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Research Article

Antiparkinsonian activity of selective MAO-B inhibitors of different chemical structures

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Abstract

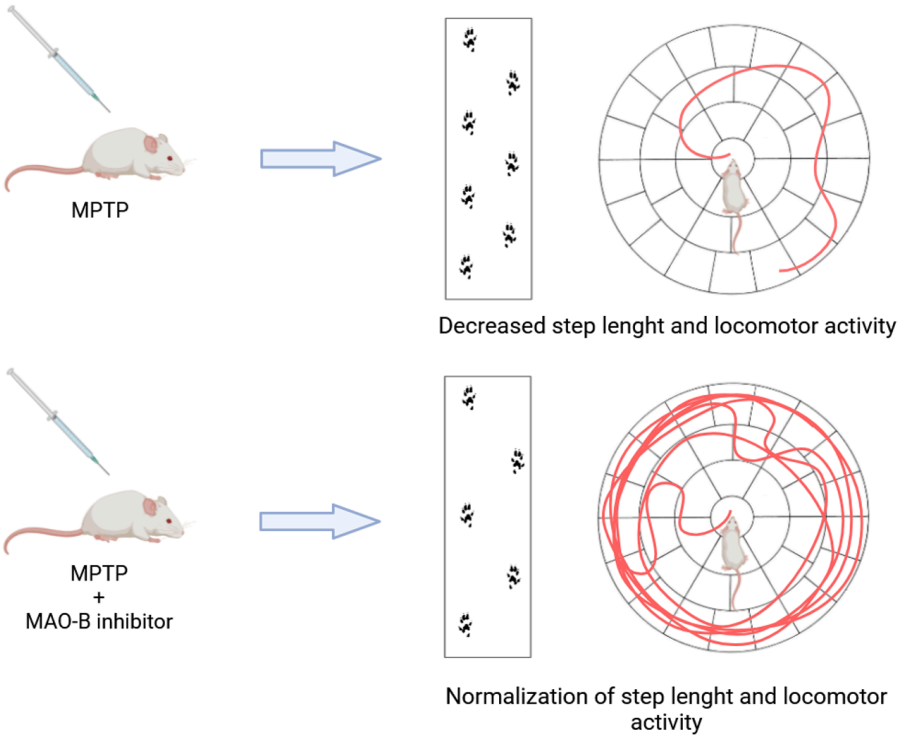
Introduction: Parkinson's disease (PD) is a chronic neurodegenerative disease of the central nervous system, the pathogenesis of which is associated with the death of dopaminergic neurons of the midbrain substantia nigra. The mainstay of therapy for PD is levodopa. However, in the initial stages of PD or in case of levodopa intolerance, MAO B inhibitors are used. **Purpose of the study** was to determine antiparkinsonian activity of newly synthesized selective MAO-B inhibitors in vivo on the model of experimental parkinsonism in white mice.

Materials and Methods: Parkinsonian syndrome in mice was modeled by systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). As the criteria for its evaluation, we used the determination of muscle rigidity severity by step length of mice and evaluation of oligokinesia severity and emotional and mental disturbances in the open field test. A total of 9 candidate compounds were studied, assigned with laboratory codes S1-S5, S9, S10, S14, and S15. Rasagiline was used as a comparison drug.

Results and Discussion: Of the 9 compounds used at a dosage of 2mg/kg, the degree of rigidity was significantly reduced by compounds S1, S9, and S15; locomotor activity was restored to the level reached through rasagiline only by compound S9; the decline in exploratory activity was prevented only by S9 and to some extent by S5.

Conclusion: Only compound S9 having benzenesulfonamide chemotype showed significant therapeutic potential in a model of experimental parkinsonism and only in relation to it additional studies can be planned.

Graphical abstract



Keywords

Parkinson’s disease, MAO-B inhibitors, experimental parkinsonism, benzenesulfonamide derivative

Introduction

Parkinson's disease is a slowly progressive chronic neurodegenerative disease of the central nervous system. The pathogenesis of Parkinson’s disease is associated with the death of neurons in the compact part of the substantia nigra, a structure that produces dopamine for the needs of the extrapyramidal system (Youdim and Riederer 2007; Chew et al. 2023). Deficiency of dopaminergic input leads to excessive inhibition of the motor centers of the cerebral cortex, which ultimately manifests itself in the form of bradykinesia, rigidity, resting tremor and postural instability, as well as a wide range of non-motor manifestations (psychotic, vegetative, cognitive, sensory, etc.). (Ramesh and Arachchige 2023). Men are more likely to develop Parkinson’s disease than women. In addition, there are genetic risk factors that may contribute to the development of the disease (Gómez-Benito et al. 2020).

