THE EFFECT OF ETHYZINE* ON THE CONDITIONED REFLEXES OF DOGS

E. K. Aganyants

From the Department of Normal Physiology (Head — Prof. P. M. Starkov) of the Kuban Medical Institute, Krasnodar

(Received September 30, 1958. Presented by Active Member AMN SSSR V. V. Parin)

Neurolytic drugs of the phenothiazine group have recently been widely used for purposes of potentiation of anesthesia and the production of hypothermia [3, 7].

After chlorpromazine and phenergan, one of the more potent members of this groups is ethyzine (synonyms: phenethazine, anergan, lisergin), which, according to the investigations of M. D. Mashkovskii and his co-workers [10], possesses antihistamine and adrenolytic actions. According to L. E. Kovalev [6], ethyzine depresses the electrical activity of the cerebral cortex.

The character of the effect of ethyzine on conditioned reflexes has not so far been studied, whereas a large number of investigations relate to chlorpromazine [1, 2, 4, 5, 12].

In view of the topical importance of this question, in our present research we set out to study the effect of ethyzine on conditioned reflexes in dogs.

EXPERIMENTAL METHOD

The investigation was carried out on 4 dogs in a conditioned reflex chamber. The dogs Valetka and Laska had conditioned reflexes to food, with short periods of delay (10 seconds), from various analyzers, and differentiation of one reflex. In Laska, besides short-delay reflexes to light, a conditioned reflex to a knocker, with a delay of 2 minutes, was developed. As unconditioned stimulus we used a meat and biscuit powder (10g). Registration of the saliva was done by the method of A. I. Makarychev [9]. At the same time, the respiratory and masticatory movements and also the stimulus and time markers were recorded on the kymograph.

In two other dogs Sil'va and Sedaya, protective respiratory conditioned reflexes were developed to a bell as positive stimulus, a bell as differential, to light and to touch. The unconditioned stimulus was ammonia, which was expelled from a system of tubes into the nostril of the animal. All the conditioned stimuli except the light were delayed for 5 seconds from the beginning of action of the unconditioned stimulus, and the light was delayed for 30 seconds.

Ethyzine was injected intramuscularly as a 1% solution in distilled water, in doses of 0.5 to 25 mg/kg body weight. The investigation of the conditioned reflexes began 15 minutes after injection of the drug, and continued for 3-6 hours.

Altogether 35 experiments with ethyzine and 6 control experiments, in which distilled water was injected intramuscularly, were carried out.

* Ethyzine is N-(2-dimethylaminoethyl)-phenothiazine hydrochloride, or phenethazine.

TABLE 1

The Effect of Ethyzine on Conditioned Reflexes in the Dog Valetka

Experiment No.	1	2	3	4	5	6
Dates of experiments	3/I-57	7/I-57	9/I-57	17/I-57	21/I-57	24/I-57
Doses of ethyzine, in mg/kg body weight	0,5	1	2	5	7	10
Metronome +240	8 10 9	10 5 8	9 0 0	9 0 5	7 0 3	8 0 0
Light	2 4 2	8 0 1	4 0 2	4 0 0	5 0 0	5 0 0
Touch	4 5 5	7 1 2	7 0 2	5 0 0	5 0 0	4 0 0
Metronome -60	0 1 0	2 0 0	0 0 1	1 0 5	0 0 0	2 0 0
Total	14 20 16	27 6 11	20 0 5	19 0 10	17 0 3	19 0 0

Note. The magnitude of the conditioned reflexes is given in drops of saliva during 30 seconds of action of the conditioned stimuli. In each experiment the first column of figures gives the initial magnitude of the reflexes, the second gives the magnitude of the reflexes 20-60 minutes after administration of ethyzine and the third gives the magnitude of the reflexes 3-4 hours after administration of ethyzine.

EXPERIMENTAL RESULTS

The observations showed that a small dose of ethyzine (0.5 mg/kg) caused disturbance of the cortical processes. Under these circumstances the positive conditioned reflexes were increased and differentiation was disinhibited. In Valetka, the magnitude of the conditioned reflexes was increased by 1-2 drops of saliva during 30 seconds of action of the stimulus, and in Laska by 2-5 drops. Differentiation in the first dog was disinhibited up to one drop of saliva, and in the second to 2 drops. In Laska, besides disinhibition of differentiation, a shortening of the inhibitory phase of the delayed conditioned reflex was observed (Tables 1 and 2).

