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Research Article

Novel mGluR4 agonist Rapitalam ameliorates motor dysfunction in mice with tau-associated neurodegeneration

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Abstract

Introduction: Tau protein is classically involved in the pathogenesis of a neurodegenerative processes, such as Parkinson's disease. This study was aimed at testing the novel mGluR4 selective agonist using it in transgenic mice with tau-associated neurodegeneration.

Materials and methods: Mice with Human P301S Tau hyperexpression were divided into 3 groups: Rapitalam 6 mg/kg and 20 mg/kg by gavage 3 times a week; and Control (Sham). The motor functions of animals were evaluated at 12th, 14th, 16th, 18th, and 20th weeks of life using the grip-test, rotarod and hanging wire test. In addition, the time of symptoms onset and death was recorded.

Research results: The use of Rapitalam at a dose of 6 mg/kg and 20 mg/kg significantly restored the holding impulse on a hanging wire, increasing it from 5.06±1.25 kg×sec to 6.42±0.97 kg×sec and 8.84±1.17 kg×sec, respectively. A similar trend was observed in the grip test: Rapitalam recovered grip strength from 28.43±5.04 N in the control group to 44.27±5.54 N (6 mg/kg) and 59.53±7.95 (20 mg/kg). Finally, the two-month use of Rapitalam neither delayed the manifestation of symptoms, nor increased the survival of mice.

Discussion: The cause of the loss of nerve cells in the mouse-tau line is autophagy. Apparently, Rapitalam is not able to simulate this process by reducing excitotoxicity, but against the background of the neurodegenerative process, it increases the activity of the nerve cells.

Conclusion: Rapitalam improves motor dysfunction in mice with tauopathy, with no effect on the survival of animals.

Keywords

Tau protein, neurodegeneration, Rapitalam, mGluR4, frontotemporal dementia, parkinsonism

Introduction

The dominant link in the pathogenesis of Parkinson's disease (PD) is an anti-toxic effect of specific protein aggregates, which contributes to synaptic dysfunction and axonal degeneration of the dopaminergic neurons of the black substance. Proteinopathy in PD combines this nosology with other conformotional diseases, including synucleopathies (Lewy's body disease, Multisys-

tem atrophy, and PD itself), taupathies (frontotemporal dementia, corticobasal degeneration, amyotrophic lateral sclerosis, parkinsonism, etc.), primary cerebral amyloidosis (Alzheimer's disease, prion diseases, etc.), and polyglutamine diseases (neurodegenerations caused by expansion of protein polyglutamine chains: Huntington's chorea, spinocerebellar ataxia, amyotrophic lateral sclerosis) (Ganguly et al. 2017).

Toxic aggregates in PD are eosinophilic deposits of abnormally folded fibrillar proteins (Lewy's bodies) (Jellinger 2018; Jellinger and Korczyn 2018). For the first time, pathological inclusions in PD were described by Konstantin Tretyakov in 1919 (Trétiakoff 1919). He found in the black substance corpuscles previously found in other areas of the brain by German-American neurologist Henry Lewy (Lewy 1912). These inclusions have become a pathologically defining feature of PD, but, as with other conformational diseases, the mechanism of formation of pathological aggregates has not been fully studied and is a combination of several processes, including aberrant inter-protein interactions (Olzscha et al. 2011), pathology of biomembrane (Butterfield and Lashuel 2010), and protein clearance disorders (Morimoto 2008). Lewy's bodies are formed from insoluble amyloid fibrils of the presynaptic α-synuclein protein, consisting of 140 amino acids (Lashuel et al. 2013).

Recently, however, evidence has been accumulated that in addition to α- synuclein, the Tau protein plays a significant role in the development of motor and cognitive disorders in PD and parkinsonism. Tau protein refers to cytoskeletal proteins and in humans is encoded by the MAPT gene located on chromosome 17q21 and containing 16 exons (Shaw-Smith et al. 2006; Furman et al. 2017; Guo et al. 2017). Tau plays a role in stabilizing microtubules, binding to the membrane, and regulating axonal transport (Gauthierkemper et al. 2011; Wang et al. 2017). Tau dissolves well in physiological conditions, but with changes in the isoforms or patterns of phosphorylation in pathological conditions, Tau proteins become insoluble and abnormally fold, causing damage to neurons and disruption of axonal transport (Alonso et al. 2001; Laurent et al. 2018). Abnormal coagulation, accumulation, and pathological aggregation of Tau are called "tauopathy" (Decker et al. 2016; Wang and Mandelkow 2016). Taupathy is the main cause of such a socially significant neurodegenerative process as Alzheimer's disease, but more and more information is being accumulated about the detection of pathological inclusions of the Tau protein in the black substance and other brain structures in PD (Arai et al. 2001; Armstrong and Cairns 2013; Jones et al. 2014; Holtzman et al. 2016). In addition, studies of genetic associations in Europeans with sporadic PD within GWAS confirmed that MAPT gene polymorphism is closely related to PD (Nalls et al. 2014; Kumaran and Cookson 2015).

