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Research of a New Atypical Neuroleptic 1-(3′,4′-Methylenedioxyphenyl) - 6,7-Methylenedioxy- 1,2,3,4-Tetrahydroisoquinoline on the Central Nervous System

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Abstract. For the first time, the synthesized derivative (3′,4′-methylenedioxyphenyl) - 6,7-methylenedioxy-1,2,3,4-tetrahydroquinoline, conventionally designated F-29, was studied for its effect on the central nervous system – anti-anxiety, motor and research activity, interaction with analeptics corazole, strychnine and on dopamine receptors. F-29 exerted, anti-anxiety, anticonvulsant, and blocked dopamine receptors.

Keywords: neuroleptic activity, anticonvulsant, haloperidol, (3′,4′-methylenedioxyphenyl) -6,7-methylenedioxy-1,2,3,4-tetrahydroquinoline, dopamine blocker.

Introduction. The last decade has seen unprecedented promotion of new antipsychotic medicines. Just like their predecessors – neuroleptics – atypical antipsychotics effectively eliminate delusional disorders, hallucinations, disorganization of thinking and other clinical manifestations of psychosis. Compared to previous generations of drugs, atypical antipsychotics are less able to cause extrapyramidal symptoms and have greater clinical efficacy [1-3]. Traditional antipsychotic drugs are effective against acute agitation and in controlling positive symptoms, and, at the same time, are not effective against cognitive disorders and negative symptoms in schizophrenia [1,4]. Atypical antipsychotics, on the contrary, have a very wide range of effectiveness, allowing to treat both positive and negative symptoms, as well as cognitive disorders [5]. In view of this, there was a need to create lighter neuroleptics, called "atypical neuroleptics". For the first time, the synthesized derivative (3′,4′-methylenedioxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroquinoline, conventionally designated F-29, showed neuroleptic properties – they have hypothermic, cataleptogenic, less pronounced inhibition of motor activity, lack of central α-adreno - and M-cholinoblocking effects and are less toxic [6] in terms of severity comparable to the activity of a closer analog of the neuroleptic haloperidol, which has motor and autonomic disorders [7], which F-29 lacks.

Materials and methods of research. All experiments were performed on white mice of both sexes weighing 18–20 g for 6-10 animals per group. Neuroleptics usually have an anti-anxiety

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effect, so the effect of F-29 and haloperidol on anxiety was studied in mice [8], in a 5-chamber maze with 2 light and 2 dark chambers (the 5th in the center). An exacerbation of the feeling of anxiety was caused by corazole 25 mg / kg p / k 1 hour after the administration of the studied substances. The duration of being in the maze is 2 minutes. In a test using a previously studied method [9], white rats (or mice) are placed in an unfamiliar environment in an "open field", where the animals feel emotional discomfort in the form of stiffness of behavior and frequent defecation. Anti-anxiety (anxiolytic) agents, eliminating the feeling of anxiety, as a rule, increase the number of intersections of square lines and the number of examined minks in comparison with" untreated " control rats for 2 minutes of experience. In the experiment, the number of visits to the squares, the number of minks examined and the number of isolated fecal boluses were calculated, according to which the research activity was evaluated. An increase in the number of line crossings and the number of minks studied indicate disinhibited behavior and increased research activity. The anxiolytic effect was also manifested by a decrease in the number of isolated fecal boluses. Interaction of F-29 with analeptics of corazole and strychnine. To identify the comparative D-blocking activity of F-29 and haloperidol, their activity was studied in tests of antagonism of these substances to the D-stimulating effect of apomorphine in 2 series of experiments: at the presynaptic and postsynaptic levels according to the methods described in the Khabriev manual [10].

Results and discussion.

1. The effect of F-29 and haloperidol on the feeling of anxiety with a single administration.

The results of the experiments are given in tab.1 indicate that the K index against the background of the introduction of F-29 and haloperidol increased by 3-4 times. The severity of the anxiolytic effect of F-29 and haloperidol was approximately the same.

Table 1.

The effect of F-29 and haloperidol on the feeling of anxiety (from corazole) in mice with a single administration.

