EXPERIMENTAL STUDIES

THE INFLUENCE OF NEUROPROTECTOR ISATIN ON HALOPERIDOL-INDUCED CATALEPSY AND PROTEOMIC PROFILE OF MICE BRAIN

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Isatin (indol-2,3-dione) is an endogenous regulator found in humans and animals. It interacts with numerous target proteins and exhibits a wide range of biological activities, including neuroprotective action in animal models of Parkinson's disease (PD) induced by administration of neurotoxins MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) or rotenone. An antipsychotic drug haloperidol, which impairs neurotransmitter balance in the nigrostriatal pathway, models dopamine deficiency and promotes the development of motor disorders characteristic of PD. In this work, the effect of two doses of isatin (10 mg/kg and 80 mg/kg) on the haloperidol catalepsy and on the proteomic profile of mice brain was investigated. The pretreatment of animals with isatin (1 h before haloperidol administration) reduced the occurrence of haloperidol catalepsy. The administration of haloperidol and also isatin with haloperidol influenced the relative content of a number of proteins associated with PD and other neurodegenerative diseases.

Keywords: isatin; neuroprotector; neurodegeneration; Parkinson's disease; haloperidol; brain; proteomic profiling

DOI: 10.18097/PBMCR1718

INTRODUCTION

Isatin (indole-2,3-dione) is an endogenous regulator found in the brain, peripheral tissues, and biological fluids of humans and animals; it exhibits a broad spectrum of biological activity due to its ability to bind to numerous target proteins [1, 2]. The neuroprotective properties of isatin have been demonstrated in mouse and rat models of parkinsonism using the neurotoxins 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone [3–5]. In both cases, isatin reduced the severity of symptoms characteristic of Parkinson's disease (PD) and influenced the brain proteome of the animals. A study comparing the profile of isatin-binding brain proteins in rats with rotenone-induced parkinsonian syndrome (PS) against the corresponding parameters in mice with MPTP-induced parkinsonism has shown that the molecular mechanisms of action of these neurotoxins differ. A comparison of isatin-binding proteins specific to animals with MPTP-induced and rotenone-induced PS (relative to control animals) showed a complete absence of proteins common to these two PD models [6]. Although the development of PS resulting from exposure to either neurotoxin is driven by mitochondrial dysfunction, the underlying mechanisms differ. In the case of MPTP-induced PS, the neurotoxin is converted — via the action of monoamine oxidase B (MAO-B) — into the methylphenylpyridinium ion (MPP^+), which is responsible for the initial disruptions in the mitochondrial respiratory chain [7]. In the case of rotenone-induced PD, the development of mitochondrial dysfunction occurs via a pathway independent of MAO and involves other proteins. However, our observations indicate that isatin administration exerts a neuroprotective effect in both models [4, 5, 8, 9].

In the context of the universality of the neuroprotective action of isatin, it is important to investigate its effects in various PD models. One such model, in which the effects of isatin have not yet been studied, is haloperidol-induced catalepsy [10]. The antipsychotic drug haloperidol acts as a dopamine receptor antagonist in the nigrostriatal pathway; a characteristic feature of haloperidol is its ability to induce a cataleptogenic state (muscle rigidity and a lack of response to external stimuli). This feature forms the basis for using haloperidol to study the motor disturbances observed in parkinsonism and to screen potential antiparkinsonian drugs in animal models [10–15].

The aim of this study was to investigate the effects of isatin on haloperidol-induced catalepsy and on the brain proteomic profile of mice.

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MATERIALS AND METHODS

Reagents

The following reagents were used in the study: isatin, ammonium bicarbonate, dithiothreitol, Tris(hydroxymethyl)aminomethane, urea, guanidine hydrochloride, sodium chloride, Triton X-100, 4-vinylpyridine, Coomassie Brilliant Blue G-250, and glycerol (Merck, USA); formic acid and sodium hydroxide (Acros Organics, USA); acetonitrile (Fisher Chemical, UK); isopropanol and trifluoroacetic acid (Fluka, USA); tris(2-carboxyethyl) phosphine (Pierce, USA); modified trypsin (mass spectrometry grade, Promega, USA); and haloperidol (Sigma-Aldrich, Germany). Other reagents of the highest available purity were from local suppliers.

