NEUROPHARMACOLOGIC ACTIVITY OF METOCLOPRAMIDE AND HALOPERIDOL WHEN INJECTED INTRAPERITONEALLY AND INTO THE CORPUS STRIATUM OF RATS

A. F. Yakimovskii

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KEY WORDS: metoclopramide; haloperidol; corpus striatum; conditioned-reflex avoidance; motor activity

The search for optimal programs of pharmacotherapy of diseases of the extrapyramidal sphere is an urgent trend in clinical neuropharmacology. To terminate hyperkinesias of varied etiology, resort is most frequently made to neuroleptics [5]. By reducing the intensity of compulsive movement, these drugs have a negative effect on the emotional-volitional and cognitive spheres, which is particularly unacceptable for the treatment of children and adolescents. One possible way of overcoming this contradiction is by the choice of new preparations not traditionally used for the treatment of patients of this group. One such drug is metoclopramide, which has been successfully used for the treatment of Gilles de la Tourette disease [2]. It has been suggested that one of the targets for metoclopramide is the striatal complex of nuclei, which are among the structures involved in the pathogenesis of most extrapyramidal diseases. However, both the pharmacologic spectrum of action of metoclopramide and the character of its direct effect on the striatum have not yet been adequately studied.

This paper gives a comparative analysis of the effect of systemic injection of metoclopramide and its injection into the corpus striatum of rats; the alternative preparation used was the neuroleptic haloperidol.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar albino rats weighing 220-250 g. In two series of experiments, altogether 36 animals were used. Each series consisted of four groups, with 4 or 5 rats in each group. A 5% ampul solution of metoclopramide (Cerucal, from "Germed," Germany) and haloperidol (from "Gedeon Richter," Hungary) was used. In series I metoclopramide (group 1) and haloperidol (group 2) were injected intraperitoneally 3 times a week on alternate days in a dose of 10 mg/kg for 3 weeks; in the control, physiological saline (group 3) or nothing (group 4) was injected. In the experiments of series II, the animals were anesthetized with hexobarbital and polyethylene cannulas filled with the preparation were introduced into the region of the rostral neostriatum, and for three weeks daily microinjections of 5 μg metoclopramide, 5 μg haloperidol, or physiological saline in a volume of 1 μl (5, 6, and 7) were given for 3 weeks; in the animals of group 8, the whole course of the operation was repeated, but no microinjections were given. The technique of microinjection was described previously [4]. In all animals a conditioned active avoidance reflex was formed before the experiments began, in a shuttle box [3]. Conditioned-reflex testing was carried out daily (on rats receiving injection of a preparation, 20 min after the injection), the level of spontaneous motor activity was determined from the number of times the animal crossed the boundaries of the squares into which the floor of the shuttle box was divided, and a test was carried out for catatonia: the time during which the "suslik posture" could be maintained on a grid tilted to an angle of 45° [6] was recorded. The aftereffect of the preparations was assessed for 3 weeks after discontinuation of the microinjection. Rats of groups 5, 6, and 7 were killed under hexobarbital anesthesia and histological and morphological investigations were carried

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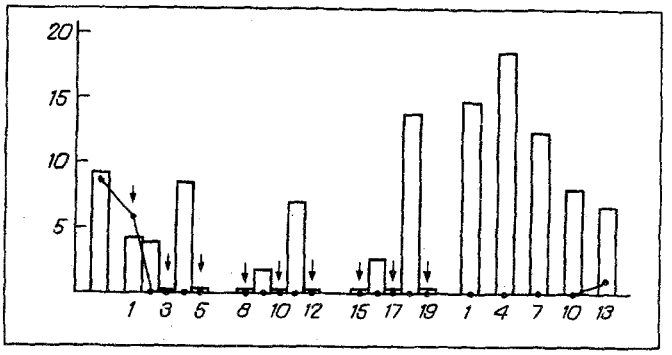

Fig. 1. Changes in level of spontaneous motor activity in rats after intraperitoneal injection of 10 mg/kg haloperidol (columns) and metoclopramide (dots joined by lines). Abscissa, number of times animal crossed boundaries of squares during 5 min of observation (arrows indicate days of injections; ordinate, days of experiments.