Treatment of the disease is lifelong; the initial therapy regimen is formed taking into account the patient’s age and the state of their mental functions. The drug levodopa is the cornerstone of Parkinson’s disease therapy. Nerve cells can use levodopa to synthesize dopamine and replenish its stores in the brain (Armstrong and Okun 2020). However, treatment begins with MAO-B inhibitors or dopamine receptor agonists (DRAs) when the disease onsets before the age of 70. The use of combination with levodopa preparations is advisable in the late stages of PD, especially in the elderly. The mechanism of therapeutic action of MAO-B inhibitors is associated with a decrease in the degree and rate of dopamine breakdown, which is normally catalyzed by the monoamine oxidase reaction (Chew et al. 2023). Drugs of this group are prescribed as monotherapy for the initial stages of Parkinson’s disease, although in case of intolerance to levodopa and DRAs, they can be prescribed in later stages of the disease. They are better tolerated than levodopa and DRAs and are often prescribed together with them. Currently, irreversible MAO-B inhibitors (selegiline and rasagiline) and reversible MAO-B inhibitors (safinamide and zonisamide) with a dual mechanism of therapeutic action, including inhibition of sodium and calcium channels with subsequent suppression of glutamate release, are used in the clinic (Jost, 2022; Vanderah, 2024).

Thus, MAO-B inhibitors play an important role in the treatment of Parkinson’s disease. They allow delaying the administration of levodopa-containing drugs, indirectly reducing the risk of developing clinically significant

late drug complications such as fluctuations and dyskinesias in patients in the early stages of the disease. MAO-B inhibitors are combined with levodopa and dopamine receptor agonists, not only enhancing their clinical efficacy, but also increasing their safety in the treatment of Parkinson's disease in advanced stages (Yan et al. 2023; Vanderah, 2024).

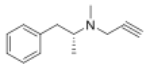
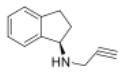
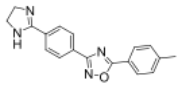
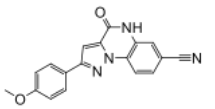
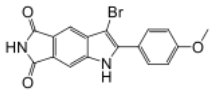
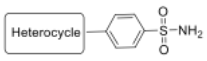
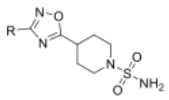
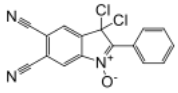
Although MAO-B inhibitors currently available on the pharmaceutical market have a high safety profile, they have relatively low efficacy, which is why there is a need to develop new drugs in this group that would have a combination of high efficacy and tolerability.

The synthesis of a number of compounds was carried out in 2017-2022 at M.V. Dorogov Pharmaceutical Technologies Transfer Center of Yaroslavl State Pedagogical University named after K.D. Ushinsky, for which higher selectivity towards MAO-B in comparison with existing drugs was determined in *in vitro* studies (Table 1). This allows us to assume that the newly synthesized compounds have high antiparkinsonian activity against the background of a decrease in their undesirable effects.

Table 1 shows that most compounds (except S5 and S14) have greater selectivity for inhibiting MAO-B over MAO-A than the reference selegiline and rasagiline; S3 has greater MAO-B inhibitory activity over rasagiline, and S2, S9, and S15 have greater MAO-B inhibitory activity over selegiline.

Purpose of the study was to determine antiparkinsonian activity of newly synthesized selective MAO-B inhibitors in vivo in a model of experimental parkinsonism in white mice.

Table 1. Comparative characteristics of newly synthesized and reference MAO-B inhibitors by the degree of selectivity of enzyme inhibition

Lab number	Compound	IC_{50}, µM	
		MAO-A	MAO-B
Selegiline		-	0.037
Rasagiline		0.412	0.0043
S1		>100	0.763 ± 0.035
S2		2.31 ± 0.123	0.071 ± 0.005
S5		0.011 ± 0.003	6.64 ± 0.222
S3		46.2 ± 11.2	0.0027 ± 0.00064
S9		79.915 ±29.96011	0.038545 ±0.01996
S15		95.215 ± 2.02940	0.00793 ± 0.00146
S4		>100	0.43625 ± 0.045
S10		>100	0.8545 ± 0.024
S14		0.418 ± 0.069	1.74 ± 0.119

Material and Methods

Model of parkinsonism

A mouse model of parkinsonism induced by systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was used to study the *in vivo* antiparkinsonian activity of newly synthesized MAO-B inhibitors. This model is most adequate to the pathogenesis and clinical picture of the disease in humans, since the intoxicant selectively damages the dopaminergic neurons of the substantia nigra. The neurotoxicity of MPTP in relation to the substantia nigra is due to its conversion by MAO-B to 1-methyl-4-phenylpyridinium, which directly exerts a neurotoxic effect (Mironov 2012). MPTP was administered to mice once intraperitoneally at a dose of 30 mg/kg.