Experimental Animals

The study was conducted using male outbred SHK albino mice (body weight 26–30 g) obtained from the Stolbovaya branch of the Scientific Center for Biomedical Technologies of the Russian Federal Medical and Biological Agency. The animals were housed in accordance with GOST 33215-2014 and GOST 33216-2014 under standard vivarium conditions: a 12-h light/dark cycle, temperature of 20–24°C, and relative humidity of 45–65%. They were kept in plastic cages with sawdust bedding (10 mice per cage) with *ad libitum* access to food and water.

Modeling of Experimental Parkinsonism in Mice

A cataleptogenic state was modeled in the mice by administration of haloperidol in accordance with the "Guidelines for Conducting Preclinical Studies of Drugs" [16]. The animals were randomly divided into four groups of 7–8 mice each:

1) Animals of the group "Control" (n = 7) received an intraperitoneal (i.p.) injection of physiological saline in an equivalent volume of 1 ml per 100 g of body weight.

2) Animals of the group "Haloperidol" (n = 8) received an i.p. injection of haloperidol (1 mg/kg).

3) Animals of the group "Isatin 10 mg/kg + Haloperidol" (n = 8) received a subcutaneous (s.c.) injection of isatin (10 mg/kg), and then (after 1h) an i.p. injection of haloperidol (1 mg/kg).

4) Animals of the group "Isatin 80 mg/kg + Haloperidol" (n = 8) received a s.c. injection of isatin (80 mg/kg) and then (after 1h) an i.p. injection of haloperidol (1 mg/kg).

The test was conducted 60 min, 120 min, and 180 min after the i.p. injection of haloperidol. The antagonism between the neuroprotective agent isatin and haloperidol was assessed based on the ability of isatin to reduce the duration of the cataleptic state in the animals [10, 14].

The animals were placed in the TS1601-RM testing apparatus for evaluating catalepsy in rodents (OpenScience, Russia). After acclimation for 2–3 min, both forepaws were gently placed on a horizontal bar (the "lecturer's posture") elevated to a height of 4 cm, and the duration of the animal's immobility was recorded. The maximum observation time was 2 min. If the animal changed its posture or moved during the observation period, it was returned to the "lecturer's posture", and the timing was restarted. A maximum of five attempts were made per time point [16].

Statistical Analysis of Results

Statistical analysis was performed using GraphPad Prism software (GraphPad Software/ Dotmatics, USA/UK). Data normality was assessed using the Shapiro-Wilk test, and homogeneity of variances was evaluated using the Levene's test. In cases of normal distribution and equal variances, analysis of variance (ANOVA) followed by Dunnett's post hoc test was used. If the distribution deviated from normality, non-parametric methods were employed: the Kruskal-Wallis test followed by Dunn's multiple comparisons test. Results are presented as the arithmetic mean ± standard error of the mean (M ± SEM). The critical significance level (Type I error) was set at $p = 0.05$.

Sample Preparation for Mass Spectrometry (MS) Analysis

Following the tests for catalepsy, the animals were decapitated under light ether anesthesia; brain homogenate lysates were obtained, and samples were prepared for mass spectrometric analysis.

The preparation of brain homogenate lysates and samples for MS analysis (protein extraction, alkylation, and trypsinolysis) has been described in details previously [4, 9].

MS Analysis

MS analysis was performed using the equipment of the "Human Proteome" Core Facilities of the Institute of Biomedical Chemistry. These included specifically, the Ultimate 3000 RSLCnano high-performance liquid chromatography system (Thermo Scientific, USA) operating in nanoflow mode coupled to a Q-Exactive HFX mass spectrometer (Thermo Scientific); the procedures of the MS analysis were described previously [6]. Bioinformatic data processing was carried out as described in [6]. Each of the proteins listed in the tables was identified in at least three independent experiments.