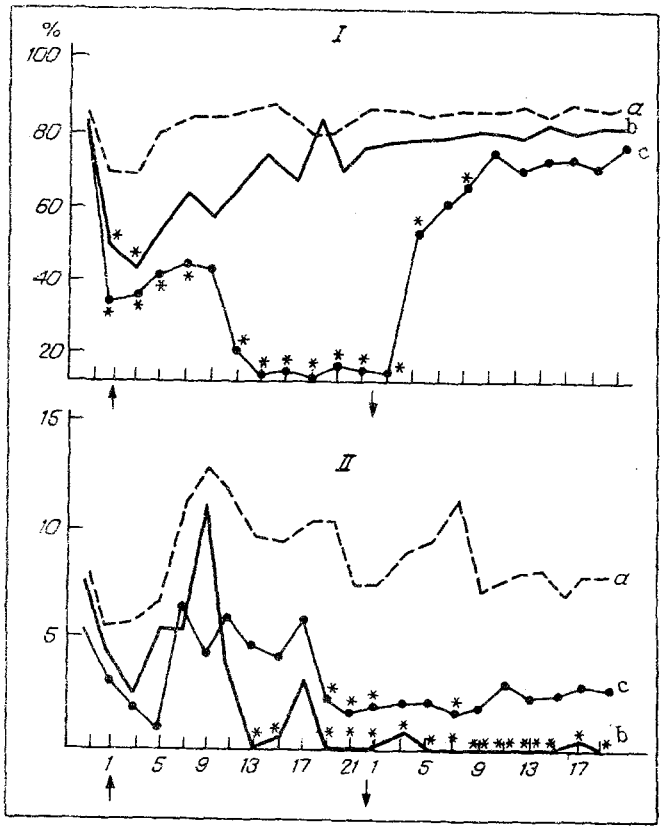

Fig. 2. Time course of realization of active avoidance reflex (I) and spontaneous motor activity (II) against background of chronic injection of physiological saline (a), 5 μg metoclopramide (b), and 5 μg haloperidol (c) into striatum. Abscissa, number of correct realizations of reflex (in per cent of conditioned stimuli presented or number of times animal crossed boundaries of squares during 5 min of observation); ordinate, days of experiments. Arrows indicate beginning and end of period of daily microinjections. Asterisk indicates days when this particular index differed from the control with injection of physiological saline, at the $p \leq 0.05$ level; two asterisks – $p < 0.01$.

out. The tips of the cannulas were located in the dorsal segments of the rostral region of the neostriatum. The numerical results were subjected to statistical analysis on a type PC/AT computer, using Student's test.

EXPERIMENTAL RESULTS

In the animals of groups 3 and 4, throughout the experiment no changes were found in the animals' behavior. In rats of groups 7 and 8, only during the first two or three days of the experiment were defects observed in the accuracy of realization of the reflex: it reached the level of 60-65% of correct responses, evidently due to residual manifestations of operative trauma. Later the behavioral parameters of the rats of these groups were indistinguishable from those for animals of groups 3 and 4.

Intraperitoneal injection of metoclopramide and haloperidol led to definite disturbances of motor behavior. A single injection of the neuroleptic blocked conditioned-reflex avoidance behavior against the background of the catatonia typical of haloperidol [1, 6]. The state of torpidity persisted in the animals for 3-4 h after each injection, but on days without injections the parameters of the reflex were unchanged compared with the normal state, and they did not exhibit catalepsy. The effects of metoclopramide on motor behavior were similar to those of haloperidol, but catatonia was not observed in the rats of this group. Disturbances of conditioned-reflex activity developed gradually and reached their peak only by the 8th-9th day of the experiments. Meanwhile, spontaneous motor activity unconnected with realization of the reflex was completely absent in these rats not only on days of injection of the drug, but also between them, and also throughout the period of observation after discontinuation of the drug (Fig. 1). These animals characteristically were in a state of relaxation, mild drowsiness, and passiveness.

