SEASONAL CHANGES IN BEHAVIORAL EFFECTS OF NEUROLEPTICS IN ALBINO RATS

M. J. Otter, É. I. Kalda, and J. P. Érik

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KEY WORDS: neuroleptics; seasonal rhythms; catalepsy; motor activity.

It has been shown [3, 4, 6, 7] that the degree of blockage of mediator systems and the corresponding behavioral effects of neuroleptics vary in the course of the 24-hour period. Seasonal changes in activity of monoaminergic systems and in behavioral effects of neuroleptics have received little study, for this situation calls for systematic research over a period of several years [5].

The aim of this investigation was to study the circennial rhythm of natural seasonal variations in spontaneous activity of metabolism of monoaminergic systems in the rat brain and the psychotropic effects of two neuroleptics: haloperidol and levomepromazine.

EXPERIMENTAL METHOD

Experiments were carried out once a week on female albino rats at 9 a.m. Before the experiments the animals were kept for 2-4 weeks under standard conditions of lighting, temperature, and diet. Orienting-motor activity was determined in the control and 30 min after a single intraperitoneal injection of haloperidol (0.5 mg/kg) and levomepromazine (5 mg/kg). Catelepsy was determined 30 min and 1, 2, 4, 6, and 24 h after injection of the drugs, using a 10-point scale [4].

The results given in this paper are the sum of data obtained in individual experiments during a calendar month in 1981, 1982, 1983, and 1984. Concentrations of dopamine (DA) and serotonin (5-HT) and of their metabolites — homovanillic acid (HVA) and hydroxyindoleacetic acid (5-HIAA) — were determined by spectrophotofluorometric methods [1, 2]. The numerical results were subjected to statistical analysis by Sutdent's t test.

EXPERIMENTAL RESULTS

Spontaneous motor activity varies in the course of the year. In the control it was increased in January, March, July, and September (Fig. 1). Initially low motor activity (February, August) was inhibited less strongly by neuroleptics than high activity. Seasonal rhythms also were observed in the recovery of motor activity after administration of neuroleptics. Initially high motor activity of rats (January, March), depressed after administration of neuroleptics, remained relatively low 24 h later. Data showing fluctuations of the cataleptogenic action of neuroleptics are given in Fig. 2.

The closed curve reflecting the cataleptogenic action of the neuroleptics in rats has peaks in the spring and fall and resembles an ellipsoid. Catalepsy (60 min later), induced by injection of haloperidol, was maximal in April and October (9.1 ± 0.9 points), whereas after administration of levomepromazine it was maximal in March (7.5 ± 1.5 points) and November (9.1 ± 1.5 points). After 4 h the maxima of haloperidol-induced catalepsy in spring and the fall and also the peak in August against the background of low motor activity were preserved. Levomepromazine-induced catalepsy passed off more rapidly in spring, whereas in October (9.7 ± 1.2 points) and November (9.4 ± 0.6 points) it remained high (Fig. 2c). "Residual" (after 24 h) catalepsy, induced by the neuroleptics, also was high in the spring and autumn months (Fig. 2d). In many cases, if the initial development of catalepsy was sluggish, it lasted longer than when marked catalepsy developed rapidly (Fig. 2a, d) [5].

Comparison of the details of the cataleptogenic action of the neuroleptics with the rate of DA and 5-HT metabolism (the HVA and 5-HIAA levels) in intact animals revealed some degree

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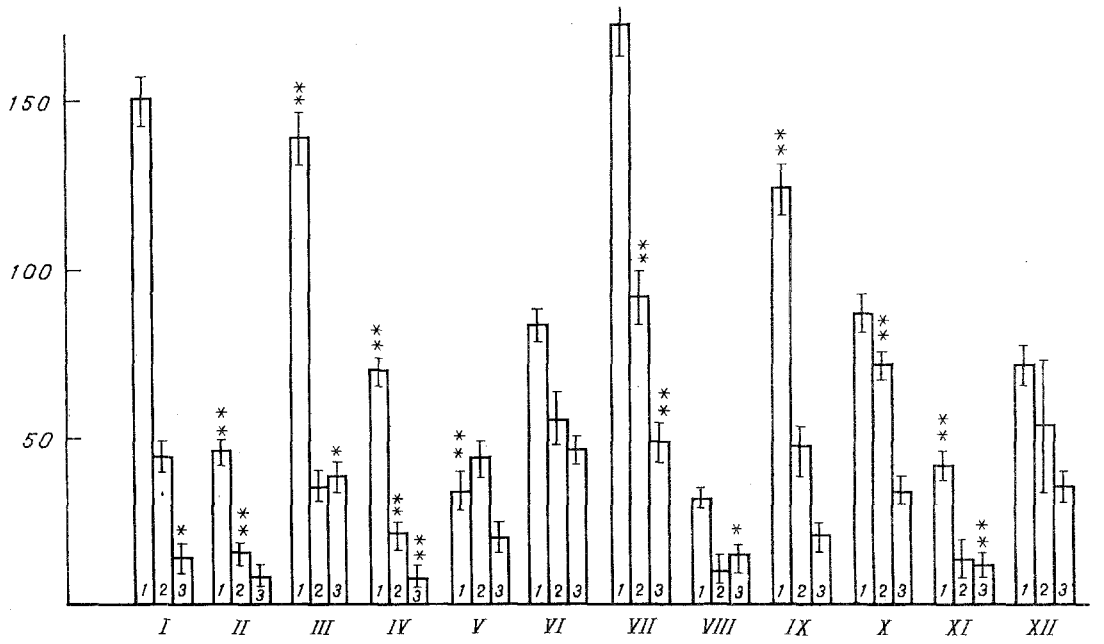

Fig. 1. Circennial rhythm of motor activity in control and after administration of haloperidol (2) and levomepromazine (3). Abscissa, months of year; ordinate, number of pulses recorded in photoelectric actometer. *P ⩽ 0.05; **P ⩽ 0.01.

