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ANTICATALEPTIC ACTIVITY OF 2-SUBSTITUTED DERIVATIVES OF 3(H)-QUINAZOLIN-4-ONE

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АНТИКАТАЛЕПТИЧЕСКАЯ АКТИВНОСТЬ 2-ЗАМЕЩЕННЫХ ПРОИЗВОДНЫХ 3(H)-ХИНАЗОЛИН-4-ОНА

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The anticataleptic effect of 2-substituted derivatives of 3(H)-quinazolin-4-one in male rats was examined using a haloperidol catalepsy test. Compounds I, II, III, IV, V, VI, and VII (laboratory codes) were administered at a dose of 0.2 of the molecular weight in mg/kg. Catalepsy was induced by administration of haloperidol (1 mg/kg). Control animals were injected with a neuroleptic solvent. In male rats, compounds IV and V limited the severity of motor disorders and showed anticataleptic activity, suggesting their possible use as antiparkinsonian treatments.

Keywords: 2-substituted derivatives of 3(H)-quinazolin-4-one, anticataleptic effect, haloperidol catalepsy

Изучено антикаталептическое действие 2-замещенных производных 3(H)-хиназолин-4-она у самцов крыс в тесте галоперидоловой каталепсии. Соединения I, II, III, IV, V, VI, VII (лабораторные шифры) вводились в дозе 0,2 от молекулярной массы в мг/кг. Каталепсию вызывали введением галоперидола (1 мг/кг). Контрольным животным вводили нейролептик и растворитель. Соединения IV, V у самцов крыс ограничивают выраженность двигательных нарушений, проявляя антикаталептическую активность. Это позволяет предположить перспективность их изучения как антипаркинсонических средств.

Ключевые слова: 2-замещенные производные 3(H)-хиназолин-4-она, антикаталептическое действие, галоперидоловая каталепсия

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An urgent problem in Russian medicine is the creation of new original, domestic, safe, and highly effective drugs for the treatment of parkinsonism, a widespread neurodegenerative disease [1]. Antiparkinsonian drugs affect the development of parkinsonism through various mechanisms, and dopamine receptor agonists are widely used as treatments. However, most antiparkinsonian agents are characterized by adverse side effects and limited effectiveness. Therefore, identification of new agents for the treatment of parkinsonism is important [2–4] and can be achieved by synthesizing new compounds and performing functional studies of their biological activity. Many quinazolinone-4 derivatives exhibit neuroprotective effects [5]. Previously, antihypoxant and analgesic effects were noted when the pharmacological activity spectrum of new 2-substituted derivatives of 3(H)-quinazolin-4-one was evaluated [6, 7]. The purpose of this study was to investigate the anticataleptic action of 2-substituted 3(H)-quinazolin-4-one derivatives.

Material and Methods. A series of experiments was performed on male white rats (77) weighing 200–220 g (6–10 in each group). The rats were housed in a vivarium, and experiments were performed in accordance with the «Rules for Conducting Work Using Experimental Animals», as well as the principles of the Helsinki Declaration. All experimental studies were carried out in compliance with bioethical standards and approved by the local ethics committee.

The specific activity of compounds was determined using an experimental model of parkinsonism: haloperidol-induced catalepsy [8–10]. Haloperidol was injected intraperitoneally (1 mg/kg).

Antagonism to neuroleptics was determined by the ability of the test substances to limit the intensity of haloperidol-induced catalepsy. The effect on catalepsy was determined by measuring the duration a rat could maintain a vertical position on a support, which was termed as the «verticalization time» (in seconds). The rat was positioned so that its front legs rested on the support (height 15 cm) («lecturer's pose»). The stagnation time of the immobile animal, which was defined as the time until the rat removed a paw from the support, was evaluated. The results were recorded at 60, 120, and 180 minutes after drug administration.

The biologically active compounds (new 2-substituted quinazolin-4-one derivatives) included seven substances synthesized by teams at the Department of Organic Chemistry of the Pyatigorsk Medical and Pharmaceutical Institute (Head of the Department, Doctor of Pharmaceutical Sciences, Professor E. T. Oganesyan and Doctor of Pharmaceutical Sciences I. P. Kodonidi) and the Scientific Research Institute of Physical and Organic Chemistry of the Southern Federal University (Senior Scientist, Candidate of Chemical Sciences A. V. Bicherov and A. A. Bicherov). Compounds (laboratory designations: I, II, III, IV, V, VI, and VII) were administered intraperitoneally at a dose of 0.2 of the molecular weight in mg/kg (I – 47.6 mg/kg; II – 53.6 mg/kg; III – 53.6 mg/kg; IV – 53.6 mg/kg; V – 56.4 mg/kg; VI – 59.2 mg/kg; VII – 75.2 mg/kg). The reference drug, levodopa (Sindopa, Sun Pharmaceutical Industries Ltd., India), was intraperitoneally administered at a dose of 10 mg/kg. The substances were introduced as a suspension, which was prepared ex tempore by dissolving the compounds in sterile distilled water with the addition of one to two drops of Tween-80 as a stabilizer. Solubilized Tween-80 and haloperidol were administered to the control group in a similar mode and volume. Haloperidol and then the test compounds were introduced at 5-minute intervals into different lateral pockets of the abdomen. The doses of the test compound, haloperidol, and the reference preparation were selected on the basis of the literature and the dose titration method [6–8, 11].

