NGF and NTF-3 could play role as agonist for TrkB: An *in silico* approach for Type 2 Diabetic Retinopathy

Vaibhav Singh[1] Archana Tiwari[2*]
[1]Student, [2]Head of Department,
Department of Biotechnology,
Rajiv Gandhi Proudyogiki Vishwavidyalaya
(State Technological University of Madhya Pradesh),
Bhopal, Madhya Pradesh-462033 India.

ABSTRACT

Type 2 Diabetic Retinopathy is a communal cause of visual damage in the world and it is a actually blinding complication of diabetes that damages the eye's retina. Type 2 Diabetic retinopathy is a complication of diabetes that distresses the blood vessels of the retina. Growth of new blood vessels, known as proliferative retinopathy, may lead to blindness through hemorrhage and scarring. A worsening of retinal blood vessels producing loss of blood vessels and leakage into the retina is known as maculopathy and leads to visual impairment and may progress to blindness. Brain-derived neurotrophic factor (BDNF) activates the receptor tropomyosin-related kinase B (TrkB) with high potency and specificity, promoting neuronal survival, differentiation, and synaptic function. In this review, main focus has been played on NTF3, NGF interactions with TrkB as NTF3 and NGF can act as agonist for TrkB, which would be helpful in retinal cell survival which would in turn help in controlling Type 2 Diabetic Retinopathy.

Keywords: Type 2 Diabetic retinopathy, Brain-derived neurotrophic factor, Tropomyosin-related kinase B, Nerve growth factor, Neurotrophin-3

INTRODUCTION

Type 2 Diabetic retinopathy (T2DR) remains a main cause of visual impairment and blindness in the worldwide with its timely detection and timely treatment capable of reducing the risk of visual loss [1]. Reasons for loss of vision are diabetic maculopathy and complications of proliferative diabetic retinopathy (PDR) such as vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma. By 2030 developing countries will face growth by 69% and industrialized countries by 20% of the number of patients with diabetes compared to 2010 [2,3,4]. Micro-angiopathy due to hyperglycemia in patients with diabetes mellitus outcomes in vascular leakage, which causes diabetic macular edema on one hand, and capillary occlusion on the other hand. Capillary occlusion then again causes retinal ischemia and increased levels of vascular endothelial growth factor (VEGF) which are

responsible for the expansion of neovascularization and the proliferative stage of diabetic retinopathy [5]. Retina is a part of central nervous system. Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, was effective in guarding retinal neurons from hyperglycemia *in vitro*. BDNF promoted neuronal cell survival. Tropomyosin-related kinase B (TrkB) is a receptor protein involved in the development and maturation of the central and peripheral nervous systems. BDNF has a great affinity for TrkB and p75 increases the interaction between BDNF and TrkB [6].

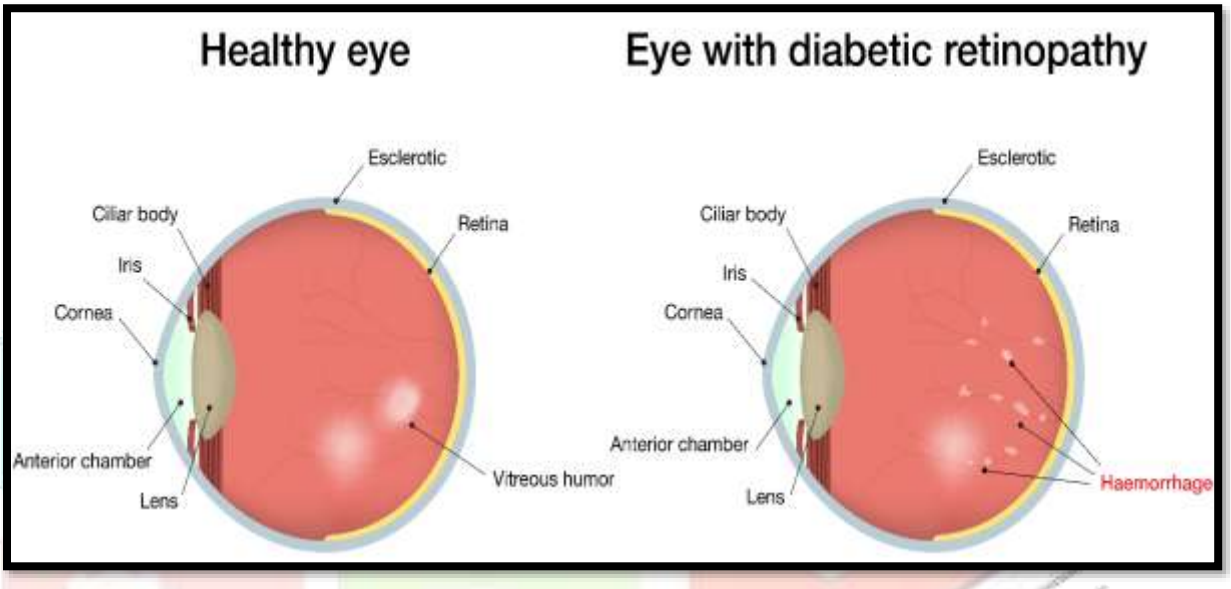

Figure1. Difference between healthy eye and Diabetic Retinopathy eye [7]

