A POSSIBLE EXPERIMENTAL EQUIVALENT OF THE HALLUCINOGENIC ACTION OF DRUGS

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One of the clearest manifestations of the action of drugs of addiction is the appearance of visual hallucinations. This effect is well known for the hallucinogens, which is why they are so called [4, 5, 8], and also for psychostimulants [6]. Work has recently been published which indicates that visual hallucinations may also arise in man as a result of the action of tranquilizers of the benzodiazepine series [7]. Models of hallucinatory reactions have been suggested in the literature, but these have mainly been integral behavioral acts, which do not allow isolation of a truly perceptual component which, in the modern view, lies at the basis of the origin of hallucinations [3]. Behavior acts of animals such as unmotivated movements cannot be assessed quantitatively and, consequently, they are unsuitable for evaluating the action of drugs. Moreover, hallucinations are a particularly subjective phenomenon and, consequently, they cannot be assessed sufficiently completely in animals. In order to evaluate the hallucinogenic action of drugs on animals it is therefore more logical to study changes in the brain function that is closest in its origin to hallucinations. Such a function is the "recognition of objective reality" [3], disturbances of which have been found in patients with hallucinations.

It was decided to study how the perception of visual stimuli is modified under the influence of drugs belonging to the three groups mentioned above: hallucinogens, psychostimulants, and tranquilizers. The hallucinogenic action of these drugs differs considerably and, consequently, it is possible in principle to attempt to draw a parallel between their hallucinogenic action and their effect on visual perception. The investigation described below was devoted to a study of these problems.

EXPERIMENTAL METHOD

Experiments were carried out on cats which were first trained by a conditioned defensive reflex method to distinguish two lines in different directions. Patterns were presented with different exposures of 5000 msec or less. It was found that discrimination between the visual stimuli could be achieved during prolonged training (3000 msec or more). Reduction of the exposure time, irrespective of the duration of training, led to a regular decrease in the percentage of correct discrimination. The minimal exposure after which statistically significant discrimination could be achieved was 500 msec. The curve of the relationship between the presentation time of the visual stimulus and the correctness of the response to it consisted ot two parts, in one of which correctness of response in the background was independent of presentation time, whereas in the other the percentage of correct responses decreased regularly with shortening of the exposure (Fig. 1). The presence of correlation between parameters of the stimulus and quality of the response to it suggests that in this case the predominant factor for the formation of the final response is the actual process of perception of the visual stimuli and not the subsequent stages of the conditioned-reflex act, leading ultimately to the response. The second part of the curve was evidently connected with a much greater number of components of the conditioned-reflex act, such as determination of the biological significance of the stimulus and decision making, each of which, in turn, is a complex, multicom-

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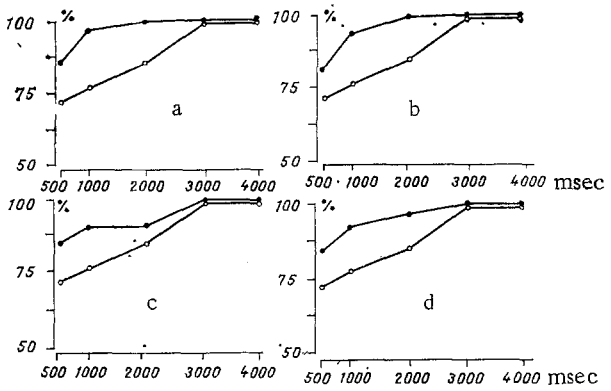

Fig. 1. Percentage of correct identification of pattern as a function of exposure in background period and after injection of tranquilizers of benzodiazepine series. Abscissa, time of presentation of pattern (in msec); ordinate, percentage of correct identifications of patterns relative to total number of presentations taken as 100. Empty circles) background; filled circles: a) phenazepam, b) clonazepam, c) diazepam, d) nitrazepam.

ponent process [1]. By the use of this technique it was thus possible to judge the action of drugs on different components of visual stimulus **evaluation.**

Besides correctness of differentiation of visual stimuli with different exposures, the latent period of the conditioned reflex also was taken into account.