The increase in the magnitude of the positive conditioned reflexes with, at the same time, disinhibition of differentiation and shortening of the inhibitory phase of the delayed reflex indicated weakening of the processes of internal inhibition. Simple observation of the animals' behavior meanwhile showed no abnormality after administration of small doses of ethyzine.

Increasing the dose of ethyzine to 1 mg/kg caused, in Valetka, a sharp fall in the conditioned reflexes to the metronome, to touch and, as far as complete extinction, to light. Differentiation was not disinhibited. A similar picture was observed in the case of Laska. In the latter, however, the action of ethyzine developed gradually, so that the changes in the cortical processes could be followed. In the first 30 minutes after administration of ethyzine, disappearance of the delayed conditioned reflex to the knocker and dishinhibition of differentiation to light up to 3 drops were observed (experiment No. 2, Table 2). The magnitude of the positive conditioned reflex to light was not altered under these circumstances.

The fact that there was marked disinhibition of differentiation to light and no change in the magnitude of the positive conditioned reflex to the same stimulus indicated considerable weakening of internal inhibition. Meanwhile, the complete extinction of the delayed conditioned reflex was evidence of a lowering of the level of excitation in the cerebral cortex. In the 30 minutes following administration of ethyzine (1 mg/kg) gross weakening of excitation was observed — the conditioned reflex to light disappeared and differentiation was not disinhibited (Table 2).

After larger doses of wthyzine were given (from 1.5 to 2.0 mg/kg), in Valetka the artificial conditioned reflexes fell to zero and differentiation also had a value of zero (Table 1). In Laska, the action of these doses

