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EFFECT OF PSYCHOTROPIC DRUGS ON DEFENSIVE CONDITIONING IN EXPERIMENTAL NEUROSIS

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Rats exposed to the prolonged action of an emotionally adverse factor (the response of a neighboring rat to nociceptive stimulation) develop neurosis as a result of which the course of defensive motor conditioning is disturbed. Benactyzine, diazepam, chlordiazepoxide, and sodium hydroxybutyrate improve the formation of defensive conditioned reflexes in neurosis of this type. Trioxazine, trifluoperazine, and amphetamine have no such action. The suggested model of experimental neurosis can be used for the study of antineurotic activity of psychotropic drugs.
KEY WORDS: neurosis; conditioned reflex; psychotropic drugs.

Tranquilizers are widely used to relieve emotional stress and to treat neurotic states. However, despite their broad common spectrum of psychotropic activity, not all tranquilizers have proved equally effective in the treatment of neuroses [1]. It is therefore important to be able to evaluate tranquilizers experimentally in order to discover and predict their therapeutic effect in neurotic states.

The object of this investigation was to study the effect of psychotropic drugs with tranquilizing properties on one form of experimental neurosis in rats.

EXPERIMENTAL METHODS

Experiments were carried out on 160 male albino rats weighing 250-350 g. The methods of the avoidance response to stimulation of the partner [5, 9] and formation of a motor defensive conditioned reflex [10] were used. The defensive conditioned reflex served as an indicator of the functional state of the CNS. Animals with a stable avoidance response to stimulation of the partner, observed not less than 10 times in succession, were chosen for the experiments. By this time the rats showed changes in behavior when put inside the chamber: a posture of alertness, sometimes accompanied by a squeak, resistance to being placed in the chamber, and jumping out of it. At the same time, autonomic somatic disorders appeared (baldness, keratitis). These phenomena form part of the picture of an experimental neurosis [7]. Experiments were carried out by the following scheme: The rat was placed for 5 min in the chamber for the avoidance response to stimulation of the partner, and then immediately transferred to the defensive conditioned reflex chamber. The conditioning stimulus was the ringing of a bell. It acted alone for 5 sec, after which an electric current was applied to the floor of a chamber (also for 5 sec) while the bell continued to ring. The rat was taught to jump onto a vertical rod and to support itself on it until the stimulus ceased to act. The intervals between stimuli were 1 min. Training continued for 10 days with daily presentation of 10 combinations. Rats not taught the avoidance response during stimulation of the partner served as the control.

Benactyzine, diazepam, chlordiazepoxide, trioxazine, sodium hydroxybutyrate, and trifluoperazine were used. Each substance was injected intraperitoneally into 10 rats with a neurosis and 10 control rats 30 min before the beginning of each training session, in daily doses, each of which causes inhibition of the avoidance response to stimulation of the partner (tranquilizing effect). Isotonic sodium chloride solution was injected into 10 rats with neurosis and 10 control rats. The number of jumps on to the rod in response to the conditioning

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TABLE 1. Effect of Psychotropic Drugs on Defensive Conditioning in Rats with Experimental Neurosis

Drug	Daily dose, mg/kg	No. of conditioned responses per experiment as percentage of total number of stimuli
None		20.6
Benactyzine	0.5	51.2†
Diazepam	1.0	39.9*
Chlordiazepoxide	3.0	39.7*
Trioxazine	30.0	27.5
Sodium hydroxybutyrate	30.0	49.5‡
Trifluoperazine	0.2	27.6
Amphetamine	1.0	37.5

*$P < 0.005$.

†$P < 0.01$.

‡$P < 0.001$.

stimulus was counted. The results were analyzed by assessment of the significance of the difference between sampling means by Fisher's criterion [8].

EXPERIMENTAL RESULTS

The experiments showed a significant disturbance of the process of formation of a motor defensive reflex to the conditioning stimulus in the rats with experimental neurosis. The number of correct responses in the experiment on the animals with neurosis was 43% less than in the control ($P < 0.05$). It was later found that in the control rats none of the drugs tested, in the doses used, had any statistically significant effect on the formation of the defensive conditioned reflex. The main experiments were then carried out and their results are given in Table 1.

