Correlations between the Pharmacokinetics and Dynamics of Pharmacological Effects of Bromantane

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 119, № 3, pp. 305-308, March, 1995
Original article submitted April 19, 1994

It is shown that there is a mathematical correlation between an integral characteristic of activity of the organism (the capacity for work), electrophysiological indexes of functioning of the brain structures, and the concentration of a novel derivative of 2-aminoadamantane, bromantane, in the brain. The nature of the correlation between integral characteristics of the organism studied on different levels is found to change depending on the time elapsed from the administration of the preparation and on its concentration in the blood or target tissue.

Key Words: *bromantane; EEG spectral analysis; psychostimulators*

Bromantane (2-[n-bromphenyl]-aminoadamantane) exhibits psychostimulating activity and produces a marked adaptogenic effect combined with immunostimulatory and detoxicating activities [6,11,14,15]. As was shown previously, therapeutic adamantane derivatives, being highly lipophilic, cross the blood-brain barrier easily and their concentration in the brain markedly exceeds that in the blood [8-10,13,16,17].

The aim of the present investigation was to study the correlations between the pharmacokinetics and dynamics of the pharmacological effects of bromantane using methods of linear and nonlinear regression. Account was taken of the fact that the majority of biological processes are governed by linear dependences only in exceptional cases and mainly by polynomials of the second and third orders [1].

MATERIALS AND METHODS

The experiment was carried out on outbred male albino rats weighing 200-250 g. Bromantane was administered *per os* in a dose of 20-100 mg/kg as 5% solution on polyethyleneglycol-400. The bromantane concentration in the blood and brain homogenates was determined by the gas-chromatography method [12]. The effect of bromantane on the duration of running was studied in repeated loadings until the rats refused to run. Rats of the experimental and control groups ran till exhausted on a treadmill with a belt speed of 55 m/min every 60 min for 24 h. The effect of bromantane on the potentials of different brain structures was examined in free-behavior rats using quantitative spectral analysis of the electroencephalogram (EEG) after Fourier. The method of implanting chronic Nichrome electrodes in the sensorimotor cortex of both brain hemispheres, in the dorsal hippocampus, and lateral hypothalamus of the left hemisphere, and the protocols for recording and processing biopotentials and for the quantitative EEG spectral analysis were described previously [2,5-7]. On the day of the experiment the bioelectrical activity of the brain was recorded using a specialized neurophysiological complex (O.T.E. Biomedica and W.A.B. Technology, Russia) before (the background) and after (1, 2, 3, 4, 5, 6, 7, and 8 h) the oral administration of bromantane.

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0007-4888/95/0003-0297$12.50

RESULTS

As was found in pharmacokinetic studies, the coefficient of bromantane distribution was 2.29 for the brain 10 min after its oral administration, which attests to the high permeability of the blood-brain barrier for this preparation. The maximal level of bromantane in the brain was recorded at 60 min, amounting to 396% of the blood concentration (k_p=3.99). The content of bromantane in the brain drops relatively quickly: just 4.26% of the maximal concentration was found after 24 h ($t_{1/2}$=7 h).

Drugs that are adamantane derivatives (midantane, adapromine, as well as bromantane) markedly affect the indexes of the EEG power ranges, characterized on the whole by a decrease of the total power and by a diminishment of the absolute power of all frequency ranges and of the amplitude of the dominating peak of power ranges (APR) of the EEG, respectively [3,4,6]. The development of this effect peaks 1-3 h after administration, this corresponding to the period of the maximal brain concentration and lasting at least 8 h after a single administration.

The correlation analysis performed using bromantane brought to light the correlations between the pharmacokinetics of the preparation in the brain and its effect on the physical capacity for work (the duration of treadmill running for repeated loadings), on the one hand, and the change of biopotentials of the different brain structures as exemplified by EEG APR, on the other (Figs. 1, 2).

The period of observation was divided into two phases corresponding to the biphasic effect of bromantane (Fig. 1, *a*, *c*). The linear and nonlinear (second- or third-order polynomial predominantly) dependences are depicted on Fig. 2 and the strength of the correlation is characterized as a function of the correlation coefficient and of the degree of reliability.

The dependence between the pharmacokinetics of bromantane in the brain and the influence of

