

Point of View about Erythropoietin in Treatment of Central Nervous System Diseases

Liu-Zhu Yang^{1,2,#}, Rui-Long Li^{2,#}, Bo Wu¹, Jin Luo², Zhong Chen^{1,#}, Xin-Ping and Yan³ and Wei Tan⁴

¹Department of Orthopedics, Southern Medical University, Zhujiang Hospital, Guangzhou, Guangdong, China

²Department of Orthopedics, Hezhou city people's hospital, Hezhou, Guangxi, China

³Department of Orthopedics, The Chinese people's liberation army 175 hospital, Zhangzhou, Fujian, China

⁴Department of Orthopedics, The third people's hospital of Huizhou, Affiliated Huizhou hospital of Guangzhou Medical University, Huizhou, Guangdong, China

#Equally contributed

Abstract

Spinal Cord Injury (SCI) is a complex process which leads to destruction of neuronal tissue and also vascular structure. Recent many studies have shown erythropoietin (EPO) has neuro-protective effects in acute SCI animal models. Alzheimer's disease (AD), Parkinson's disease (PD) and SCI belong to central nervous system diseases, a few studies also indicated that EPO may be effective for AD and PD. In this a short review article, we provide a short overview of the animal and human studies on rEPO in SCI, AD and PD. Further clinical studies should reveal whether derivatives and variants of EPO provide any benefits over the clinical application EPO to against SCI, AD and PD in the experimental studies.

Keywords: Erythropoietin; Spinal cord injury; Alzheimer's disease; Parkinson's disease

Many previous studies have shown that erythropoietin (EPO) inhibits oxidative stress and glutamate release [1,2], regulates inflammation [3], decreases lipid peroxidation [2] and increases blood flow and tissue oxygenation [4] and nitric oxide production [5,6] in various animal models. EPO is a glycoprotein cytokine which is produced mainly by the fetal liver and adult kidney and involved in regulation of red blood cell production. EPO exerts its effects through interaction with EPO receptor (EPO-R), which belongs to the type I family of single-transmembrane cytokine receptors [7]. The expression of EPO and EPO-R was observed in the brain and spinal cord after injury and regulated by tissue hypoxia [8-10]. In addition, proinflammatory cytokines also induce EPO-R expression, but restrain endogenous EPO production [10]. So it means that the high expression of EPO-R was immediately induced after central nervous system injury, whereas endogenous EPO expression is inhibited. A previous study found that EPO can enhance differentiation of neural progenitor cells expressing a high level of EPO-R toward the oligodendrocyte-lineage cells, through activation of cyclin E and Janus kinase 2 pathways [11]. So it is possible that high expression of EPO-R provides an opportunity for application of exogenous EPO to against central nervous system diseases. Nerve growth factor (NGF) and platelet-derived growth factor (PDGF)-B act as protective agents through rescuing neuronal cells after injury of specific neuronal pathways [12]. The recent studies shown that administration of EPO can repair injured tissue and recovers neurological by increasing expression of NGF and (PDGF)-B [13,14].

Spinal Cord Injury (SCI) is a catastrophic sudden and devastating event associated with high mortality and morbidity and high social and economic burden. The pathogenesis of SCI is a very complex process which causes destruction of neuronal tissue and vascular structure. Currently, researchers usually divided the pathogenesis of SCI into two phases including the acute and secondary phase. The acute phase is caused by direct disruption of tissues which cause limited neuronal death surrounding the lesion epicenter and damage to axons and blood vessels at the site of injury that results in vasoconstriction, hemorrhage and ischemia [15]. The secondary phase usually involves a cascade of secondary damage, including fluid-electrolyte imbalance, regional blood flow alterations, glutamate-induced excitotoxicity, free radical generation,

