DYNAMICS OF MINUTE RHYTHMS IN CATALEPSY AND THE ROLE OF THE DAILY HALOPERIDOL SCHEDULE IN TOLERANCE FORMATION

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The writers showed previously that haloperidol-induced catalepsy is a nonstationary process in time and its oscillatory structure is significantly modified by antiparkinsonism drugs and by damage to the corpus striatum [2, 3]. The principles governing modification of the rhythm reflect the degree of stability of the side effect of the neuroleptics.

In the investigation described below, having the prognostic value of the approach in mind, the character of evolution of the time course of catalepsy was determined during the development of tolerance to haloperidol. The importance of the daily schedule of administration of the neuroleptic for the character of the ensuing tolerance was studied at the same time.

EXPERIMENTAL METHOD

Altogether 52 experiments were carried out on 23 noninbred female albino rats weighing 180-200 g. To assess the neuroleptic catalepsy, the animals were made to hang by their forelimbs on a horizontal rod continuously for up to 2-4 h. Depending on the duration of holding on to the rod, the intensity of catalepsy was judged. On the basis of the results the primary time course (chronogram), smoothed beforehand by the sliding mean method [7], was plotted on a graph. To detect the oscillatory process, the resulting curves were subjected to autocorrelation and spectral analysis by the Nairi-2 computer. The Wilcoxon–Mann-Whitney method [4] was used for statistical analysis of the data. Haloperidol was injected intraperitoneally, daily for 2 weeks, in accordance with several different schedules: animals of group 1 (11 rats) received a single dose of 2 mg/kg of the neuroleptic at a strictly fixed time of day (8 a.m.), the six rats of group 2 received the drug three times a day (at 8 a.m. and 2, and 8 p.m.) in a dose of 0.7 mg/kg per injection, and the six rats of group 3 received a single injection of 2 mg/kg of the drug, but with a daily shift of the time of injection through 2 h (at 8 and 10 a.m., 12 noon, 2 and 4 p.m., then again at 8 a.m., and so on). The severity of catalepsy in all the animals was assessed at 5-7 p.m. on the 1st and 14th days of chronic administration of the neuroleptic, and also on the day after the end of its administration. The investigation was conducted during the winter (December–February) with maximal standardization of the experimental conditins (illumination, feeding, and maintenance of the rats).

EXPERIMENTAL RESULTS

The animals developed distinct catalepsy 1 week after the beginning of chronic administration of haloperidol, and it continued throughout the 24-h period irrespective of when the last injection was given. Later the disturbances of muscle tone in some of the rats gradually diminished and tolerance developed.

According to previous observations [2], a number of phases can be distinguished in the primary chronograms of catalepsy associated with acute injection of the standard doses of haloperidol: initial — progression of the neuroleptic effect with a high-amplitude peak and irregular waves, the phase of stabilization of the process, when a well marked rhythmic activity appeared with predominance of waves in the 2-4, 5-7, and 8-12 min bands, and a phase of gradual extinction of catalepsy.

