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Review Article

(Epi)genetic Aspects of Metabolic Syndrome Pathogenesis in Relation to Brain-derived Neurotrophic Factor Expression: A Review

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Abstract

A key element in the pathogenesis of metabolic syndrome (MetS) is the reprogramming of hypothalamic cells at the genetic level (in the prenatal phase), which leads to neuroinflammation. We hypothesize that alterations in the structure of hypothalamic neurons mediated by (epi)genetic alterations are directly related to impaired expression/production of neurotrophins and neurotransmitters that control the metabolism of substances in the brain and periphery, including brain-derived neurotrophic factor (BDNF). The aim of this review is to describe the molecular genetic and epigenetic role of BDNF in the development of MetS. Articles entered into the National Library of Medicine Medline database via the PubMed interface were used to create this review. We attempted to include as much literature as possible, including reviews, animal studies, cell culture studies, and clinical trials. Studies on BDNF point to its role in metabolic processes, including glucose, insulin, and cholesterol homeostasis. Evidence-based studies show that multiple genes in close proximity to BDNF are involved in the development of MetS. Studies aimed at analyzing BDNF in metabolic diseases using different biological samples will reveal clear pathophysiological links between processes in the brain and in the periphery.

Keywords: Metabolic syndrome; Brain-derived neurotrophic factor; MetS; Obesity; Hypothalamus; Epigenetics; Histones.

Abbreviations: AKT, protein kinase B; AMPK, 5′-adenosine monophosphate-activated protein kinase; ARC, arcuate nucleus; Bax, B-cell lymphoma 2-like protein 4; BBB, blood-brain barrier; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CREB, cyclic adenosine monophosphate response element-binding protein; DRP1, dynamin-related protein 1; ERK, extracellular signal-regulated kinase; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HFD, high-fat diet; HMGSR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IR, insulin resistance; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MetS, metabolic syndrome; MFF, mitochondrial fission factor; miR, microRNA; NF-kB, nuclear factor kappa B; NTRK2, neurotrophic receptor tyrosine kinase 2; p75NTR, p75 neurotrophin receptor; PCK, phosphoenolpyruvate carboxykinase; PGC-1a, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; PINK1, phosphatase and tensin homolog-induced kinase 1; PLCg, phospholipase C gamma; POMC, pro-opiomelanocortin; PRKAA, protein kinase adenosine monophosphate-activated catalytic subunit alpha; PRKN, parkin; PVH, paraventicular nucleus; TrkB, tropomyosin B kinase receptor.

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Introduction

Metabolic syndrome (MetS) is a complex and multifactorial disease of the 21st century that affects 20–25% of the world's population.[1] The components of MetS include obesity, type 2 diabetes mellitus, hyperinsulinemia, insulin resistance (IR), hypercholesterolemia, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and systemic metabolic inflammation, which lead to severe disease and premature mortality.[2]

The hypothalamus is the major brain structure that regulates eating behavior and plays a key role in the development of MetS. The primary role of the brain (hypothalamus) in the development of MetS has been confirmed by the proven link between the development of psychoneurotic disorders and MetS.[3] MetS is also associated with the development of cancer.[4] The development of both diseases can be mediated by a malfunction of the hypothalamus and brain structures.

Structural and molecular changes are observed when analyzing the brain of MetS patients and its components against a background of increased aging.[5] The early manifestation of MetS is associated with a decrease in brain tissue integrity (according to magnetic resonance imaging data), changes in serum high-density lipoprotein cholesterol (HDL-C), triglycerides, body mass index

(BMI), and diastolic blood pressure. Frontotemporal morphometric disturbances are also observed in MetS. In addition, changes in the convolutions of the cerebral cortex (responsible for reward, taste, and impulse regulation related to food) are associated with brain functions and behaviors that increase the risk of MetS.[6]

Molecular genetic studies on animal models and meta-studies conducted on large cohorts of MetS patients have identified many aspects and signaling pathways involved in the development of the disease, but an effective drug that can prevent and stop the global spread of MetS has not yet been proposed, even after a series of clinical trials. This is because we do not fully understand the specific cause of MetS. New areas of science that have developed rapidly over the last decade (e.g., epigenetics and transgenerational inheritance) point to another fundamental reason for the development of MetS, linking the internal and external aspects of pathogenesis and allowing us to look at deeper connections when studying this disease. At the same time, transient changes in the genome (e.g., methylation and acetylation), which can be inherited among generations and stabilized due to environmental factors, may play a key role in MetS.