proinflammatory cytokine production, etc. These pathogenesis changes finally lead to neurons injury or death. There is no a good therapeutic method for patients with SCI to date. Over the past few decades, methylprednisolone (MP) has been regarded as the first choice and only available treatment for SCI patients and must be given to patients within 8 h after injury. Currently, MP is no longer the standard of care and merely a treatment option or in some medical centers, abandoned altogether due to possible non-ignored severe side effects of high doses of MP [16]. The extensive studies have reported EPO has neuro-protective effects in animal models with acute SCI [15,17-25]. Our previous study also got a similar result [26]. However, the animals are very different from human, many studies have got good results in animal models, but it may not be effective for patients. Does EPO show the neuroprotective effects for patients with acute SCI? Recently, a few studies have reported the results of EPO treatment of acute SCI in the clinic. In 2011, a retrospective study suggested that EPO can provide the neuroprotective against acute SCI and no complications are observed [27]. In this study, 27 patients with acute SCI received EPO and MP and 36 patients with acute SCI got treatment with MP within 2 h after injury, the patients got EPO 1000U/per via intramuscular injection, three times per week (at the 2nd, 4th and 6th day) and treated for 8 weeks consecutively [27]. MP was given to the patients according to the NASCIS III protocol [28], this study also shown that EPO combined with MP could be better improved neurological function [27]. A previous case report also shown EPO has neuroprotective effect in post-operation cervical SCI. In this case report, patient got Darbepoetin alpha (a long-action EPO derivate) 100 mcg, subcutaneous daily for three times at seven days after trauma and no complications were found [29]. In addition, a single-blind randomized

*Corresponding author: Zhong Chen, Department of Orthopedics, Southern Medical University, Zhujiang Hospital, Guangzhou, Guangdong, China, Tel: +86-15778448908; E-mail: czjkd2013@sina.com

Received March 27, 2017; Accepted April 12, 2017; Published April 19, 2017

Citation: Yang LZ, Li RL, Wu B, Luo J, Chen Z, et al. (2017) Point of View about Erythropoietin in Treatment of Central Nervous System Diseases. J Alzheimers Dis Parkinsonism 7: 320. doi: 10.4172/2161-0460.1000320

Copyright: © 2017 Yang LZ, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

trial study was performed by Costa et al. [30], they assessed the superiority of EPO versus MP in improving clinical outcome of acute SCI, a total of 19 patients were conducted: 8 patients who got MP treatment according to the NASCIS III protocol [28] were randomized to MP and 11 received EPO iv (500 U/kg, repeated at 24 and 48 h) to EPO and all patients got drugs treatment 8 h after injury. Their data shown EPO can promote neural functional recovery. Moreover, no patients experienced serious adverse effects [30]. However, Alibai et al. [31] reported a contrary result with the previous [30], in their study, 20 patients with acute traumatic cervical SCI less than 8 h after injury were included and all the patients received standard regimen of MP [28], then patients were randomly divided into EPO and placebo group, 14 patients from EPO group received EPO in a dosage of 500 U/kg as bolus dose followed by another 500 UI/kg administered 24 h after the first dose and 6 patients received injection of placebo (normal saline) in two same intervals. They study suggested that administration of EPO cannot improve behavioral outcomes of patients with traumatic cervical SCI and no participants experienced serious adverse effects [31]. There are main four points different between two studies: (a) In the first study, SCI patients from experiment group receive EPO three times (repeated at 24 and 48 h), but in the second study SCI patients only receive EPO two times (repeated at 24 h). Acute SCI patients get EPO frequency that may affect the final clinical results. It is well-known that frequency of drugs given to patients are very important to gain good clinical results; b) Patients with traumatic cervical or thoracic SCI and grade A or B of the American Spinal Cord Injury Association Impairment Scale are conducted in the first study, while only patients with cervical SCI are studied in the second study. The degree and location of SCI determine the extent and future outlook of SCI patients; (c) SCI patients in the experiment group from the first study only receive EPO treatment and control group get MP treatment, while SCI patients from experiment group receive EPO and MP treatment and control group get MP treatment in the second study. EPO combined MP whether better promote neural functional recovery as compared to single EPO or MP treatment, it need more studies to prove that conclusion. In addition to previous reasons, the sample size of those two studies are too small, it may also cause the inconsistent results of those two studies. The neuroprotective effects of EPO for patients with acute SCI are controversial, so further clinical researches are necessary. Currently, our team is also assessing the neuroprotective effects of EPO in the clinical setting.

