PHENAZEPAM-INDUCED DISSOCIATED STATE OF REVERSIBLE AMNESIA

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In the modern view a dissociated state is behavior dissociated from normal, during which a skill or conditioned reflex is manifested only after administration of a drug during administration of which this type of behavior was formed [4, 6, 14], and substances inducing dissociation are defined as a special kind of stressors, affecting the formation and storage of information in the system [1, 4]. The range of substances capable of inducing a dissociated state is quite wide, but it includes only centrally acting substances such as barbiturates, alcohol, meprobamate, psychostimulants, narcotics, and general anesthetics [1, 3, 10, 12, 13]. The ability of tranquilizers to induce a state of dissociation is not yet clear. Data are available only on their use as discrimination factors, and there are also isolated reports in the western literature on the possibility learning arising during administration of chlordiazepoxide [8, 9, 11].

The object of this investigation was to study the ability of the benzodiazepine tranquilizer phenazepam to induce a dissociated state and to discover the principles governing the formation and extinction of this phenomenon.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 280-300 g in a T maze [2]. After the habituation procedure (free behavior in the maze for periods of 20 min daily for 3 days) a conditioned drinking reflex was formed in the rats, consisting of visiting the right (target) compartment of the maze where there was a bowl containing water. The daily training session consisted of seven visits. The conditioned stimulus was the click produced by opening the door. The criterion of reflex formation was error-free identification of the target compartment with a visiting time of not more than 5 sec. To induce a dissociated state in the animals with a stable conditioned reflex, the same response was again formed but against the background of phenazepam (0.5 or 2 mg/kg daily, intraperitoneally, 30 min before each session).

EXPERIMENTAL RESULTS

The study of the time course of formation of the dissociated state showed that the animals were able to negotiate the maze both after taking the drug and under normal conditions (24 h after its withdrawal). After administration of phenazepam for 3 days, the appearance of the conditioned reflex in the rats with and without the drug was virtually indistinguishable. After training for 2 weeks, against the background of phenazepam, a considerable disturbance of the conditioned reflex was found in the rats under normal conditions, but administration of phenazepam only partially abolished this disturbance, evidence of a transition period in the formation of dissociated learning. After daily administration of phenazepam for 2-3 weeks a dissociated state arose, characterized by the fact that the conditioned reflex formed in the rat was exhibited only against the background of phenazepam (Fig. 1). When the action of the drug ceased (after 2 h or more) the animals did not exhibit the conditioned reflex, i.e., in the normal state complete amnesia had arisen relative to the skill formed in the rats during its administration, but the amnesia was reversible in character. After administration of phenazepam, the animals again visited the target

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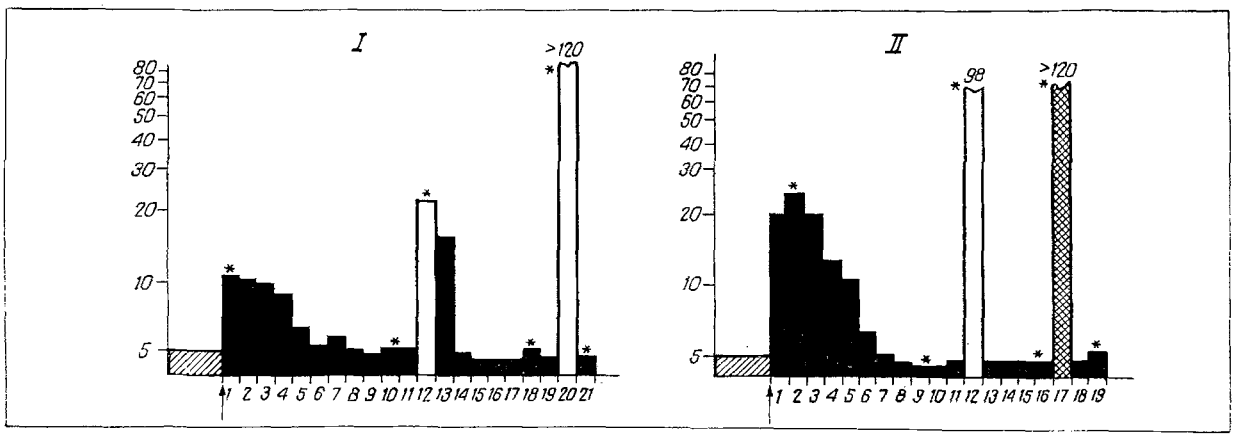

Fig. 1. Time course of formation of dissociated state during administration of phenazepam in doses of 0.5 (I) and 2 mg/kg (II). Shaded columns — time of reflex before beginning of phenazepam administration; black columns — time of reflex during daily administration of phenazepam (recording made 30 min later); unshaded columns — time of reflex without phenazepam administration (dissociation); cross-hatched columns — time of reflex in animals trained during administration of phenazepam in a dose of 2 mg/kg, when given a dose of 0.5 mg/kg. Abscissa, daily training sessions; ordinate, mean duration of reflex (in sec). Arrow indicates beginning of daily administration of phenazepam.

