Obesity Medicine 17 (2020) 100189

Contents lists available at ScienceDirect

Obesity Medicine

journal homepage: www.elsevier.com/locate/obmed

Review

Role of brain derived neurotropic factor in obesity

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ARTICLE INFO

Keywords:
Brain derived neurotrophic factor (BDNF)
Obesity
Appetite suppression
Homeostasis
Polymorphism
Hyperphagia

ABSTRACT

Purpose: Correlating abasement in brain derived neurotrophic factor (BDNF) and cognated energy homeostasis together with obesity and metabolic syndrome in both human and animal models. In this review, we focus on the evidence for BDNF as regulator of satiety and body weight; analysing the latest evolvement of BDNF functions via the help of published research results, data and meta-analysis.

Key findings: Neurotrophic factors such as BDNF and CNTF are essential for body weight management. Mutations in the gene of BDNF and impairment of activation of its receptor TrkB results in austere obesity, insatiable appetite and less energy expenditure. Severe obesity was found to cause BDNF haploinsufficiency and it is the foundation for hyperphagia and obesity linked with some patients with the Wilms' tumor, aniridia, genitourinary disorders, and mental retardation (WAGR) syndrome. The WAGR syndrome is an infrequent disease and repercussions from two distinct alleles of this specific gene, sporadically dimensioned, interconnecting deletions on chromosome 11 that extend into the BDNF gene in few of the investigated cases.

Conclusion: The current article reviews the sophisticated resemblance of BDNF in obesity and the consequences of BDNF gene in metabolic disorders. The cytoprotective action of BDNF clearly explains its role other neurological diseases as well where the basic mechanism involved is protection of neuronal cells. BDNF faces a limitation in clinical administration due to its lower bioavailability, shorter half-life and poor penetrability through blood brain barrier.

1. Introduction

Obesity is the largest prevailing and augmenting at an exponential measure, leading to increased fatality along with retrenchment of life expectancy, amidst the autonomous risk considerations in cardiovascular disorders. Being overweight is a diseased state, neoterically cognated with depressed type of inflammatory disposition. Recent investigations suggest breakthrough of elemental influences as dominant subsidizing factors for obesity. Neurons, immune cells, adipocytes, endothelial cells and monocytes and tissues such as brain and blood are the prime synthesizing locations of neurotrophin, BDNF (Amadio et al., 2017). It is a key regulator of energy balance and imparts an efficient contribution in neural protection and synaptic recreation. This prominent gene acts as a key to fullness and more energy expenditure in mammals as found by a study related to induction of recombinant human BDNF intra-cerebroventricularly for examination of its effect of cholinergic neurons but instead delivered results of depreciated body weight in adult rat. Genetic evidence was collected from various mutant mice to support the result of suppression in appetite and low levels of food intake (Xu and Xie, 2016). Hence conclusion was drawn from several other experimental studies conducted on rats that upon deletion of the BDNF gene lead to severe obesity and insatiable appetite (Leonardo Sandrini et al., 2018) (Fig. 1).

1.1. Genesis of BDNF

BDNF is a part of the neurotrophin series of maturation factors along with nerve growth factor (NGF); neurotrophins-3 (NT-3), NT4/5 and NT-6. BDNF is generated in the endoplasmic reticulum (ER) as a 32–35 kDa precursor protein (pro BDNF) that goes through the Golgi apparatus and trans-Golgi network (TGN). In the lipid raft related sorting receptor carboxy-peptidase E (CPE), pro-BDNF is sorted by vesicles and then transported into activity-dependent secretion by postsynaptic dendrite. The terminal area of pro-BDNF is cut by a different protein convertase enzyme to form 13 kDa biologically active mature BDNF (mBDNF).(Kernie SG et al., 2000).