BDNF and TrkB

BDNF is a member of the neurotrophin family of growth factors and is significant in the development, differentiation and maintenance of neurons. Previous studies have discovered that BDNF is critical for photoreceptor cells and the repair of injury to the retina and the optic nerve. BDNF encourages survival in injured RGCs induced by axotomy or retinal ischemia, and also promotes regeneration of the nerve fiber [8, 9]. In addition, BDNF encourages the survival of retinal interneurons and is important for forming phenotypes and synaptic connections in the developing retina [10]. Tropomyosin-related kinase B (TrkB) is a receptor protein involved in the development and maturation of the central and peripheral nervous systems. BDNF has a great affinity for TrkB and p75 increases the interaction between BDNF and TrkB. Upon ligand-binding, TrkB undertakes homodimerization, autophosphorylation and activation. It then recruits and activates several downstream effectors to regulate gene expression and protect neurons. Members of the TrkB downstream signaling cascade, including ERK/MAPK and PI3K/PKB, have been reported to be responsive to BDNF [11, 12].

The interaction study of brain-derived neurotrophic factor (BDNF) with its tropomyosin-related kinase receptor B (TrkB) is involved in fundamental cellular processes including neuronal proliferation, differentiation and survival [13].

7, 8-Dihydroxyflavone

Flavonoids are a naturally arising class of chemicals, which are plentiful in fruits and vegetables and exert diverse biological effects. Recent studies have recognised that a flavonoid derivative, 7,8-DHF acts as a high-affinity tropomyosin related kinase receptor B (TrkB) agonist that incites receptor dimerization and autophosphorylation and activation of downstream signalling *in vivo*. This compound has been revealed to be highly neuroprotective in numerous disease conditions. 7, 8-Dihydroxyflavone (7,8-DHF) is a TrkB receptor agonist, and treatment with this flavonoid derivative conveys about an enhanced TrkB phosphorylation and encourages downstream cellular signalling [14].

NGF and NTF3

Nerve growth factor (NGF) is important for the development and maintenance of the nervous system. Extracellular ligand for the NTRK1 and NGFR receptors, triggers cellular signaling cascades through those receptor tyrosine kinase to regulate neuronal proliferation, differentiation and survival. NGF is initially in a 7S, 130-kDa complex of 3 proteins - Alpha-NGF, Beta-NGF, and Gamma-NGF (2:1:2 ratio) when expressed. This form of NGF is also referred to as proNGF (NGF precursor). The gamma subunit of this complex acts as a serine protease, and cleaves the N-terminal of the beta subunit, thereby activating the protein into functional NGF. NGF is involved primarily in the growth, as well as the maintenance, proliferation, and survival of nerve cells (neurons). In fact, NGF is critical for the survival and maintenance of sympathetic and sensory neurons, as they go through apoptosis in its absence. However, numerous current studies suggest that NGF is also involved in pathways besides those regulating the life cycle of neurons [15].