Alzheimer's disease (AD) is the progressive neurodegenerative disease of aging which is characterized by progressive memory loss and decline cognitive dysfunction and it is the most frequent form of dementia [32,33]. The common symptoms of AD include progressive cognitive decline, irreversible memory loss, disorientation, language impairment, and emotional instability [34]. AD is becoming a growing problem around the world with a rapidly aging population in the developed world and increasing life expectancy in the developing world [35-37]. Recent report shows it affects approximately 35,000,000 people all over the world and 5,000,000 new cases are increased every year [34]. This disease is a serious threat to the old people and next only to heart disease, cancer and stroke in the cause of death in the elderly. Currently, there are no effective therapies against AD due to complex disease etiology and unclear pathological mechanism. It is well-known that amyloid beta ($A\beta$) is a key molecule in AD and it is critical to develop a treatment that can arrest the $A\beta$ -induced pathologic progression of AD. Li et al. [38] study suggested that mice treated EPO (1000 U/kg) attenuated $A\beta$ 42-induced cognitive deficits and tau hyperphosphorylation at multiple AD-related sites through the regulation of glycogen synthase kinase- β and the $A\beta$ 42-induced mitochondrial dysfunction and apoptosis in

brain. To the best of our knowledge, no literatures report about EPO treatment of AD patients. In the future studies, researchers should try to apply EPO into treatment of AD patients.

Parkinson's disease (PD) is a common neurodegenerative disease with complex clinical features [39]. The main symptoms of PD include bradykinesia, tremor and postural instability [40] and can severely affect quality of patients' life. It is well-known that the serious degeneration of the dopamine (DA) neurons in substantia nigra pars compacta is key to cause PD [41-44]. The traditional therapies for PD are only based on DA-enhancing strategies which provide symptomatic relief during the disease's early stages, but it can't improve neural functions. Moreover, patients with PD need be a long term medication. Thus, preventing apoptosis of the striatal DA neurons is critical to cure PD. Currently, EPO has been regard as a potential therapeutic candidate for treatment of PD due to its neuroprotective effects [14,17-26]. Some preclinical studies has been done in order to observe the neuroprotective effects of EPO treatment of PD [5,6,45,46]. A previous report shows that EPO can inhibit 6-hydroxydopamine-induced neuron death in *in vitro* and *in vivo* models of PD through activating the phosphatidylinositol 3-kinase/Akt signalling pathway and the downstream substrate FoxO3a [46]. Furthermore, in the rat models of PD, EPO can markedly suppress apoptosis of striatal neurons and significantly improve neurological function [46]. EPO has protective and treating effect in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced neurotoxicity in this mouse model of Parkinson's Disease via increasing nitric oxide production [5,6]. In addition, Carelli et al. [47] study shows that EPO, whether ectopically administered or released by neural precursors, does reverse MPTP-induced Parkinsonism in mice. Unilateral stereotaxic injection of erythropoietin-releasing neural precursor cells can rescue degenerating striatal DA neurons and promote behavioral recovery [47]. Recently, two studies in humans have investigated safety and efficacy of EPO treatment of PD patients. Pedroso et al. [48] reported that 10 PD patients gained EPO (60 U/Kg) administration via subcutaneously once a week for five weeks. This dosage was safe and well tolerated. Moreover, some variables such as motor function, cognitive status and mood gained better clinical results as compared to the baseline pretreatment assessment [48]. In the whole study, three patients experienced mild adverse events: precordial discomfort and hypertension in one; leg fatigue in another; renal colic in a third and these complications cannot threat life [48]. In the second study, 13 PD patients got EPO (40,000 IU) treatment twice a week for five weeks [49]. At 12 months after administration, EPO exerted beneficial effects on non-motor symptoms but not on motor function. Moreover, no serious adverse effects were observed in the whole study [49]. In summary, EPO might be a good candidate for the treatment of PD, but more high quality studies in PD patients are needed.

AD, PD and acute SCI all belong to central nervous system diseases which reduce quality of life and increase the economic burden. Moreover, there are no effective therapeutic strategies for AD, PD and SCI. Currently, EPO gains more and more attention from the researchers and they think EPO may be an effective therapy for those diseases due to its neuroprotective action. However, many problems about EPO treatment of AD, PD and SCI are needed to further studies before EPO is widely applied in the clinic, such as complications, optimal dosage, therapeutic time window, etc. Although the previous studies have shown the different doses of EPO treatment of central nervous system diseases are safe and no serious adverse effects [27,29-31,48,49], the possible serious complications caused by EPO should be not ignored, especially for the patients with hypertension or increased blood clotting. Timely monitoring blood pressure and blood coagulation function may help

to reduce risk of stroke and blood clots. Current studies are unable to provide a standard therapeutic strategy for AD, PD and SCI. In our opinion, further studies in the clinic are needed, especially, high quality studies should be encouraged to conduct. Furthermore, the mechanism of EPO how to cross the blood-brain barrier (BBB) remains unclear. It might be a specific receptor mediated translocation of EPO into the central nervous system [50]. Oxidative stress increase the BBB permeability by decreasing the expression of low-density lipoprotein receptor-related protein 1 and up-regulating receptor for advanced glycation end products in BBB [50-52]. The exact mechanism of EPO over the BBB should have more attention from researchers in the future. If we find the mechanism of EPO over the BBB, we will develop a new type of EPO analogues which can quickly across the BBB to reach nidus to *repair the damaged nerves*.