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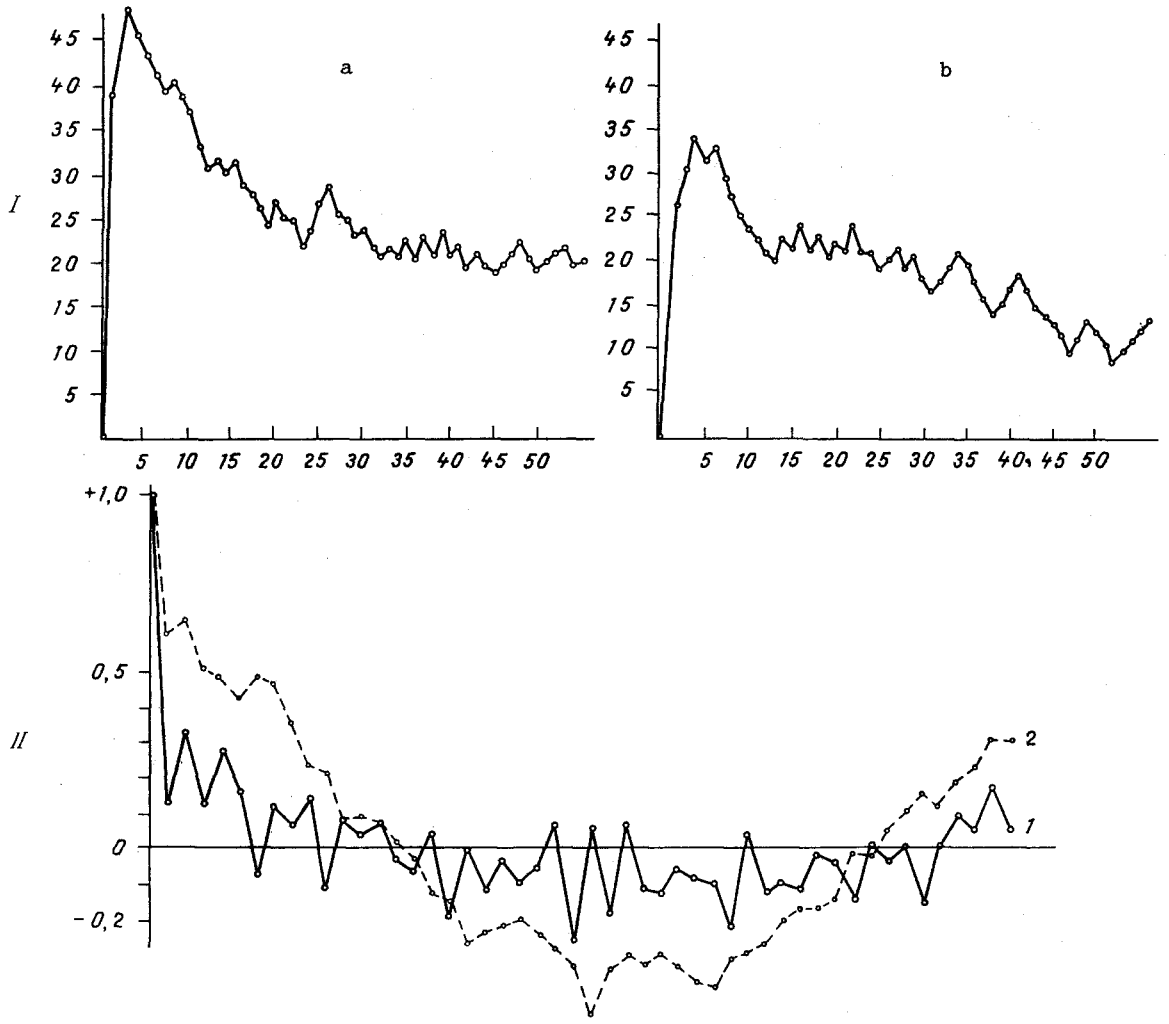

Fig. 1. Characteristics of time course of haloperidol-induced catalepsy during tolerance formation. I) Primary changes in catalepsy on 1st day (a) and on 14th day (b) of chronic administration of haloperidol (2 mg/kg at 8 a.m.) to rat No. 16. Abscissa, time from beginning of recording (min); ordinate, duration of catalepsy (in days); II) autocorrelation analysis of the same experiments (data for stabilized region of changes from 30th through 120th minutes). 1) Effect on 1st day, 2) on 14th day.

The same kind of phasic structure was maintained also during chronic administration of the neuroleptic, but the time course of catalepsy in the tolerant animals underwent a definite evolution. Its particular features were studied most fully in the experiments of group 1, using the most traditional form of administration of the drug, namely in a single dose at a fixed time of day. With this experimental schedule, after the end of the injections 100% of the rats showed adaptation to haloperidol in the form of a sharp decrease in the intensity of catalepsy (mean values of data for the whole experiment).

A typical feature of tolerance was marked weakening of the peak rise of the initial phase of action of the drug. The amplitude of this peak could be reduced or its duration could be greatly shortened (Fig. 1, I). However, the most interesting changes took place in the phase of stabilization of catalepsy, with a change in its rythmic characteristics. The time structure of the process under these circumstances was transformed differently in different animals.