There are six different Tau protein isoforms, and the differences between them are due to alternative splicing of the MAPT mRNA gene (Goedert et al. 1989). The domains responsible for binding to microtubules consist of several repeating sequences. The six isoforms are divided into two categories depending on the number of these repeats, namely 3R and 4R. The 3R Tau Isoform has three repeats, and 4R has four (Hogg et al. 2003). Each of the repeats is able to bind to microtubules, and the more repeats the protein contains, the more affinity it will have with them (Kumaran et al. 2007). Therefore, compared to 3R Tau, it is much easier for 4R Tau to bind and polymerize microtubules. Progressive supranuclear paralysis and cortical basal degeneration associated with PD are characterized by 4R Tau deposits in neurons and microglia (Flament et al. 1991). Also, patients suffering from X-linked parkinsonism syndrome were found to have severe 4R-tauopathy in the striated body (Poorkaj et al. 2010)

As mentioned, one of the main reasons for the accumulation and formation of Tau aggregates is the hyperphosphorylation of the molecule (Pascual et al. 2017; Barthélemy et al. 2020). Phosphorylation of the Tau protein affects its ability to bind to and stabilize microtubules (Chohan et al. 2005; Prokopovich et al. 2017). When Tau is hyperphosphorylated, the architectonics of microtubules is disrupted, which ultimately leads to disruption of their transport capacity. Disruption of transport function is especially significant for neuronal cells due to their high polarity and the importance of communication between different cell compartments. The body of a neuronal cell contains the nucleus, endoplasmic reticulum, Golgi apparatus, and lysosomes, which are the main sites of protein metabolism, whereas synapses specialize in releasing and re-capturing neurotransmitters. An extensive network of microtubules, which makes up the cell network of the cytoskeleton, connects two regions of the neuron, allowing for multidirectional movement of transport vesicles from the body to the axonal processes.

The Tau protein appears to be easily phosphorylated due to 85 potential phosphorylation sites, and 20 protinkinases have been characterized that may be associated with its phosphorylation (Duka et al. 2013). In the case of a healthy human brain, Tau protein contains only two or three phosphorylated amino acid residues, whereas in the neurodegenerative process, there are much more of them (Hanger et al. 2009). Additional studies show that the most likely mechanism underlying hyperphosphorylation is either an increase in protein kinase activity or a decrease in proteinphosphatase activity (Noble et al. 2011). In addition, the recent data show that abnormally folded Tau can move from cell to cell, via a prion-like mechanism, which also contributes to the formation of aggregates (Clavaguera et al. 2017).

This study is aimed at evaluating the effect of the new antiparkinsonian drug Rapitalam on the motor functions of mice with the 1137 C-->T mutation in the gene encoding the Tau protein. This mutation leads to the P301S amino acid substitution, and in humans is associated with the development of such an autosomal dominant neurodegenerative disease as frontotemporal dementia with parkinsonism-17 (LVDP-17) (Sperfeld et al. 1999). LVDP-17 is characterized by an impaired emotional and cognitive status, as well as extrapyramidal disorders in

the form of tremor, muscle rigidity, and bradykinesia (Hulette et al. 1999; Ghetti et al. 2015).

Transgenic mice with the Human P301S Tau mutation were first obtained under the guidance of Michel Goedert in 2002 (Allen et al. 2002; Hernandez et al. 2019). Four copies of the mutant gene were subcloned under thy1 promoter, resulting in a four-fold neuro-specific hyper-expression of the aberrant human Tau protein. At the age of 5–6 months, homozygous animals of this line develop a neurological phenotype, which is characterized by general muscle weakness, tremor, and severe paraparesis. Raised by the tail, mice cannot extend their hind limbs, and most animals also have eye inflammation.