EXPERIMENTAL RESULTS

The minimal doses at which an effect of the hallucinogens LSD and Δ9-tetrahydrocannabinol (Δ9-THC) was observed were 40 μg/kg and 1.5 mg/kg, respectively; with these doses differentiation of short stimuli was impaired whereas differentiation of long stimuli remained at the background level. With an increase in doses to 100 μg/kg and 3 mg/kg, respectively, differentiation of both short and long stimuli was impaired. The latent period of the conditioned reflex was reduced by administration of LSD and increased by Δ9-THC. With a further increase in the doses of the drugs the reflex to single stimuli was inhibited.

Minimal doses of psychostimulants (amphetamine, cocaine, Sydnocarb, and Catinon), with which an effect on differentiation was found, were 0.2, 0.5, 1.5, and 0.5 mg/kg, respectively. The effect was the same for all these drugs except Catinon. Differentiation of short stimuli improved and differentiation of long stimuli remained at the background level. After administration of Catinon, differentiation of short stimuli was impaired. The latent period of the conditioned reflex was shortened. If the doses of the drugs were doubled differentiation of both short and long stimuli was impaired. The latent period of the conditioned reflex remained shorter than in the background. The exception to this series of drugs was cocaine, after injection of which differentiation of long stimuli was not impaired.

The minimal doses after which effects of the tranquilizers of the benzodiazepine series were found (diazepam, nitrazepam, phenazepam, and clonazepam) were 0.04, 0.02, 0.01, and 0.005 mg/kg, respectively (Fig. 1). In these doses all tranquilizers were found to improve perception of short stimuli, without changing perception of long stimuli. The latent period of the conditioned reflex was lengthened after injection of nitrazepam and diazepam and remained at the background level after administration of phenazepam and chlonazepam. If the doses of the drugs were doubled differentiation of short stimuli, as before, remained at a higher level than in the background. The latent period of the conditioned reflex was lengthened. After administration of the tranquilizers in any of the doses tested, differentiation of visual stimuli was never completely suppressed, even though with large doses the conditioned reflex to a single stimulus was suppressed.

The following conclusions can thus be drawn from these experiments. Hallucinogens impair both the perception of the physical parameters of visual stimuli and also their subsequent processing. Psychostimulants improve the perception of visual stimuli in minimal doses, but in larger doses they impair both the perception of visual stimuli and the process of

their subsequent recognition. Tranquilizers in minimal doses improve visual perception but impair it when the dose is increased; however, whatever the dose they never disturb completely the processes which lead ultimately to adequate response to external stimuli.

A parallel can thus be detected between the intensity of changes in visual stimulus analysis and the intensity of the hallucinogenic action of the drugs.

The intensity of the disturbances of subsequent stimulus analysis, which is closely linked with extrasensory factors [3, 6] during the action of hallucinogens and psychostimulants, and the absence of these disturbances during the action of tranquilizers, are particularly characteristic from this point of view. This fact is in good agreement with modern views on the origin of hallucinations, according to which they are not a disturbance of the functioning of an analyzer of any one particular modality, but they are connected with changes in the more general aspects of brain activity such as emotions and memory and figurative thinking [2].

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A GABA-ERGIC CORTICAL COMPONENT IN THE ACTION OF PIRACETAM AND THE CETYL ESTER OF GABA

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The high efficacy of piracetam in different types of psychoneurological pathology makes the study of the mechanism ofits action imperative. The ability of piracetam to exert a marked effect on memory functions has led to the suggestion that it acts on the cortex. To elucidate the possible role of GABA-ergic structures of the cortex in the mechanism of action of piracetam, it seemed a useful approach to analyze its effect by means of a test which the writers developed previously in order to detect GABA-ergic inhibition in the cortex, namely the recovery cycle of evoked cortical responses. The object of the present investigation was to use this test to study piracetam and its interaction with bicuculline, a blocker of GABA-ergic receptors, and with strychnine, a blocker of glycinergic receptors, and also to compare the effects of pracetam and the cetyl ester of GABA (CEGABA) — a compound whose GABA-mimetic effect was demonstrated previously [5, 8, 13]. It was also decided to study these substances from the point of view of their action on the main biochemical parameters of the GABA system: its level, and activity of enzymes of synthesis and deactivation.

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