Effect of Fluctuating Currents on the Time Course of Apomorphine-Induced Stereotypy in Rats

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Any pharmacological reaction has a fluctuating (rhythmic) nature and, thus, various external rhythmogenic influences can be used to control it. To verify this assumption formulated by us earlier [2], we studied the efficiency of fluctuating currents on the time-course of apomorphine-induced stereotypy in rats. This model is considered to be a stable oscillatory phenomenon [4]. As fluctuating currents, we used a noise voltage comprised of pulses of random amplitude and phase which has been successfully applied in the treatment of somatic diseases [1,6].

MATERIALS AND METHODS

Experiments were performed on 20 nonpedigree albino rats with a body weight of 150-200 g during the winter period (January-February). The rhythmic character of stereotyped behavior was assessed according to a previously described methodology [4]. Monotonic motion automatisms established after administration of a standard dose of apomorphine (1 mg/kg, intraperitoneally) were counted every minute during 1-1.5 h. The primary chronograms were further mathematically processed using a special computer software package developed in our laboratory. The following parameters were assessed: phase and duration of apomorphine-induced stereotypy, its average value (mesor), and the variation coefficient (ΔX). to investigate the wave dynamics of the pharmacological response, we carried out a spectral analysis of chronograms according to 20 harmonics. To administer the fluctuating currents, a flexible collar with two electrodes attached to a power supply was placed around the rat's neck. The voltage was chosen individually (it was lower than the voice reaction threshold). Six daily 10-min sessions of fluctuating currents were carried out in the experimental group (10 rats). In the control group of animals fluctuating currents was simulated under the same conditions. Before the experiments, the starting (initial) time-course of stereotypy was determined in all the animals. On the 7th day after fluctuating currents or its simulation the effect of apomorphine was assessed again. The animals were kept under standard conditions with access to food and water ad libitum in a natural light regime. The experiments were performed at a fixed time of the day (14-16:00 h).

The results were processed statistically using the Student and Wilcoxon-Mann-Whitney tests.

RESULTS

In accordance with our previous data [2], the time course of the apomorphine-induced stereotyped behavior for continuous registration displayed a wave character with a wide range of minute oscillations from 2-3 to 20-40 min. More frequent and low-

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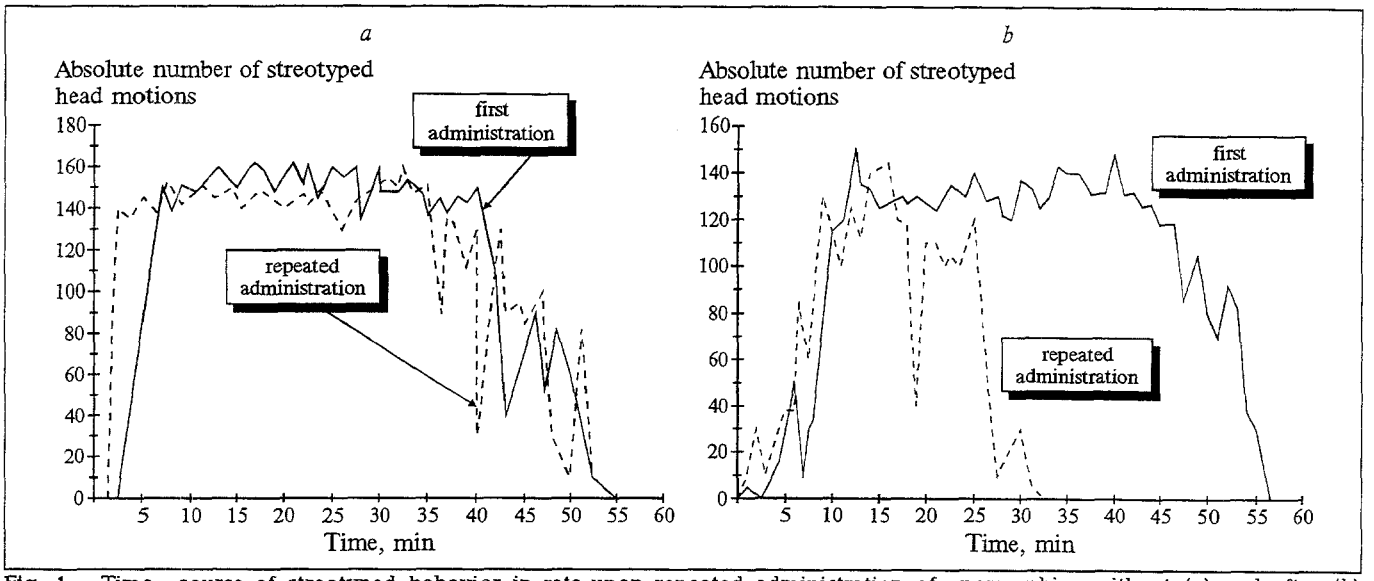

