receptor blocker muscimol, if administered under conditions of tolerance to phenazepam, caused disappearance of the tolerance and the development of marked muscle relaxation phenomena in all animals (Fig. 1). Lonetil, calcium valproate, sodium hydroxybutyrate, inosine, and nicotinamide had the property of partly preserving tolerance developing to phenazepam.

In the experiments of series II, when phenazepam was injected after the development of tolerance to other drugs (on the 10th day of administration of the drugs), it was found that phenazepam was able to replace diazepam completely and nicotinamide partly. Meanwhile injection of phenazepam into animals tolerant to meprobamate or phenobarbital led to the appearance of muscle relaxation in 100% of mice.

In the experiments of series III injection of phenazepam alternated with administration of the other drugs. Injection of phenazepam into the same animals alternately with meprobamate, atarax, chlorpromazine, or phenobarbital (phenazepam one day, the replacement drug for one day) revealed superposition of the effects of the drugs: each drug acted independently, apparently quite apart from the rest. For instance, the muscle-relaxing effect of phenazepam during alternation of the drugs disappeared by the 2nd-3rd day of its administration, whereas the effects of chlorpromazine, meprobamate, atarax, and phenobarbital remained stable in 100% of animals even on the 10th day of administration of the drugs (Fig. 2). By contrast, during alternation of phenazepam and drugs of the benzodiazepine series (diazepam or lorazepam) the drugs acted interconnectedly and the pattern of tolerance was the same as when phenazepam was given alone. Of drugs of nonbenzodiazepine structure, nicotinamide and calcium valproate produced partial cross tolerance when given alternately with phenazepam (in the initial stages of development of tolerance).

Complete cross tolerance with phenazepam, as reflected in the muscle-relaxing effect, was thus produced only by drugs with benzodiazepine structure. Neuroleptics, ethanol, tranquilizers with a different chemical structure (meprobamate, atarax), and muscimol (an agonist of GABA-ergic receptors) could not replace benzodiazepines. Partial cross tolerance with phenazepam was exhibited by nicotinamide, inosine, calcium valproate, and lonetil.

These results indicate the high selective specificity of the phenomenon of cross tolerance to benzodiazepines. An interesting rule was discovered: ability to replace benzodiazepines is a property of substances (nicotinamide, inosine) which bind with sufficient affinity to benzodiazepine receptors [5, 8, 10] and, conversely, substances unable to bind (tranquilizers with nonbenzodiazepine structure, neuroleptics, ethanol) [11] do not produce cross tolerance. There is also evidence that during prolonged administration of benzodiazepines regions of their specific binding are modified [4, 9]. These observations indicate the possible involvement of adaptive mechanisms at the level of interaction between the drug and its receptor in the process of development of tolerance to benzodiazepines.

Inosine and nicotinamide are nowadays regarded as possible endogenous ligands of benzodiazepine receptors [5, 8, 10]. They produce benzodiazepine-like effects and have the property of binding with the benzodiazepine receptor. The presence of partial cross tolerance when these drugs are used with benzodiazepines points to their affinity for these drugs and is evidence in support of the hypothesis [8, 10] that these substances may have a role as endogenous ligands. The development of tolerance to benzodiazepines does not evidently involve the receptor system for GABA, because muscimol, a direct agonist of GABA-receptors, is not concerned in the process of development of tolerance.

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