



EDITORIAL

Protective potential of NeuroEPO: there is still a lot to be explored

Potencial protector de la NeuroEPO: queda aún mucho por explorar

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How to cite this article

Fernández Peña G, Pérez Hernández CL, Fernández Romero T. Protective potential of NeuroEPO: there is still a lot to be explored. Rev haban cienc méd [Internet]. 2022 [cited]; 21(4):e5000. Available from: <http://www.revhabanera.sld.cu/index.php/rhab/article/view/5000>

Received: July 15, 2022
Approved: July 25, 2022

Erythropoietin (EPO) is a glycoprotein whose most recognized function is the regulation of erythropoiesis. EPO binds to receptors on erythroid progenitor cells and promotes survival, proliferation, and differentiation into mature erythrocytes.⁽¹⁾ For decades, human recombinant erythropoietin (rhuEPO) replacement therapy has changed the course of anemia secondary to chronic kidney disease. However, the current interest of the scientific community in EPO is not focused on its hematopoietic function.

Beyond the kidney and the liver, expression of EPO and its receptor has been detected in the brain, lung, vascular endothelium, heart muscle, skeletal muscle, and adipose tissue, among others. There is evidence that under conditions of hypoxia, trauma or inflammation, the local production of EPO is essential for the protection and repair of the injured tissue; EPO has been reported to exhibit antioxidant, anti-inflammatory, angiogenic, antiapoptotic, and immunomodulatory activity, which supports its cytoprotective effects.^(1,2)

The availability of rhuEPO has facilitated the discovery of the non-hematopoietic functions of EPO and has stimulated its evaluation as a therapeutic candidate for several alterations of the central nervous system and the cardiovascular system, among others. However, the clinical use of rhuEPO as a cytoprotector has been limited in part by the stimulation of erythropoiesis, so variants that preserve cytoprotective effects without hematopoietic effects have been developed.⁽²⁾

There are variants of EPO with low sialic acid content that have a greater hepatic clearance and shorter half-life in blood. Consequently, these variants loss the hematopoietic effect but preserve the cytoprotective effect.⁽²⁾ Among these hyposialic variants is NeuroEPO, produced by the Center for Molecular Immunology (CIM), Havana, Cuba, which has demonstrated to exert neuroprotective effects in pre-clinical and clinical studies.

In *in vitro* studies of glutamate-induced neuronal damage, the treatment with NeuroEPO decreased apoptosis with reduction of oxidative stress, restoration of the Bcl-2/Bax ratio and inhibition of caspase activation.^(3,4) In the same way, *in vivo* preclinical studies have shown neuroprotective effects of NeuroEPO; in models of Alzheimer's disease, it decreased memory alterations, oxidative stress, neuroinflammation and apoptosis,^(5,6) and in models of cerebral ischemia, it reduced mortality and favored sensory and motor function, with decreased neuronal death and areas of injury.^(7,8,9)



The neuroprotective effects of NeuroEPO have also been evaluated in clinical trials with favorable results. In a randomized Phase I clinical trial in healthy volunteers, the administration of NeuroEPO was shown to be safe and well tolerated.⁽¹⁰⁾ In patients with Parkinson's disease, NeuroEPO was well tolerated⁽¹¹⁾ and improved the cognitive sphere,^(12,13) as evidenced by the electroencephalogram.⁽¹⁴⁾ In patients with spino-cerebellar ataxia type 2, NeuroEPO was well tolerated for six months, with a reduction in the clinical manifestations of motor and cognitive alterations.⁽¹⁵⁾ In mild to moderate Alzheimer's disease there is evidence of clinical improvement in patients receiving NeuroEPO.⁽¹⁶⁾

Among the researchers who have participated in the evaluation of the neuroprotective effect of NeuroEPO are professors from the Institute of Basic and Preclinical Sciences "Victoria de Girón" (ICBP) of the University of Medical Sciences of Havana. One of its results was recently published, under the title "*Intranasal administration of NeuroEPO does not affect the structure of respiratory mucosa in Wistar rats*".⁽¹⁷⁾ In the article, Suárez Borrás *et al.* report that intranasal administration of 300 µg/kg of NeuroEPO for 28 days to Wistar rats does not produce changes in the histological structure of the respiratory mucosa or in the lymphatic tissue associated with the nasal mucosa.

On the other hand, evidence has promoted an increase in research on the benefits of EPO in diabetes mellitus. In this sense, for several years our research group of the Department of Biochemistry of this Institution has evaluated the potential cytoprotective role of NeuroEPO in this metabolic disorder.

In a result of our research,⁽¹⁸⁾ a hypoglycemic effect of NeuroEPO was reported in rats with streptozotocin-induced diabetes, following administration of a single dose of 0,5 mg/kg subcutaneously. The benefits in glucose homeostasis were related to an insulinotropic mechanism, which also shows synergism with the action of insulin in the treatment of hyperglycemia.

Another article published recently with the title "*Protective effect of NeuroEPO on the reproduction of diabetic rats*",⁽¹⁹⁾ in which the results of the administration of NeuroEPO to pregnant diabetic rats are shown. Three dose levels were evaluated, on alternate days, for a total of six doses. The study shows that the lowest dose used, 0,5 mg/kg, not only reduced hyperglycemia, which confirms the hypoglycemic effect of NeuroEPO, but also decreased gestational losses, evidencing a beneficial effect on the reproduction of diabetic rats.

Currently, our group continues to delve into the influence of NeuroEPO on glucose homeostasis, metabolic control and complications in diabetic rats, as well as the mechanisms involved. The potential of NeuroEPO as cytoprotector opens up new research perspectives on the benefits that this product of Cuban biotechnology could offer, not only in conditions of the nervous system and diabetes mellitus, but also in other diseases.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Authors' contributions

All authors participated in the writing-original draft, as well as writing-review and editing, and have read, reviewed, and approved the final version of the article.