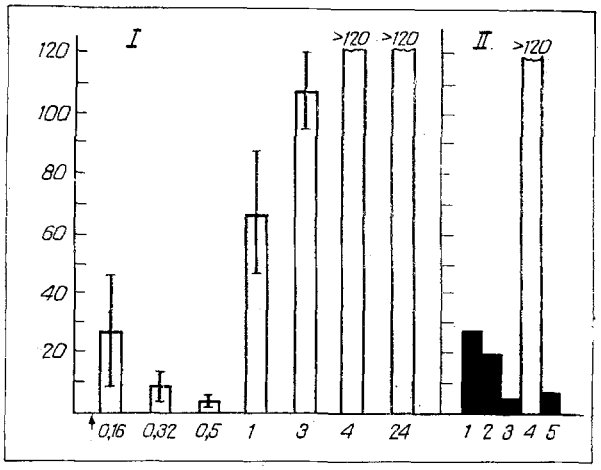

Fig. 2. Dependence of intensity of dissociated state on time factor. I) Dependence of intensity of dissociated learning on time interval between administration of phenazepam (2 mg/kg) and recording of reflex. Abscissa, time (in h) after injection of phenazepam; ordinate, time of reflex (in sec). II) Reproduction of dissociated state 45 days later. Abscissa, training sessions accompanied by administration of 2 mg/kg phenazepam after an interval; ordinate, time of reflex (in sec). Remainder of legend the same as to Fig. 1.

compartment with great accuracy.

The depth of the dissociated state depended on the dose of phenazepam: the higher the dose, the more marked the sedative inhibitory action when a single dose was given, the more clearly dissociation was exhibited (Fig. 1). For instance, when training was given against the background of phenazepam in a dose of 0.5 mg/kg a dissociated state developed on the 21st day of administration of the drug, compared with the 14th day when the dose given was 2 mg/kg. Furthermore, if the dose given to animals with dissocated learning in response to

TABLE 1. Effect of Phenazepam on Conditioned Reflex Formation in a T Maze

Day of injection of drug	Reflex performance time, sec	
	control	phenazepam 0.5 mg/kg
1	113,05 (105,46—120,64)	128,22 (121,09—135,85)
2	112,27 (105,25—119,29)	111,11 (97,94—124,28)
3	107,38 (96,42—118,34)	107,11 (88,99—125,23)
4	110,44 (102,29—118,59)	102,33 (84,76—119,90)
5	103,94 (95,37—112,51)	103,33 (85,49—121,17)
6	96,22 (87,23—105,21)	98,00 (79,88—116,12)
7	95,33 (84,23—106,43)	85,88 (59,25—112,51)
8	83,11 (70,04—96,18)	55,33 (24,86—85,80)
9	78,88 (63,84—93,92)	55,77 (23,38—88,16)
10	59,16 (42,86—75,46)	48,66 (16,27—81,05)
11	42,44 (25,85—59,03)	—
12	35,50 (18,15—52,85)	—
13	30,88 (14,15—47,61)	8,11 (0,15—16,07)
14	20,77 (4,04—37,35)	2,75 (1,19—4,31)
15	28,72 (11,99—45,46)	3,11 (1,74—4,48)
16	17,33 (3,11—31,53)	3,55 (2,18—4,92)
17	16,66 (1,90—31,42)	
18	8,3 (4,1—12,5)	
19	4,6 (2,7—6,5)	
20	4,5 (6—5,5)	

2 mg/kg of phenazepam was reduced to 0.5 mg/kg, reflex formation was impaired. This suggests that the dissociated state was determined by the degree of saturation of the animal with the drug. The depth of dissociated learning also largely depended on the time interval between administration of phenazepam and recording of the reflex (Fig. 2). Optimal visiting behavior was observed 30 min after administration of phenazepam, i.e., under the same temporal conditions as those during which dissociated learning was formed. With shorter intervals the reflex was manifested less clearly, possibly on account of incomplete absorption of the drug. With an increase in the time interval between administration of phenazepam and recording of the effect, gradual weakening of the reflex was observed, and after 4 h complete amnesia of the skill of visiting the bowl of drinking water was observed and persisted for a long time (72 h or more).

Since the conditioned reflexes formed in rats with the maze with positive reinforcement as a rule disappear 28-30 days after training [1, 6], and since the skill can be restored only under special conditions, testing for extinction of the reflex was carried out 1-1.5 months after the last session of dissociated learning. During this period the animals were kept in the vivarium without the drug. Investigations showed that in the case of training accompanied by phenazepam (2 mg/kg) the length during which it was preserved was considerably increased: the rats still continued to visit the drinking bowl after injection of phenazepam even 40 days or more after the complete cessation of training (Fig. 2).

Since one of the requirements of drugs for use in dissociated learning is inability to substantially modify the fixation and storage of information [1, 13, 14], the effect of phenazepam on the rate of formation of a conditioned maze reflex was studied. Phenazepam (0.5 mg/kg), injected daily from the 1st day of training, not only did not disturb the process of reflex formation, but actually speeded up the fixation and stabilization of the skill (Table 1).

The investigations showed that when training was accompanied by phenazepam administration a dissociated state appeared, in which the reflex was exhibited only during administration of the drug and not without it, i.e., under normal conditions.

There is no unanimity at present regarding the mechanism of onset of a dissociated state as a result of set of specific changes in the coding and recall of information [1, 4, 12, 14]. It can be tentatively suggested that when training is accompanied by phenazepam administration, the system connected with performance of the maze reflex under normal conditions is blocked, new connections are formed, and on their basis a new functional system performs the conditioned-reflex activity, but only if the drug is present in the body. The results shed light on the character of amnesia observed in man and animals after administration of large doses of benzodiazepines [5, 7], whose development was hitherto

inexplicable. Loss of memory in these cases is evidently connected with the onset of a dissociated state, and information received under these conditions is not recalled when the drug has disappeared from the body, i.e., under normal conditions.

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