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ROLE OF THE GABA-ERGIC COMPONENT IN THE DEVELOPMENT OF THE TRANQUILIZING EFFECT IN CATS

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GABA (if administered in a manner bypassing the blood–brain barrier) and its derivatives (the GABA-mimetic muscimol, inhibitors of GABA transaminase) [10] are known to exhibit an inhibitory effect on locomotor activity, investigative behavior, and conditioned reflexes in animals. Some structural analogs of GABA have found clinical application as tranquilizers (fenibut, sodium hydroxybutyrate, fepyron) [8]. The mechanism of action of the benzodiazepine tranquilizers is linked with their allosteric effect through specific receptors on the system regulating affinity of the GABA receptor for endogenous GABA [9]. However, the question of the role of the GABA-ergic component in the development of the tranquilizing effect is not yet clear. On the psychophysiological plane the tranquilizing effect is manifested as a broad spectrum of behavioral changes in which emotional, activating, and sedative components can be distinguished; consequently, to assess the role of the GABA-ergic component in the manifestation of the tranquilizing effect on behavior, models taking into account the complex structure of this phenomenon must be used.

The aim of the present investigation was to evaluate changes in the spectrum of emotional-behavioral reactivity of animals (cats) under the influence of n-dipropyl acetate (n-DPA), which raises the brain GABA concentration [12], by comparison with diazepam, which has a similar effect on the brain GABA concentration [6].

EXPERIMENTAL METHOD

The spectrum of emotional-behavioral reactivity was assessed in chronic experiments on cats by the method described in detail previously [3]. A state of anxiety and fear was induced by stimulation of the emotiogenic zones of the hypothalamus through implanted electrodes, by peripheral electrical stimulation of the skin, or by placing the animal a second time in an emotionally meaningful aversive situation (conditioned-reflex fear response) [5]. Interpretation of the significance of the response manifestations and their quanti-

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TABLE 1. Effect of n-DPA on Spectrum of Emotional and Behavioral Reactivity of Cats Initially and when Modified by Aversive Stimulation (M ± m)

Spectrum of emotional and behavioral reactivity	Initial spectrum	After injection of n-DPA	After aversive stimulation	
			before injection of n-DPA	after injection of n-DPA
Fear	1,4±0,3	0,14±0,09*	2,7±0,6*	0,1±0,06*
Anxiety	0,9±0,3	0	3,0±0,3*	0,3±0,2*
Negativity	0,7±0,5	1,6±1,0*	4,2±0,2*	2,3±0,8*
Aggressiveness	2,2±0,5	1,1±0,4	1,8±0,7	2,1±0,5
Readiness for conflict	3,4±0,7	2,7±0,3	2,1±0,9	2,9±0,3
Competitive ability	2,6±0,9	1,3±0,7	0	1,6±0,5*
Manifestation of satisfaction	2,5±0,4	1,1±0,4*	0	0,4±0,2
Playing, hunting	0,4±0,1	0	0	0
Food motivation	2,7±0,5	0	0	0
Kindness or contact with partner	1,3±0,5	2,2±0,3	0	0,9±0,3
Orienting reaction	2,3±0,2	1,4±0,2*	2,3±0,3	1,3±0,1*
Investigative activity	2,4±0,4	1,0±0,2*	0	0,2±0,1
Motor activity	1,9±0,1	1,2±0,1*	1,6±0,4	1,2±0,1
Initiative	2,4±0,3	0,9±0,3*	0,8±0,6*	0,9±0,1
Hypertonus	0	0	2,3±0,8	0
Muscle relaxation	0	0	0	0

Legend. Numbers in columns give mean abundance of feature (in points) and error of mean, asterisk denotes significance of difference at $P < 0.05$.

tative evaluation (on a five-point system) were based on evaluation tables [3] followed by statistical analysis of the results. Experiments were carried out on nine male cats weighing 3-3.5 kg, with a normal spectrum of emotional-behavioral reactivity and with an active form of behavior, exhibiting adequate responses of fear, anxiety, and aggressiveness, with well-marked investigative behavior, exhibiting positive emotions to stroking, and with a dominant form of behavior in the group with their partners (type 1 according to our own classification) [2].

