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NORMALIZING EFFECT OF ANTIDEPRESSANT IMIPRAMINE ON CHANGES IN CIRCADIAN MOVEMENT PATTERN OF PINEALECTOMIZED RATS AFTER A CHANGE IN TIMING OF THE PERIOD OF DAYLIGHT

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The ability of antidepressants to interfere with the function of the pineal gland has been noted and is recognized as an important element of the psychotropic activity of these substances [1, 3]. Most studies of this type have been carried out by the use of biochemical methods, and for that reason they have left mainly unanswered the question of to what degree the changes taking place involve the specific properties of the gland. In the modern view the pineal gland above all adjusts the various physiological processes to external environmental conditions changing in accordance with the duration of the photoperiod [7].

In this investigation the effect of an antidepressant was studied on disturbances of adjustment of the circadian rhythm of motor activity of rats following a shift of several hours in the time of the photoperiod in animals after pinealectomy.

EXPERIMENTAL METHOD

Experiments were carried out on 40 noninbred male and female albino rats weighing 220-280 g. The circadian rhythm of spontaneous motor activity was studied in an actograph, whereby the number of journeys made by the animal around its individual cage (30 × 12 × 12 cm) could be recorded continuously. Each journey was recorded graphically on a moving paper tape, as a result of which an actogram covering a period of several days was obtained. It was divided into equal 3-hourly sections and the number of journeys in these areas was counted. The results were used to construct individual chronograms. For overall assessment of the results the mean values of motor activity were counted during the same time cuts for the group of animals. Cosinor analysis was carried out, with the construction of confidence ellipses for the group

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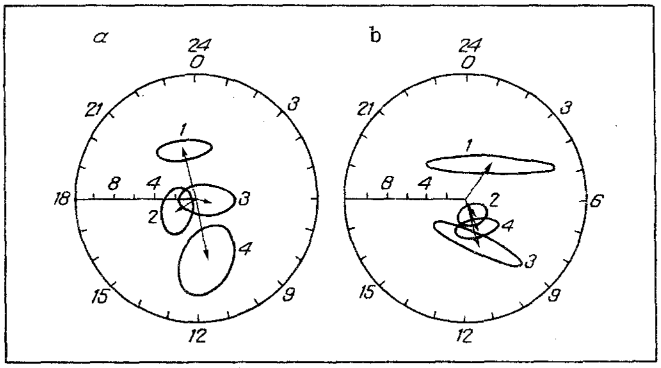

Fig. 1. Effect of pinealectomy on readjustment of circadian rhythm of motor activity of rats during a shift of photoperiod. a) Time course in intact, b) pinealectomized rats. Ellipses of confidence values of parameters of circadian rhythm shown on 24-h dial for 3 days before (1) and on 1st-2nd (2), 3rd-4th (3), and 5th-6th days after shift of photoperiod through 10 h. Left side of circle gives scale for measuring amplitude of circadian rhythm (arrow connecting center of circle with center of ellipse of errors); direction of arrow determines acrophase of rhythm on 24-h time scale.

of rats. Amplitude versus frequency characteristics of the rhythm were determined within the range of oscillations with a period of from 20 to 28 h in the course of 6 days and the same time after a change of photoperiod was determined. Finally, individual changes in amplitude and acrophase in individual animals were estimated by the method of serial time cuts [5]. Experiments were carried out on intact and pinealectomized animals. Pinealectomy was performed under pentobarbital anesthesia by a method developed in the writers' laboratory [6]. The animals were used in the experiments not earlier than 1 month after the operation. Under these circumstances all the rats were kept initially under conditions of an ordinary fixed photoperiod (light:darkness 12:12), the light being turned on at 8 a.m. and off at 8 p.m. The animals were fed daily at 8-10 a.m. This was followed by a shift of the photoperiod to 10 a.m. (after a short day lasting 2 h), with the light turned off at 10 a.m. and on at 10 p.m. Reorganization of the circadian rhythm in accordance with the new photoperiod was assessed in the course of 1 week. Equal numbers of intact and pinealectomized animals began chronic daily intake of the antidepressant imipramine (10 mg/kg, intraperitoneally) began 1 week before the shift of photoperiod, and the injections continued for the same period after the end of the shift. Control rats received physiological saline on the same schedule. The experimental results were subjected to statistical analysis by personal computer.

EXPERIMENTAL RESULTS

In connection with the ethologic features of rats, leading a nocturnal mode of life, they exhibited typical circadian activity with a maximal number of journeys during darkness and minimal during daylight. After the time shift of the photoperiod a smooth, step by step transition of the circadian rhythm was observed. During the first 2 days the original circadian curve of locomotion had a tendency to continue, although its maximum was shifted through 18-21 h, followed by reduction of motor activity in the late nocturnal hours. On the 3rd-4th day the rhythm was disturbed, and subsequently normalized by the 5th-6th day, which corresponded to a new position of the acrophase. The rhythm described above was clearly revealed by cosinor analysis (Fig. la). To this it must be added that in a study of amplitude–frequency characteristics of the circadian pattern of motor activity on days before the change of photoperiod, the 24-hourly component predominated. After the phase shift of the photoperiod, two components now were seen, with longer (26-28 h) and shorter (20-24 h) periods.