Drug, dose	The time spent in the bright compartment	The time spent in the dark compartment	Number of camera-to-camera transitions	Ratio of time spent in light and dark compartments

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1st control (corazole 25 mg / kg s/c)	38	72	6,2	0,53
F-29 0.1 mg / kg inside + corazole	92	28	15	3,3
F-29 1 mg/kg inside+ corazole	84	36	11,4	2,7
F-29 10 mg/kg inside + corazole	74	46	9,6	1,6
2nd control (corazole 25 mg / kg s/c)	35	75	6,8	0,43
Haloperidol 0.1 mg/kg inside + corazol	97	23	7,0	3,8
Haloperidol 1.0 mg/kg inside + corazol	88	32	23	2,5
Haloperidol 10.0 mg/kg + corazol	65	55	16	1,2

2. The effect of F-29 on DA and research activity of rats in the "open field" test.

In the "open field" test, F-29 significantly increased the number of intersections of squares and the number of minks examined compared to the control group, and at the same time reduced the number of isolated fecal boluses. The obtained first 2 indicators are a manifestation of increased research activity, and the 3rd is a manifestation of the anti-anxiety (anxiolytic) effect of substances that should be manifested in neuroleptics (see table 2).

Table 2.

The impact of F-29 on research and development activities

Drug, dose	motor activity %	research activity %	number of fecal boluses %
control (aq. dest.)	100	100	100
0.1 mg / kg inside	240	164	25

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1,0 mg/kg inside	294	209	50
10 mg/kg inside	110	60	80

3. Interaction of F-29 with analeptics

3.1. Experiments with corazol

The effect of F-29 on the convulsive effect of corazole was studied in 3 series of experiments with the preliminary administration of F-29 at doses of 10 mg / kg iv, as well as at doses of 1.0 and 5.0 mg/kg orally. Corazole was administered at a dose of 75 mg / kg p /c. In the control experiment, seizures occurred in all animals (100%) after a latent period of 3.3 min.and 3 out of 6 mice fell (50%). Against the background of F-29 10 mg/kg i.p., seizures occurred only in 6 out of 6 (100%) with a latent period of 6 minutes. Death occurred in all the mice. Thus, there was a certain antagonism of F-29 in the latent period at a dose of 10.0 mg / kg to the effect of corazole and increased the death of animals.

In the second and third series of experiments with the introduction of F-29 in doses of 1.0 and 5.0 mg/kg. In mice, with preliminary administration of F-29 at doses of 1.0 and 5.0 mg/kg orally, convulsive readiness began after 7.8 and 9.7 minutes, respectively. Convulsions were observed in both groups, respectively, in 4 out of 6 (67%) and 3 out of 6 (50%) animals. The study showed that F-29 at a high dose (10 mg/kg) shows synergism, and in small (therapeutic) doses antagonism to the convulsive action of corazole.

3.2. Experiments with strychnine

The experiments were carried out on white mice. F-29 was administered in doses of 10.0 mg / kg i / p for 30 minutes. before the administration of strychnine. In the control experiment, seizures from strychnine were observed in 2 out of 6 mice, and both mice died from the first attack. Against the background of F-29, there were no seizures in any of the 6 mice, which indicates the antagonism of F-29 to the convulsive action of strychnine.

In another experiment, F-29 was administered at a dose of 3.0 and 10.0 mg/kg orally 1-1.5 hours before the administration of strychnine 1.1 mg/kg p / K. Attention was paid to the latent period of the onset of seizures, the number of seizures and the death of mice. In the control experiment, from a dose of strychnine of 1.1 mg/kg n/a, seizures occurred in all 6 mice with a latent period of 7.7 minutes. Seizures were one-time attacks and in all cases were accompanied by the death of mice. Against the background of F-29 at a dose of 3 and 10 mg/kg orally, convulsions and death of mice were not observed. Thus, it can be considered that the substance showed antagonism to strychnine seizures.

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4. The effect of F-29 and haloperidol on D-receptors.

As indicated, the neuroleptic effect of haloperidol and other neuroleptics is primarily due to the blockade of D-receptors [11, 12, 13]. The classic D-receptor stimulator is apomorphine.