Contribution

Liu-Zhu Yang and Rui-Long Li have equally contributed.

References

- Ozturk E, Demirbilek S, Kadir But A, Saricicek V, Gulec M, et al. (2005) Antioxidant properties of propofol and erythropoietin after closed head injury in rats. *Prog Neuropsychopharmacol Biol Psychiatry* 29: 922-927.
- Solaroglu I, Solaroglu A, Kaptanoglu E, Dede S, Haberal A, et al. (2003) Erythropoietin prevents ischemia-reperfusion from inducing oxidative damage in fetal rat brain. *Childs Nerv Syst* 19: 19-22.
- Chen G, Shi JX, Hang CH, Xie W, Liu J, et al. (2007) Inhibitory effect on cerebral inflammatory agents that accompany traumatic brain injury in a rat model: A potential neuroprotective mechanism of recombinant human erythropoietin (rhEPO). *Neurosci Lett* 425: 177-182.
- Cetin A, Nas K, Büyükbayram H, Ceviz A, Olmez G (2006) The effects of systemically administered methylprednisolone and recombinant human erythropoietin after acute spinal cord compressive injury in rats. *Eur Spine J* 15: 1539-1544.
- Genc S, Kuralay F, Genc K, Akhisaroglu M, Fadiloglu S, et al. (2001) Erythropoietin exerts neuroprotection in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated C57/BL mice via increasing nitric oxide production. *Neurosci Lett* 298: 139-141.
- Genc S, Akhisaroglu M, Kuralay F, Genc K (2002) Erythropoietin restores glutathione peroxidase activity in 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine-induced neurotoxicity in C57BL mice and stimulates murine astroglial glutathione peroxidase production in vitro. *Neurosci Lett* 321: 73-76.
- Kasper C (2003) Erythropoietin. In: Thomson AW, Lotze MT (eds) *The cytokine handbook*. Elsevier, London 1: 149-166.
- Li Y, Juul SE, Morris-Wiman JA, Calhoun DA, Christensen RD (1996) Erythropoietin receptors are expressed in the central nervous system of mid-trimester human fetuses. *Pediatr Res* 40: 376-380.
- Sirén AL, Knerlich F, Poser W, Gleiter CH, Brück W, et al. (2001) Erythropoietin and erythropoietin receptor in human ischemic/hypoxic brain. *Acta Neuropathol* 101: 271-276.
- Nagai A, Nakagawa E, Choi HB, Hatori K, Kobayashi S, et al. (2001) Erythropoietin and erythropoietin receptors in human CNS neurons, astrocytes, microglia and oligodendrocytes grown in culture. *J Neuropathol Exp Neurol* 60: 386-392.
- Chō YK, Kim G, Park S, Sim JH, Won YJ, et al. (2012) Erythropoietin promotes oligodendrogenesis and myelin repair following lysocleithin-induced injury in spinal cord slice culture. *Biochem Biophys Res Commun* 417: 753-759.
- Deller T, Haas CA, Freiman TM, Phinney A, Jucker M, et al. (2006) Lesion-induced axonal sprouting in the central nervous system. *Adv Exp Med Biol* 557: 101-121.
- Fumagalli F, Madaschi L, Brenna P, Caffino L, Marfia G, et al. (2008) Single exposure to erythropoietin modulates Nerve Growth Factor expression in the spinal cord following traumatic injury: comparison with methylprednisolone. *Eur J Pharmacol* 578: 19-27.
- Hong Z, Hong H, Chen H, Wang Z, Hong D (2011) Investigation of the protective effect of erythropoietin on spinal cord injury in rats. *Exp Ther Med* 2: 837-841.
- Tator CH (1995) Update on the pathophysiology and pathology of acute spinal cord injury. *Brain Pathol* 5: 407-413.
- Priestley JV, Michael-Titus AT, Tetzlaff W (2012) Limiting spinal cord injury by pharmacological intervention. *Handb Clin Neurol* 109: 463-484.
- Celik M, Gökmen N, Erbayraktar S, Akhisaroglu M, Konak S, et al. (2002) Erythropoietin prevents motor neuron apoptosis and neurologic disability in experimental spinal cord ischemic injury. *Proc Natl Acad Sci U S A* 99: 2258-2263.