In heterozygous mice, a similar phenotype develops at the age of 12–14 months. Immunohistochemical staining with antibodies to the phosphorylated Tau protein reveals a large number of immunopositive neurons in all areas of the brain, including the hypocampus, frontal and temporal cortex. The largest amount of mutant protein is found in the spinal cord and brain stem. The electron microscopy reveals a large number of pathological filaments in neurons, whose filaments have an approximate diameter of 5–15 nm, are randomly oriented and are not connected to the plasma membrane. Morphological studies in mice of this line show a decrease in the size and number of neurons, reactive astrocytosis, and de-innervation atrophy of muscle fibers (Allen et al. 2002).

Materials and methods

Evaluation of the effectiveness of Rapitalam on the Tau-associated neurodegeneration model

Animals

To study the effectiveness of Rapitalam as a tool for the prevention and treatment of motor Parkinson-like disorders in hereditary proteinopathy, 45 male mice with hyper-expression of the aberrant human Tau gene were used. Homozygous mice with the human P301S Tau mutation were used in the experiment at the age of 8 weeks. The animals were divided into 3 equal groups: 1) Rapitalam 10 mg/kg by gavage 3 times a week for 2 months; 2) Rapitalam 20 mg/kg by gavage 3 times a week for 3 months; 3) solubilizer (propylene glycol) in an equivalent volume 3 times a week for 3 months. As a control without pathology, 15 wild-type male C57BL/6J background mice were used. The experiment was conducted in compliance with the requirements of the Russian Federation Law 267 “On Protection of Animals from Cruel Treatment” of 24.06.1998, the rules of laboratory practice in preclinical studies in Russia (GOST 3 51000.3–96 and GOST P53434–2009) and The European Community Directive (86/609 EC).

Motor functions tests

All the tests aimed at evaluating the motor functions were performed at the same time of the day. The mice were kept under reverse light conditions in order to conduct a test during the maximum daily activity of both the animals and the researchers. The conditions of the working chambers, including temperature, illumination, and humidity, were standardized. Before the beginning of the tests, the animals underwent the procedure of handling and training to the working chambers. After working with each animal, all the surfaces were deodorized to reduce distractions. To identify the cumulative effect or the development of tolerance to the drug, the procedures aimed at evaluating motor functions were performed at the 12th, 14th, 16th, 18th, and 20th weeks of life.

Hanging wire test

The animals were carefully lifted by the tail and pulled to the middle of a metal wire 55 cm long and 2 mm thick, located at a height of 35 cm from the bedding below. After the animal grasped the middle of the wire with its forelimbs, the tail was released, the timer was started, and the holding impulse was evaluated (body weight in kg x latency of time to fall in seconds). Each animal was tested three times, with an interval of ≥ 60 seconds between the attempts. Then the arithmetic mean was calculated for each parameter (Aartsma-Rus and van Putten 2014) (Fig. 1).

Figure 1. General view of the animal during the “hanging wire” test. **Note:** the picture shows that the mouse is trying to pull up its hind legs and fix itself on the wire with four limbs or climb on it.

Evaluation of the grip strength

Each animal was lifted by the tail and placed with its four limbs on a rolling grid connected to a stationary electronic dynamometer, so that the mouse was placed with the rostral part of the body to the dynamometer, and the caudal part to the researcher. Then the animal was pulled by the tail towards the researcher until the animal's limbs "slip" off the bar of the rolling grid. The maximum tensile force (N) of the dynamometer was used as an integral parameter. Each animal was subjected to the described procedure three times, then calculating the arithmetic mean of the grip strength for three attempts (Aartsma-Rus and van Putten 2014) (Fig. 2).

Rotating rod test

To assess the level of movement coordination, the time of animals holding onto a rotating rod was estimated (Panlab, Spain). For that, mice were lifted by the tail and placed onto the rod (band width 50 mm, rod diameter 30 mm), set to rotate at a speed of 1 revolution per 8 seconds. Along with that, the latency time we recorded from the beginning of the movement to the fall of the animal (Ayton et al. 2013), and the arithmetic average of the holding time on the rod from the three best attempts out of 6 was evaluated (Bruch et al. 2017). Previously, the animals had been trained to walk on a drum, leaving them on the working surface of the rod, rotating at a speed of 1 revolution per 15 seconds, five times for 1 minute a day for 5 days.