The choice of n-DPA as pharmacological analyzer of the role of the GABA-ergic component was determined by the fact that this compound, unlike inhibitors of GABA-transaminase, has a selective action on the mediator compartment of GABA, causing an increase in the level of the amino acid mainly in terminals of GABA-ergic neurons [1]. The n-DPA was injected intraperitoneally in 2% sterile starch mucilage, in a dose of 50-200 mg/kg; diazepam was given enterally in a dose of 0.5-2 mg/kg.

EXPERIMENTAL RESULTS

In a dose of 200 mg/kg, n-DPA evoked a characteristic complex of emotional and behavioral manifestations which can be described as a tranquilizing effect. In the original spectrum of behavioral reactivity, after administration of n-DPA (Table 1) the initiative of motivated behavior, investigative activity, and motor responses were reduced. The slight manifestations of anxiety and fear due to the experimental situation were abolished practically completely. The spectrum of emotional reactivity was narrowed. The behavioral manifestations of positive emotions were weakened and food motivation was reduced. The status of the animal in the group was unchanged, it retained control of its own territory, although the level of conflict as a result of interdependent behavior was lowered because of an increase in passive equanimity.

The conditioned-reflex response of fear and emotional strain, manifested as increased anxiety and defensive-protective and vocal reactions, adynamia, muscular hypertonus, loss of orienting and investigative activity, and competitive interactions with partners, was depressed after administration of n-DPA. Manifestations of anxiety and fear were abolished completely, but active defensive and protective reactions were preserved. The muscular hypertonus disappeared and motor and investigative activity was unchanged. Manifestations of positive emotions were not increased.

More distinct changes were observed in the fear and anxiety response induced by aversive stimulation (Table 1). After preliminary administration of n-DPA not only the abundance, but also the duration of the behavioral manifestations of fear and anxiety was sharply reduced. Negative-reinforcing properties of stimulation, assessed on the basis of refusal of the hungry animal to take food immediately after aversive stimulation, were reduced. The status of the animal in their group was restored. Manifestations of positive emotions, depressed during the period of the anxiety and fear reaction, were restored but not completely. Activation of investigative behavior and of motor activity did not occur.

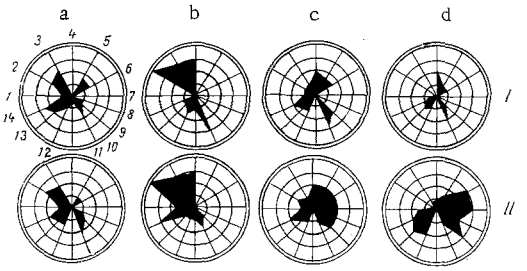

Fig. 1. Comparison of dynamics of tranquilizing action of n-DPA and diazepam on models of anxiety and fear. a) Initial spectrum of emotional and behavioral reactivity, b) spectrum after aversive electrodermal stimulation, before injection of n-DPA and diazepam, c, d) the same against the background of n-DPA (I) in doses of 50 and 200 mg/kg, respectively, and of diazepam (II) in doses of 0.5 and 2 mg/kg, respectively; 1) aggressiveness, 2) fear, 3) anxiety, 4) negativity, 5) investigative activity, 6) manifestations of satisfaction, 7) playing, 8) hunting, 9) kindness, 10) readiness for conflict, 11) inadequacy of response, 12) initiative, 13) motor activity, 14) orienting reaction.