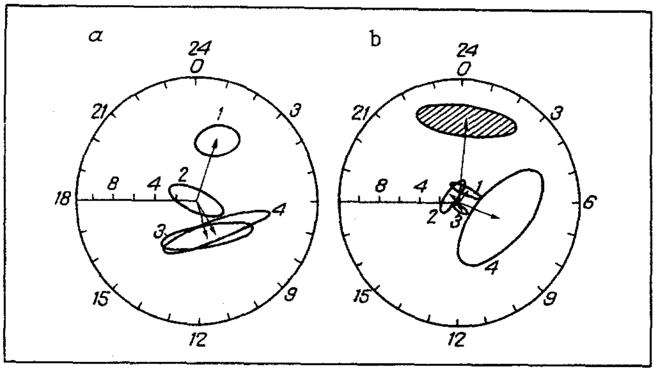

Fig. 2. Limitation by imipramine of disturbances caused by pinealectomy in reorganization of circadian rhythm of motor activity of rats following a shift of photoperiod: a) readjustment of rhythm during chronic administration of antidepressant; b) the same, in pinealectomized animals. Shaded ellipse indicates initial characteristic of circadian rhythm in pinealectomized rats before administration of drug. Remainder of legend as to Fig. 1.

Pinealectomy caused no significant change in the normal rhythm of the animals' circadian activity although there was a certain tendency for the amplitude of the oscillations and the zone of migration of the acrophase of the rhythm to increase. The change in photoperiod, however, revealed a different time course of adjustment of the circadian rhythm from that in the control. During the first 2 days of the shift to the new photoperiod, a steplike migration of the acrophase was observed. On following days it maintained the same position, during appreciable fluctuations in amplitude of the rhythm itself (Fig. 1b). This kind of step could also be found by the study of individual adjustment of the rhythm by the method of serial time cuts. Moreover, calculation of amplitude versus frequency characteristics of pinealectomized rats revealed no splitting of the circadian rhythm into two components during the first 6 days after the shift of photoperiod could be found.

Imipramine, in agreement with previous observations [2] modified somewhat the circadian rhythm of motor activity of the intact animals with a shift of acrophase to later night hours (Fig. 2a). Meanwhile the antidepressant impaired the natural dynamics of resynchronization of the circadian locomotion with the new lighting schedule after shift of the photoperiod. The rhythm disturbance took place more rapidly during the first 2 days, and on subsequent days the formation of the new photoperiod lagged behind the control values (compare Figs. 1a and 2a). In other words, in that situation a distinct pharmacogenic effect must have developed in the mechanisms of rhythm reorganization.

However, against the background of pinealectomy, the action of the antidepressant appeared differently. Imipramine restored the normal time course of the adjustment of circadian rhythm, which resembled migration of the acrophase in intact animals. Since the substance reduced the amplitude of the circadian fluctuations of activity appreciably, it was logical to expect acceleration of desynchronization of the rhythm with the step of the acrophase toward its new location. Nevertheless, this was not observed. On the contrary, disturbance of the original rhythm was clearly retarded (Fig. 2b). During the first 2 days, despite the fall of amplitude, the original curve of activity followed by the smooth formation of a new rhythm was observed, although its acrophase was still far from the expected position. Just as in the control, splitting of the amplitude–frequency characteristic curve of the rhythm into two periodic components again took place.

Thus pinealectomy prevents the normal sequence of reorganization of the circadian rhythm after a shift of photoperiod through several hours. The original pattern of the rhythm, which was not changed as a result of the operation, is highly resistant to a phase shift of photoperiod. Under these conditions the antidepressant imipramine, which itself accelerates disturbance of the rhythm in the first stages of transition to the new pattern of activity, largely restores the normal, smooth readjustment of the rhythm when disturbed by pinealectomy.

Defects found in the organization of the circadian motor activity of rats after pinealectomy closely resemble disturbances which, as we described previously [4], caused various types of depression-inducing factors under similar conditions (chronic pain stress, reserpine). In that way, pinealectomy induces disturbances on this model that closely resemble a depressive state. The specific character of such disturbances also is confirmed by their disappearance under the influence of imipramine.

On the other hand, as will be evident, the pineal gland does not determine the ability of the antidepressant to interfere with the chronobiological phenomenon we are studying, and this compels a search for an extrapineal object to which the action of the drug can be applied. The possibility cannot be ruled out that the central pacemaker of circadian oscillations, namely the suprachiasmatic nuclei of the hypothalamus, plays the role of such an object. They are known to be actively involved in adaptation to a new pattern of illumination [8] and, at the same time, large quantities of labeled imipramine accumulate in the nuclei [9]. Hence, the pharmacologic effect may be the result of normalization of pacemaker function and/or abolition of the defect in its relations with the secondary oscillating structures of the brain.

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