1.2. BDNF structure

BDNF has around 11 exons and span around 70 kb with the

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https://doi.org/10.1016/j.obmed.2020.100189
Received 14 January 2020; Received in revised form 22 January 2020; Accepted 25 January 2020

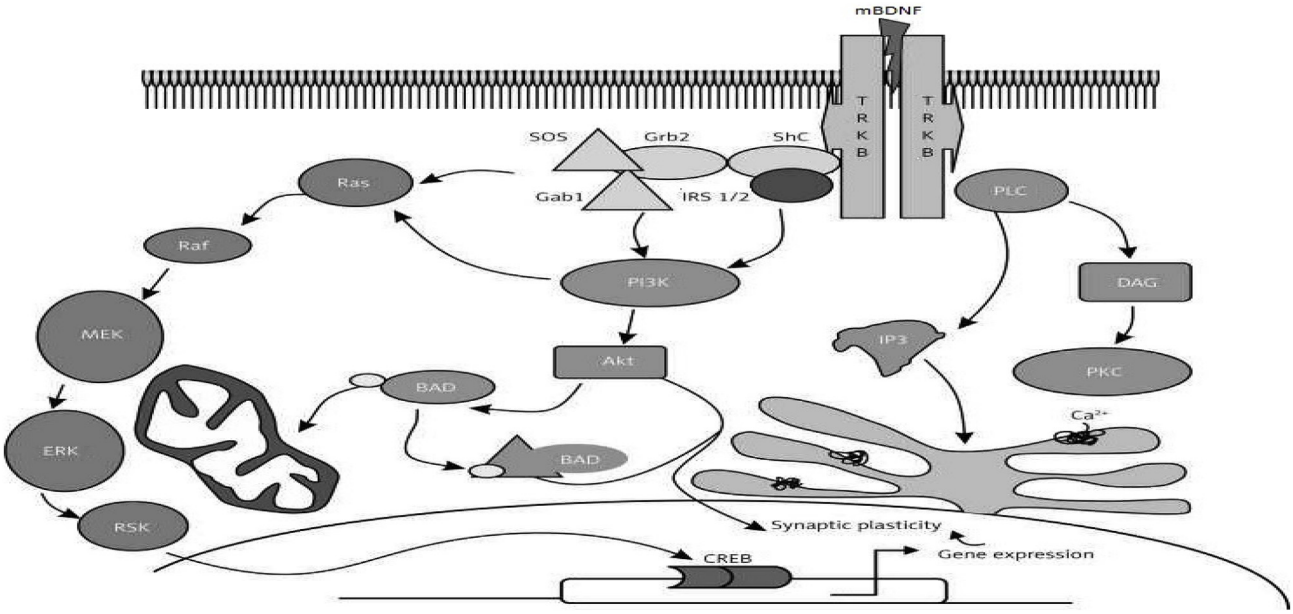

Fig. 1. Mechanism of action of BDNF protein.

recognised transcription sites initiating at 9 exons, each of which is associated with a functional promoter. Structural homology of BDNF is in relation to NGF and NT3/4/5 with similar 50% amino acid. The neurotrophins are homodimers that are associated non-covalently to signal proteins and initial codons accommodating N-linked glycosidation sites in pro regions (Juliette Gray et al., 2006). Chromosome-11 is the site of location for BDNF gene in case of rats and authorized by tissue related promoters I, II, III, IV. Among these, promoters I and III are coordinated by severe stimulatory elements and transcription of promoter III transpire by binding to calcium transcription factors. Apart from human axon VIIB and VIII, all other axons present in humans have been expressed in mouse and rats. Cryptic splicing occurs within the exon II of rats to form exon IIA, B and C gene (Betley et al., 2013). The expression of transcript BDNF is circulated by various promoters. On the other hand, structure of human BDNF shows congruency to that of mouse and rats. Transcription of almost 8 mRNAs take place out of which expression of exons I-III occurs in brain while that of exon IV in heart and lungs. The manifestation of BDNF mRNA in brain has been authenticated by miscellaneous in-situ experiments. The level of such expressions are markedly low at the time of foetal development, gradually increase after the birth and decreases in case of adults. (Friedman J, 2014).

1.3. Obesity

Obesity is major healthcare concern worldwide; contributions include genetic, environmental and behavioral factors. Abnormal and excessive fat accumulation is the key characteristics of identification of this condition called obesity. It is a very common condition with crores of reported cases every year (G Y Liao et al., 2012). Physical and mental disorders risk is augmented due to obesity. Familial history, above average body weight, troubled sleeping pattern, sleep apnoea, varicose veins, osteoarthritis and gallstones are some of the symptoms. When BMI (body mass index) is 30 or higher then obesity is diagnosed. Hyperplasia and hypertrophy are the key factors helping in characterisation of obesity. Fat gets deposited in adipose tissue due to the fact that subject was taking augmented caloric intake. Progression of adipocytes occurs due to some key elements such as attenuated plasma, hyperplasia, hypoxia, macrophagal inflammation. Also presence of anti-oxidants gets highly diminished in case of obese patients and hence healing process is very much delayed (Gajewska E et al., 2014).