RESULTS AND DISCUSSION

The Effect of Isatin on Haloperidol-Induced Motor Impairments in Mice

Haloperidol administration resulted in the development of catalepsy, which persisted and increased during the observation period (Table 1). Isatin reduced the severity of haloperidol-induced catalepsy in mice. The dynamics of changes in haloperidol-induced catalepsy depended on the isatin dose. During the first hour of observation (following haloperidol administration), the duration of the cataleptogenic state in mice treated with 10 mg/kg isatin and 80 mg/kg isatin was 1.3 and 1.7 times shorter ($p < 0.05$), respectively, than in the "Haloperidol" group animals (Table 1). Although the observed effect of isatin diminished during the subsequent observation period, it did not disappear completely by the end of the experiment. This was manifested as a 1.4-fold reduction ($p < 0.05$) in the duration of catalepsy in mice treated with 80 mg/kg isatin two hours after haloperidol administration, and a 1.4-fold reduction ($p < 0.01$) in mice treated with 10 mg/kg isatin three hours after the haloperidol administration (Table 1).

The Effects of Haloperidol and Isatin on the Brain Proteome Profile of Mice

Administration of haloperidol to mice (1 mg/kg i.p.) induced significant changes in the relative levels of 14 brain proteins; most of them are associated with neurodegenerative diseases (Table 2). The most pronounced (almost 10-fold) increase in the relative content was observed for mitochondrial carbamoyl phosphate synthase, an enzyme, playing a key role in ammonia detoxification via the synthesis of carbamoyl phosphate. A deficiency of this enzyme causes hyperammonemia, leading to multiple disorders, including neurodegeneration [17–19]. The level of fructose-bisphosphate aldolase increased more than fivefold. Along with certain other glycolytic enzymes, aldolase is a direct target of dopamine. This and some other can be modified during their interaction with dopamine thus underlying their importance for significance in PD [20]. Administration of haloperidol led to a 4.6-fold increase in the level of betaine-homocysteine methyltransferase. This enzyme participates in homocysteine metabolism, thereby reducing its concentration in the blood. Elevated blood homocysteine levels are characteristic of PD patients [21–23].

The group of brain proteins demonstrating a marked decrease in their relative content (2.2–2.6-fold) after haloperidol administration included the Alzheimer's disease biomarker neuronal pentraxin 1, tetraspanin, synaptotagmin, and the eS17 protein of the small ribosomal subunit. All these proteins are known to be associated with neurodegeneration (see references in Table 2).

Administration of 10 mg/kg isatin before haloperidol administration influenced the relative content of 30 proteins. The functions of the majority of these proteins include cytoskeleton formation, exocytosis, signal transduction, and the enzyme activity regulation. Most of these proteins were downregulated and only nine were upregulated (Table 3). In addition to the previously mentioned carbamoyl phosphate synthase and betaine-homocysteine methyltransferase (their relative content increased more than 15-fold and 3-fold, respectively), this group included mitochondrial alcohol dehydrogenase, plectin, alpha- and beta-globins, 17-beta-hydroxysteroid dehydrogenase, synaptic Ras GTPase-activating protein 1 (synGAP1), and monoamine oxidase B (MAO-B). Administration of isatin and haloperidol was accompanied by a 2- to 3-fold increase in the relative content of these proteins compared to control. The change in the relative content of MAO-B is particularly interesting. This enzyme is directly involved in dopamine metabolism and MAO-B inhibitors are widely used in the therapy of PD [3, 24, 25]. However, the other upregulated brain proteins are also linked in some way to neurodegeneration, including PD and Alzheimer's disease (AD) (Table 3). The brain proteins with the decreased relative content (2- to 4-fold) in animals of this group are also related to neurodegeneration. These include alpha- and beta-synucleins, neuronal pentraxin 1, myelin basic protein, mitochondrial ATPase inhibitor,

