ROLE OF DIFFERENT PARTS OF THE RAT STRIATUM IN ORGANIZATION OF SHORT-TERM (MINUTES) FLUCTUATIONS OF STEREOTYPED BEHAVIOR AND TOLERANCE IN AMPHETAMINE USERS

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The psychosislike state with monotonous motor automatisms, induced in animals by large doses of amphetamine, has a distinctly oscillatory nature [4]. Analysis of the time course of this type of stereotyped behavior has proved a promising method of, on the one hand, understanding the chronobiological nature of psychopathology and, on the other hand, for predicting the character of evolution of a psychopharmacologic effect [2, 6]. This provides the motivation for a study of the neurophysiological mechanisms of rhythmicity, including elucidation of the role of different parts of the corpus striatum, which make different contributions to the organization of stereotypy, in its genesis [3].

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 180-220 g. Stereotyped behavior was produced by an injection of a standard dose of amphetamine (5 mg/kg, intraperitoneally) and recorded oscillographically by the method described previously [2]. By counting the number of monotonous movements of the animal's head every minute, it was possible to construct primary chronograms, which were then subjected to spectral and histographic analysis, by the use of an original computer program, developed in the writers' laboratory.

The characteristics of the time course of the pharmacological response to acute and chronic (5 mg/kg daily for 2 weeks) administration of the substances were compared in 12 intact rats and 23 animals after preliminary destruction of brain structures. Under pentobarbital anesthesia various parts of the striatum and extrastriatal formations were damaged electrolytically 10 days before the first determination [1]. Throughout the period of the investigation the rats were kept under standard conditions (temperature, light and darkness, diet), and with free access to food and water. The experiments were done at the same time of day, during summer months (June, July). The results were subjected to statistical analysis by the Wilcoxon-Mann–Whitney test.

At the end of the experiment the animals were anesthetized and killed. After fixation of the brain tissue in 10% formalin solution the volume of the lesion was determined (in per cent of the total volume of the structure) and its location, in accordance with coordinates of an atlas of the rat brain [7], were determined in serial brain sections.

EXPERIMENTAL RESULTS

After a single injection of amphetamine the rats developed stereotyped behavior with the usual range of motor automatisms (monotonous head turning, licking, nibbling), which lasted for about 3 h. According to analysis of the rhythmic structure of the process, on the primary chronograms it corresponded to oscillations with different amplitude–frequency characteristic curves (Figs. 1 and 2). Bilateral electrolytic injury to the striatum modified both the amplitude and the stability of the amphetamine stereotypy, and also its rhythmic components. The intensity of the changes depended on the volume and location of the lesion within the nucleus.

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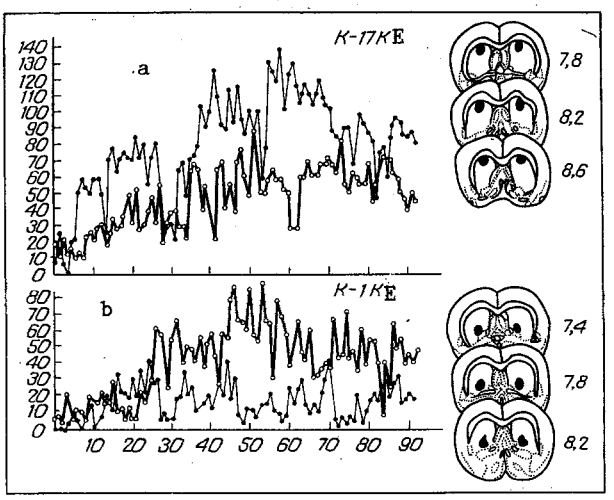

Fig. 1. Different kinds of reorganization of amphetamine stereotypy after damage to different parts of the striatum in individual rats. Primary chronograms, constructed from the results of minute by minute assessment of frequency of stereotyped head movements in a rat following a single (bold line) and chronic (thin line) administration of amphetamine, are shown as curves. a) Changes in stereotypy following injury to dorsal, and b) ventral parts of striatum. Ordinate, frequency of stereotyped head movements (during 1 min); abscissa, time of recording (in min).