Fig. 1. Time–course of streotyped behavior in rats upon repeated administration of apomorphine without (*a*) and after (*b*) fluctuating currents.

amplitude motion automatisms corresponded to the steady-state pharmacological response. In addition, we registered a marked decrease in the locomotor activity of the animals and their reaction to external stimuli. As stereotypy attenuated,high-amplitude waves in the primary chronograms (Fig. 1, *a*) appeared that correlated with appearance of licking, grooming, and locomotion.

Even a superficial comparison of the chronogram shape in response to the initial injection of apomorphine revealed a significant difference in the individual pharmacological sensitivity of the rats. In one-third of the cases we observed a strongly marked stereotypy with an average mesor value, determined from the frequency of head motions, reaching 123±7.3 motions/min. The variation coefficient was rather high: ΔX=133.7±8.4 motions/min. In other rats the behavioral disorders were less marked (stereotypy mesor 70.4±10.0 and ΔX=102.8±16.3 motions/min).

The repeated administration of apomorphine in the control rats subjected to the simulated fluctuating currents was accompanied by a slight overall strengthening of hypokineses. This phenomenon could be considered an indicator of sensitization of the postsynaptic dopamine receptors that is usually ascribed to apomorphine [9]. However, judging from the individual analysis of the stereotypic time course, this tendency can by no means always be traced. The rats with enhanced initial reaction to the drug usually responded to the second injection of apomorphine by attenuation of stereotypy. On the other hand, in 40% of the initially hypoactive animals their stereotypic behavior was enhanced and in 30% of cases it remained unaltered.