Table 1. The effect of isatin on haloperidol-induced catalepsy in mice

Groups of mice, doses and routes of administration of substances	Catalepsy duration, s		
	1 h after haloperidol administration	2 h after haloperidol administration	3 h after haloperidol administration
Control, saline, i.p.	1.7±1.4***	9.0±3.8***	6.3±3.7***
Haloperidol, 1 mg/kg, i.p.	91.8±11.6	108.1±4.9	118.1±1.9
Isatin 10 mg/kg, s.c. + Haloperidol 1 mg/kg, i.p.	70.6±14.2	89.9±9.7	**84.3±12.1****
Isatin 80 mg/kg, s.c. + Haloperidol 1 mg/kg, i.p.	**54.1±5.9***	**78.4±12.4***	105.8±6.9

Data represent M ± SEM. Statistically significant changes vs the Haloperidol group are indicated in bold and marked with asterisk(s): * – $p < 0.05$; ** – $p < 0.01$,*** – $p < 0.001$, respectively.

Table 2. Changes in the relative content of brain proteins of mice treated with 1 mg/kg haloperidol vs control

#	Uniprot accession number	Uniprot gene name	Uniprot protein name	Functions	Localization	-LOG(P-value)	Fold change	Association with neurodegeneration
1	Q8C196	*Cps1*	Carbamoyl-phosphate synthase [ammonia], mitochondrial	6	N, MCh, M	7.90	9.67	[17–19]
2	Q3UER1	*Aldob*	Fructose-bisphosphate aldolase	1	C	5.33	5.60	[20]
3	O35490	*Bhmt*	Betaine-homocysteine S-methyltransferase 1	6	N, C	4.63	4.60	[21–23]
4	A8DUV1	*Hbat1*	Alpha-globin	2	ECS	4.59	3.82	[31, 32]
5	Q6P8Q0	*Gsta13*	Glutathione S-transferase	4	C	2.70	3.24	[33]
6	A0A338P799	*Syngap1*	Synaptic Ras GTPase activating protein 1 homolog (rat)	3	M	4.49	2.45	[34]
7	Q3UWG5	*Cd81*	Tetraspanin	2	M	4.55	0.46	[35]
8	Q62443	*Nptx1*	Neuronal pentraxin-1	3	V, EPR	3.47	0.44	[36, 37]
9	Q5DTI3	*Syt2*	Synaptotagmin	2	V	2.88	0.40	[38, 39]
10	Q9CRB	*Tppp3*	Tubulin polymerization-promoting protein family member 3	2	C	5.70	0.40	[40–42]
11	Q5M9J2	*Hint2*	Histidine triad nucleotide binding protein 2	3	MCh	5.18	0.40	—
12	Q5M9L7	*Rps17*	Small ribosomal subunit protein eS17	6	C	5.58	0.39	[43, 44]
13	Q6ZQA0	*Nbeal2*	Neurobeachin-like protein 2	4	EPR	3.31	0.19	—
14	P11881	*Itpr1*	Inositol 1,4,5-trisphosphate-gated calcium channel ITPR1	2	C, V, EPR	2.74	0.18	[45]

Here and in other tables the numbers in the column “Function” indicate the following functional groups of proteins:
1. Proteins/enzymes involved in the processes of energy generation and carbohydrate metabolism.
2. Proteins involved in the formation of the cytoskeleton, transport and exocytosis.
3. Proteins involved in signal transduction and regulation of enzyme activity regulation.
4. Antioxidant and protective proteins/enzymes.
5. Proteins involved in the regulation of gene expression, cell division, and differentiation.
6. Enzymes involved in metabolism of proteins, amino acids and other nitrogenous compounds.
7. Enzymes involved in lipid metabolism.
Localization: C – cytoplasm, N – nucleus, M – membranes, PM – plasma membranes, EPR – endoplasmic reticulum, P – peroxisomes, MCh – mitochondria, L – lysosomes, E – endosomes, V – vesicles, ECS – extracellular space.

thymosin beta-4, astrocytic phosphoprotein PEA-15, stathmin, neuromodulin, A-kinase anchor protein 5, microtubule-associated proteins, and others; all are linked to neurodegeneration, particularly to PD (Table 3 and references cited there).