A key element in the pathogenesis of MetS might be the reprogramming of hypothalamic cells at the genetic level (in the prenatal phase), which leads to neuroinflammation. At the same time, neuroinflammation of the hypothalamus, which occurs in those who consume a Western diet, leads to the development of peripheral inflammation and creates a vicious cycle of neuro-/meta-inflammation.[7] The hypothalamus also regulates the body's endocrine functions and cholesterol metabolism, which are impaired in MetS. We hypothesize that alterations in the structure of hypothalamic neurons mediated by (epi)genetic alterations are directly related to impaired expression/production of neurotrophins and neurotransmitters that control the metabolism of substances in the brain and periphery, including brain-derived neurotrophic factor (BDNF).

The aim of this review is to describe the molecular genetic and epigenetic role of BDNF in the development of MetS. Articles entered into the National Library of Medicine Medline database via the PubMed interface were used to create this review. Articles of interest were searched by citation and keywords (e.g., metabolic syndrome and BDNF, metabolic syndrome and hypothalamus, hypothalamus/blood and BDNF, cholesterol and brain, cholesterol and BDNF, metabolic syndrome and epigenetic theories, obesity and BDNF, obesity and hypothalamus, obesity and Developmental Origins of Health and Disease, obesity and transgenerational epigenetic inheritance, mtDNA/histone/microRNA (miR)/methylation/mutation and BDNF, BDNF and treatment), and automatically suggested related articles were also considered. We attempted to include as much literature as possible, including reviews, animal studies, cell culture studies, and clinical trials.

Epigenetics as a missing link in the pathogenesis of MetS

Epigenetic theories on the development of MetS

Transgenerational inheritance, fetal reprogramming, the Barker hypothesis, and the theory of developmental origins of health and disease consider the influence of environmental factors on the development of organ systems in the offspring and their relationship with the risk of developing diseases in adulthood and in subsequent generations. Transgenerational epigenetic inheritance describes the influence of stress to which parents are exposed (e.g., hunger, life threat, and separation from parents) on phenotypic changes in methylation processes in their offspring (e.g., three or more generations in the female line or two or more generations in the male line).[8] The important role of transgenerational inheritance in the development of MetS has been confirmed by studies showing a high risk of developing MetS components in the offspring against a background of the same pathologies in the parents.[9] This could play a key role in the formation of the hypothalamic structures: arcuate nucleus (ARC), paraventricular nucleus (PVH), lateral hypothalamic area, dorsomedial hypothalamic nucleus, and ventromedial nucleus of the hypothalamus, which receive and integrate metabolic signals from the peripheral organs and thus regulate the body's energy homeostasis.[10]

In addition, the prenatal period is crucial for the formation of hypothalamic structures involving signaling cascades (e.g., Notch-Hes1/5-Mash1-Ngn2/3-Nhlh2/PC1) and hormones (e.g., leptin, ghrelin, and insulin). First, the processes of neurogenesis are set in motion, then the nuclei differentiate. ARC melanocortin neurons project to different brain regions and regulate feeding behavior and energy metabolism.[11] Pro-opiomelanocortin (POMC) neurons are activated under conditions of high energy availability (e.g., elevated blood insulin and leptin levels) and release a peptide that is converted to alpha-melanocyte-stimulating hormone: When it interacts with melanocortin-4 receptors, the process of food intake is inhibited. A Western diet has been shown to lead to impaired glucose sensing in POMC neurons, altered mitochondrial dynamics, and inhibition of POMC firing as a result of impaired Ca^{2+} processing.[12] Moreover, agouti-related peptide/neuropeptide Y neurons release gamma-aminobutyric acid and positively regulate feeding behavior.[13] In this case, acute activation of agouti-related peptide neurons leads to impairment of systemic insulin sensitivity.

