Short Communication

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2019.22.003724

Experimental Autoimmune Encephalomyelitis: Corrective Properties of Metabolic Therapy

Irina V Okunevich*

Department of Neuropharmacology of Federal State Budgetary Scientific Institution, Institute of Experimental Medicine, Russia

***Corresponding author:** Irina V Okunevich, Institute of Experimental Medicine, Department of Neuropharmacology of Federal State Budgetary Scientific Institution, 197376 St. Petersburg, Russia

ARTICLE INFO

Received: October 18, 2019

Published: October 23, 2019

Citation: Irina V Okunevich, Experimental Autoimmune Encephalomyelitis: Corrective Properties of Metabolic Therapy. Biomed J Sci & Tech Res 22(2)-2019. BJSTR. MS.ID.003724.

Keywords: Multiple Sclerosis; Experimental Autoimmune Encephalomyelitis; Corrective Properties; Protective Action; Antioxidant Triafen

ABSTRACT

A pronounced neuroprotective and immune-modulating effects of the new drug Triafen (Trf), which corrects the manifestations of Experimental Autoimmune Encephalomyelitis (EAE) on an adequate model of severe comorbid disease - Multiple Sclerosis (MS), was established. The synthetic drug Trf was obtained in a more optimized way and is a structural analogue of the effective antioxidant Hypoxen that is widely applied in urgent medicine of Russia as a metabolic corrector of hypoxia. In present investigation Trf was used for chronic administration to guinea pigs for 35 days, orally at a dose of 50 mg/kg. The EAE model was created by immunizing 75 adult animals with an encephalitic mixture in Freund's complete adjuvant. We studied mortality, a number of immunological parameters, the clinical picture of neurological complications and the severity of Central Nervous System (CNS) damage in experimental and control guinea pigs. In the experiments, a significant decrease in mortality and a pronounced protective effect of the drug Trf on neurological symptoms in experienced guinea pigs was shown. The positive effect of Trf on the migration activity of leukocytes and antibodies was found, and its ability to reduce the content of lipid peroxidation products in the blood was also noted.

Introduction

It is known that Multiple Sclerosis (MS) is an organic heterogeneous disease with the progressive complex symptoms and multifocal lesions of conducting neural pathways, triggers of which are environmental factors. The main therapy of MS patients is aimed at stopping the autoimmune inflammatory process by immune modulating and anti-inflammatory drugs, since it is destructive damage to the myelin sheaths of the nerve fibers by the own immune system that leads to the development of neurological complications in young people [1]. The multiplicity of regimens of MS dictates the need to further search for new approaches to the pharmacological correction of this disease. Due to the activation of oxidative stress in the complex therapy of MS, the use of multifunctional drugs with protective and antioxidant effects is justified. Earlier, in an experiment we detected anti-inflammatory activity in an antihypoxant and an antioxidant Hypoxen that is widely applied in Russian medical practice as a metabolic corrector in urgent conditions (cardiogenic shock, blood loss, myocardial infarction and others) [2,3]. In this paper, we studied another active synthetic compound - Triafen (Trf) - a new formulation of the Hypoxen preparation, obtained in a modern synthetic optimized way.

Aim of the Present Study

The main target was to identify the ability of antioxidant Trf to influence the severity of immunological and neurological disorders in the course of MS modeling.

Materials and Methods

The experiments were conducted in 120 adult male guinea pigs (with initial body mass 300-350 g) obtained from the science nursery "Rappolovo" (Leningrad region).The model of experimental autoimmune encephalitis (EAE) was used as the most adequate method of MS reproduction, which allows studying pathological processes in the CNS. EAE was caused by a single subcutaneous inoculation into the paw pads of guinea pigs of an encephalitogenic mixture - the main myelin protein from the spinal cord of a bull, in

complete Freund's adjuvant. A few days later the animals developed T-lymphocytic infiltration of the brain, demyelination of the nerve endings occurred, and paralysis occurred. The drug being studied Trf was orally administered with a probe at a dose of 50 mg/kg daily for 35 days, starting from the 2nd day after immunization. The experiments were carried out in two series of 75 adult male guinea pigs (with final body mass 350-370 g). In the first series, in 2 experimental groups of 15 animals in 30 guinea pigs, mortality was determined after the administration of an inducing sensitizing agent and the protective effect of Trf was evaluated.

In the second series of experiments, a study was conducted on the effectiveness of the drug Trf on 45 guinea pigs, which were divided into 3 groups of 15 individuals: 1-intact, 2 - the pathological model (EAE), 3 - EAE + Trf. The severity of the disease was assessed by Clinical Index (CI) in points from 0 to 6 by the presence of paresis and paralysis in animals. Neurological symptoms and the state of the nerve endings of the peripheral and central parts of the central nervous system were studied visually and morphologically in experimental animals. After immunization, blood samples were taken from guinea pigs five times for testing for antibodies against myelin basic protein. The migration activity of peripheral blood leukocytes and the reaction of inhibition of leukocyte migration were evaluated after incubation of heparinized blood at 37°C for 24 hours. At the end of the experiment, guinea pigs were removed from the experiment by rapid decapitation. In the serum of animals, the content of lipid oxidative products - diene conjugates and malonic dialdehyde (MDA) was studied. Statistical data processing was performed using univariate analysis ANOVA test, at $p < 0.05$.

