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POSSIBLE DISPARITY BETWEEN ADEQUACY OF BEHAVIOR AND MOTOR AUTOMATISMS IN AMPHETAMINE STEREOTYPY IN CATS

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Stereotyped behavior arising in animals receiving large doses of amphetamine is nowadays regarded as one of the most adequate models of psychopathology [3, 7, 8]. This state, because of high sensitivity to neuroleptics, is widely used for the screening of new antipsychotic drugs. The criterion of specificity of action of the drugs in this case is limitation of motor automatisms accompanying the stereotypy. Meanwhile, as the authors cited above have shown, in some cases disparity may arise between the intensity of the motor disturbances in amphetamine stereotypy and the adequacy of the animals' behavior.

EXPERIMENTAL METHOD

Experiments were carried out on 17 cats of both sexes weighing 2-4 kg. Stereotyped behavior induced by amphetamines was assessed by two methods. In animals kept in a chamber measuring 60 X 60 X 60 cm external indices of stereotypy were considered first. The number of automatized movements (turning the head from side to side, nodding it up and down, movements around the chamber, sniffing) were counted three times in the course of 1 min at different times after injection of the drug. Immediately after this the cats were allowed to move freely around the experimental room, where the adequacy of their behavior was determined by means of a series of natural test stimuli (calling by name, response to stroking, playing with a paper "butterfly"). The response to each test was assessed by a 5-point system. For example, for play behavior it appeared as follows: 0 points — no response to the "butterfly," 1 point — having seen the "butterfly," the cat at once lost interest, 2 points — the cat watched the butterfly for a long time but without starting to play, 4 points — the cat started to play, stretched out its paw, but did not pursue the object, 5 points — the cat pursued the "butterfly," and tried to catch it. The averaged total of points for different tests constituted the index of adequacy.

Altogether there were four series of experiments (six experiments on six animals in each series). In series I the cats received only amphetamine, in increasing doses (from 0.25 to 2.0 mg/kg) with an interval of 25 min, and in the next three series, against the background of a dose of amphetamine at the threshold level for stereotypy, one of the drugs inhibiting amphetamine stereotypy was given repeatedly (every 15 min) until this was completely abolished: haloperidol — 0.125, 0.25, and 0.5 mg/kg; clozapine — 0.25, 0.5 and 1.0 mg/kg; metoclopramide — 0.5, 1.0, and 2.0 mg/kg. In the experiments of series V the adequacy of the animals' behavior was assessed during administration of gradually increasing doses of haloperidol only. The drugs were given intraperitoneally, and the numerical results were subjected to statistical analysis by Student's t-test (at the $P < 0.05$ level).

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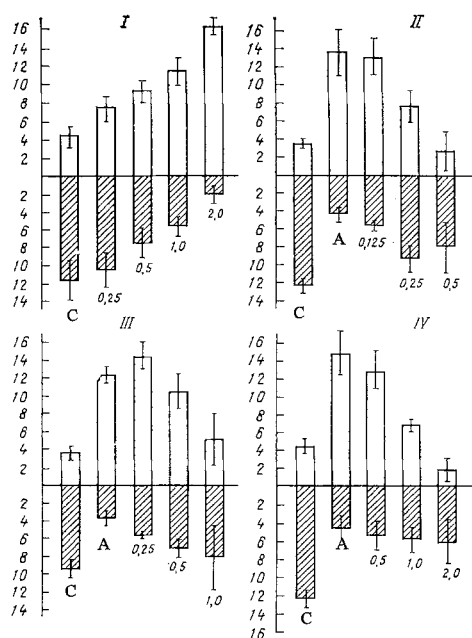


Fig. 1. Unequal effect of neuroleptic and metoclopramide on different indices of amphetamine stereotypy. Top row of columns in each graph represents index of animals' motor activity, assessed as number of head movements (per minute); bottom row represents index of adequacy of animals' behavior determined as mean total of points for three responses to test stimuli. C) Control (before administration of drugs); A) action of dose of amphetamine at threshold level for stereotypy (0.5 mg/kg); numbers beneath columns indicate doses of drugs. I) effect of increasing doses of amphetamine; II, III, and IV) effect of haloperidol, clozapine, and metoclopramide respectively on amphetamine stereotypy.

EXPERIMENTAL RESULTS

Gradual cumulation of amphetamine led to the progressive development of stereotyped behavior. Under these conditions a high degree of correlation was found between the expressiveness of the motor automatism and the adequacy of the animals' behavior.