Furthermore, transgenerational effects may be mechanistically mediated by small RNAs, DNA methylation, histone modification, and cellular reprogramming in the hypothalamus. In DNA methylation, DNA methyltransferases, which use S-adenosylmethionine as a methyl donor, add a methyl group to the fifth position of cytosine to form 5-methylcytosine.[14] An increased DNA methyltransferase level correlates with increased gene expression. DNA demethylation is an active enzymatic process that aims to remove/modify the methyl group of 5-methylcytosine to form unmodified cytosine. The ten-eleven translocation methylcytosine dioxygenase family, activation-inducible cytidine deaminase, growth arrest- and DNA damage-inducible protein 45α, and thymine DNA glycosylase are involved in this process.[15]

Histones are proteins that interact with each other and form an octamer around which DNA is wrapped. The N-terminal tails of histones can undergo post-translational modifications that alter the structure of chromatin and affect gene transcription.[16] Mammals have small amounts of N6-methyldeoxyadenosine.[17]

Environmental factors in the prenatal period influence the process of DNA methylation of placental cells and alter gene expression.[18] Methylated histones can be maintained during cell division, and the complex responsible for methylation of histone H3 on lysine 27 can be fixed on chromatin by DNA replication and passed down through generations. Additionally, the process of RNA interference plays an important role in the regulation of gene expression and influences enzymes that modify histones and binding proteins.[19]

Fetal reprogramming examines the effects of the intrauterine environment on the health of future generations. For example, famine suffered by parents (e.g., in the Netherlands during 1944–1945 and the Great Chinese Famine) is associated with the development of

obesity in offspring, hypercholesterolemia, and cardiovascular disease.[20] Moreover, high methylation of genes associated with cholesterol transport and aging (e.g., *IL10*, *LEP*, *ABCA1*, *GNASAS1, MEG3*, *INSIGF2*) but low methylation of insulin growth factor 2 has been found.[21]

According to the "Barker hypothesis," the mother's eating behavior influences neuropsychiatric changes in the offspring and contributes to hyperactivation of the hypothalamic reward system and to overeating.[22] Studies in newborns and animals have confirmed Barker's postulate about the link between intrauterine developmental delay and a high risk of developing components of MetS and the inheritance of defects across generations.[23] Presumably, catch-up growth in the neonatal period in children with intrauterine developmental delay is associated with a high ratio of low-density lipoprotein cholesterol to HDL-C, against a background of changes in circulating cholesterol acceptors in the blood serum.[24] Furthermore, type 2 diabetes mellitus and maternal gestational diabetes provoke placental methylation of genes regulating mitochondrial function and inflammation.[22]

The concept of transgenerational epigenetic inheritance is related to the theory of developmental origins of health and disease, which emphasizes the role of the environment during intrauterine life in predisposition to disease in adulthood by altering the number of copies of mtDNA.[25] The above studies confirm the role of (epi)genetic changes in the hypothalamus in MetS in offspring.

The epigenetic role of maternal obesity

A high-fat diet (HFD) negatively affects the organs of the reproductive system of the maternal body and contributes to a pro-inflammatory phenotype of the cells. The effects of maternal obesity on the hypothalamus of the offspring are similar to those seen in adults.[26] Inflammatory mediators and fatty acids pass through the blood-brain barrier (BBB) and trigger inflammation of the hypothalamus in the fetus.[27] Molecular mechanisms include alterations in synoptic neuronal communication; increased alanine, adenosine, and glutamine levels mediating lipotoxicity; impaired signaling from cerebrospinal fluid; and insulin, phosphoinositide 3-kinase/protein kinase B, adenosine monophosphate-activated protein kinase, and forkhead box transcription factor 1/2 signaling.[28] In addition, the work of the cells that line the medial elevation are in contact with the BBB and protect against obesity—the tanycytes—is disrupted.[28]

Changes in the hypothalamus precede the development of metabolic disorders in the children of obese mothers.[29] Moreover, astrocyte gliosis is associated with hypothalamic dysfunction (neuroinflammation) and induces meta-inflammation, IR, and fetal obesity.[30] Perinatal levels of glucose, insulin, leptin, and free fatty acids also can cause changes in the hypothalamus. In animals, a maternal HFD has been shown to lead to a high expression of peptide tyrosine tyrosine and a low expression of POMC in the hypothalamus, resulting in high food intake.[31] Furthermore, excessive weight gain during pregnancy is associated with the measurement of genome methylation sites in cord blood and has been linked to obesity in the offspring at a later age.[32]