The predominant form of tolerance in group 1 (83% of cases) was progressive slowing of the rhythmic fluctuations and a fall in amplitude of the waves on the primary chronogram, irrespective of their period. This state of affairs was clearly revealed by autocorrelation analysis (Fig. 1, II). The number of waves in the 2-4 and 5-7 min ranges on the spectral density curve of the stabilized regions of the chronograms was reduced, with a parallel increase in the slow-wave component (Fig. 2, I). This shift was statistically significant ($p<$

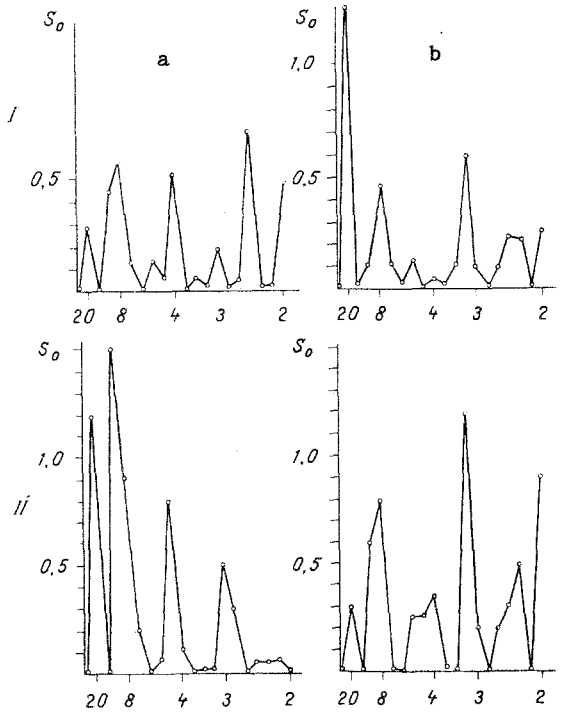

Fig. 2

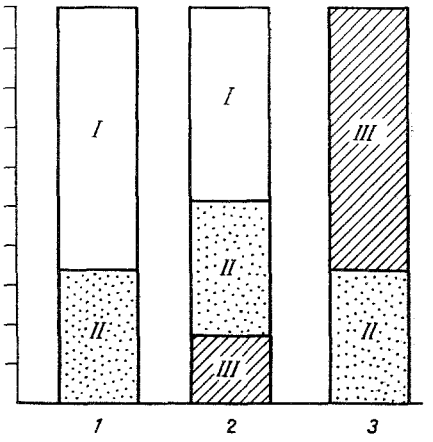

Fig. 3

Fig. 2. Time structure of neuroleptic tolerance based on data of spectral analysis with an increase in low-frequency (I) and high frequency (II) components. I (rat No. 16) and II (rat No. 10) — spectral density of stabilized regions of primary changes in different rats receiving haloperidol at the same time of day. a, b) Effects on 1st and 14th days of injection of neuroleptic respectively. Abscissa, period of waves (in min); ordinate, spectral density.

Fig. 3. Intensity of tolerance in animals receiving haloperidol by different schedules, after end of chronic administration. Ratio (in %) between numbers of cases with different degrees of tolerance and its absence in animals of groups 1, 2, and 3 of experiments respectively (mean data for six animals in each group). I) Tolerance; II) weak tolerance; III) absence of tolerance.

0.05). Furthermore, in rats with this type of tolerance, high-frequency oscillations were clearly dominant on the chronograms obtained during acute administration of the neuroleptics.

Much less frequently (17% of cases) the animals of this group had a different pattern of adaptive response. Tolerance formation was accompanied by an increase in the short-period (2-4 min) oscillations (especially if they were few in number in the control), and this shift was also statistically significant. The number of waves with a period of 5-7 min, on the other hand, showed a tendency to decrease (Fig. 2, II).