1.4. Other names for BDNF gene

- Abreneurin
- ANON2
- Neurotrophin
- BULN2

1.5. Chromosomal location of BDNF

Cytogenic location: 11p14.1, which is the short (p) arm of chromosome 11 at position 14.1.

Molecular location: base pairs 27,654,893 to 27,722,030 on chromosome 11 (*Homo sapiens* updated annotations release 109.20190607 (Yang, Q Li et al.,0.2017).

1.6. Mechanism of action

- **Receptors of BDNF Protein**

BDNF being a component of NT series with several other nerve growth factors are important for growth of nervous system by circulating neuronal repair, neurotransmission, synaptic activity and plasticity of central and peripheral nervous system. P75 NT, a cell exterior receptor for BDNF that exist to cancer necrosis superfamily whereas TrkB i.e. tyrosine kinase receptor resides in tropomyosin series which operates antagonistic to that of neuron (Vigers AJ et al., 2012). Pro-BDNF mobilizes neuronal apoptosis and with an increased compatibility towards p75. Oppositely, developed BDNF has attenuated affinity with TrkB receptor and increases differentiation along with maturation of neurons, synaptic plasticity and cell survival (Williams KW, Elmquist JK, 2012). Abbreviated TrkB and full-length TrkB are receptor isomers of TrkB that are asserted completely in brain, apart from this full length TrkB is included in onset of intracellular signalling and TrkB precipitates activation of intracellular signalling pathways and circulates concentration of extracellular BDNF. (MC_4-R) receptor responsible for causing a reduction in taking of food and developed expenditure of energy is also a receptor of BDNF.

- **Activation of TrkB**

Neurotrophic tyrosine kinase in mammals is ciphered by NTRK2 gene. TrkB with an external sphere with a lot of sites of

glycosylation, an exclusive transmembrane segment and an internal sphere recognised by TrkB activity (Wang C et al., 2010). After activation, many small G proteins, including RAS along with MAP kinase, PI3-kinase and Phospholipase-C-γ (PLC-γ) pathways are circulated. The activation of TrkB takes place in 2 min, and deactivation takes place in 30 min after activation in the spinal cord. TrkB receptor-mediated signaling is regulated via occurance of mediators in these signaling pathways that circulate localization of different signaling constituents (Sohn JW et al., 2013).

- **Activation of secondary messengers**
  Neurotrophin's actions are controlled through the activation of the TrkB series of receptors TrkA-C and the p75 neurotrophin receptor. The huge pre-synaptic p75 NTR has the dual role of modulating TrkB receptor binding, Ras-mediated activation of ERK and neurite outgrowth and activating c-jun N-terminal kinase (JNK), leading to apoptosis in a variety of neurons. The secondary messengers which are activated in the spinal cord by BDNF signaling include the MAP/ERK pathway, proto-oncogene c-fos and nitric oxide (NO)-producing neurons (W Ito et al., 2011).
- **Ras/MAPK/ERK pathway**

When a ligand (BDNF) binds to the TrkB receptor, it results in dimerization and auto-phosphorylation of tyrosine residues to form a docking site for src-homology 2-domain containing adaptor protein (Shc) and phospholipase C (PLC) (T J Bartness et al., 2014). Once Shc is docked with the receptor and bound to adapter protein Grb2 by guanine nucleotide-releasing factor SOS, Ras activates the following signaling pathways: Ras/MAPK-ERK pathway, PI3–K pathway and PLC pathway. Ras is linked to Grb2 by the guanine nucleotide-releasing factor SOS. MAPK/ERK is essential for neurogenesis and promotes survival in two ways: by induction of prosurvival genes and inhibition of proapoptotic (BAD) proteins (Sobia Rana et al., 2018).