Test compounds and dosages

A total of 9 candidate compounds, assigned with laboratory codes S1-S5, S9, S10, S14 and S15, were studied. The selective MAO-B inhibitor Rasagiline was used at a dose of 2 mg/kg as a comparator drug. The studied compounds were administered at the same dose. All drugs were administered intragastrically as a suspension 30 minutes before the administration of MPTP.

Animals

120 white male mice of the ICR (CD-1) line weighing 25-30 grams, kept at a temperature of 22±2 C, humidity 55±5%, in a 12/12 hour light cycle, with unlimited access to food and water were used for the study. The animal study was approved by the independent Ethics Committee of Yaroslavl State Medical University of the Ministry of Health of the Russian Federation, Minutes No. 6 dated September 14, 2023.

The study design was a comparative study of the effectiveness of the test substances on the proposed model in 12 groups of 10 mice each, with one group of healthy animals: the first group was intact mice, the second group was a control group – the animals were administered with MPTP, but without treatment; the third group – treatment with rasagiline; groups 4 through 12 – treatment with the test substances.

Methods of research

The following indicators were used as criteria for evaluating the effectiveness of drugs: assessment of the severity of muscle rigidity 15 minutes after the administration of MPTP by the length of the animals' steps in cm and assessment of the severity of oligokinesia and emotional-mnestic disorders 1.5 hours after the administration of MPTP in the open field test.

The severity of muscle rigidity was assessed 15 minutes after the administration of MPTP based on the step length of the animals in comparison with in the intact group. The animals' forepaws and hindpaws were painted with non-toxic paints of different colours for this purpose, and then they were put into a narrow box (height of walls 8 cm, width 8 cm, length 50 cm), the floor of which was lined with white paper. The distance between the tracks of the forepaws and hindpaws in 5 steps of the animal was measured. The steps at the beginning and end of the alley were not taken into account.

The open field device is a round white arena with an opaque side 32 cm high, 63 cm in diameter, divided into 4 rows of sectors. At the intersection of the sectors, there are "holes" (black circles drawn on the field) on the floor. The following parameters were recorded: horizontal activity (number of sectors crossed by the animal), vertical activity (number of rises on hindpaws with or without support on the wall), exploratory activity (number of looks into "holes"), emotional-behavioural activity – grooming (number and duration of paws approaching the mouth, licking them, cleaning the front part of the muzzle and body) and defecation (number of excrements).

Statistical analysis

The obtained results were subjected to statistical processing using the BIOSTATISTICS program. The Student's t-test (if there was normal distribution) and the nonparametric Wilcoxon test (if there was no normal distribution) were used for between-group comparisons. Student's t-test with Bonferroni correction was used for multiple comparisons. The reliability of intragroup differences was determined using the paired Student's t-test. Differences were considered significant at $p < 0.05$ (Glantz, 1998).

Results and Discussion

The average step length in the intact control group was 6.24±0.20 cm, and with the introduction of MPTP it significantly decreased to 5.29±0.18 cm – by 15% (Table 2). The use of the reference drug rasagiline for the treatment of animals allowed us to normalize their step length to 6.18±0.14 cm, which increased it by 17% ($p<0.05$) compared to that in the group receiving only MPTP.

Table 2. Step length of mice in cm when administered test compounds at a dose of 2 mg/kg

Groups	Step length. cm
Intact	6.24±0.20
Control	5.29±0.18*
Rasagiline	6.18±0.14**
S1	6.03±0.18**
S2	6.14±0.48
S3	5.85±0.20
S4	5.37±0.10*
S5	5.55±0.09*
S9	6.24±0.18**
S10	5.53±0.06*
S14	5.75±0.18
S15	6.20±0.22**

Note: * – significant difference from intact animals; ** – significant difference from control animals.

Of the 9 compounds studied, substances S1, S9 and S15 restored the average step length reliably in relation to the control group: the step length in treated mice significantly increased by 12-18% compared to that in the control group. A tendency towards normalization of this indicator (there was no reliability in relation to both intact and control animals) was observed in compounds S2, S3 and S14. The step length of the treated subjects increased in relation to the control group by 8-16% in this case. The use of compounds S4 and S10 was ineffective: the step length in animals of these groups remained significantly lower than in healthy mice.

The animal's horizontal activity in the open field test is primarily an indicator of locomotor activity and to a much lesser extent indicates their exploratory activity; low levels of horizontal activity may indicate stress or anxiety in the animal. Administration of MPTP to mice caused a significant 3-fold decrease in horizontal activity; rasagiline prevented this: this indicator decreased by only 24% ($p>0.05$) and was significantly – by 2.3 times – higher than in the control. Compound S9 significantly increased horizontal activity – by 1.9 times, but it remained significantly lower – by 37% – than in the intact control. A tendency to increase this indicator (there is no reliability in relation to either healthy or sick animals) by 49% was observed when using S2. The administration of the remaining drugs (S1, S3, S4, S5, S10 and S14) was ineffective (Table 3).