Administration of 80 mg/kg isatin before haloperidol influenced the relative content abundance of 26 brain proteins. As was the case of administration of 10 mg/kg isatin, the most of these proteins are involved in cytoskeleton formation and exocytosis, or in signal transduction and the regulation of enzyme activity (10 proteins in each category). An increase in the relative content was observed for only 6 proteins. In addition to the previously mentioned carbamoyl phosphate synthase and 17-beta-hydroxysteroid dehydrogenase (their relative content increased nearly 14-fold and 2.5-fold, respectively), the proteins included cytochrome *c* oxidase subunit 5A, calcium ATPase, and mitochondrial ATP synthase subunit f. Their relative levels increased 2- to 3-fold (Table 4). Dysfunction of cytochrome *c* oxidase (the rate-limiting enzyme of the mitochondrial respiratory chain) leads to oxidative stress and is a hallmark of PD and AD [26]. Reduced levels of calcium-ATPase were detected in a *Drosophila melanogaster* PD model PD [27]. Oxidative modifications of ATP synthase are characteristic of PD, AD, and Huntington's diseases, and this enzyme is considered as a potential pharmacological target for treating these diseases [28].

Table 3. Changes in the relative content of brain proteins of mice treated with 10 mg/kg isatin and after 1 h with 1 mg/kg haloperidol vs control

#	Uniprot accession number	Uniprot gene name	Uniprot protein name	Functions	Localization	-LOG(P-value)	Fold change	Association with neurodegeneration
1	Q8C196	*Cps1*	Carbamoyl-phosphate synthase [ammonia], mitochondrial	6	N, MCh, M	8.93	15.74	[17–19]
2	Q54AH9	*Hbb-b2*	Beta-2-globin	2	ECS	4.01	9.09	[31, 32]
3	O35490	*Bhmt*	Betaine-homocysteine S-methyltransferase 1	6	N, C	1.97	3.74	[46, 47]
4	A8DUV1	*Hbat1*	Alpha-globin	2	ECS	4.06	3.01	[31, 32]
5	Q9CZS1	*Aldh1b1*	Aldehyde dehydrogenase X, mitochondrial	4	MCh	1.71	2.65	[48]
6	E9Q3W4	*Plec*	Plectin	2	C	3.53	2.31	[49]
7	Q8BW75	*Maob*	Amine oxidase [flavin-containing] B	6	MCh	3.71	2.23	[3, 24, 25]
8	A0A338P799	*Syngap1*	Synaptic Ras GTPase activating protein 1 homolog (rat)	3	M	6.06	2.20	[34]
9	Q3UHW2	*Hsd17b4*	Hydroxysteroid (17-beta) dehydrogenase 4	7	P	11.17	2.06	[50]
10	Q91ZZ3	*Sncb*	Beta-synuclein	3	C	2.36	0.49	[51, 52]
11	Q3UNH4	*Gprin1*	G protein-regulated inducer of neurite outgrowth 1	3	PM	6.20	0.48	—
12	E9PV44	*Atp5if1*	ATPase inhibitor, mitochondrial	3	MCh	3.99	0.48	[53]
13	Q6ZWX2	*Tmsb4x*	Thymosin beta	3	C	4.24	0.47	[54, 55]
14	Q62048	*Pea15*	Astrocytic phosphoprotein PEA-15	3	C	4.75	0.47	[56]
15	Q3UST4	*Nptx1*	Neuronal pentraxin-1	3	V, EPR	2.06	0.46	[37, 53]
16	Q543N3	*Lasp1*	LIM and SH3 domain protein 1	2	C	7.06	0.45	[57, 58]
17	B6ZHC9	*Epb41l1*	Erythrocyte protein band 4.1-like 1	2	C	6.56	0.44	[59]
18	Q5M9L7	*Rps17*	Small ribosomal subunit protein eS17	6	C	3.29	0.44	[43, 44]
19	Q3UY00	*S100b*	Protein S100	3	C, N, ECS	2.34	0.42	[60, 61]
20	P26645	*Marcks*	Myristoylated alanine-rich C-kinase substrate	2	PM, C	6.13	0.40	[62, 63]
21	D3Z1Z8	*Stmn1*	Stathmin	2	C	5.76	0.40	[64, 65]
22	D3YVF0	*Akap5*	A-kinase anchor protein 5	3	M	7.76	0.39	[66–68]
23	P06837	*Gap43*	Neuromodulin	3	C, M	7.01	0.37	[69]
24	O55042	*Snca*	Alpha-synuclein	3	C, M, N	5.70	0.37	[70, 71]
25	A0A411P8U6	*Mbp*	Myelin basic protein	4	M	5.37	0.33	[72, 73]
26	A0A0A6YVU8	*Adrm1b*	Adhesion regulating molecule 1B	6	C, N	2.07	0.31	[74]
27	Q8R5J9	*Arl6ip5*	PRA1 family protein 3	2	PM, C	2.36	0.27	[75, 76]
28	Q7TSJ2	*Map6*	Microtubule-associated protein 6	2	C, V	8.88	0.26	[77–80]
29	Q547J4	*Mapt*	Microtubule-associated protein	2	C	7.38	0.25	[77–79]
30	P20357	*Map2*	Microtubule-associated protein 2	2	C	6.37	0.15	[77–79]