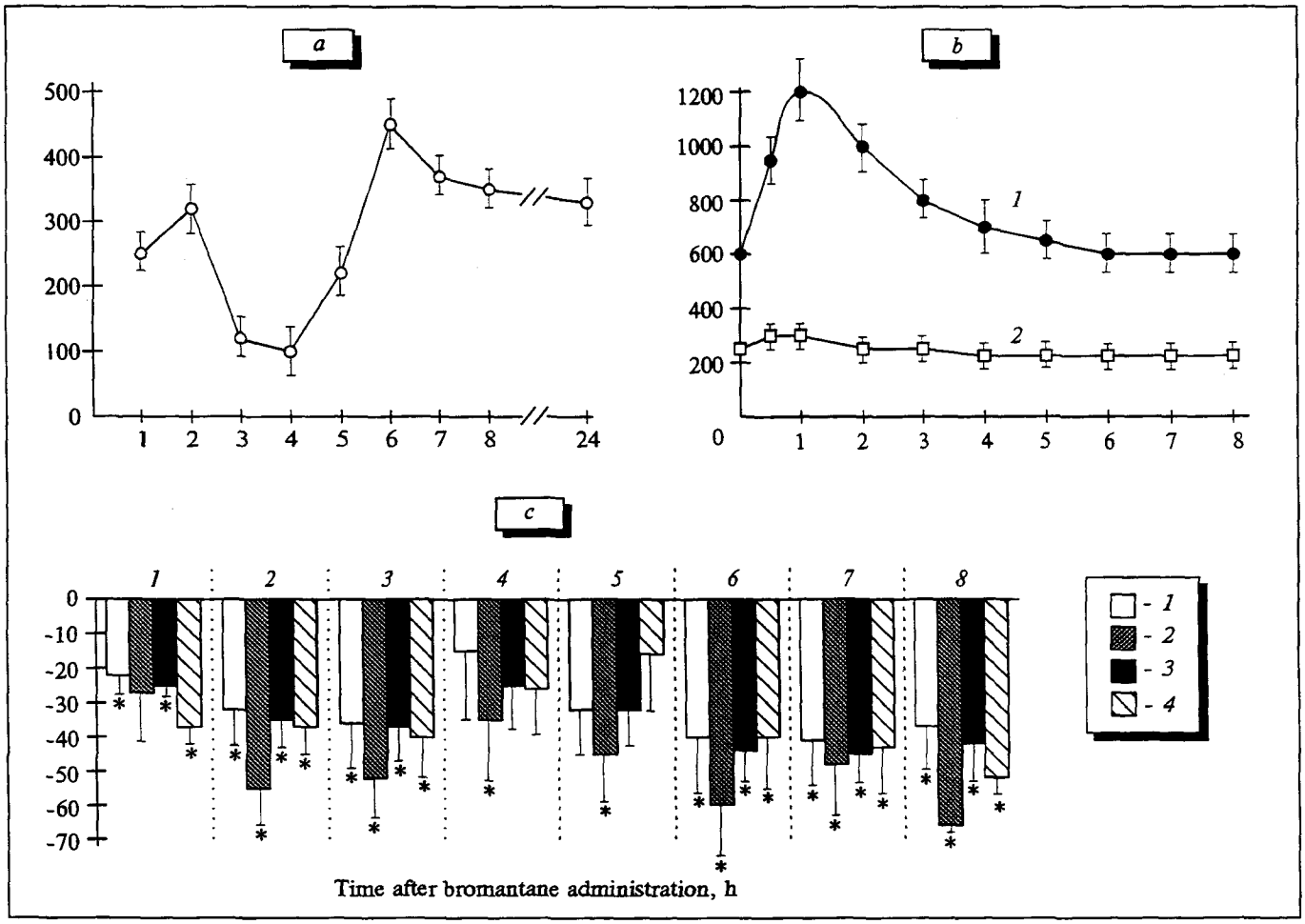

Fig. 1. Pharmacokinetic and pharmacodynamic characteristics of bromantane. *a*) effect of bromantane on the duration of treadmill running (in % of control) for repeated loadings; *b*) kinetic curve of bromantane content in the brain (ng/g, *1*) and in the plasma (ng/ml, *2*) of rats after oral administration of bromantane. *c*) effect of bromantane on EEG APR (μV^2/Hz) after Fourier for the left (*1*) and right (*2*) hemispheres, hippocampus (*3*), and hypothalamus (*4*). * $p<0.05$.

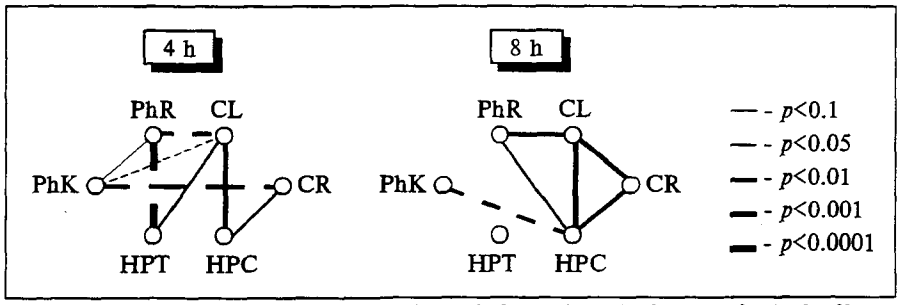

Fig. 2. Correlations between pharmacokinetics (*PhK*) of bromantane in the brain and dynamics of pharmacological effects. Variation of amplitude of dominating peak of EEG power spectrum affected by bromantane; cortex of the left (*CL*) and of the right (*CR*) hemispheres; *HPC*: dorsal hippocampus; *HPT*: lateral hypothalamus of left hemisphere. *PhR*: influence of bromantane on duration of treadmill running for repeated loadings. Solid line depicts linear dependence, dotted line nonlinear dependence.

the preparation on the level of physical work capacity during the first 4 h of observation is governed by the linear regression $y=0.41x-189.8$ ($r=0.84$, $p<0.1$). The dependence between the pharmacokinetics of bromantane and its effect on EEG APR of the left sensorimotor cortex is described by the second-order polynomial ($r=0.915$, $p<0.1$).