Fatty acids (e.g., oleic acid and palmitic acid) and triglycerides have been shown to increase the expression of lipoprotein lipase in astrocytes *in vitro*, which promotes the formation of free fatty acids.[33] A HFD leads to aging of the hypothalamus and amygdala, thus inducing the expression of markers of cell aging and excessive accumulation of lipid droplets in microglia with the formation of cells with the phenotype of accumulation of lipids in senescence (perilipin 2-positive cells).[34,35] In aging mice, lipids are detected in neurons, astrocytes, appendix cells, and ionized calcium binding adaptor molecule 1-positive cells. Additionally, in cultures of mouse hypothalamic cells and the N9 cell line, stimulation by lipopolysaccharide was accompanied by an accumulation of lipid droplets.[34] The aging human hippocampus contains lipid droplets and high numbers of ionized calcium binding adaptor molecule 1-positive and perilipin 3-positive cells.[34] Moreover, high numbers of senescent proinflammatory chemokine (C-X-C motif) ligand 1-positive/interleukin 6-positive/perilipin 2-positive cells (40% astrocytes, 19% microglia) have been demonstrated to be associated with genome instability and to localize near the left ventricle around the periaqueductal gray region of the brain in mice on a HFD.[35]

A HFD induces infiltration of monocytes/macrophages from the bone marrow into the central nervous system and hypothalamus (in the ARC), increasing the number of microglial cells and promoting neuroinflammation.[36] Hypothalamic macrophages can be generated from visceral adipose tissue under *in-vitro* conditions in mouse models.

Neonatal overfeeding (as well as ghrelin, leptin, and glucose treatment) in mice leads to the development of IR in ARC neurons. In addition, maternal obesity is thought to alter the sensitivity of the hypothalamus to fatty acids and their metabolism in the ARC and PVH.[37] Analysis of umbilical cord blood and the neonatal body composition showed associations between maternal obesity and hyperglycemia as well as intrauterine fetal IR. Maternal glucose intake in those with gestational diabetes mellitus (GDM) altered fetal brain activity in association with gliosis in the ARC observed in early pregnancy.[38] Maternal GDM also caused the increased expression of POMC in the ARC in female offspring, leading to metabolic changes in adult offspring (Wistar rats).[39]

It has been shown that postnatal epigenetic maturation of the ARC occurs in genomic regions that are associated with BMI in humans and depends on the cell type and sex.[40] miRs regulate phenotypic changes in offspring under the influence of the maternal environment. The expression of 30% of the miRs localized in the ARC changes in the postnatal period.[41] At the same time, miR-103/107 is required for the conversion of progenitor cells expressing *POMC* into mature neuropeptide Y neurons.[42]

The offspring of obese female mice exhibit altered levels of axon growth-controlling signals (e.g., netrin receptors Dcc and Unc5d) in the ARC compared to the offspring of normal-weight mice, against a background of reduced innervation of PVH-neuropeptide Y fibers. Injury to the semaphores and a novel system in the hypothalamus also led to early obesity in fish, mice, and humans. This is mediated by the presence of 40 rare semaphore 3 signal transduction variants that are associated with impaired signaling in melanocortin chains in humans with severe obesity.[43]

The Notch signaling pathway regulates neurogenesis in the hypothalamus and is activated in the neonatal period by a decrease in the expression of the proneuronal transcription factor *Mash* in the offspring of obese mothers.[31] Thus, maternal obesity leads to hypothalamic dysfunction in their offspring through epigenetic reprogramming and negative effects on the integrity of the BBB.[44]

The epigenetic role of paternal obesity

Paternal obesity is associated with changes in epigenetic marks in their offspring. A high paternal BMI is associated with hypomethylation of differentially methylated regions of some genes that regulate pre/postnatal growth (e.g., *IGF2*, *PEG3*, and *NNAT*) in the umbilical cord blood leukocytes of the offspring, leading to metabolic disorders.[45]

In male mice, the offspring of obese fathers, a genetic disorder of hepatic lipogenesis has been observed. In rats, the sex-specific transgenerational effects of paternal obesity and a disruption of the hypothalamic-pituitary-gonadal axis have been described.[45] Mechanistically, paternal obesity alters the structure (quality) of the seminal fluid and modifies the sperm epigenetically, disrupting the transcription/translation of genes in the fetus. Epigenetic marks of the sperm can affect DNA methylation, histone modification, small (long) noncoding RNAs, tRNAs, and miRs in the offspring, which have a negative impact on the metabolic and reproductive processes of subsequent generations.