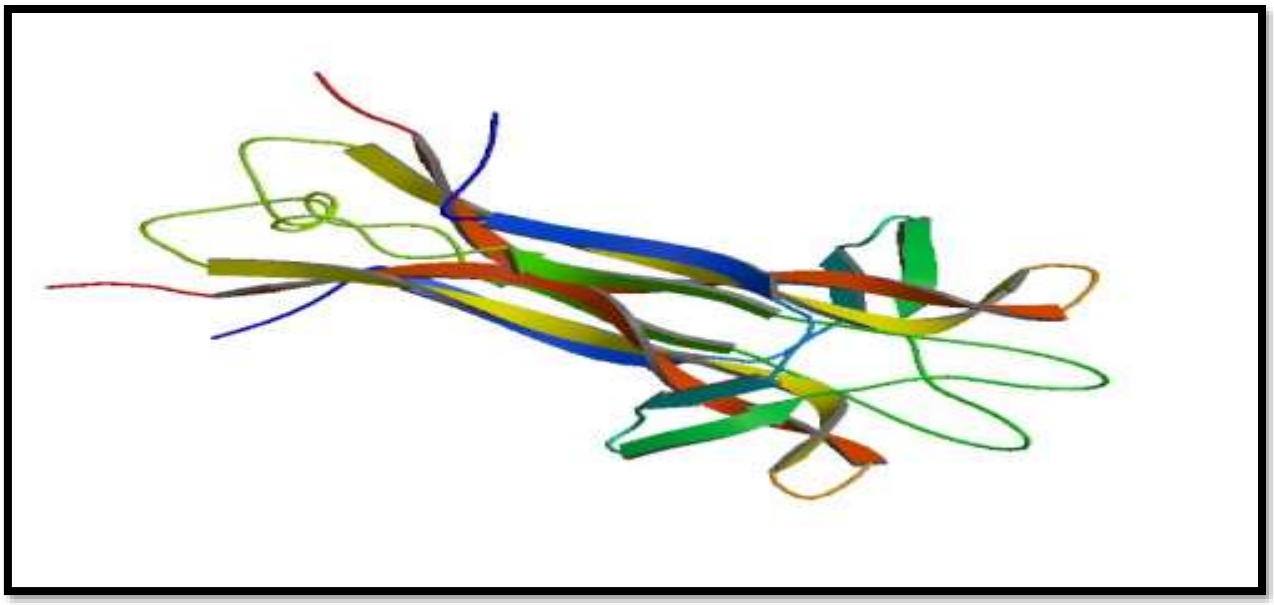

Figure2. Structure of NGF [16]

Neurotrophin-3 is a protein that in humans is encoded by the **NTF3 gene**. The protein encoded by this gene, NT-3, is a neurotrophic factor in the NGF (Nerve Growth Factor) family of neurotrophins. It is a protein growth factor which has activity on certain neurons of the peripheral and central nervous system; it helps to maintaining the survival and differentiation of existing neurons, and inspires the growth and differentiation of new neurons and synapses. NT-3 was the third neurotrophic factor to be categorized, after nerve growth factor (NGF) and BDNF (Brain Derived Neurotrophic Factor) [17, 18]. NT-3 is unique in the number of neurons it can possibly stimulate, given its ability to activate two of the receptor tyrosine kinase neurotrophin receptors [19].

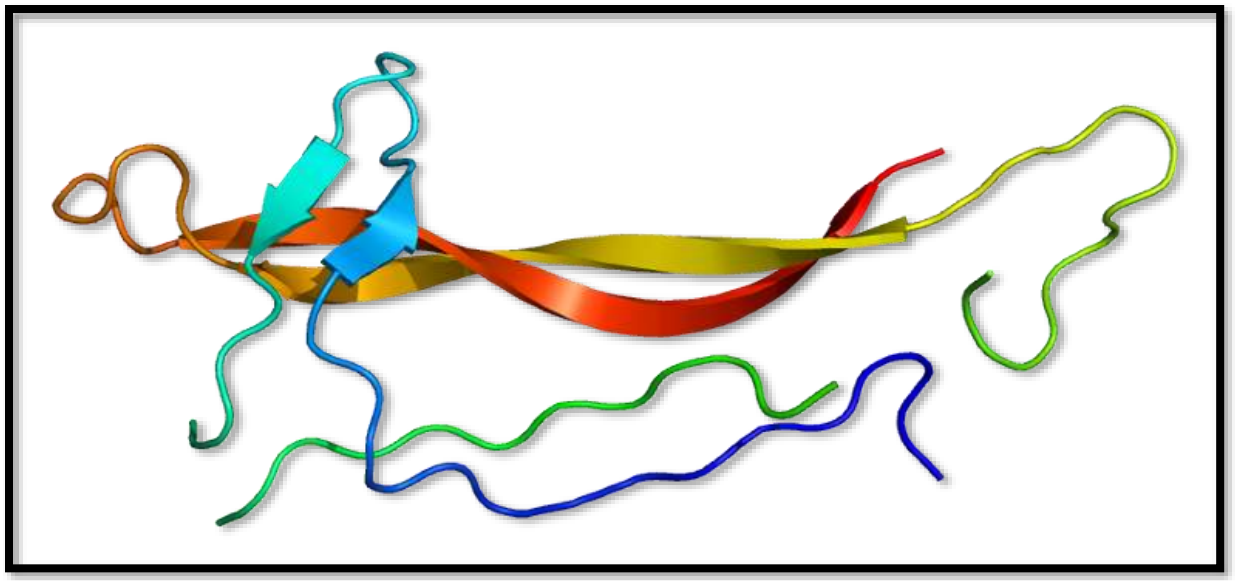

Figure3. Structure of NTF3 [20]

CONCLUSION

In past studies, it has been reported that BDNF activated TrkB for cell survival signals. Likewise, 7, 8-Dihydroxyflavone was used as TrkB receptor agonist, enhanced TrkB phosphorylation and promotes downstream cellular signalling. In this review, as a novel approach it was hypothesized that NGF and NTF3 can also act as agonist for TrkB as both of them are similar to BDNF (predicted with help of ProBis bioinformatics tool). NGF and NTF3 could be helpful in controlling T2DR as they will bind to TrkB and thus will promote cell survival signals in diabetic retina. In future study, NGF and NTF3 will be docked with TrkB for studying the interactions of NGF and NTF3 with TrkB with the help of various online bioinformatics online tools, which would be great beneficial for controlling T2DR.

