COMPARATIVE AND ONTOGENIC PHYSIOLOGY

Modeling of Schizophrenia with Levodopa+Carbidopa

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Abstract—Experimental modeling of mental disorders on animal helps both to reveal mechanisms of the appearance of pathology and to direct the ways of effective methods of its treatment. The goal of the present work was to create a new model of schizophrenia by oral Levodopa+Carbidopa (LC) administration. Introduction of LC to rats was found to induces a significant decrease of emotional reactions, hypersensitivity to sound stimuli, a reduction of exploratory activity, stereotype behavior, and motor hyperactivity in occasional rats. It is concluded that the LC administration to rats may be used as an alternative dopaminergic model of schizophrenia on animals.

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INTRODUCTION

Experimental modeling of mental disorders on animals helps both disclosing mechanisms of the appearance of pathology and envisaging effective methods of its treatment. In opinion of Lipska and Weinberger [1], the experimental modeling of schizophrenia can represent the disease at three levels: (1) to reproduce the causal factor (for example, the genetic defect and the subsequent pathologic process underlying the disease), (2) to simulate phenomenology (for example, a set of productive or negative symptoms of schizophrenia), (3) to predict response to the already accessible medicinal drugs (for example, antipsychotics).

Phenomenology (semiotics) of schizophrenia is known to consist in three groups of symptoms: productive, negative, and cognitive. The productive symptoms reflect the excess or disturbance of the normal function including the conceptual disorganization, hallucinations, and unusual content of thoughts. The negative symptoms reflect the loss or a decrease of normal functioning including the flattened affect, alogia, anhedonia, a decrease of feeling of goal, a decreased social activity, motor disturbances. The cognitive symptoms are currently considered the main features of schizophrenia and include disturbances of the attention and of rate of processing of information, of visual, verbal, and social learning, of working memory and of executive functions. At present there are many different approaches to modeling of schizophrenia [2]:

— pharmacologic, based on the dopamine model (DA model);
— models of disturbance of development of the nervous system:
  • the models testing etiological theories (prenatal protein deprivation, pre- and perinatal infectious effects, etc.),
  • the models of disturbance of neurogenesis,
  • the models of perinatal stress,
• the models of neonatal damage
  — models of the glutamatergic hypofunction;
  — genetic models.

Some models reproduce to the greater degree the productive symptoms (DA models), others—negative and cognitive (for example, models of disturbance of neurogenesis). In some models (for example, in the model of neonatal destruction of hippocampus), authors try to reproduce maximally the whole complex of the schizophrenic symptoms.

One of theories of schizophrenia is based on the fact of hyperactivity of the dopamine (DA) neurotransmission system in striatum, which can result from an increase of the number of D₂ receptors that have a high affinity to DA or from an enhanced presynaptic accumulation of DA in striatum [3, 4]. Besides, the DA hyperactivity in schizophrenia was also recorded in the prefrontal cortex [5]. It was demonstrated that the productive symptoms in experimental schizophrenia on the animal models can be produced due to activation of D₂ receptors [2]. The DA agonist amphetamine producing hyperactivity in animals also provokes psychoses in people [6, 7]. The hyperactivity in animals is explained by an increased DA activation in the mesolimbic system, especially in nucleus accumbens [8]. Owing to similarity between the schizophrenia and amphetamine psychoses, the amphetamine introduction was widely used for modeling of schizophrenia in animals, particularly of positive symptoms [9].

Amphetamine is a psychostimulator and is included in the List of narcotic drugs and psychotropic substances (List II), which extremely restricts its use in the Russian Federation. In this connection, to create model of schizophrenia in the experiment on animals, it was decided to use other dopamine agonists. For this purpose, we have chosen the anti-Parkinsonian preparation Nacom© whose composition includes dopamine precursors—Levodopa and Carbidopa, an inhibitor of peripheral DOPA-decarboxylase, decreasing production of dopamine in peripheral tissues, which indirectly leads to an increase of the amount of Levodopa entering CNS. Thus, the goal of this study was to create a new model of schizophrenia with aid of peroral Levodopa+Carbidopa (LC) administration.

MATERIALS AND METHODS

The work was carried out on 80 adult male rats aging 10–11 weeks, with the body mass of 180–200 g.

There were performed 3 series of the experiments. In the first two series, the experimental rats \((n = 10)\) were treated perorally with 500/50 mg/kg, respectively, of Levodopa+Carbidopa (further—LC), while the control rats \((n = 10)\)—water. In the third series the experimental rats were treated with LC at doses 250/25 mg/kg \((n = 10)\), 500/50 mg/kg \((n = 10)\), and 750/75 mg/kg \((n = 10)\), the control rats \((n = 10)\)—water.

The animals were tested 1.5 h after the administration in the “open field” for 3 min. The “open field” represents an arena 600 × 600 mm with rims 150 mm in height, separated in 16 squares with 5 “burrow” orifices illuminated with incandescent lamp 60 W at the height of 1 m. Six parameters were recorded: the latent period of way out from the starting square, horizontal activity (the number of crossed squares), vertical activity (stands), glancing down into orifices, grooming, boluses, urinations, as well as the reaction to the sound stimulus was recorded (a blow with packer on the wall of arena at the distance of 20 cm from the animal) in scores: 0—the absence of reaction, 1—shuddering, 2—jumping.

For the statistical analysis the ANOVA Mann—Whitney U test was used.

RESULTS AND DISCUSSION

For the first 30 min after the LC administration, apnea, piloerection, hypersalivation, and increased diuresis were observed in all animals. After 1.5 h, there were preserved all symptoms, except for tachypnea.

The motor activity (the number of the crossed squares and stands) of rats treated with LC turned out to be quite variable: it was higher in the first series, as compared to the control, in the second did not differ, and in the third, at administration of LC at a dose of 500/50 mg/kg it was lower than in control. The total activity in all three series did not differ significantly from that in control animals (Fig. 1).

Marked individual differences were revealed in