4.1. Effect of F-29 on presynaptic D-receptors.

Experiments were conducted on male rats with the introduction of apomorphine 0.05 mg / kg s/c. In control animals on the background of apomorphine, stereotypical yawning movements were observed for 30 minutes, with an average number of 9.8 in the group; taken as a control. It is believed that the appearance of yawning movements is associated with the blockade of presynaptic D-receptors, leading to increased release of dopamine into the synaptic cleft, which leads to an increase in the number of yawning stereotypical movements. Amid a preliminary introduction of f-29 in a dose of 0.3 mg/kg s/c number severnyh movements against apomorphine decreased from 9.8 to 5.6 (blockade 43%); in a dose of 0.4 mg/kg and 2.3 (77%); a dose of 0.5 – was completely absent. The ED50 of the antagonism of the action of F-29 to the action of apomorphine calculated graphically was 0.32 mg / kg s/c.

In experiments with haloperidol, from a dose of 0.1 mg / kg s/c the average number of yawns decreased from the control 9.8 to 5.4; from a dose of 0.2 – 2.4; and from a dose of 0.3 were absent, and the ED50 was 0.13 mg/kg s/c. In this test, haloperidol was 2.5 times higher than F-29 in its presynaptic D-blocking action. However, in terms of acute toxicity, F-29 is 4.2 times less toxic than haloperidol [6].

4.2. The effect of substances on postsynaptic D-receptors was studied in experiments on mice in which apomorphine (2 mg/kg s/c) caused stereotypical movements in the form of verticalization [9].

The essence of the experience is to ensure that the background of the stimulant D-receptors with apomorphine, there are a number of stereotypical movements, most of which is climbing the inner wall of the mesh cap, and this stereotype is expressed in the form of points: 4 points – when the animal climbed on a wire wall all 4 legs; 3 - points - when the mouse tried to climb on a wall 3 feet. The postures of the mice against the wall with the support of 2 forelegs on the wall were not taken into account, since this behavior was also observed in control mice. Observations were carried out before the end of the manifestation of climbing stereotypes in our experiments for up to 1 hour. A graph was built based on the points received. Maximum score – (20 points) it was given to control mice when all 5 mice climbed on the wall with all 4 legs for 1 min of observation; 18 points - if 3 mice climbed on the wall with 4 legs, and 2 only tried to climb with

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3 legs. In the conducted experiments, the highest number of points was noted against the background of the control experiment when one apomorphine was administered 20 minutes after administration, then the severity of stereotypy decreased. Against the background of the action of neuroleptics with their D-antagonizing effect, the severity of stereotypes decreased depending on their activity, the administered dose and the duration of the experience. The number of points in the control experiment for 50 minutes of observation was 72, against the background of F-29 0.3 m / kg-48 points or 33% less; against the background of 0.5 mg/kg-25 points or 65% less. Based on these data, the ED50 of the D-blocking action of F-29 was calculated graphically, which was 0.41 mg / kg orally. In experiments with haloperidol, the ED50 for haloperidol was 0.11 mg / kg s/c, i.e. F-29 was 3.6 times inferior to haloperidol in terms of D-blocking activity.

The analysis of the obtained data indicates that both compared substances act unidirectionally, i.e. both drugs block both presynaptic and postsynaptic D-receptors. F-29 in both tests was inferior to haloperidol in D-blocking action at the postsynaptic level by about 3 times.

Conclusion. Conducted psychopharmacological studies of a synthetic compound, conventionally called F-29, revealed pharmacological properties. In the anti-anxiety test, F-29 and haloperidol in the same doses of 0.1 and 1.0 mg/kg orally showed almost the same anti-anxiety activity. It had an anticonvulsant effect. The difference in the doses of pre - and postsynaptic D-blocking effects in F-29 and haloperidol is significant, but it is leveled by 4.2 times less pronounced acute toxicity of F-29. The presented differences between F-29 and haloperidol indicate that F-29 belongs to the representatives of a new popular class of atypical neuroleptics. F-29 has prospects of becoming one of the original atypical neuroleptic therapeutic drugs devoid of some of the side effects of haloperidol, which is one of the" dirty drugs " [11].

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