- Boran BO, Colak A, Kutlay M (2005) Erythropoietin enhances neurological recovery after experimental spinal cord injury. *Restor Neurol Neurosci* 23: 341-345.
- Arishima Y, Setoguchi T, Yamaura I, Yone K, Komiya S (2006) Preventive effect of erythropoietin on spinal cord cell apoptosis following acute traumatic injury in rats. *Spine (Phila Pa 1976)* 31: 2432-2438.
- Cetin A, Nas K, Büyükbayram H, Ceviz A, Olmez G (2006) The effects of systemically administered methylprednisolone and recombinant human erythropoietin after acute spinal cord compressive injury in rats. *Eur Spine J* 15: 1539-1544.
- Fang XQ, Fang M, Fan SW, Gu CL (2009) Protection of erythropoietin on experimental spinal cord injury by reducing the expression of thrombospondin-1 and transforming growth factor-beta. *Chin Med J (Engl)* 122: 1631-1635.
- Wang Y, Yao M, Zhou C, Dong D, Jiang Y, et al. (2010) Erythropoietin promotes spinal cord-derived neural progenitor cell proliferation by regulating cell cycle. *Neuroscience* 167: 750-757.
- Ning B, Zhang A, Song H, Gong W, Ding Y, et al. (2011) Recombinant human erythropoietin prevents motor neuron apoptosis in a rat model of cervical sub-acute spinal cord compression. *Neurosci Lett* 490: 57-62.
- Cerri G, Montagna M, Madaschi L, Merli D, Borroni P, et al. (2012) Erythropoietin effect on sensorimotor recovery after contusive spinal cord injury: An electrophysiological study in rats. *Neuroscience* 219: 290-301.
- Jin W, Ming X, Hou X, Zhu T, Yuan B, et al. (2014) Protective effects of erythropoietin in traumatic spinal cord injury by inducing the Nrf2 signalling pathway activation. *J Trauma Acute Care Surg* 76: 1228-1234.
- Yang L, Yan X, Xu Z, Tan W, Chen Z, et al. (2016) Delayed administration of recombinant human erythropoietin reduces apoptosis and inflammation and promotes myelin repair and functional recovery following spinal cord compressive injury in rats. *Restor Neurol Neurosci* 34: 647-663.
- Xiong M, Chen S, Yu H, Liu Z, Zeng Y, et al. (2011) Neuroprotection of erythropoietin and methylprednisolone against spinal cord ischemia-reperfusion injury. *J Huazhong Univ Sci Technolog Med Sci* 31: 652-656.
- Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, et al. (1997) Administration of methylprednisolone for 24 or 48 h or tirilazad mesylate for 48 h in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. *National Acute Spinal Cord Injury Study*. *JAMA* 277: 1597-1604.
- Nekoui A, Abdolmohammadi S, Sheded D, Blaise G (2015) Neuroprotective effect of erythropoietin in post-operation cervical spinal cord injury: Case report and review. *Anesth Pain Med* 5: e28849.
- Costa DD, Beghi E, Carignano P, Pagliacci C, Faccioli F, et al. (2015) Tolerability and efficacy of erythropoietin (EPO) treatment in traumatic spinal cord injury: A preliminary randomized comparative trial vs. methylprednisolone (MP). *Neurol Sci* 36: 1567-1574.
- Alibai EA, Baghban F, Farrokhi MR, Mohebbi N, Ashraf MH (2015) Effects of human erythropoietin on functional outcome of patients with traumatic cervical cord injury: a pilot randomized clinical trial. *Bull Emerg Trauma* 3: 79-85.
- Bosco D, Fava A, Plastino M, Montalcini T, Pujia A (2011) Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. *J Cell Mol Med* 15: 1807-1821.
- Albert MS (1996) Cognitive and neurobiologic markers of early Alzheimer disease. *Proc Natl Acad Sci U S A* 93: 13547-13551.
- Alzheimer's Association (2011) 2011 Alzheimer's disease facts and figures. *Alzheimers Dement* 7: 208-244.
- Kawas CH, Corrada MM (2006) Alzheimer's and dementia in the oldest-old: A century of challenges. *Curr Alzheimer Res* 3: 411-419.