REFERENCES

1. Shaw, J. E., Sicree, R. A., & Zimmet, P. Z. (2010). Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes research and clinical practice*, *87*(1), 4-14.
2. World Health Organization. (2004). Diabetes action now: an initiative of the World Health Organization and the International Diabetes Federation.
3. Stefánsson E, Bek T, Porta M, Larsen N, Kristinsson JK, Agardh E. Screening and prevention of diabetic blindness. Acta Ophthalmol Scand. 2000;78:374–385.
4. Hammes, H. P. (2013). Optimal treatment of diabetic retinopathy. *Therapeutic advances in endocrinology and metabolism*, *4*(2), 61-71.
5. Bhat, M., Pouliot, M., Couture, R., & Vaucher, E. (2014). The kallikrein-kinin system in diabetic retinopathy. In *Recent Developments in the Regulation of Kinins* (pp. 111-143). Springer International Publishing.
6. Yoshii, A., & Constantine-Paton, M. (2010). Postsynaptic BDNF-TrkB signaling in synapse maturation, plasticity, and disease. *Developmental neurobiology*, *70*(5), 304-322.
7. http://nuasupplements.com/range-products/nuadha-vision/diabetic-retinopathy/?lang=en
8. Mey, J., & Thanos, S. (1993). Intravitreal injections of neurotrophic factors support the survival of axotomized retinal ganglion cells in adult rats in vivo. *Brain research*, *602*(2), 304-317.
9. Peinado-Ramon, P., Salvador, M., Villegas-Perez, M. P., & Vidal-Sanz, M. (1996). Effects of axotomy and intraocular administration of NT-4, NT-3, and brain-derived neurotrophic factor on the survival of adult rat retinal ganglion cells. A quantitative in vivo study. *Investigative ophthalmology & visual science*, *37*(4), 489-500.

10. Pinzón-Duarte, G., Arango-González, B., Guenther, E., & Kohler, K. (2004). Effects of brain-derived neurotrophic factor on cell survival, differentiation and patterning of neuronal connections and Müller glia cells in the developing retina. *European Journal of Neuroscience*, *19*(6), 1475-1484.
11. Hetman, M., Kanning, K., Cavanaugh, J. E., & Xia, Z. (1999). Neuroprotection by brain-derived neurotrophic factor is mediated by extracellular signal-regulated kinase and phosphatidylinositol 3-kinase. *Journal of Biological Chemistry*, *274*(32), 22569-22580.
12. Almeida, R. D., Manadas, B. J., Melo, C. V., Gomes, J. R., Mendes, C. S., Graos, M. M., ... & Duarte, C. B. (2005). Neuroprotection by BDNF against glutamate-induced apoptotic cell death is mediated by ERK and PI3-kinase pathways. *Cell Death & Differentiation*, *12*(10), 1329-1343.
13. Massa, S. M., Yang, T., Xie, Y., Shi, J., Bilgen, M., Joyce, J. N., ... & Longo, F. M. (2010). Small molecule BDNF mimetics activate TrkB signaling and prevent neuronal degeneration in rodents. *The Journal of clinical investigation*, *120*(5), 1774.
14. Chitranshi, N., Gupta, V., Kumar, S., & Graham, S. L. (2015). Exploring the molecular interactions of 7, 8-dihydroxyflavone and its derivatives with TrkB and VEGFR2 proteins. *International journal of molecular sciences*, *16*(9), 21087-21108.
15. Freeman, R. S., Burch, R. L., Crowder, R. J., Lomb, D. J., Schoell, M. C., Straub, J. A., & Xie, L. (2004). NGF deprivation-induced gene expression: after ten years, where do we stand?. *Progress in brain research*, *146*, 111-126.
16. http://www.rcsb.org/pdb/explore.do?structureId=1bet
17. Maisonpierre, P. C., Le Beau, M. M., Espinosa, R., Ip, N. Y., Belluscio, L., Suzanne, M., ... & Yancopoulos, G. D. (1991). Human and rat brain-derived neurotrophic factor and neurotrophin-3: gene structures, distributions, and chromosomal localizations. *Genomics*, *10*(3), 558-568.
18. Maisonpierre, P. C., Belluscio, L., Squinto, S., Ip, N. Y., Furth, M. E., Lindsay, R. M., & Yancopoulos, G. D. (1990). Neurotrophin-3: a neurotrophic factor related to NGF and BDNF. *Science*, *247*(4949), 1446-1452.
19. Entrez Gene: NTF3 neurotrophin 3
20. https://en.wikipedia.org/wiki/File:Protein_NTF3_PDB_1b8k.png