Time of the disease manifestation and death

For bioethical reasons, when developing severe paresis, the animals were euthanized by an overdose of anesthesia. To assess the effect of Rapitalam on the rate of disease manifestation, the dates of euthanasia or natural death of each animal were recorded, and after comparison with the dates of birth, a Kaplan-Meyer curve was constructed. To reduce the amount of censored data, wild animals were not included in the analysis. Statistical differences between the groups were determined in pairs using the Cox F-test.

Research result

Hanging wire test

When performing the hanging-wire test, mice with the Human p301s Tau mutation are prone to a distinct de-

Figure 2. General view of the animal in the working chamber when determining the grip strength.

terioration in the motor functions. It was found that after the 16th week of life, transgenic animals by the 20th week of life showed more than a twofold decrease in the holding impulse (Table 1, Fig. 1). At the same time, the use of Rapitalam at a dose of 6 mg/kg statistically significantly restored this indicator from 5.06±1.25 kg×sec to 6.42±0.97 kg×sec. The use of Rapitalam at a dose of 20 mg/kg increased this indicator to 8.84±1.17 kg×sec, which was statistically significantly higher than not only the same indicator of the control group, but also that of the group with the use of Rapitalam at a dose of 6 mg/kg (Table 1, Fig. 3), which indicates the dose-dependent nature of the pharmacological effect.

Thus, the hanging-wire test showed that Rapitalam at doses of 6 mg/kg and 20 mg/kg dose-dependently improves motor functions, partially restoring muscle endurance and the ability of mice to perform complex non-stereotypical movements.

Determination of the grip strength

When determining the grip strength using a rolling grid connected to a dynamometer, there was a similar trend as in the previous test towards a distinct decrease in neuromuscular control of the fingers of the forelimbs and hind limbs from the 12th to the 20th week, which was manifested by a more than three-fold decrease in the grip strength by 20th week in the control group of animals. Against the background of the use of Rapitalam at a dose of 6 mg/kg, this process was slowed down, which led to the restoration of the grip strength to 44.27±5.54 N compared to 28.43±5.04 N in the control. Similarly to the previous block, an increase in a Rapitalam dose to 20 mg/kg resulted in a statistically significant increase in the effect (Table 2, Fig. 4).

Rotating-rod test

The rotating-rod test had less representative results than the previous study blocks in mice with the Human p301s Tau mutation. So, the test confirmed a progressive loss of coordination and ability to balance in transgenic animals, but the use of Rapitalam led to a statistically significant increase in the holding time on the rotating rod only at the 20th week and only in the group with a higher dose of the drug. However, despite the lack of statistically reliable re-

Table 1. The Effect of Rapitalam on the Holding Impulse that Characterizes the Motor Functions of Animals When Tested at the 12th, 14th, 16th, 18th and 20th weeks of life (M±m).

Group	Ratio of the holding impulse (grams×sec/100)				
	12 weeks	14 weeks	16 weeks	18 weeks	20 weeks
Wild type	13.96±0.31	17.49±0.36	17.06±0.41*	16.92±0.45*	17.14±0.71*
Control	12.72±0.18	17.07±0.50	13.81±0.37	9.22±1.30	5.06±1.25
Rapitalam 6 mg/kg	12.87±0.45	16.77±0.53	14.58±0.63*	11.43±1.05*	6.42±0.97*
Rapitalam 20 mg/kg	12.51±0.35	16.94±0.41	15.77±0.42*#	12.73±1.27*#	8.84±1.17*#

Note: * – p<0.05 when compared with the control group; # – p<0.05 when compared with the Rapitalam 6 mg/kg" group.

Table 2. The Effect of Rapitalam on the Holding Impulse Coefficient that Characterizes the Motor Functions of Animals WhenTested at the 12th, 14th, 16th, 18th and 20th weeks of life (M±m).

Group	Grip strength (H)				
	12 weeks	14 weeks	16 weeks	18 weeks	20 weeks±
Wild type	106,73±4.57	119.33±5.44	111.27±5.17*	114.47±4.13*	119.33±5.85*
Control	103.60±5.68	113.53±4.48	84.73±3.41	73.00±4.66	28.43±5.04
Rapitalam 6 mg/kg	105.07±4.16	114.73±5.45	90.07±5.79	74.27±5.91	44.27±5.54*
Rapitalam 20 mg/kg	106.87±5.08	115.40±4.65	99.47±5.88*#	91.60±4.73*#	59.53±7.95*#

Note: * – p<0.05 when compared with the control group; # – p<0.05 when compared with the Rapitalam 6 mg/kg group.