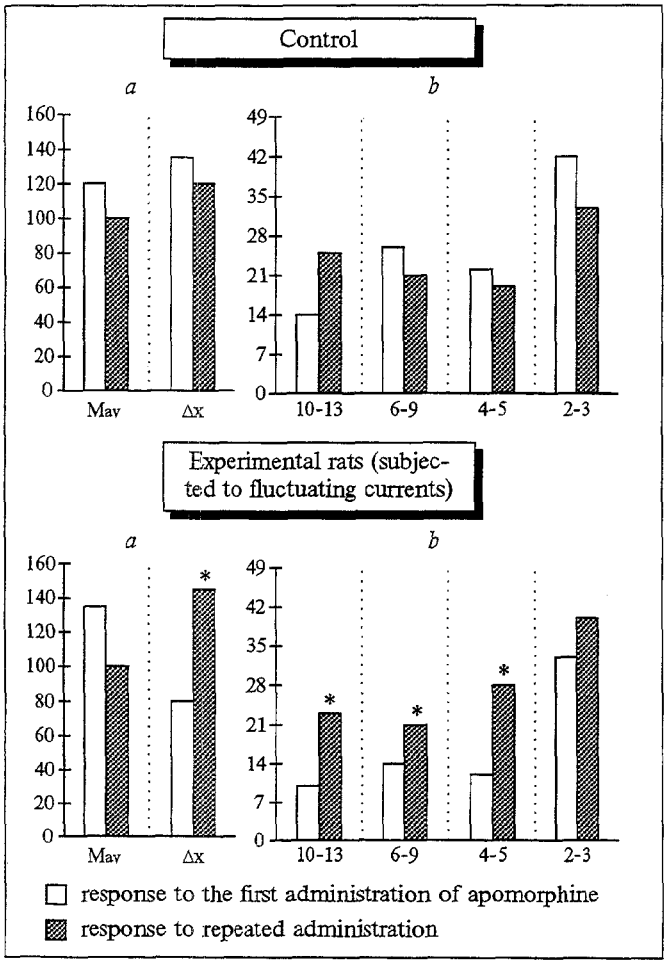

Fig. 2. Effect of fluctuating currents on static (*a*) and spectral (*b*) characteristics of stereotypy in rats that responded to repeated administration of apomorphine by attenuation of motion automatisms. *a*) average values of mesor (M_{av}) and variation coefficient (ΔX). Ordinate: frequency of head motions per min; *b*) average number (abscissa) of minute range waves in time course of the apomorphine - induced stereotypy.Asterisk: statistically reliable ($p<0.05$) shift in comparison with the results of the primary testing.

According to the summary data, the behavioral disorders against the background of fluctuating currents were less strongly manifested after the repeated administration of apomorphine. All the animals became more aggressive and reacted more rapidly to the external stimuli with streotyped head motions; grooming and washing reflexes became more frequent. At the same time, the stereotypy mesor dropped from 126±5.2 to 110.5±10.3 motions/min and the variation increased to 120.4±15.4 motions/min. According to spectral analysis, the power of the minute range of oscillations increased, especially in the high-frequency region of the spectrum.

Evaluation of the individual sensitivity of the animals showed that after fluctuating currents atenuation of stereotypy (Fig. 1, *b*) was recorded in a higher number of cases (60%) in comparison with the control. Moreover, the chronobiological approach made it possible to reveal peculiarities of reorganization in the oscillatory process accompanying attenuation of stereotypy.

As shown by a comparison of the control and experimental rats that responded to the repeated administration of apomorphine by an attenuation of stereotyped behavior and a monotypic decrease of the reaction mesor, these changes correlated with a nonuniform reorganization of the time-course of stereotypy (Fig. 2). In these cases fluctuating currents led to a considerable expansion of the variation range. The spectrum of the pharmacological effect was also different: in the experimental group of animals a regular increase of oscillatory power in a wide frequency range occurred. The number of 4-5 and 6-9 min waves reliably increased.

Proceeding from our previous observations [3], we believe that this reorganization of streotyped behavior may serve as an indicator of its low stability and subsequent ready destruction, leading to the formation of tolerance to the drug.

The probable reason underlying the destabilizing effect of fluctuating currents on apomorphine-induced behavioral shifts may be the triggering of some adaptational mechanisms by external stimuli. For instance, the pineal body possesses some adaptive properties [7]. On the one hand, it is known to be highly reactive to physical factors [8], while on the other, removal of the pineal body prevents the development of pharmacoresistance. This is reflected in the time course of the effect of psychotropic substances by a reduction of the fraction of minute fluctuations with high and average frequency. The epiphyseal hormone melatonin gives the opposite results [4].

Thus, an external rhythmogenic influence can lead to a disorganization of the pharmacological response and a reduction of its stability in time.

REFERENCES

1. S. Kh. Azov, *Fluctuating currents in Experiment and Clinical Practice* [in Russian], Stavropol (1985).
2. E. B. Arushanyan and K.B. Ovanesov, *Byull. Eksp. Biol.*, **101**, № 6, 704-707 (1986).
3. E. B. Arushanyan and A. V. Popov, *Farmacol. Toksikol.*, № 1, 17-19 (1990).
4. E. B. Arushanyan, N. Yu. Binatova, A. V. Popov, and A. P. Popova, *Ibid.*, № 4, 8-11 (1991).
5. E. B. Arushanyan, *Eksp. Klin. Farmakol.*, № 4, 67-69 (1992).
6. A. F. Gavrilenko and L. V. Yashchenko, *Voprosy Kurortologii*, № 1, 36-39 (1991).
7. V. D. Slepukhin and V. G. Pashinskii, *The Pineal Body and Adaptation of the Organism* [in Rusian], Tomsk (1982).
8. J. L. Bardasano, S. Cos, *et al.*, *J. Hirnforsch.*, **30**, 39-43 (1943).
9. W. Riffee, R. E. Wilcox, D. Vaughn, R. V. Smith, *Psychopharmacology*, **72**, 146-149 (1982).