- **IRS-1/PI3K/AKT pathway**
  Other paths involved in BDNF actions include activation of insulin receptor substrate-1, PI-3K and protein kinase B. RAS suppresses apoptosis via PI3K; PI3K activates AKT, which shows pro-apoptotic proteins in the cytoplasm far from their transcriptional target. Inhibition of part of the Ras-PI3K-Akt pathway diminishes survival of sympathetic neurons in culture in the presence of NGF, showing that the PI3K pathway has a crucial role in activation of pro-survival genes responsible for cell survival (Shah BP et al., 2014)
- **PLC/DAG/IP3 pathway**

The protein PLC-γ is phosphorylated after BDNF docks with the Trk receptor and this has consequences to breakdown of membrane lipids to inositol 1,4,5 triphosphate (IP3), which has an increase in intracellular calcium concentration and diacylglycerol (DAG). DAG, in turn, regulates protein kinase C, which is required for the MAPK/ERK signal implicated in neurite outgrowth (Richard D,2015).

1.7. Regulation of BDNF activity

The expression of BDNF mRNA is ruled by neuronal approach that occurs via glutamatergic synapse activation. Such synaptic activities are activated by receptor antagonists of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) that attenuates levels of mRNA which encodes for BDNF in cortex and hippocampus (Marosi, K.; Mattson, M.P, 2014). Expression of BDNF mRNA is increased by light, osmotic and whisker stimulation in visual cortex, hypothalamus, and somatosensory barrel cortex respectively. Physical exercise along with electrical stimuli also enhances expression of BDNF in hippocampus thus preventing Alzheimer development plus improving memory. The functioning of hippocampus is regulated due to interaction of BDNF with oestrogen, together forming oestrogen-NPY-BDNF trio (Neetu, M. et al., 2012).

On the other hand, blockade or stimulation of glutamate or GABAergic receptors lead to decreased level of BDNF mRNA in hippocampus while any changes in neuronal activity can directly affect the expression of BDNF (Leshan RL et al.,. 2012). Any physiological activity induced by light enhances the expression of this mRNA in visual cortex. The activity of BDNF can be antagonised by using TkB-IgG OR Anti-BDNF antiserum in case of inflammatory hypersensitivity and neuropathic pain. This further explains the use of antibody mediated agonism of TrkB as a pharmacological approach for nerve injury to enhance the survival of retinal ganglionic cells (Nakazato M et al., 2003). Studies reported that antagonists for neurotropin alter the molecular topology and act against the BDNF by preventing the activation of neurotropin induced pathway via MAPK pathway. In addition to this, production of endogenous NO (nitrous oxide) downregulates the production of BDNF via activating cGMP signal transduction in hippocampal neurons causing regulation of calcium release by the protein kinase (Leonardo Barros et al., 2019).

1.8. Plasma levels of BDNF

The BDNF levels and plasma levels show a negative linkage when studies were done via several experiments on depressed as well as controlled patients. Although there are no reasonable relation with BMI. There is an affirmative connection between BDNF levels and total cholesterol, diastolic blood pressure, body mass index, triglyceride and mass of adipose tissues in the body.(Kunugi H et al., 2001). The level of BDNF in plasma of healthy volunteers is about 92.5 pg/ml and is comparatively higher in women showing a decrease with the advancement of age. This further suggested the reason behind low mortality rate in women which increase with the reduction in BDNF levels. It is found in various parts of brain and helps in supporting the functioning and survival of neurons. Various other sources include liver, spleen, heart, lungs and gastrointestinal tract, vascular smooth muscle and fibroblasts. Certain studies proved that the level of BDNF was higher in organs like colon, lung and urinary bladder in comparison to brain (Juliette Gray et al., 2006).

1.9. Regulation of physiological condition due to BDNF

Energy homeostasis is maintained by food intake that is controlled by multiple molecules and hormonal signalling. BDNF acts as one of the key protein that regulates body weight as well as food intake and its intra-cerebroventricular infusion on rats clinically treated weight gain in case of rats (Kong D et al., 2012). Recent studies also confirmed reduction in food intake induced by BDNF which causes a dose dependent suppression in appetite that could be attributed to hypothalamic serotonergic mechanism. In addition to this, BDNF also regulates food intake in obese patients. Human studies presented a decreased TrkB receptor functioning due to missense mutation in both neurotropin-4/5 and BDNF causing severe obesity leading to decrease in its level in humans with decreased insulin level (Koh-Banerjee, P. et al., 2004).

