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Letter to the Editor

Brain derived Neurotrophic factor: Is it spreading wings from Neurological to Metabolic Disorder

Dear Editor ,

Since the time of its discovery in 1982 from pig brain, Brain derived neurotrophic factor (BDNF) has been a topic of great interest for the researchers specially for its role in various neurological disorders like Alzheimer's, Parkinson's, Huntington's disease and also various neuropsychiatric disorders like Schizophrenia, bipolar mood disorder [1]. BDNF is a 14 k Da basic protein (pI=9.99) of 252 amino acids (AAs). It is synthesized as a 30 k Da precursor molecule which has got 18 AAs long hydrophobic signal sequence and a prosequence of 112 AAs containing, N-glycosylation site. BDNF has got 50% analogy with nerve growth factors (NGF), neurotropins; NT-3, NT-4, and NT-5. BDNF gene is located on human chromosome 11 p and consists of four 5'exons (I-IV) with distinct promoter site and one 3'exons (V). Eight distinct BDNF mRNA are transcribed which are selectively expressed in neural and extraneural tissues. Transcripts that contain exons I-III express predominantly in brain, whereas transcripts with exon IV are expressed in lung and heart [2-3].

Though BDNF is known to be active predominantly in homodimer form, a less active heterodimer form of BDNF and NT-3 has also been discovered in vaccinia virus system [4]. BDNF acts on tyrosine related kinase B (TrkB) receptor present in central nervous system, hypothalamus and other organs. It initiates signal transduction via activation of *TrkB* which elicit various intracellular signaling pathways including mitogen- activated protein kinase (MAPK) or extracellular signal regulated protein kinases (ERKs), phospholipase Cg, and phosphoinositide 3 kinase (PI3K) pathway [5].

Recently the role of BDNF in various metabolic disorders is drawing much attention of the researchers. Karezewan et al [6] have shown lower serum BDNF level in young non obese subjects with low insulin sensitivity. It was also found that BDNF levels are increased in newly diagnosed female patients of Type 2 DM and correlated its concentration with the obesity [7].

Earlier, the role of BDNF in regulating glucose metabolism via modulation of energy balance was shown in experimental diabetic mice models. BDNF is shown to enhace glucose utilization in peripheral tissues of diabetic mice. Sympathetic innervations of brown and white adipose tissue are thought to regulate the energy output [8]. Interestingly, physical activity has been shown to increase BDNF concentration and insulin sensitivity, the BDNF level correlated with physical exercise, insulin sensitivity and memory [9].

It is logical to ask –why in low BDNF, one subset of patients develop neurological disorders without Diabetes Mellitus and another subset develop Diabetes Mellitus without neurological disorders. Is it the level of BDNF or subtype if any of the BDNF or any polymorphism in disease prone individual is responsible for such varied manifestation?

It also raises a very important question, whether schizophrenics are more prone to insulin resistance and diabetes and if yes; is it BDNF which is the link? To answer these concerns more programmed studies are needed which link BDNF level with insulin sensitivity in various affective disorders. Also important to find out whether it is a cause or effect association of BDNF with metabolic disorder like insulin sensitivity. It has been very recently proposed that total and phosphorylated MAPK as specific markers of Insulin signaling pathway [10]. With the consideration of this previous evidence, it appears more interesting to relate BDNF (which elicit MAPK activation) with insulin resistance and development of diabetes, its progression and associated complications. Further, as physical activity has been reported to favor BDNF levels and insulin sensitivity and our research experience (un-published) of finding high diabetes associated atherogenic risk factors

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in urban population versus rural subjects, it would be interestingly important to study the role of physical activity and stress related factors in relation to BDNF, insulin sensitivity among diabetics from urban and rural regions. Furthermore, as the precursor molecule for BDNF is known to contain N-glycosylation site, we hypothesize and hence appeal for research focusing on the formation, measurement and the role of glycosylated BDNF, if any, on the pathophysiology of diabetes.

In a nutshell, it is opined that BDNF is an important neurotropin with lots of its hidden potential to reduce the pathogenesis of not only many neurological disorders but also may prove useful to many metabolic disorders like insulin resistance. It may be a therapeutic target of such disorders in future generation.

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References

1. Balaratnasingam S, Janca A. Brain Derived Neurotrophic Factor: a novel neurotropin involved in psychiatric and neurological disorders. Pharmacol Ther. 2012; 134(1): 116-24.
2. Chao MV, Bothwell M. Neurotrophins: to cleave or not to cleave. Neuron. 2002; 33(1): 9-12.
4. Timmusk T, Palm K, Metsis M, Reintam T, Paalme V, Saarma M, Persson H. Multiple promoters direct tissue-specific expression of the rat BDNF gene. Neuron. 1993; 10(3): 475-89.
5. Jungbluth S, Bailey K, Barde YA. Purification and characterisation of a brain-derived neurotrophic factor/neurotrophin-3 (BDNF/NT-3) heterodimer. Eur J Biochem. 1994; 221(2): 677-85.
6. Numakawa T, Suzuki S, Kumamaru E, Adachi N, Richards M, Kunugi H. BDNF function and intracellular signaling in neurons. Histol Histopathol. 2010; 25(2): 237-58.
7. Karczewska-Kupczewska M, Strączkowski M, Adamska A, Nikołajuk A, Otziomek E, Górska M, Kowalska I. Decreased serum brain-derived neurotrophic factor concentration in young nonobese subjects with low insulin sensitivity. Clin Biochem. 2011; 44(10-11): 817-20.
8. Suwa M, Kishimoto H, Nofuji Y, Nakano H, Sasaki H, Radak Z, Kumagai S. Serum brain-derived neurotrophic factor level is increased and associated with obesity in newly diagnosed female patients with type 2 diabetes mellitus. Metabolism. 2006; 55(7): 852-7.
9. Yamanaka M, Tsuchida A, Nakagawa T, Nonomura T, Ono-Kishino M, Sugaru E, Noguchi H, Taiji M. Brain-derived neurotrophic factor enhances glucose utilization in peripheral tissues of diabetic mice. Diabetes Obes Metab. 2007; 9(1): 59-64.
10. Vivar C, Potter MC, van Praag H. All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis. Curr Top Behav Neurosci. 2013; 15: 189-210.
11. Shiva, Senthil Kumar, Xian Liu, Haifei Shi. Estrogen Facilitates Insulin Signaling in a Leptin-Dependent Manner. Endocr Rev. 2012; 33 (03_MeetingAbstracts): SAT-207.