Vertical activity is the second most important indicator of locomotor activity and also indicates active exploration of the environment. Its low level is associated with increased anxiety. Administration of MPTP to mice caused a reliable 5-fold decrease in vertical activity; although rasagiline prevented this: the rats' activity still decreased by 1.9 times ($p<0.05$); at the same time, this indicator was reliably 2.6 times higher than in the control. S9 had a tendency to increase vertical activity by 49% (not significantly in relation to either healthy or sick animals). Administration of S1, S3, S3, S4, S5, S10, S14 and S15 was ineffective. Thus, S9 contributed to a greater degree to the restoration of locomotor activity in mice administered with MPTP. The therapeutic effect of the remaining compounds was absent or did not reach the level of significance.

A common analogue of exploratory behavior in the open field test is the animal looking into "holes". This primarily indicates its interest in the new environment and its assessment of its safety. The introduction of MPTP significantly reduced this type of behavioral activity – by 2 times; however, when using rasagiline, although it prevented a significant decrease in exploratory activity in mice with modeled parkinsonism, there was a tendency (by 1.5 times) for it to decrease (Table 3).

Only S9 (healthy animal level) and to some extent S5 of the study drugs prevented the decline in research activity. The administration of the other substances was ineffective.

Grooming and defecation are a emotional-behavioural part of the test, with short grooming being an indicator of stress reduction, while long grooming indicating the development of anxiety in the animal. The administration of the neurointoxicant reliably reduced both the level of emotional reactivity and stress tolerance. Neither rasagiline nor the studied drugs contributed to their restoration.

Table 3. Open field test with the introduction of test compounds at a dose of 2 mg/kg

Group	Horizontal activity	Vertical activity	Grooming		Research activity	Emotional reactivity
			Short	Long		
Intact	111.6±11.5	16.6±1.8	0.4±0.1	0.6±0.2	4.8±0.8	0.4±0.1
Control	37.1±7.1*	3.3±0.7*	0.1±0.1*	0.4±0.1	2.4±0.4*	0.1±0.1*
Rasagiline	85.1±8.6**	8.7±2.1*/**	0*	0.3±0.2	3.2±0.8	0.2±0.1
S1	17.9±5.3*/**	0.3±0.2*	0*	0*	0.1±0.2*/**	0
S2	55.2±25.8	0*/**	0*	0.2±0.2	2.5±0.6	0
S3	41.2±19.3*	4.0±2.0*	0.5±0.5	0.3±0.3	1.1±0.7*	0
S4	15.0±6.5*/**	1.0±0.6*	0*	0	0.5±0.4*/**	0
S5	32.5±6.8*	0.7±0.4*	0*	0.2±0.2	3.2±0.6	0
S9	69.2±12.6*/**	8.0±3.6	0*	0.7±0.2	4.5±1.3	0.1±0.2
S10	5.0±3.3*/**	0*/**	0*	0	0.2±0.2*/**	0
S14	37.9±27.8*	2.7±1.2*	0*	0*	0.6±0.5*/**	0
S15	31.9±6.5*	2.3±0.6*	0.1±0.2	0.1±0.2	0.6±0.6*/**	0

Note: *– significant difference with intact animals; ** – significant difference with control animals.

Conclusion

It is an axiom of preclinical research that the results of *in vitro* experiments are not always reproducible with data obtained on a living object. Therefore, *in vivo* experiments determine the future fate of new compounds as possible drugs. Based on this, a study of the pharmacological activity of the lead compounds (according to *in vitro* data) was conducted on animal models of neurodegenerative diseases at a dosage of 2mg/kg. Thus, the highest inhibitory activity to MAO-B was revealed *in vitro* in S1 (1.5 times higher than in rasagiline) and in S15. But neither compound proved to be a leader in the treatment of experimental Parkinsonism: they prevented the development of rigidity (the average step length of mice), and were ineffective in restoring the open field indices.

Of all the studied compounds, only benzenesulfonamide derivative S9 was comparable to rasagiline in preventing the development of rigidity and oligokinesia in animals for all studied parameters and was superior to the reference drug in correcting exploratory activity.

S1 and S15 significantly relieved muscle rigidity. A tendency towards normalization of this indicator, as well as horizontal activity (there was no reliability in relation to both intact and control animals) was observed when using compound S2. Compounds S3 and S14 showed a tendency to decrease the level of rigidity. The remaining compounds (S4 and S10) had no therapeutic effect.

Thus, only compound S9 based on the benzenesulfonamide chemotype showed significant therapeutic potential in the experimental parkinsonism model, and only in relation to it, is it advisable to plan additional studies.

Conflict of interest

The authors declare the absence of a conflict of interests.

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Data availability

All of the data that support the findings of this study are available in the main text.

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