1.10. Correlation of obesity and BDNF

BDNF protein, a regulator of appetite, when produced in decreased levels in brain due to the fact of a variation in BDNF gene exposes people to obesity. Major role of BDNF is to produce “feeling of fullness”. Comparison of a subjects BDNF gene combination –CC, CT OR TT-was done with disorders such as obesity, BMI, body-fat percentage etc. research provided evidence that C allele of BDNF gene is related to obesity in subjects (J J An et al., 2015). GIT and other advancing and nubile circumferential tissues illustrate BDNF, TrkB and p75. Deprivation of GI tissues BDNF in embryos and neonates could misalign the development of vagal GI afferents and consequently disrupt its regulation because vagal GI afferents sustain the major proportion of

signals from GIT to brain involved in circulation of feeding. Neurotrophic elements are investigated for their pursuit of nurturing neuronal differentiation and continuation, axonal and dendritic augmentation, and synaptic development and plasticity. Along with BDNF, evidences have implicated an alternative neurotrophic factor, ciliary neurotrophic factor (CNTF), in the predominance of human body weight (Kernie SG et al., 2000). Transfiguration in the genes for BDNF and its receptor TrkB lead to appalling obesity in humans. Clearly from above discussed factors and all the analysis up-to-date suggest that depreciation in the levels of BDNF in human body leads to obesity.

1.11. Clinical implication of BDNF

Research from worldwide justifies the vital portrayal of BDNF and its clinical implications in neurological diseases like Alzheimer's, bipolar diseases, Huntington disease and obesity. Depression can be improved by physical exercise as it increases the BDNF level in brain. Stimulatory action of TrkB expression is enhanced by lithium in turn enhancing expression of BDNF mRNA supporting its role in bipolar disorder while over-expression of the same in hippocampus causes seizures and epilepsy of temporal lobe (Neetu, M. et al., 2012). It activates PLC pathway and modulated the functioning of gastrointestinal system, showing its therapeutic action in dyspepsia and irritable bowel syndrome. BDNF levels in plasma act as bio markers for autism disorder detection which significantly decreases during its early stages. It also maintains the energy homeostasis which explains its role in diabetes mellitus, metabolic syndrome and obesity where both central and peripheral actions of BDNF prevent type 2 diabetes mellitus. Thus BDNF administration could prove to be a therapeutic approach in management as well as prevention of metabolic syndrome, obesity (Brunoni AR et al., 2008).

In experimental mice, BDNF receptor depletion causes obesity and severe hyperphagia. It is also an important mediator for MC_4-R signalling and thus prevents T2DM development in them. BDNF treatment is used in improving sensitivity to insulin as it decreases glucose and HbA1c insulin levels in diabetic mice and also reduces food intake causing loss in body weight. BDNF can be used for antilipidemic and antidiabetic treatment. However, its intrathecal and peripheral administration may cause certain side effects such as progression of tumour and metastasis in human malignancies (Huanhuan Wang. Etal., 2017).

2. Conclusion and future perspectives

The activity of BDNF receptor not only modulates the synaptic activity along with suppression of apoptosis, but also enhances neurogenesis in body. It also participates in pathogenesis of diabetes mellitus and certain cardiovascular diseases thus maintaining inflammation, lipid and glucose level in the body. The deficiency of this protein is related to increased body weight thus its external administration increases the expenditure of energy and decreases food intake showing its intricate role in obesity. The cytoprotective action of BDNF clearly explains its role other neurological diseases as well where the basic mechanism involved is protection of neuronal cells (Hall, K. D. et al., 2012). The secretion of BDNF by gut also explains its participation in various gut related disorders while various attempts to increase its production with the help of various co-factors like dexamethasone and vitamin B_{12} regulates its expression. Thus the endogenous peptides of BDNF can be exploited as a novel protein for understanding its role in health and other metabolic disorders. Altogether, we can say that BDNF participates in upgrading body glucose level and enhancement of energy expenditure. However, BDNF faces a limitation in clinical administration due to its lower bioavailability, shorter half-life and poor penetrability through blood brain barrier. Also, intrathecal or intravenous injection did not produce any reliable effects and caused an inflammatory state along with alteration of the circulating cytokines (Gao and Horvath, 2014). The experimental studies conducted so far focused on alteration in plasma glucose, insulin and lipid levels after administration of BDNF but does not present changes in inflammatory markers in obesity. Thus, further experiments and investigations are called for to understand the contribution of BDNF and its effect in obesity.

Funding source

Any funding was not received for this present review.

Declaration of competing interest

The author declares no conflict of interest in preparing the present review.

Acknowledgement

The present study received no funding from any source or any governing body.

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