According to morphological verification considerable injuries to the striatum (30-35% of its volume or more) were accompanied by gross behavioral defects in the form of general inhibition, often interrupted by short bursts of motor activity. Against this background, the action of amphetamine as a whole was greatly weakened. Because of this, such cases (four rats) were eliminated from the further study.

Limited destruction of the striatum (under 20% of the volume of the nucleus) did not cause significant disturbances in the rats' spontaneous behavior. Abnormalities observed in individual rats disappeared 7-10 days after the operation. Meanwhile amphetamine stereotypy under conditions such as these could undergo distinct, sometimes opposite, changes. Judging by the results of analysis of the morphological material, the location of the zone of injury played a decisive role in this respect.

Destruction predominantly of the rostro-dorsal parts of the nucleus led to weakening of motor automatisms. In this group (five rats) amphetamine induced stereotypy in only 60% of the animals. They still possessed increased locomotor activity 2 weeks after the operation and they were more aggressive than intact rats. External stimulation readily interrupted the stereotypy in these animals. The mean frequency of stereotyped head movements throughout the experiment (mesor) was 35 ± 8.6 turns per minute (compared with 52.6 ± 6.1 in the control); the maximal amplitude of the effect (79.6 ± 13.2 turns per minute compared with 117.4 ± 8.1 in intact rats) also was lower. Spectral analysis in the course of stereotypy revealed limitation of the power of the waves in the minute band and a statistically significant decrease in short-term (2-3 min) fluctuations (Figs. 1a and 2a).

Limited damage to the ventral parts of the striatum (three rats) had a rather different effect on the action of amphetamine. Compared with the animals of the first group they appeared tranquil, with no signs of evident aggressiveness. Although the mesor of stereotypy and its maximum were both reduced (37.6 ± 1.6 and 82.3 ± 7.2 turns per minute respectively), differences also were noted in the course of the rhythmic process. With lesions of this kind the power of the 2-3-min oscillations was not reduced but, on the contrary, it was increased, but there were no changes in the remaining components (Figs. 1b and 2a).

Meanwhile local destruction of the central parts of the corpus striatum (three rats) had little effect on the sensitivity of the animals to amphetamine. The mean value of stereotypy was close to values found in the intact group (51 ± 12.4 turns per minute). Only a tendency, not statistically significant, was found toward some degree of weakening of power of the 10-13 min oscillations. In precisely the same way, destruction of the extrastriatal brain formations was not reflected in either the intensity or the time course of stereotypy. In four rats with analogous defects in the suprastriatal cortex and septum, these parameters did not differ from results obtained with intact rats.

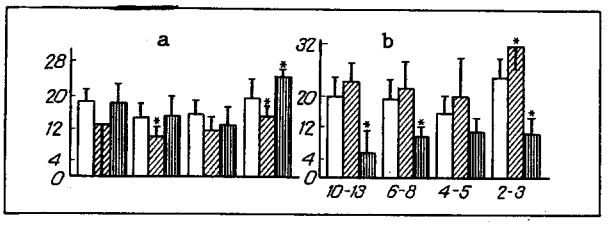

Fig. 2. Spectral characteristics of stereotyped behavior in groups of animals with lesions in different parts of the striatum. Columns indicate mean power of oscillations in minute band on primary chronograms of stereotypy during acute (a) and chronic (b) amphetamine administration: unshaded — intact rats, obliquely and vertically shaded — striatectomized animals with lesions in the dorsal and ventral parts of the striatum respectively. Ordinate, power of waves (conventional units); abscissa, period of waves (in min). Asterisk indicates statistically significant differences ($p < 0.05$) between results for intact and striatectomized rats.