A more rigid dependence described by the second-order polynomial ($r=0.977$, $p<0.01$) is found for the pharmacokinetics of bromantane in the brain and the dynamics of EEG APR in the right hemisphere.

The dependence between the effect of the preparation on work capacity and the dynamics of EEG APR of the left hemisphere cortex is described by the second-order polynomial ($r=0.947$, $p<0.1$), whereas that between the influence of bromantane on work capacity and the dynamics of EEG APR of the hypothalamus against the background of the preparation is described by the second-order polynomial ($r=0.9995$, $p<0.0001$).

The results of correlation analysis showed that the dependences between the EEG dynamics in different brain structures against the background of bromantane during the first 4 h of observation are described by linear regressions as follows:

1) $y=0.623x+18.9$ ($r=0.841$, $p<0.05$) for EEG APR of the left hemisphere cortex and EEG APR of the hypothalamus;

2) $y=0.612x+13.67$ ($r=0.97$, $p<0.001$) for EEG APR of the left hemisphere cortex and EEG APR of the hippocampus;

3) $y=2.04x-18.48$ ($r=0.896$, $p<0.05$) for EEG APR of the right hemisphere cortex and EEG APR of the hypothalamus.

When the observation period is prolonged to 8 h after bromantane administration, some of the correlations lose their significance and new ones develop, while the dependence between the effect of the preparation on the level of work capacity and the dynamics of the activity of the left hemisphere cortex, described by the second-order polynomial in the 4-h observation, is described by the linear regression $y=-8.75x-6.801$ ($r=-0.65$, $p<0.05$) for the 8-h observation.

The 8-h observation yielded correlations with a high degree of reliability, described by linear regression equations as follows:

1. $y=-10.15x-89.12$ ($r=-0.698$, $p<0.05$) for the dynamics of EEG APR of the hippocampus and the effect of the preparation on physical work capacity;
2. $y=0.866x+8.01$ ($r=0.933$, $p<0.001$) for the dynamics of EEG APR of the hippocampus and the dynamics of EEG APR of the left hemisphere;
3. $y=1.34x+1.64$ ($r=0.815$, $p<0.05$) for the dynamics of EEG APR of the hippocampus and the dynamics of EEG APR of the right hemisphere.

The dependence between bromantane pharmacokinetics in the brain and the dynamics of EEG APR of the hippocampus during 8 h of observation is described by the second-order polynomial ($r=0.69$, $p<0.005$).

The linear dependence between the dynamics of activity of the cortex of the left and right hemispheres ($y=1.16x+12.25$, $r=0.762$, $p<0.001$) during 8 h after bromantane administration probably reflects the more synchronous (synphase) activity of these regions against the background of the preparation.

On the whole, the findings reveal a mathematical correlation between an integral characteristics of the organism's activity (the capacity for work), electrophysiological indexes of functioning of the brain structures, and the drug concentration in the target tissue.

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Spermatogenesis in Rats After Administration of the Anthracycline Antibiotic Pharmorubicin

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 119, № 3, pp. 308-310, March, 1995
Original article submitted April 4, 1994

It is established that Wistar rat testes demonstrate stable morphological changes attended by a diminishment of the stem cell population, depletion of the other layers of the spermatogenic epithelium, a decrease of the number of tubules with meiosis stage XII, and intensified desquamation of epithelial cells during 30 days after administration of pharmorubicin in the maximal permissible dose. The depletion of the stem cell population may result in long-term damage to the reproductive function and manifest itself long after antibiotic treatment.

Key Words: *testis; spermatogenesis; pharmorubicin*

Antitumor antibiotics from the anthracycline family are widely used in the drug therapy of malignant neoplasms [4,5]. Their marked antiblastomic effect is known to be accompanied by a toxic effect on cell systems of the organism with a rapid rate of renewal such as the bone marrow, and gastrointestinal epithelium, as well as the reproductive tissues [1,3,5,6]. Yet information on the effect of anthracycline antibiotics on the reproductive organs is scant and controversial.

The aim of the present investigation was to study the effect of the anthracycline antibiotic pharmorubicin (PR) on rat spermatogenesis.

MATERIALS AND METHODS

Experiments were carried out on 60 male Wistar rats weighing 110-130 g, 10 of which were controls. PR was injected i.v. at the maximal permis-

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0007-4888/95/0003-0300$12.50