36. Helzner EP, Scarmeas N, Cosentino S, Tang MX, Schupf N, et al. (2008) Survival in Alzheimer disease: A multiethnic, population-based study of incident cases. *Neurology* 71: 1489-1495.
37. Larson EB, Yaffe K, Langa KM (2013) New insights into the dementia epidemic. *N Engl J Med* 369: 2275-2277.
38. Li YP, Yang GJ, Jin L, Yang HM, Chen J, et al. (2015) Erythropoietin attenuates Alzheimer-like memory impairments and pathological changes induced by amyloid β 42 in mice. *Brain Res* 1618: 159-167.
39. Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J (2011) Epidemiology and etiology of Parkinson's disease: A review of the evidence. *Eur J Epidemiol* 26 Suppl 1: S1-S8.
40. Obeso JA, Rodriguez-Oroz MC, Goetz CG, Marin C, Kordower JH, et al. (2010) Missing pieces in the Parkinson's disease puzzle. *Nat Med* 16: 653-661.
41. Ham A, Kim DW, Kim KH, Lee SJ, Oh KB, et al. (2013) Reynosin protects against neuronal toxicity in dopamine-induced SH-SY5Y cells and 6-hydroxydopamine-lesioned rats as models of Parkinson's disease: Reciprocal up-regulation of E6-AP and down-regulation of α -synuclein. *Brain Res* 1524: 54-61.
42. Villalba RM, Smith Y (2013) Differential striatal spine pathology in Parkinson's disease and cocaine addiction: A key role of dopamine? *Neuroscience* 251: 2-20.
43. Wilson JM, Levey AI, Rajput A, Ang L, Guttman M, et al. (1996) Differential changes in neurochemical markers of striatal dopamine nerve terminals in idiopathic Parkinson's disease. *Neurology* 47: 718-726.
44. Gardoni F, Bellone C (2015) Modulation of the glutamatergic transmission by Dopamine: A focus on Parkinson, Huntington and Addiction diseases. *Front Cell Neurosci* 9: 25.
45. Jia Y, Mo SJ, Feng QQ, Zhan ML, Ouyang LS, et al. (2014) EPO-dependent activation of PI3K/Akt/FoxO3a signalling mediates neuroprotection in *in vitro* and *in vivo* models of Parkinson's disease. *J Mol Neurosci* 53: 117-124.
46. Erbaş O, Çınar BP, Solmaz V, Çavuşoğlu T, Ateş U (2015) The neuroprotective effect of erythropoietin on experimental Parkinson model in rats. *Neuropeptides* 49: 1-5.
47. Carelli S, Giallongo T, Viaggi C, Latorre E, Gombalova Z, et al. (2017) Recovery from experimental parkinsonism by intrastriatal application of erythropoietin or EPO-Releasing neural precursors. *Neuropharmacol pii: S0028-3908(17)30127-2*.
48. Pedroso I, Bringas ML, Aguiar A, Morales L, Alvarez M, et al. (2012) Use of Cuban recombinant human erythropoietin in Parkinson's disease treatment. *MEDICC Rev* 14: 11-17.
49. Jang W, Park J, Shin KJ, Kim JS, Kim JS, et al. (2014) Safety and efficacy of recombinant human erythropoietin treatment of non-motor symptoms in Parkinson's disease. *J Neurol Sci* 337: 47-54.
50. Brines ML, Ghezzi P, Keenan S, Agnello D, Lanerolle NCD, et al. (2000) Erythropoietin crosses the blood-brain barrier to protect against experimental brain injury. *Proc Natl Acad Sci* 97: 10526-10531.
51. Srikanth V, Maczurek A, Phan T, Steele M, Westcott B, et al. (2011) Advanced glycation end-products and their receptor RAGE in Alzheimer's disease. *Neurobiol Aging* 32: 763-777.
52. Jaynes B, Provias J (2008) Evidence for altered LRP/RAGE expression in Alzheimer lesion pathogenesis. *Curr Alzheimer Res* 5: 432-437.