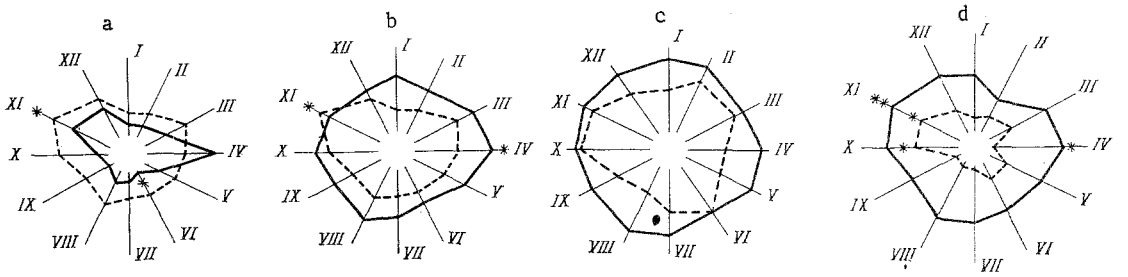

Fig. 2. Circennial rhythm of catalepsy induced by haloperidol (continuous line) and levomepromazine (broken line), 30 min (a) and 1 h (b), 4 h (c), and 24 h (d) after injection of neuroleptics. Roman numerals denote months of the year. Diameters represent arithmetic mean values of intensity of catalepsy (in points). Each point obtained by summation of intensity of catalepsy in 24-36 animals on average.

of negative correlation (Fig. 3) [4].

Haloperidol increased the HVA concentration, and levomepromazine the 5-HIAA concentration, and the lower their concentrations at this time in the brain of the control animals, the greater the increase [3]. The greater increase in concentration of these metabolites usually correlated with marked development of catalypsy: Haloperidol-induced catalepsy developed more intensively when the HVA concentation was low (January, June) in the brain of intact rats, but levomepromazine-induced catalepsy developed when the 5-HIAA concentration was minimal (in spring and the fall).

Seasonal fluctuations in the action of neuroleptics are considered to be due to endogenous seasonal neurobiological and pharmacokinetic factors [3].

Seasonal rhythms of cataleptogenic action, like circadian rhythms, are thus determined by rhythms of activity of dopaminergic and serotoninergic processes in the brain. When the rate of metabolism of monoamines and the concentrations of their metabolites in control rats are low, an increase in their turnover under the influence of neuroleptics is high, and is accompanied by the simultaneous rapid and powerful development of catalepsy. If the rate of monoamine metabolism is high, an increase in the concentration of metabolites of monoamines after injection of neuroleptics and the development of catalepsy are delayed. A definite

role in this situation is evidently played by the general increase in the intensity of metabolism of rodents in spring and fall. Data showing that activity of adaptive reactions of rodents is weaker in the spring and fall [1] are in good agreement with the powerful development of catalepsy in these seasons [1].

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IMMUNOLOGIC AND PHARMACOLOGICAL ACTIVITY OF ATROPINE–PROTEIN CONJUGATES

V. K. Kozlov and A. Ya. Bespalov

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Antibodies specific for low-molecular-weight pharmacologically active compounds are widely used in practical and experimental medicine and, in particular, in pharmacology. To obtain specific antibodies, animals are immunized with artificial conjugated antigens (conjugates), in which low-molecular-weight pharmacologically active substances play the role of hapten determinants of immunochemical specificity. Protein conjugates of atropine have previously been used to obtain antibodies specific for atropine, and to develop a method of quantitative radioimmunoassay of the cholinolytic in biological fluids [9, 13]. However, the activity of these conjugates as inducers of a humoral immune response specific for atropine, and also the time course of specific antibody formation to these antigens have not been studied. There is no information in the literature on pharmacologic activity of atropine conjugates.

The aim of this investigation was to study immunologic (induction of atropine-specific antibody formation) and pharmacological (cholinolytic) activity of atropine conjugates when injected into experimental animals, within a wide dose range.

EXPERIMENTAL MEHOD

Experiments were carried out on 500 non-inbred and inbred (CBA) mice weighing 16-20 g and on 20 rabbits, of different sexes, weighing 2-3 kg. The atropine conjugates were synthesized under conditions similar to those described previously: p-carboxyphenylazoatropine–bovine serum albumin (PCPAA-BSA) by the method in [13], atropine hemisuccinate–BSA (AHS-BSA) by the method in [9]. The number of hapten groups on the carrier (epitopic density) was determined spectrophotometrically. The PCPAA-BSA conjugate has 10, the AHS-BSA conjugate had 6 epitopes of chemically modified atropine. For immunization of the mice and rabbits, the conjugates were injected mixed with Freund's complete adjuvant, in doses of 0.5 to 10 mg/kg, subcutaneously: Mice received two injections at an interval of 7 days; rabbits

Departments of Pharmacology and Chemistry, Institute of Toxicology, Ministry of Health of the USSR, Leningrad.

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