Thus according to the results, functionally different parts of the corpus striatum in rats, as also in cats [3], make different contributions to the formation of stereotyped behavior. The results indicate that the nucleus is involved not only directly in the organization of amphetamine stereotypy, but also through its pacemaker mechanisms [5] it determines certain rhythmic components of the pharmacologic effect differently. Evidence in support of this view is given by observations on the same animals during chronic amphetamine administration.

In the case of repeated administration of amphetamine the time course of stereotypy showed a different evolution, details of which were described previously [2]. In this case, some rats showed strengthening, but others weakening of the response to amphetamine, inversely proportionally to its initial intensity. As the above facts show, this connection was disturbed in the striatectomized animals.

It was shown that a lesion of the dorsal striatum regularly led to enhancement of the motor manifestations after chronic amphetamine administration (Fig. 1a). In all the rats of this group, compared with animals undergoing acute administration of amphetamine, lengthening of the stereotypy (on average from 1.5 to 3 h) was observed, with an increase in the value of its mesor (to 82 ± 7.2 turns per minute). A sharp increase in power of the waves in the minute band, especially in the high-frequency part of the spectrum, discovered by spectral analysis, also was significant (Fig. 2b).

Another picture was found after destruction of the ventral zone of the nucleus. Although in intact rats with low initial values of the mesor of stereotypy, repeated administration of amphetamine was invariably accompanied by potentiation of the pharmacologic response, and the animals of this group reacted differently. Despite the low amplitude of stereotypy in the case of acute administration, the effect of amphetamine continued to weaken under the influence of repeated injections of the drug. The mesor of stereotypy fell to extremely low values (17.5 ± 2.1 turns per minute). Meanwhile the power of the rhythmic components of stereotypy also fell statistically significantly for many harmonics at the same time (2-3-min, 6-8-min, and 10-13-min waves; Fig. 2b).

According to our previous observations, from the functional and pharmacologic point of view the cat caudate nucleus is a heterogeneous formation. Among others, zones differently involved in the organization of specific activity of neuroleptics and amphetamine can be distinguished in the nucleus. It has also been postulated that the dorsal and ventral zones of the striatum share competitive relations with one another [6]. The results of the present study as a whole confirm this view and this means that the chronobiological approach can be used to deepen our understanding of the nature of striatal heterogeneity.

As has been shown, the dorsal and ventral zones of the corpus striatum in rats are responsible for different rhythmic components of amphetamine stereotypy. In particular, short-term fluctuations of stereotyped behavior in the course of time evidently depend on integrity of the dorsal zones of the nucleus, for just as their destruction weakens, damage to the functionally antagonistic ventral zones, on the contrary, strengthens the power of the 2-3-min oscillations.

Meanwhile, according to results of previous observations, the considerable abundance of the 2-3-min waves in response to acute administration of amphetamine is a condition of the rapid formation of tolerance to the drug [2]. Consequently, we may speak of the predominant contribution of strictly defined areas of this brain structure to the development of drug resistance. In

fact, in animals with injury to the rostro-dorsal striatum adaptation to amphetamine is much less marked, whereas after ventral lesions, on the contrary, it is significantly stronger than in the intact group.

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ACTION OF BEFOL AND ITS DERIVATIVES ON MONOAMINE OXIDASE FROM DIFFERENT SOURCES

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Progress in the study of the toxic action of pyridine derivatives, which is important for our understanding of the mechanism of onset of Parkinsonism, has again emphasized the difficulty of studying the biological properties of monoamine oxidases (MAO) [11]. The presence of at least two isozymes, namely MAO of types A and B, in biological objects has been established, and the ratio between them differs even in the same organ of animals of different types, and their physiological role has not yet been explained [14]. Furthermore, multiple forms of MAO, not identical with MAO of types A and B, also exist [9, 10, 12, 13].

In the investigation described below, in order to study the mechanism of action of the new antidepressant befol – *p*-chloro-N-(2-morpholinobutyl)benzamide [4] – its action on MAO of tissues containing different amounts of the A and B isozymes (bovine and rat brain, human placenta and platelets) was investigated and the antimonoamine-oxidase activity of various benzamide derivatives similar to befol also was compared.

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