Just as with systemic injection of haloperidol, microinjections of the drug into the corpus striatum led to disturbance of the conditioned avoidance reaction and to reduction of motor activity (Fig. 2c). Catatonia was not observed under these circumstances, but chronic blockade of the dopamine receptors of the striatum induced a state resembling the akinetic syndrome in the rats, with elements of rigidity of the skeletal musculature, characteristic of neuroleptic-induced Parkinsonism [8]. A characteristic feature of the rats was kyphosis, and they sat motionless and responded negatively to touch. They remained capable of responding to the conditioned stimulus, but the time taken to perform the reflex was increased and the rats were unable to leave the "dangerous" half of the chamber and they received an electric shock often on the boundary between the zones through their hind limbs. The state thus described developed gradually and was exhibited most clearly in the 2nd and 3rd weeks of the experiments. After intrastriatal injection of metoclopramide, the accuracy of performance of the reflex was impaired only during the first 4-5 days of the experiments (Fig. 2b). Conversely, spontaneous motor activity during this period was at the normal level – it began to decrease in the second week of the investigation and was virtually completely suppressed throughout the subsequent period of observation. The external behavior of the rats of this group resembled animals with systemic injection of metoclopramide.

The character of the conditioned-reflex changes and motor disturbances in the rats of group 1 is evidence of the neurotropic properties of metoclopramide when injected intraperitoneally, and it casts doubt on the view that it penetrates with difficulty through the blood-brain barrier [7]. The similarity of the effects of systemic and intracerebral injection of metoclopramide in principle suggests involvement of the neostriatum in the behavioral changes in rats in response to intraperitoneal injection of the drug. Meanwhile the time of exhibition of these basic effects of metoclopramide, namely diminution of motor activity and disturbance of conditioned-reflex avoidance – differed significantly in the two series of experiments. For instance, after intraperitoneal injection of metoclopramide, movements around the chamber unconnected with performance of the reflex disappeared completely after the first injection, whereas realization of the reflex was disturbed later – in the second week of the experiment. An opposite relationship was observed after microinjections of metoclopramide into the striatum: relatively mild disturbances of conditioned-reflex behavior were observed only in the first 4-5 days of the experiments, whereas distinct hypokinesia was established on the 10th-11th days of the experiments. These differences could indicate a role of the neostriatum mainly in the antihyperkinetic effects of metoclopramide. The fact that realization of the conditioned-reflex skill following microinjections of metoclopramide into the striatum is not significantly impaired, is important in principle. In addition, no manifestations of catatonia or rigidity of the musculature, so characteristic of the effects of haloperidol, were recorded in rats receiving metoclopramide. These data confirm the view expressed above that the action of metoclopramide on the dopaminergic system of the brain is qualitatively different from that of neuroleptics [2, 9]. The properties of metoclopramide described above are evidence of its effect on the neostriatum and

they permit it to be recommended for the treatment of diseases in which the use of neuroleptics is undesirable, for example, in children with neurological diseases or to terminate L-dopa-induced hyperkinesias without the risk of aggravating the basic symptoms of Parkinsonism.

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SYSTEMIC AND REGIONAL HEMODYNAMICS DURING AUDIOGENIC CONVULSIONS IN RATS GENETICALLY PREDISPOSED TO EPILEPSY

M. N. Ivashev, O. S. Medvedev, V. B. Koshelev, and T. V. Ryasina

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Experiments on Krushinskii-Molodkina (KM) rats have shown that during a convulsion induced by interrupted acoustic stimulation the animals developed subdural and subarachnoidal hemorrhages [1, 2, 9]. The mechanism of onset of these hemorrhages is not yet clear. In our view, changes in the systemic blood pressure (BP) during a convulsion may be the cause of hemorrhage into the brain.

The aim of this investigation was to study changes in BP, the heart rate (HR), and the blood flow in the brain, heart, liver, kidneys, and other organs during convulsions.

EXPERIMENTAL METHOD

Experiments were carried out on six KM rats, bred in the Faculty of Biology, Moscow State University. The rats, weighing 250-300 g, were anesthetized with pentobarbital (30-40 mg/kg) for insertion of polyethylene catheters: through the right carotid artery into the left ventricle and through the femoral artery into the abdominal aorta.

Laboratory of Experimental Pharmacology, Institute of Experimental Cardiology, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR. Department of Human and Animal Physiology, Faculty of Biology, M. V. Lomonosov State University, Moscow. Laboratory of Pathological Anatomy, Research Institute of Neurology, Academy of Medical Sciences of the USSR.

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