Table 4. Changes in the relative content of brain proteins of mice treated with 80 mg/kg isatin and after 1 h with 1 mg/kg haloperidol vs control

#	Uniprot accession number	Uniprot gene name	Uniprot protein name	Functions	Localization	-LOG(P-value)	Fold change	Association with neurodegeneration
1	Q8C196	*Cps1*	Carbamoyl-phosphate synthase [ammonia], mitochondrial	6	N, MCh, M	6.91	13.94	[17–19]
2	P12787	*Cox5a*	Cytochrome *c* oxidase subunit 5A, mitochondrial	1	MCh	3.23	3.07	[26]
3	S4R1C4	*Atp2b2*	Calcium-transporting ATPase	2	PM, M	2.52	2.64	[27]
4	Q3UHW2	*Hsd17b4*	Hydroxysteroid (17-beta) dehydrogenase 4	7	P	5.91	2.47	[50]
5	P56135	*Atp5mf*	ATP synthase subunit f, mitochondrial	1	MCh	2.49	2.33	[28]
6	S4R286	*Anks1b*	Ankyrin repeat and sterile alpha motif domain containing 1B	3	C, N	3.40	2.12	—
7	D3YVF0	*Akap5*	A-kinase myristoylated protein 5	3	M	5.04	0.50	[66–68]
8	P26645	*Marcks*	Myristoylated alanine-rich C-kinase substrate	2	PM, C	3.49	0.49	[62, 63]
9	O55042	*Snca*	Alpha-synuclein	3	C, M, N	3.95	0.47	[70, 71]
10	Q8BG51	*Rhot1*	Mitochondrial Rho GTPase 1	3	MCh	1.64	0.47	[29]
11	Q5M8N0	*Cnrip1*	CB1 cannabinoid receptor-interacting protein 1	3	M	2.91	0.46	[81]
12	Q9Z0P5	*Twf2*	Twinfilin-2	2	C	4.50	0.45	[30]
13	Q6ZWR0	*Rap2b*	Ras-related protein Rap-2	3	E, M	2.09	0.39	[82]
14	Q547J4	*Mapt*	Microtubule-associated protein	2	C	4.06	0.38	[77–79]
15	Q9D8B4	*Ndufa11*	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 11	1	MCh	6.04	0.37	[83]
16	D3Z1Z8	*Stmn1*	Stathmin	2	C	6.38	0.36	[64, 65]
17	Q3UWG5	*Cd81*	Tetraspanin	4	M	3.24	0.34	[35, 84]
18	Q7TSJ2	*Map6*	Microtubule-associated protein 6	2	C, V	7.65	0.30	[77–80]
19	C9K0Y6	*Gria3*	Glutamate receptor	3	PM	4.45	0.28	[85]
20	Q62048	*Pea15*	Astrocytic phosphoprotein PEA-15	2	C	7.66	0.27	[86]
21	Q8BHZ0	*Cyria*	CYFIP-related Rac1 interactor A	3	M	2.24	0.25	[87]
22	Q62443	*Nptx1*	Neuronal pentraxin-1	3	V, EPR	3.34	0.21	[37, 53]
23	P20357	*Map2*	Microtubule-associated protein 2	2	C	5.10	0.18	[77–79]
24	P68181	*Prkacb*	cAMP-dependent protein kinase catalytic subunit beta	3	C, PM, M, N	5.74	0.18	[88, 89]
25	Q6ZQA0	*Nbeal2*	Neurobeachin-like protein 2	2	EPR	2.82	0.18	—
26	Q9JKD3	*Scamp5*	Secretory carrier-associated membrane protein 5	2	PM, M, V	4.25	0.17	[90]