Comparison of the effects of n-DPA and diazepam revealed significant differences (Fig. 1). In both cases a distinct antiphobic (relieving anxiety) action was exhibited. In this sense the pharmacological effect of n-DPA, like that of diazepam, can be described as tranquilizing. However diazepam, within a certain dose range, has what is described as an activating action (activation of motor and investigative activity, of motivated behavior previously inhibited by fear), and it also strengthens manifestations of positive emotions. Under the influence of n-DPA (50 mg/kg) no such activating effect was observed, but after administration of a dose of 200 mg/kg the sedative components of the tranquilizing effect dominated (a reduction of emotional reactivity and of orienting-investigative activity). This corresponds to the view that GABA-ergic mechanisms do not play a decisive role in the development of the activating action of the benzodiazepines, whereas the sedative component of their action is the result of potentiation of GABA-ergic processes [1, 13]. In cats, n-DPA does not activate positive emotions, but in rats neither bicuculline nor muscimol changes brain self-stimulation reactions or disturbs the activating effect of diazepam in relation to this reaction [4]. GABA-ergic mechanisms are evidently not connected primarily with the functional activity of the positive reinforcing systems of the brain. n-DPA in cats causes little change in negativity due to central aversive stimulation (whereas diazepam depresses it significantly), and in rats the GABA transaminase inhibitor does not affect the latent period of active avoidance in response to stimulation of "punishing" zones of the brain, whereas muscimol actually lengthens the period of after-inhibition in a conflict situation [1]. This points to the negligible role of GABA-ergic mechanisms in the functioning of negative reinforcement systems.

Regulatory effects on GABA-ergic systems responsible for control of emotional states (fear, anxiety) may take place by at least two different mechanisms: by activation of benzodiazepine receptors which, thanks to the special modulating system, can change the affinity of GABA receptors for the endogenous mediator [9], and also through enhancement of the synaptic function of GABA, i.e., through an increase in the content of endogenous GABA in the "mediator compartment" of the GABA-ergic terminals and an increase in presynaptic liberation of GABA. The increase in affinity of the GABA receptor for the liberated endogenous mediator, effected through benzodiazepine receptors, evidently gives more precise modulation in systems in which GABA neurons are activated functionally or in which a deficiency of mediator is exhibited [9]. It has been shown [11] that n-DPA causes a selective increase in the GABA concentration in nerve endings. Inhibitors of GABA transaminase cause an overall increase in the level of functional activity of GABA neurons. The sedative effect predominates in the animals' behavior against this background. In light of these views it is possible to explain the anxiety-relieving effect of n-DPA despite the very weak or absent effect of inhibitors of GABA transaminase [7]. Total activation of GABA receptors is evidently not an adequate condition for the develop-

ment of an anxiety-relieving effect. Aminoacetic acid, which raises the GABA level in the brain by 200%, or muscimol does not induce a selective tranquilizing effect [1, 7]. As the observations described above show, substances of the n-DPA type, which behave mainly as regulators of the GABA system, and which differ in the mechanism of their action from benzodiazepines, may have a more adequate influence on emotional and behavioral processes.

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THE ACTIVATING EFFECT OF SMALL DOSES OF HALOPERIDOL

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KEY WORDS: haloperidol; small doses; activating effect; inhibition.

In recent years many investigators have directed their efforts toward the study of the mechanisms of action of neuroleptics of the butyrophenone series and, in particular, of haloperidol. This drug is widely used in the treatment of schizophrenia and it differs from other neuroleptics in the fact that its antipsychotic action is not accompanied by any marked depriming effect. It has been shown that haloperidol can exert a tranquilizing action, which has been found both clinically [11] and experimentally [9], and in this respect it exhibits similarity with tranquilizers of the benzodiazepine series. Since we know that the benzodiazepine tranquilizers, if administered in small doses, are characterized by an activating action, exhibited as facilitation of impulse summation in the nervous system [5] or as increased motor activity [3] and EEG desynchronization [6], it is interesting to examine whether haloperidol, in small doses, also possesses such an activating effect.

The object of this investigation was to study the effects of small doses of haloperidol by the use of screening tests and electrophysiological indices.

EXPERIMENTAL RESULTS

The effect of haloperidol in doses of 0.05-0.15 mg/kg on the motor activity of rats and mice (in groups of five animals at a time) was investigated by means of an Animex actometer (LKB, Sweden). The animals'

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