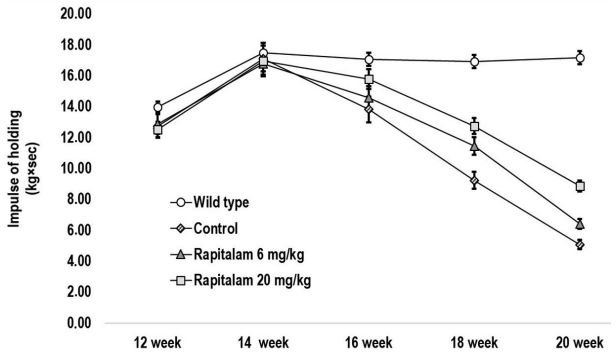

Figure 3. Effect of Rapitalam on the dynamics of the holding impulse coefficient in mice from the 12th to the 20th week of life.

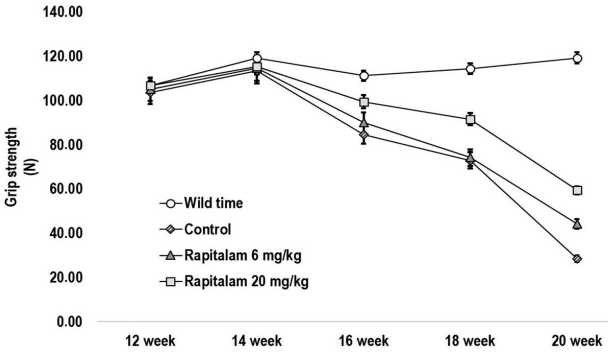

Figure 4. Influence of Rapitalam on the dynamics of grip strength from the 12th to the 20th week of life.

Table 3. Effect of Rapitalam on the Holding Time on a Rotating Rod When Tested at the 12th, 14th, 16th, 18th, and 20th weeks of life (M±m).

Group	Holding time on the rotating rod (seconds)				
	12 weeks	14 weeks	16 weeks	18 weeks	20 weeks ±
Wild Type	140.60±24.06*	149.27±28.46*	145.07±27.69*	144.67±17.66*	139.67±20.17*
Control	136.07±24.90	124.47±13.58	125.07±14.60	86.60±12.08	68.36±10.93
Rapitalam 6 mg/kg	127.87±26.72	121.80±11.64	119.27±12.38	102.00±20.58	80.33±16.06
Rapitalam 20 mg/kg	124.60±23.48	117.00±10.79	116.87±12.47	100.33±16.55	85.27±9.47*

Note: * – p<0.05 when compared with the control group; # – p<0.05 when compared with the Rapitalam 6 mg/kg group.

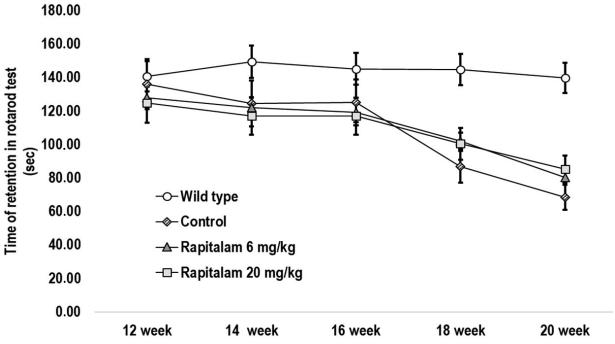

Figure 5. Influence of Rapitalam on the dynamics of the ability to stay on a rotating rod from the 12th to the 20th week of life.