In the most identified brain proteins of the group of animals treated with 80 mg/kg isatin their relative content decreased from 2- to 5-fold (Table 4). Virtually all of these proteins are associated with neurodegeneration. They include alpha-synuclein, neuronal pentraxin 1, astrocytic phosphoprotein PEA-15, stathmin, A-kinase anchor protein 5, and microtubule-associated proteins; these were also observed in the group treated with a lower dose of isatin (Tables 3 and 4). Other proteins linked to neurodegeneration were specific to the group of mice treated with 80 mg/kg isatin before haloperidol administration. These include mitochondrial Rho GTPase 1 (MIRO1), encoded by a PD candidate gene [29], and twinfilin-2 [30].

In the case of rotenone-induced PS in rats, we observed motor impairments characteristic of PS and changes in the relative abundance of 86 proteins belonging to various functional groups. Administration of the neuroprotectant isatin reduced the severity of PS and altered the levels of these proteins, which included a significant proportion of mitochondrial proteins [9, 91].

Summarizing the data on the functions and localization of proteins with altered relative content in the haloperidol-induced catalepsy model, one can see that mitochondrial proteins represent a rather small proportion: only 2 out of 14 listed in Table 2, 4 out of 30 in Table 3, and 5 out of 26 in Table 4. No changes in the relative abundance of proteins involved in the regulation of gene expression, cell division, or differentiation were observed in any of the animal groups studied. The vast majority of proteins, showing significant level changes across all three animal groups compared to the control group, were associated with the cytoskeleton and exocytosis, or were involved in signal transduction and the regulation of enzyme activity (Tables 2–4).

A comparison of MS data from experiments using rotenone [9, 91] and haloperidol (the present study) revealed a change in the relative content of only one protein common to both experimental models (Tables 5, 6). This protein is tetraspanin, a transmembrane protein involved in numerous cellular processes, including cell migration, protein transport, membrane integrity, and the regulation of signal transduction [92]. It plays a significant role in the metabolism of the amyloid precursor protein, a key player in the AD pathogenesis [93]. Tetraspanin also protects dopaminergic neurons against degeneration in a 6-hydroxydopamine-induced PD model the *Caenorhabditis elegans* nematode [35].

A comparison of proteins whose relative content changed upon isatin administration in animals with rotenone-induced parkinsonism and haloperidol-induced catalepsy revealed an overlap of five proteins: alpha-synuclein, stathmin, astrocytic phosphoprotein PEA-15, tetraspanin, and microtubule-associated protein 6. They all (particularly alpha-synuclein) are associated with neurodegeneration (Table 6 and cited references there).

CONCLUSIONS

Isatin is an endogenous regulator present in humans and animals; it exhibits numerous biological and pharmacological effects through interactions with various target proteins. Its neuroprotective activity

Table 5. Changes in the relative content of brain proteins vs control in animal experiments with rotenone and haloperidol

Uniprot accession number	Uniprot gene name	Uniprot protein name	Functions	Localization	Changes in the relative content		Association with neurodegeneration
					Rotenone	Haloperidol	
Q6P9V1	*Cd81*	Tetraspanin	4	M	3.25	0.46	[35]

Table 6. Changes in the relative content of brain proteins vs control in animals treated with isatin + rotenone and isatin + haloperidol experiments with rotenone and haloperidol