The results were statistically analyzed using Microsoft Office Excel 2007, (Microsoft, USA), BIOSTAT (S. A. Glantz, McGraw Hill, USA) and STATISTICA 10 (StatSoft, USA). The normality of the primary data distribution was evaluated using the Shapiro-Wilk criterion. Statistically significant differences were confirmed using the Kruskal-Wallis and Wilcoxon–Mann–Whitney U criteria. Data of experimental groups and groups treated with the levodopa preparation were compared with results of the control group of animals treated with haloperidol alone. Differences with $p<0.05$ were considered statistically significant.

Results and Discussion. In control rats treated with the solvent and haloperidol, catalepsy became pronounced at the 60th minute of testing, persisted through the 120th minute, and had intensified by the 180th minute (Table). Therefore, observations in all groups of animals are presented at the 60th, 120th, and 180th minutes of testing.

The levodopa preparation attenuated catalepsy only at 120 minutes after haloperidol administration, which is consistent with the results of Voronina et al. [8].

Compounds I, II, VI, and VII did not decrease the severity of catalepsy. Moreover, compounds I, II, VI, and VII even increased the duration of the «lecturer pose» of animals at the 60th minute of the test (Table).

Table

Effect of 2-substituted 3(H)-quinazolin-4-one derivatives on the intensity of haloperidol-induced catalepsy (mean; Q25 %, 75 %)

Compound	Duration of animal «freezing» in the «lecturer» position after haloperidol injection (c)		
	at 60 minutes	at 120 minutes	at 180 minutes
H	18.5 (14, 101.5)	83 (35, 128.5)	52 (25, 220.5)
I + H	141 (67, 192)*	163 (70, 456)	130 (70, 222)
II + H	178 (73, 203)*	114 (84, 329)	102 (46, 133)
III + H	117 (61, 181)	96 (55, 120)	195 (78, 268)
IV + H	4.5 (0, 10)**	113 (68, 156)	57.5 (33, 97)
V + H	27 (12, 71.5)	22.5 (16, 73.5)*	26.5 (9.5, 63.5)*
VI + H	142 (75, 169)*	50 (30 , 78)	85 (29, 136)
VII + H	87 (71, 171)*	102 (35, 161)	154 (45, 298)
Levodopa + H	34 (1, 205)	36 (18, 120)*	204.5 (103, 528)

Note: H – Haloperidol 1 mg/kg. Statistically significant differences compared with the control group of male rats that received haloperidol: * $p<0.05$; ** $p<0.01$.

Male rats administered compound IV exhibited a decrease in motor disorders at the 60th minute of catalepsy compared with the control group administered the neuroleptic alone. Catalepsy was attenuated by 79.9 %, resulting in a statistically significant difference ($p<0.01$). Treatment with compound V led to a decrease in catalepsy intensity at the 120th minute (44.3 %, $p<0.05$) and the 180th minute (65.1 %, $p<0.05$) of observation.

The results showed that the new 2-substituted derivatives of 3(H)-quinazolin-4-one, compounds IV and V, reduced the intensity of motor disorders in the haloperidol-induced catalepsy test in male rats, thus revealing their anticataleptic activity. The influence of compound IV, which appeared in the 60th minute of testing, was short-lived because no differences from control group rats were

observed at the 120th and 180th minutes of the study. The anticataleptic effect of substance V appeared later and was noted in the 120th minute, when the most pronounced extrapyramidal disorders were induced by haloperidol. Additionally, the effect of decreasing catalepsy at the 120th minute was even more distinct than that of levodopa. The effect of compound V was also manifested at the 180th minute of testing. Therefore, its effect was more prolonged than that of the reference drug.

Meanwhile, the antihypoxic effects of compounds II, IV, and V and the analgesic activity of compounds I–IV, VI, and VII were shown in tests with chemical stimuli (formalin test and «acetic roots» test) [6, 7]. The properties of compounds IV and V, in particular the antihypoxic, analgesic, and anticataleptic effects, make them interesting candidates for further development of antiparkinsonian preparations, considering the neurodegenerative nature of disease development and the pronounced pain syndrome in the clinical picture of Parkinson's disease [12–15].

Conclusions. At the examined dose of 2-substituted derivatives of 3(H)-quinazolin-4-ones (0.2 of the molecular weight in mg/kg of compounds IV and V), motor disorder expression in the haloperidol catalepsy test was limited in male rats, indicating the anticataleptic activity of these compounds. The most optimal anticataleptogenic profile was observed for compound V. Its effect was more pronounced and prolonged than that of the reference antiparkinsonian drug, levodopa. Thus, 2-substituted derivatives of 3(H)-quinazolin-4-one (compounds IV and V) are promising candidates for further study as possible antiparkinsonian agents.

Experimental animal procedures. The study was performed in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental or Other Scientific Purposes (Strasbourg, 1986; ed. Strasbourg, 2006) and in accordance with international legislation on the protection of animals used for scientific purposes (Directive 2010/63/EU). The maintenance and use of animals for experimental purposes was performed in accordance with the international rules «Guide for the Care and Use of Laboratory Animals – 8th edition, 2011». The study protocol was approved by the Local Ethical Committee.

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