Results and Discussion

In the first series of experiments, a single injection of the immunizing mixture caused the sickness rate in 100% of the guinea pigs of the control group (EAE). This led to the appearance of characteristic neurological symptoms in these animals in the form of ataxia, motor paresis and paralysis, pelvic organ disorders, cerebellar disorders. The clinical index at the peak of the disease was 4.6 points, the cumulative index of 53.1%, which characterized the course of EAE in this experience as severe. Mortality in the control group (EAE) was 30%. In the group of animals receiving an additional drug Trf, only 6.6% of the animals died. In the second series of experiments, as a result of chronic administration of the test substance, in the group of guinea pigs (EAE + Trf), only 5 individuals showed clinical signs of damage. The number of limb paralysis was 73.5% lower than in the group with pathology. It is important to emphasize that in 10 guinea pigs (66.5%) of the group receiving the study drug, there were no neurological disorders at all.

For pathological changes in the central nervous system in the control group of animals (EAE) was characterized by demyelination of the nerves, most pronounced in the spinal cord and, especially, in the lumbosacral region. Inflammatory infiltration consisted mainly of monocytes and lymphocytes in the lumbosacral spinal cord and in the interior of the white matter of the brain. It is interesting to note that in animals receiving Trf, the greatest safety of the myelin sheaths of neurons was found. In the group of animals treated with Trf, the frequency of detection of circulating complexes was the smallest, and the peak production of antibodies fell on the 21st day. The size of the migration zones of immunocompetent cells prevailed in the pathological group (EAE). The results obtained indicate the available immune-protective ability Trf. When analyzing the peripheral blood of experimental guinea pigs, an increase of 2.5 times the accumulation of MDA products and diene conjugates in the serum (group 2) compared with intact animals (group 1) and a significant decrease in their content in the EAE+Trf group of experimental animals. These results demonstrate and confirm the presence of antioxidant action of Trf.

Findings

1) In the Triafen+ EAE experimental group there were more surviving healthy guinea pigs and individuals with a minimum of neurological disorders and degenerative damage. The degree and size of the migration zones of immunocompetent cells were minimal. Thus, it was shown the presence of low toxicity, the protective immuno-neurological and anti-inflammatory effects of Trf.

2) A 29% decrease in the content of lipid peroxides - diene conjugates and a 30% concentration of malondialdehyde (MDA) in the serum of guinea pigs with Trf in comparison with animals without treatment was found. The results indicate the ability of Triafen to reduce the degree of development of lipid peroxidation processes in modeling multiple sclerosis.

3) We assume that the corrective action of the drug Triafen is not only due to a decrease in the degree of oxidative stress and a decrease in the level of peroxide products, but it is based on the anti-hypoxic and anti-inflammatory effect of the studied drug, which is present in Triafen as an active analogue of the drug Hypoxen.

4) The pronounced inhibition of the exponent of development of autoimmune encephalomyelitis under the influence of antioxidant Triafen, found in these experiments, when modeling Multiple Sclerosis without disturbing the protective functions of the immune system, expands our understanding of its pharmacological activity as polytropic drug of metabolic type of action.

Conclusion

The obtained protective corrective effects of antioxidant Triafen (Trf) are similar in action to statins - known lipid-lowering and anti-atherosclerotic drugs. Statins in the experiment suppress adhesion molecules, slow down the proliferation of T- and B-lymphocytes. In EAE model in mice, they can inhibit the

development of paralysis of the limbs. In addition, statins have anti-inflammatory and neuro-protective effect, slowing down the degeneration of oligodendrocyte precursors. It is well-known that immuno-pathological process in Multiple Sclerosis is complex in nature and course, autoimmune reactions cause an inflammatory process and lead to diffuse degenerative changes in axons and neuron death, an excessive concentration of reactive oxygen forms and oxidative products occur, so targeted specific complex therapy is necessary. In this case, the application of pharmacological agents with antioxidant, anti-hypoxic and anti-inflammatory activity [2,3] in the complex therapy of Multiple Sclerosis (MS) can be very useful. We suppose and believe that further development of new multifunctional drugs as antioxidants for the treatment of Multiple Sclerosis with minimal side effects is necessary to use and has prospects in clinical practice.

References

1. Sternberg Z (2016) Promoting sympathovagal balance in multiple sclerosis; pharmacological, non-pharmacological, and surgical strategies. Autoimmunity Reviews 5(6): 113-123.
2. Khnychenko LK, Okunevich IV (2015) Experimental assessment of inflammatory effect of Hypoxen. Reviews on clinical pharmacology and drug therapy 13(3): 35-38.
3. Shabanov PD, Zarubina IV, Novikov VE, Tzygan VN (2010) Metabolic correctors of hypoxia. – St.-Petersburg: Inform-Navigator pp. 912.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2019.22.003724

Irina V Okunevich. Biomed J Sci & Tech Res