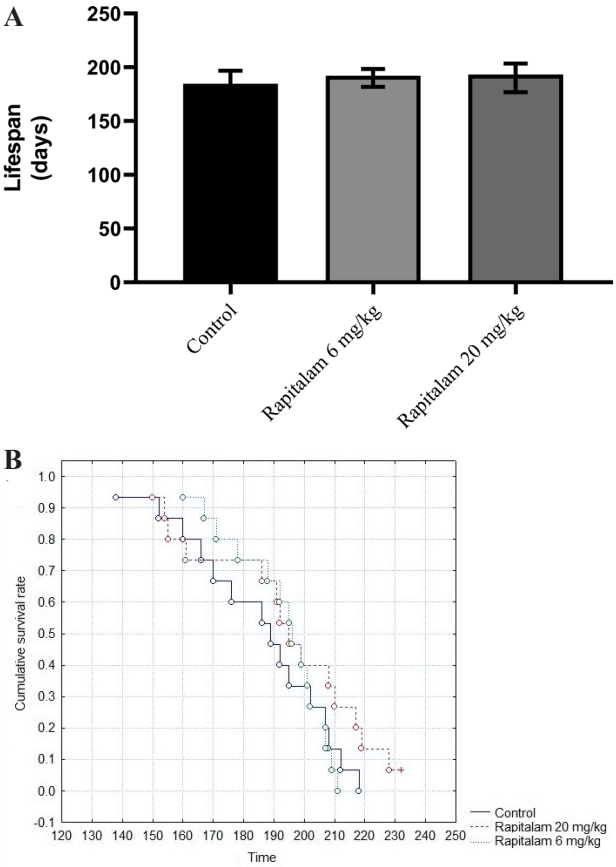

Figure 6. Effect of the course use of Rapitalam at doses of 6 and 20 mg/kg 3 times a week for 3 months on the time of disease manifestation and death of animals. **Note: A)** average time of death or disease manifestation; **B)** the Kaplan-Meyer Curve, which characterizes the survival function.

sults, when studying the data obtained in the groups using the drug, there was an obvious tendency to normalize the indicator at weeks 18 and 20 (Table 3, Fig. 5).

Thus, Rapitalam at doses of 6 and 20 mg/kg demonstrated low efficiency when conducting the rotating rod test, or rather the test itself has a low sensitivity to changes in motor skills associated with the effects of the drug.

Time of the disease manifestation and death

The obtained results demonstrate that the course use of Rapitalam at doses of 6 and 20 mg/kg 3 times a week for 3 months does not have a statistically significant effect on animal mortality (Fig. 6) when comparing groups by the Cox F-criterion. So, in the control group, the average age of death was 184.73 ±23.72 days, in the groups using Rapitalam at doses of 6 and 20 mg/kg –192.20±16.16 and 193.13±27.31 days, respectively (Fig. 6).

Discussion

Rapitalam is a selective mGluR4 receptor agonist. mGluR4 is involved in the presynaptic regulation of the synthesis and release of glutamate in the pale globe and the black substance. It is known that the basis of the Parkinson's tremor is an increased stimulating effects of the pale globe and the black substance on the thalamus. Activation of mGluR4 receptors in these structures leads to the elimination of imbalance between the inhibitory and excitatory pathways by enhancing GABA-ergic inhibition. Our previous studies showed that Rapitalam has a pronounced antiparkinsonian activity on the model of oxotremorin-induced tremor in rats (Avdeeva 2019).

In addition, Rapitalam demonstrated a significant neuroprotective activity in a model of the global brain ischemia in rats (Avdeeva et al. 2019).

This present study shows that Rapitalam at doses of 6 and 20 mg/kg 3 times a week for 3 months contributes to a marked improvement in motor functions in the mouse model of Tau-associated degeneration, but does not lead to a statistically significant increase in the life expectancy of animals. These results can be explained by the fact that by increasing the compensatory capacity of neurons in the basal ganglia and motor cortex by targeting mGluR4 receptors, Rapitalam does not affect the main link of the pathological process – neuronal degeneration due to mitochondrial dysfunction and axonal transport disorders. It is known that in the Human P301S Tau mouse line, neuronal death occurs without the participation of apoptosis: with an almost two-fold decrease in the number of motor neurons in this line, there is neither apoptosis-specific DNA fragmentation in neurons, nor the activation

of caspase-3 (Allen et al. 2002). The most likely cause of the loss of nerve cells in this mutation is autophagy of neurons. Apparently, Rapitalam cannot simulate this process by reducing calcium excitotoxicity or due to its other effects, but against the background of the neurodegenerative process, Rapitalam increases the functional activity of the surviving nerve cells.

Conclusion

This study confirmed that a selective mGluR4 receptor agonist improves motor dysfunction in mice with taupathy. Despite the fact that Rapitalam had no statistically significant effect on animal survival, the results obtained indicate that this drug can affect the pathogenetic cascades of neuronal damage in the toxic effect of pathological aggregates of abnormally folded proteins. This activity allows recommending this drug for further studies of antiparkinsonian and neuroprotective effects.

Conflict of interest

The author declare no conflict of interest.

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