The development of tolerance depended essentially on the schedule of administration of the neuroleptic. In the case of triple injections (group 2) it developed somewhat less frequently — in 87% of animals, whereas in the case of a daily change in the time of each injection (group 3) it appeared in only 34% of rats. Statistical analysis confirmed the significance of differences between the groups. To judge from the mean values of catalepsy, the degree of tolerance also was unequal (Fig. 3). It is an important fact that the second type of tolerance described, when high-frequency fluctuations with a period of 2-4 min appeared on the chronograms, was found more often in the animals of group 3 (in 60% of cases) than in the rats of group 1.

Our chronobiological approach to the evaluation of haloperidol catalepsy thus indicates that neuroleptic tolerance can be formed in different ways and that its character depends on the daily schedule of administration of the drug.

The results of a previous investigation [3] suggested a relationship between the contribution of particular waves in the minute band to the rhythmic structure of catalepsy and the state of the monoaminergic systems of the brain. It was postulated that an increase in short-

period (2-4 min) waves is an indication of strengthening of noradrenergic transmission whereas an increase in the number of 5-7 min waves was taken to be the result of activation of striatal mechanisms.

It was pointed out above that the most widespread version of tolerance in the animals of group 1 was strengthening of the slow-wave component with a decrease in amplitude and number of the other waves. It can accordingly be concluded that one method of formation of resistance to the neuroleptic must be progressive weakening of striatal hyperactivity, which is regarded as the principal factor of catalepsy [1], with simultaneous limitation of noradrenergic processes. This view is confirmed by data showing a decrease in neuronal activity of the locus coeruleus in rats during the development of tolerance to haloperidol [9].

At the same time, the results suggest that resistance to the drug may develop on account of the activation of brain mechanisms which actively counteract the cataleptogenic effect. This is shown by an increase in the proportion of high-frequency waves in the time structure of catalepsy in a number of tolerant rats. Usually this phenomenon accompanies the natural disturbance of catalepsy after acute injection of the neuroleptic or against the background of the anticataleptogenic action of dopa [3]. The possibility likewise cannot be ruled out that this form of tolerance must be less stable.

As the results show, the rate of development of tolerance to haloperidol is largely dependent on the daily schedule of administration of the neuroleptic. Prevention and the overcoming of resistance to psychotropic drugs is an urgent problem in contemporary psychiatry. Various approaches to its solution have been suggested and, in particular, a change in the dosage of the neuroleptics or in the duration of the course of treatment [5, 8]. Administration of the drug with a daily shift of the time schedule must evidently be regarded as one such method. We recorded fewest such cases of tolerance in group 3, when the time of injection of the standard dose of haloperidol was changed. Under such conditions it is probably more difficult for the so-called "expectancy response" to arise, in the form of premature readiness of the adaptive response to expected contact with xenobiotics [6]. Our observations also show that the schedule of haloperidol administration is reflected in the form of tolerance, and consequently in the possibility of effective overcoming of tolerance.

LITERATURE CITED

1. É. B. Arushanyan and V. A. Otellin, The Caudate Nucleus [in Russian], Leningrad (1976).
2. É. B. Arushanyan and A. P. Popova, Byull. Éksp. Biol. Med., No. 1, 89 (1986).
3. É. B. Arushanyan and A. P. Popova, Chemistry, Pharmacology, and Clinical Aspects of Neuroleptics [in Russian], Tartu (1986), pp. 22-23.
4. E. V. Gubler, Computerized Methods of Analysis and Diagnosis of Pathological Processes [in Russian], Leningrad (1978).
5. A. M. Zharkovskii and A. V. Belyakov, Farmakol. Toksikol., No. 5, 22 (1983).
6. V. N. Reushkin, Cybernetics of the Living [in Russian], Moscow (1985), pp. 54-80.
7. V. Yu. Urbakh, Biometric Methods [in Russian], Moscow (1964).
8. R. J. Carey and J. De Veaugh-Geiss, Psychopharmacology, 82, 164 (1984).
9. T. G. Dinan and G. Aston-Jones, Brain Res., 325, 385 (1985).