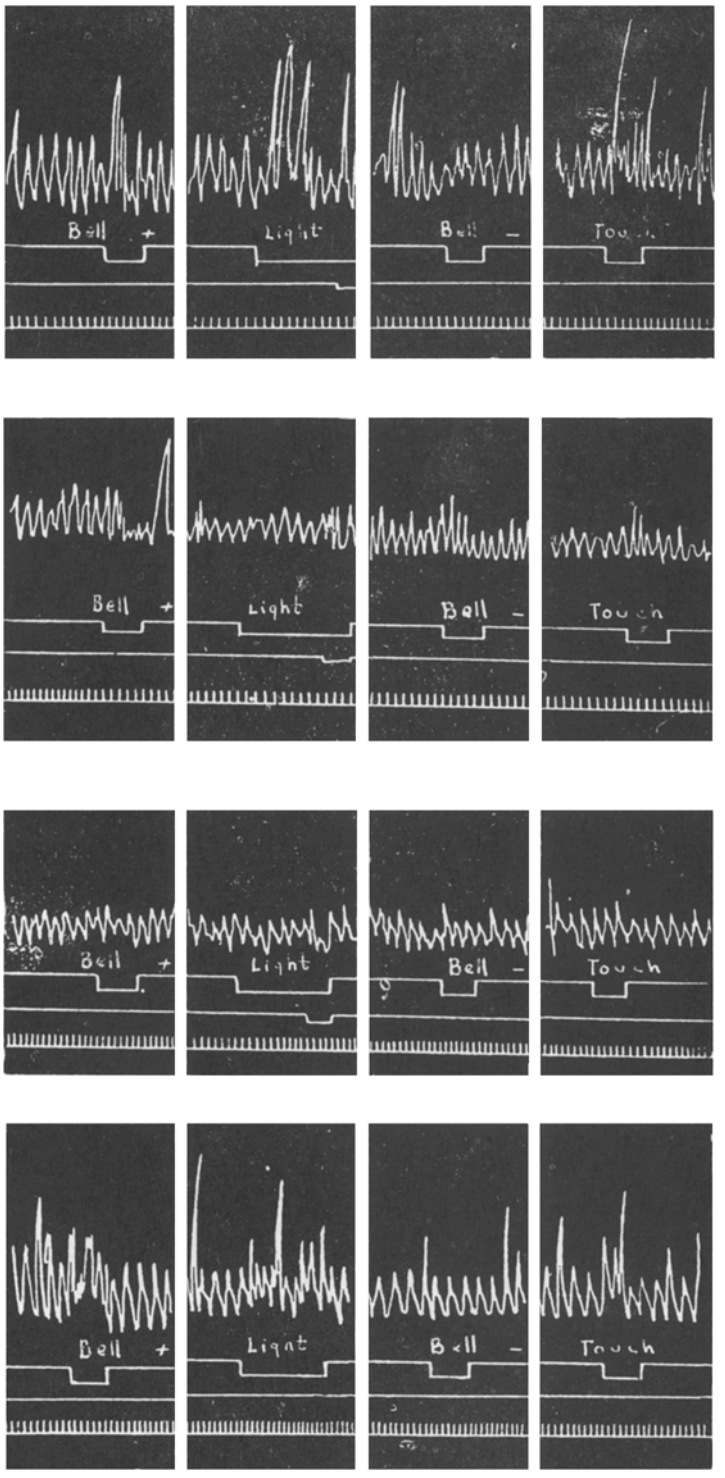
TABLE 2

The Effect of Ethyzine on Conditioned Reflexes in the Dog Laska

Experiment No.	1			2				3			4			5			6		
Dates of experiments	21/XII 1956			24/XII 1956				26/XII 1956			29/XII 1956			2/I 1957			5/I 1957		
Doses of ethyzine, in mg/kg body weight	0,5			1				1			1,5			1,5			2		
Metronome	0002	0022	0002	0012	0000	0000	0012	0001	0013	1024	0002	0002	0004	0104	0016	1004	0004	0010	0002
Light +	3	8	4	4	4	0	3	6	4	3	4	2	4	7	3	5	3	6	0
Light -	0	2	0	1	3	0	1	1	1	1	0	2	0	3	0	1	1	1	1
Total	5	14	6	8	7	0	6	8	9	11	6	6	8	15	10	11	8	8	3

Experiment No.	7			8			9			10			11			12		
Dates of experiments	15/I 1957			18/I 1957			21/I 1957			24/I 1957			28/I 1957			30/I 1957		
Doses of ethyzine, in mg/kg body weight	3			5			7			10			15			25		
Metronome	0002	0014	0002	0003	0000	0010	0046	0000	0001	0026	0000	0001	0014	0000	1001	0004	0001	0010
Light +	4	2	4	5	0	1	3	0	0	5	1	0	4	0	0	2	0	1
Light -	0	0	0	0	0	0	1	0	0	0	0	1	0	0	1	0	0	0
Total	6	7	6	8	0	2	14	0	1	13	1	2	9	0	3	6	1	2

Note. The delayed conditioned reflex to the metronome is given in drops of saliva during each 30 seconds of action of the stimulus (for 2 minutes altogether). The magnitude of the conditioned reflex to light and of differentiation are also given in drops of saliva in 30 seconds of action of the stimuli. The remaining explanatory notes are as in Table 1.



The effect of ethyzine on the conditioned defensive respiratory reflexes in the dog Sil'va. Significance of the curves (from above down): pneumogram, conditioned stimulus marker, unconditioned stimulus marker, time marker (3 seconds). Legend: a) Before injection of ethyzine; b) 40 minutes after injection of 3 mg/ kg of ethyzine; c) 40 minutes after injection of 10 mg/ kg of ethyzine d) on the 4th day after injection of ethyzine.

(1.5-2.0 mg/kg) was less pronounced than that of the lower dose (1 mg/kg) (Table 2). This fact was evidence that the dog was becoming habituated to the doses of ethyzine which we were using.

In subsequent experiments, in order to avoid the development of the habituation factor, the successive increase of the doses of ethyzine was carried out more quickly.

When the dose of ethyzine was increased to 5 mg/kg, changes were observed in the general behavior of the animals. The reactions to their names and to the sight of the experimenter were diminished. When not on the apparatus they lay down more, and when standing and walking they staggered and moved their paws clumsily, although they jumped up on to the bench quite independently.

Investigation of the conditioned reflexes under these circumstances showed a sharp diminution of excitation. The conditioned reflexes to all the stimuli completely disappeared in both dogs, and differentiation was not disinhibited in 5 to 7 tests, and in the remaining two it was disinhibited by one drop of saliva.

On increasing the doses of ethyzine to 7, 10, 15 and 25 mg/kg the conditioned reflexes fell to zero in the first 30 minutes after administration of the drug, and were absent throughout the whole period of observation (3-6 hours). At the same time the dogs became sluggish and reacted feebly to external stimuli. Refusal to eat was not observed in any of the experiments.

It must be pointed out that ethyzine, in the doses which we used, besides leading to extinction of the salivatory conditioned reflexes, caused a parallel fall in the magnitude of the unconditioned salivatory reflex to a portion of meat and biscuit powder from 40 to 32 drops on the average in Valetka and from 56 to 47 drops in Laska. The fall obtained in response to doses of ethyzine from 7 to 25 mg/kg was especially marked.