#	Uniprot accession number	Uniprot gene name	Uniprot protein name	Functions	Localization	Changes in relative content			Association with neurodegeneration
						Rotenone + isatin	Haloperidol + 10 mg/kg isatin	Haloperidol + 80 mg/kg isatin	
1	Q62048	*Pea15*	Astrocytic phosphoprotein PEA-15	2	C	3.25	0.47	0.27	[86]
2	D3Z1Z8	*Stmn1*	Stathmin	2	C	2.46	0.40	0.36	[64, 65]
3	O55042	*Snca*	Alpha-synuclein	3	C, M, N	64.00	0.37	0.47	[70, 71]
4	Q7TSJ2	*Map6*	Microtubule-associated protein 6	2	C, V	5.66	0.26	0.30	[77–80]
5	Q6P9V1	*Cd81*	Tetraspanin	4	M	3.48	—	0.34	[35]

has been demonstrated in various experimental models of neurodegenerative diseases, including MPTP-induced parkinsonism in mice and rotenone-induced parkinsonism in rats [3–5]. In this study, we demonstrated that isatin reduced the manifestations of haloperidol-induced catalepsy and influenced the relative levels and profiles of proteins associated with neurodegeneration (including PD and other disorders). These results confirm previous findings indicating that isatin exerts its neuroprotective effect in various experimental models of PD through interactions with distinct sets of target proteins.

ACKNOWLEDGMENTS

Mass spectrometry analysis was carried out using the equipment of "Human Proteome" Core Facilities of the Institute of Biomedical Chemistry (Russia).

FUNDING

The work was performed within the framework of the Program for Basic Research in the Russian Federation for a long-term period (2021–2030) (no. 122030100170-5).

COMPLIANCE WITH ETHICAL STANDARDS

Animal maintenance and care were conducted in accordance with GOST 33215-2014 "Guidelines for the maintenance and care of laboratory animals. Rules for facility equipment and procedure organization" (Reissue), GOST 33216-2014 "Guidelines for the maintenance and care of laboratory animals. Rules for the housing and care of laboratory rodents and rabbits" (Reissue), and the Recommendations of the Board of the Eurasian Economic Commission no. 33 dated November 14, 2023, "Guidelines on working with laboratory (experimental) animals during preclinical (non-clinical) studies".

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Received: 03.06.2026.
Revised: 23.06.2026.
Accepted: 02.07.2026.

ВЛИЯНИЕ НЕЙРОПРОТЕКТОРА ИЗАТИНА НА ИНДУЦИРОВАННУЮ ГАЛОПЕРИДОЛОМ КАТАЛЕПСИЮ И ПРОТЕОМНЫЙ ПРОФИЛЬ МОЗГА МЫШЕЙ

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Изатин (индол-2,3-дион) — эндогенный регулятор, присутствующий в организме человека и животных. Благодаря способности взаимодействовать с многочисленными белками-мишенями, изатин демонстрирует широкий спектр биологической активности, в том числе проявляет нейропротекторное действие в моделях болезни Паркинсона (БП) у грызунов с использованием нейротоксинов МФТП (1-метил-4-фенил-1,2,3,6-тетрагидропиридина) и ротенона. Антипсихотический препарат галоперидол, нарушая баланс нейромедиаторов в нигростриатном пути, моделирует дефицит дофамина и способствует развитию двигательных нарушений, свойственных БП. В данной работе исследовали действие двух доз изатина (10 мг/кг и 80 мг/кг) на индуцированную галоперидолом каталепсию и на протеомный профиль мозга мышей. Предварительное введение изатина (за 1 ч до введения галоперидола) снижало выраженность галоперидоловой каталепсии. Введение галоперидола и изатина совместно с галоперидолом оказывало влияние на относительное содержание ряда белков, ассоциированных с БП и другими нейродегенеративными заболеваниями.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: изатин; нейропротектор; нейродегенерация; болезнь Паркинсона; галоперидол; мозг; протеомное профилирование

Финансирование. Работа выполнена в рамках Программы фундаментальных научных исследований в Российской Федерации на долгосрочный период (2021–2030 гг.) (№ 122030100170-5).

Поступила в редакцию: 03.06.2026; после доработки: 23.06.2026; принята к печати: 02.07.2026.