All tranquilizers except trioxazine improved the formation of the motor defensive reflex in the animals with neurosis. Sodium hydroxybutyrate, which possesses tranquilizing properties [4], also improved the formation of this reflex, an effect which corresponds to the spectrum of action of tranquilizers of the benzodiazepine series and benactyzine. Trifluoperazine had no effect on the learning process under these conditions.

The results are in agreement with statements in the literature that benzodiazepine derivatives restore conditioned-reflex activity to normal when disturbed by emotional stress, whereas phenothiazine derivatives do not possess these properties [11].

Hence, although all the psychotropic drugs listed above have many common properties in the spectrum of their pharmacological activity (inhibition of the avoidance response to stimulation of the partner [4, 5], inhibition of motivated aggression [3], abolition of the aftereffects of emotional stress after a response of rage and fear [2]), their effect on defensive conditioning in experimental neurosis is by no means identical.

It was interesting to discover how CNS stimulants, notably amphetamine, would affect the formation of the conditioned defensive reflex during neurosis. The writers have found that amphetamine has no effect, in any phase, on the avoidance response to stimulation of the partner, but in a dose of 1 mg/kg, given repeatedly, it has a moderate stimulating effect on this response, i.e., it potentiates the after-effects of emotional stress [5, 6]. Consequently, both positive and negative effects of amphetamine on the learning process could be expected in animals with neurosis. However, the experiments showed that it had no statistically significant effect whatever on this process (Table 1).

The results of this investigation show that trioxazine and trifluoperazine do not restore higher nervous activity to normal in the type of experimental neurosis studied, whereas the other tranquilizers used in this investigation, are, on the contrary, highly effective, in full agreement with clinical data [1].

The suggested model of experimental neurosis can thus be used to demonstrate antineurotic activity in psychotropic drugs.

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EFFECT OF MORPHINE AND AZIDOMORPHINE ON CORTICAL UNIT ACTIVITY

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In acute experiments on unanesthetized curarized cats and rats morphine and azidomorphine, in analgesic doses, inhibited spontaneous and bradykinin-evoked unit activity in the sensomotor cortex. The depriming action of both drugs was abolished by nalorphine. It is suggested that the inhibitory action of morphine and azidomorphine is due to their direct action on the cerebral cortex.

KEY WORDS: morphine; azidomorphine; single unit activity; sensomotor cortex.

New drugs (fentanyl, etorphine, and azidomorphine), with an analgesic activity several orders of magnitude higher than that of morphine, have recently been obtained. The effect of fentanyl and etorphine on the nervous system has received little study and no data are available on the direction of action of azidomorphine [4] in the CNS in general. The role of the sensomotor cortex in the response to nociceptive stimulation in cats and rats has been established in investigations by many workers [1, 3, 8]. It is also known that injury to the somatosensory cortex in man leads to the loss of pain sensation [5].

In this investigation the effect of azidomorphine* and morphine on spontaneous single unit activity of the sensomotor cortex and activity evoked by nociceptive stimulation was studied. The effect of nalorphine, an antagonist of the narcotic analgesic, on the effects of morphine and azidomorphine also was investigated.

EXPERIMENTAL METHOD

Experiments were carried out on 15 cats weighing 2-3 kg and 10 rats weighing 250-300 g. Tracheotomy and catheterization of the veins and arteries were performed under ether anesthesia. The animal was then fixed in a special frame, immobilized with anatruxonium (0.1-0.2 mg/kg), and artificially ventilated. Unit activity in the sensomotor cortex was derived by glass microelectrodes with a tip 1-3 μ in diameter and recorded continuously throughout the experiment on the PP-15 scaler–printer. Intraarterial injection of bradykinin (10 μg) was used as a method of specific nociceptive stimulation [6]. Morphine, azidomorphine, and nalorphine were injected intravenously. Control experiments showed that the drugs tested, in the doses used, caused virtually no change in the arterial pressure.

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