The rapid extinction of the salivatory conditioned reflexes with the action of comparatively small doses of ethyzine (1 mg/kg) did not enable the course of the changes in the cortical processes with large doses of the drug to be studied. Accordingly, as an index of the higher nervous activity, we used the conditioned defensive respiratory reflexes, which have been found in our laboratory to be more resistant to the action of chlorpromazine than the salivatory conditioned reflexes.

The experiments showed that ethyzine, in a dose of up to 2 mg/kg, did not affect the defensive respiratory reflexes. Doses of ethyzine of 3-5 mg/kg gave an appreciable effect in both dogs – the conditioned reflexes to the bell and touch were severely weakened and the conditioned reflex to light disappeared altogether. With these doses, differentiation was disinhibited. On increasing the dose of ethyzine to 7 mg/kg, in addition to the disturbances already mentioned, extinction of the conditioned reflex to touch was observed. Disappearance of the conditioned reflex to the bell, as a strong stimulus, took place when the dose of ethyzine reached 10 mg/kg. In the following experiments, when higher doses (12-15 mg/kg) of this drug were given, the disturbance of the respiratory conditioned reflexes was less pronounced on account of habituation of the dogs (see figure). The unconditioned defensive respiratory reflex to ammonia was sharply diminished by large doses of ethyzine (10-15 mg/kg) but did not disappear completely.

The rate of recovery of the conditioned reflexes after ethyzine depended on the dose of the drug, on the type of conditioned reflex and on the degree of habituation of the dogs. Recovery of the salivatory conditioned reflexes with a dose of ethyzine of 0.5 mg/kg took place 3-4 days after its administration, and with doses of 1-3 mg/kg within the first 24 hours. During the recovery period, paradoxical and ultraparadoxical hypnotic phases appeared; After doses of ethyzine of 5-7 mg/kg, the conditioned reflexes were restored to normal on the third day. With higher doses (10-15 mg/kg) recovery was prolonged to 4-5 days.

Recovery of the defensive conditioned respiratory reflexes followed a more rapid course, being completed with doses of ethyzine of 3-5 mg/kg in 3-4 hours, and after 10-15 mg/kg during a period of 3 days.

It must be pointed out that in control experiment in which distilled water was injected intramuscularly into dogs, their conditioned reflex activity was unchanged.

Analysis of the results described above shows that the disturbance of the function of the cerebral cortex in dogs develops under the influence of a comparatively small dose of ethyzine (0.5 mg/kg). This dose has a selective effect on the process of internal inhibition and evidently does not affect the process of excitation. Internal inhibition is weakened, causing disinhibition of differentiation, shortening of the inhibitory phase of the delayed conditioned reflex and also an increase in the magnitude of the conditioned reflexes to positive stimuli. On increasing the dose of ethyzine to 1 mg/kg, besides weakening of the internal inhibition, a decrease in the strength of the process of excitation takes place. The positive conditioned reflexes are considerably diminished or completely extinguished.

On increasing the doses of ethyzine further, to 3-25 mg/kg, the weakening of the cortical processes increases progressively, which leads to complete extinction not only of the salivatory reflexes but also of the more stable defensive conditioned respiratory reflexes to reinforcement with ammonia. Changes in the unconditioned salivatory and respiratory reflexes take place with higher doses of ethyzine (1-10 mg/kg) than in the conditioned reflexes (0.5-3.0 mg/kg).

As we know, the study of the mechanism of action of anesthetics and hypnotics on the functions of the central nervous system has shown that anesthetics cause primary weakening of the higher form of cortical inhibition, and then lower the level of the process of excitation [8, 11, 13]. These changes in the activity of the cerebral cortex develop in response to doses of anesthetics and hypnotics which are not sufficiently large to cause disturbances of subcortical functions.

Comparison of these findings with the results of our investigation shows that the initial effect of ethyzine on the function of the cerebral cortex is similar to the action of anesthetics.

SUMMARY

The author studied the effect of ethyzine on the salivatory food and protective respiratory conditioned reflexes in 4 dogs. There is evidence that the disturbance of the cerebral cortex function sets in when ethyzine is administered in a dose of 0.5 mg/kg. This weakens the process of internal inhibition but has no effect on the excitation process. Positive conditioned reflexes become increased, differentiation — disinhibited, while the inhibitory phase of the delayed reflex is shortened. 1-25 mg/kg of ethyzine provokes a progressive weakening of the cortical processes with the conditioned reflexes dropping to zero. The conditioned reflexes become less intense when higher doses of the preparation (1-10 mg/kg) are given.

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