After a minimal dose of the drug (0.25 mg/kg) no stereotypy was present although the number of movements increased. This was because the main indicator of motor activity in the control was the number of head movements of non-stereotyped character, which increased in frequency as a result of amphetamine. Meanwhile the cats responded adequately to the test stimuli. When the dose was doubled, most animals formed a clear stereotypy, in the form of monotonous repetition of certain actions (Fig. 1). The amplitude, frequency, and range of motor automatisms could vary in individual cases, but the most constant element was monotonous movements of the head in various directions. Meanwhile the adequacy of the cats' behavior was disturbed, with depression of their responses to stimuli. Limitation of play behavior was observed soonest of all, and the response to stroking lasted longer. With an increase in the dose of amphetamine (to 1.0 mg/kg and, in particular, to 2.0 mg/kg) the phenomena described above increased even more.

Against the background of stereotypy induced by the threshold dose of amphetamine the effect of neuroleptics with different types of action were compared. The traditional (classical) neuroleptic haloperidol was compared with an "atypical" preparation, namely clozapine, which induces slight extrapyramidal disorders [5]. Metoclopramide which, as an antiemetic, readily induces dystonia and dyskinesia, but at the same time has a weak antipsychotic action [6], also was used for analysis.

Haloperidol in a low dose (0.125 mg/kg), not altering the spontaneous behavior of the animals, did not cause significant changes in the motor manifestation of stereotypy. In some cats the number of automatized movements could increase whereas in others, on the other hand, it decreased a little, but when added together these changes canceled each other out. Meanwhile haloperidol improved the response to stimuli (Fig. 1). The animals began to respond weakly to being called by name, they enjoyed being stroked, but this was the case with 4 of the 6 cats in which external signs of stereotypy

were not appreciably changed. If, however, its intensity increased, there were no disturbances of adequacy. With an increase in the dose to 0.25 mg/kg of the neuroleptic, the effect of amphetamine was distinctly modified. Not only was the number of head movements reduced, but the pattern of the stereotypy also appeared different. The cats were no longer fixed in one position, they moved around the chamber more often, and occasionally performed grooming movements. Meanwhile the adequacy of the animals' behavior improved significantly, to judge by the character of their responses to tests. Admittedly, it was noted that play behavior was the most difficult to recover. In a large dose (0.5 mg/kg) haloperidol appeared outwardly to abolish the amphetamine stereotypy almost completely. Nevertheless, the responses to stimuli were not expressed to the same degree as initially. According to the results of the control investigation, with increasing doses of the neuroleptic alone, starting with 0.5 mg/kg by itself it led to natural limitation of the psychoemotional state of the cats. Consequently, under the influence of haloperidol the two criteria by which stereotypy was assessed as a rule changed parallel to each other. This parallel trend was not found when clozapine was used. This neuroleptic restored adequacy of behavior but disturbed stereotyped movements less strongly. After administration of the drug in a dose of 0.25 mg/kg motor activity actually increased significantly and the stereotypy assumed an unrestricted form. Despite this, the animals became distinctly more adequate in behavior: They responded better to being called and to stroking and in a few cases they showed interest in the "butterfly." With an increase in the dose of the drug a tendency could be detected for the motor manifestations of stereotypy to be restricted, without, however, reaching significant values. Meanwhile the adequacy of behavior was restored even more clearly and in two animals it returned to the initial level. After administration of clozapine in a dose of 1 mg/kg amphetamine stereotypy was absent with respect to both these indices.

Unlike clozapine, metoclopramide (1.0 mg/kg) depressed motor automatisms clearly without restoring the normal adequacy of the cats' behavior. They responded extremely sluggishly to being called and to stroking, and play with the object was completely inhibited. A higher dose of the drug (2.0 mg/kg) added very little to this picture, although externally the stereotypy disappeared completely. The cats usually sat in one position, sometimes covering their eyes, and they responded weakly to the test stimuli.

Whereas the traditional neuroleptic haloperidol caused almost parallel weakening of the motor manifestations of stereotypy and improvement in the adequacy of the animals' behavior, clozapine and metoclopramide thus acted differently on the two indices. The "atypical" neuroleptic clozapine, with its weak effect on motor activity, restored the animals' normal psychoemotional state earlier, whereas metoclopramide, with its modest antipsychotic properties, on the contrary, abolished the motor automatisms first of all. Accordingly, when new neuroleptics are being screened by the use of a model of amphetamine stereotypy, it will be evident that it is not sufficient to take account only of disappearance of the external manifestations of this phenomenon.

There are at least two probable causes of the uncoupling of the two indices of stereotypy. An important role in its formation is played by defects in the function of the caudate nucleus [1]. Morphologically and functionally this structure is heterogeneous [2, 4], and its different zones may be differently involved in the regulation of mental processes and movement both under normal conditions and under the influence of amphetamine. Unlike haloperidol, clozapine and metoclopramide can cause dissociation of the indices of stereotypy, evidently because of their unequal action on different parts of the nucleus. Yet another explanation may be that these drugs have different effects on the functions of caudate and extra-caudate brain mechanisms.

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