PHARMACOLOGICAL MODELS OF THE SPECIFIC ROLE OF THE DOPAMINERGIC AND SEROTONINERGIC BRAIN SYSTEMS IN LATENT INHIBITION

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Repeated presentation of a conditioned stimulus before its combination with the unconditioned stimulus delays the subsequent development of the conditioned reflex. This phenomenon has been called latent inhibition (LI) and it is widely used at the present time as a test of selective attention in animal experiments [6].

Participation of central monoamines in LI has been demonstrated. For instance, D-amphetamine, administered before an experiment in combination with hypersensitivity of dopamine receptors or para-chlorophenylalanine, disrupt LI [9, 10]. This is evidence also of different mechanisms of involvement of the dopaminergic (M) and serotoninergic (5-HT) systems in the process of negative learning during preexposure to the stimulus, which is probably accompanied by reduction of DA activity and enhancement of 5-HT activity. Consequently, an artificial change in their activity, creating the conditions for LI, and evaluation of this state, using not one, but several parameters [1], enable a pharmacological model to be created.

Considering data in the literature and our own suggestions, an attempt was undertaken to obtain a pharmacological model of LI in a conditioned avoidance task, using preparations selectively modifying activity of the DA or 5-HT systems, and to analyze interaction between them.

EXPERIMENTAL METHOD

Experiments were carried out on 103 male Wistar rats weighing 180-200 g. A conditioned passive avoidance reflex (CPAR) was formed in one combination [5]. The latent period (LI) of passage from the lit half of the chamber into the dark half (punishable), in which the animals were subjected to electrodermal stimulation (0.75 mA, 2 sec) and were quickly transferred to their home cage, was recorded. "Psychogenic" amnesia was induced by keeping the animal after reinforcement in the dark half of chamber for 5 min [8]. Preservation of CPAR was tested at various intervals from 1 to 14 days (period of observation 180 sec). The effect of LI was achieved by preliminary training in habituation to the conditioned stimulus (20 preexposures in the experimental chamber), by a program developed previously [1], and it was evaluated relative to several characteristics of the CPAR: weak reproduction of the response to the 1st, and self-potentiation to the second testing, and resistance to spontaneous extinction and to amnesic influences.

All preparations were injected intraperitoneally in physiological saline. Haloperidol ("Gedeon Richter," Hungary), DA-receptor blocker — in a dose of 0.5 mg/kg was given 1 h before training. Sertraline ("Pfizer," USA), a blocker of 5-HT reuptake, in a dose of 5 mg/kg was given 1 h before training or, in combination with the DA reuptake blocker bupropion ("Sigma," USA), which was given in a dose of 30 mg/kg 30 min before training.

The following groups of animals were included in the experiment: control without preexposure (a, n = 19) and with 20 preexposures to the conditioned stimulus (b, n = 20), experimental with injections of haloperidol (c, n = 21), sertraline (d, n = 22), and sertraline + bupropion (e, n = 21). Each group consisted of two subgroups (I and II). Animals of the first subgroups were subjected only to training, those of the second to a combination of training with amnesic influences.

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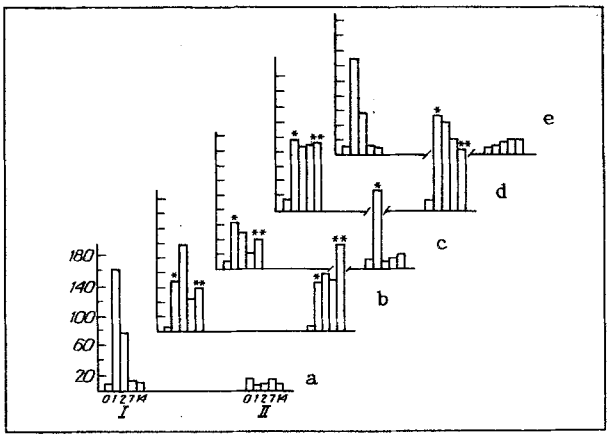

Fig. 1. Effect of preparation on preservation of CPAR. *$p < 0.05$. Compared with corresponding control. **$p < 0.05$ compared with corresponding initial value. Remainder of explanation in text.

The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

The results are given in Fig. 1. Comparison of the mean values of CPAR reproduction by the animals without preexposure (a, I) and with 20 preexposures (b, I) to the conditioned stimulus shows that preliminary habituation to the conditioned stimulus led to statistically significant weakening of recall of the conditioned reflex, recorded 24 h later. On the 2nd day after training, self-potentiation of CPAR was observed in animals of subgroup b, I, whereas simultaneously in the control (a, I) extinction began, leading to disappearance of the statistically significant difference in recall of the conditioned reflex in these subgroups ($p > 0.05$). On the 7th and 14th days after training the average value of LP of passage in subgroup a, I no longer differed from that on the corresponding initial day ($p > 0.05$). If preexposure took place (b, I) the reflex was not extinguished. Amnesic influences immediately after training caused amnesia in the control subgroup a, II, whereas in control subgroup b, II recall remained at the same level as the reflex observed in subgroup b, I at all times of testing ($p > 0.05$). Thus after 20 preexposures to the conditioned stimulus LI was observed in group b: weak recall of the conditioned reflex at the 1st testing, its self-potentiation at the 2nd testing, prolonged preservation at the established level (b, I), and resistance to amnesic influences (b, II).

The groups examined above were controls for all the other groups without preexposure to the conditioned stimulus, but with injection of the drugs. Analysis of the character of preservation of CPAR after training (I) and a combination of training with amnesic influences (II), against the background of haloperidol (c) and sertraline (d) enables an analogy to be drawn between the action of the drugs on memory and preliminary habituation (b). Just as during LI, the conditioned response was less well recalled, but it remained at the same level until the end of the experiment (c, I; d, I). A well-marked antiamnesic effect of both drugs also was observed (c, II; d, II) 24 h after a combination of training with amnesic influences ($p < 0.05$ compared with control amnesia, a, II). However, combined administration of sertraline and bupropion, with an interval of 30 min, did not change the preservation of CPAR (e, I) and did not prevent the development of amnesia (e, II; $p > 0.05$) compared with control group a. In other words, simultaneous activation of the 5-HT and DA systems had no effect on preservation of the conditioned reflex and did not prevent the development of anmesia.

Thus analysis of the results showed that the two models are sufficiently close to the original and can be used for the discussion of the neurochemical mechanisms maintaining the habituation process or inhibiting attention to a repeatedly presented stimulus, resulting in the appearance of LI.

The overwhelming majority of investigators consider that DA plays a leading role in habituation to new stimuli [4, 7, 11], but some studies suggest a role of serotonin in this process, and also that it may have a modulating influence on the processes under discussion [2]. Thus weakerdng of investigative activity during repeated presentation of a new environment was disturbed by parachlorophenylalanine [3]. The results of disturbance of LI when preexposure to the stimulus was used also were

similar in thecase of activation of the DA system or blockade of the 5-HT system [9, 10]. Repeated presentation of unreinforced stimuli at the preexposure stage is probably accompanied by lowering of the level of activity of the DA system and enhancement of that of the 5-HT system. This suggestion is confirmed by data on the effects of haloperidol or sertralin, injection of which perhaps accelerated the process of depression of attention to the new situational stimulus, and evoked LI after its combination with the unconditioned reinforcement. It is difficult as yet to say which of the two systems under examination is leading and which is modulating. Only one thing is clear at present, namely that the two systems under examination are in close interaction. This is clearly demonstrated by the example of the effect of bupropion, injected 30 min after sertraline. Ultimately the simultaneous activation of the two systems had no effect on formation and preservation of the CPAR or the creation of amnesia, compared with the control (group a).

Thus the results of this investigation showed that this approach to the study of the neurochemical mechanisms of selective attention is promising and will enable the contribution of each of the transmitter systems of the brain, and also the possible versions of interaction between them, to be analyzed more quickly.

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