BDNF and the hypothalamus in MetS

Biology of BDNF in the brain

BDNF in the hypothalamus controls neuroendocrine and autonomic processes and plays a protective role against pathologies such as obesity and cancer.[46] Various factors (e.g., inflammation) cause the release of BDNF from brain cells (e.g., neurons, astrocytes, and microglia) or its storage in vesicles (e.g., endosomes).[47] Some studies have shown no association between hypothalamic expression of BDNF and changes in the energy status of the body (as opposed to the cortical structures of the brain), but other studies emphasize the important and poorly understood role of BDNF in the ventromedial hypothalamus as an appetite suppressant (anorexigenic factor).[48,49]

BDNF formation

The precursor of pre-proBDNF is formed in the endoplasmic reticulum and then transported to the Golgi apparatus, where it is cleaved by endoproteolytic proteases. The sorting line, carboxypeptidase E, is responsible for the movement/intracellular transport and sorting of BDNF. Endogenous BDNF is transported anterograde and stored in presynaptic vesicles. Convertases regulate the release of BDNF.[50] BDNF synthesized in the periphery enters the brain through the BBB and acts on the areas of the ventral membrane (e.g., hypothalamic-pituitary-adrenal axis and nucleus accumbens) that regulate the body's metabolism.[51]

Receptors

BDNF exerts a postsynaptic effect on neurons by interacting with the tropomyosin B kinase receptor (TrkB, encoded by the *NTRK2* gene) and a receptor from the tumor necrosis factor family—p75 neurotrophin receptor (p75NTR).[52] As a result of the contact of BDNF with the pre/post-synaptic TrkA receptor, the Ras/Raf-mitogen-activated protein kinase, phosphoinositide 3-kinase/protein kinase B, and phospholipase C gamma-phosphoenolpyruvate carboxykinase signaling pathways are activated. Inhibition of BDNF/TrkB signaling leads to neuronal damage, cellular apoptosis, inhibition of autophagy, and inflammation.[53]

Induction of p75NTR activates the c-Jun N-terminal kinases and nuclear factor kappa B. Deletion of p75NTR in mice was associated with increased energy expenditure and prevented the development of obesity in mice on a HFD. Under hypoxic conditions, BDNF activates p75NTR, leading to neurodegeneration.[54]

It is assumed that the neuroprotective role of BDNF is to restore mitochondrial functions by activating mitophagy and reducing oxidative stress. The protective role of BDNF for mitochondrial biogenesis has been noted in myocytes, astrocytes, and microglia. In the brain, BDNF increases the number of mitochondria in the cell due to the influx of Ca^{2+} and activation of mitophagy through calmodulin-dependent protein kinase, cyclic adenosine monophosphate response element-binding protein, and peroxisome proliferator-activated receptor gamma coactivator 1-alpha, and it also activates the mitogen-activated protein kinase kinase-mitogen-activated protein kinase pathway, regulating mitochondrial respiration. BDNF and peroxisome proliferator-activated receptor gamma coactivator 1-alpha jointly regulate the amount of energy substrates and the formation of synaptic connections in the brain. Mitochondrial homeostasis is also regulated by proBDNF and receptors (p75NTR).[55]

Studies in humans and animals have shown an unclear relationship between the expression of BDNF in the brain and in the periphery. A study of serum BDNF levels in severely obese patients from Saudi Arabia showed a significant correlation between a low BDNF expression and a high BMI.[56] A negative correlation also was found between plasma BDNF levels and IR. Similar results were obtained in experimental animals with diabetes and obesity. The introduction of BDNF into the intracerebroventricular/intraventromedial nucleus of the hypothalamus inhibited hyperglycemia in rats. In addition, a low BDNF concentration in the peripheral blood of obese patients was associated with a visual response to a food signal, resulting in increased food craving.[57] Moreover, amniocentesis revealed a negative correlation between the maternal prepregnancy BMI and the BDNF concentration, confirming the effect of BDNF at the fetoplacental interface (Fig. 1).[58]

BDNF and cholesterol metabolism in the brain

Cholesterol is necessary for the formation of neuronal membranes, synaptogenesis, cytosolic transport/release of vesicles (neurotransmitters), and the work of neurotrophin receptors (e.g, TrkB and p75NTR). Cholesterol biosynthesis in the brain occurs independently *in situ* in astrocytes/neurons and is regulated by two overlapping biochemical pathways, as demonstrated by Bloch and Canducha-Russell.[59] 3-Hydroxy-3-methylglutaryl-coenzyme A reductase catalyzes the limiting step of cholesterol biosynthesis, and cytochrome P450 46A1 promotes the excretion of cholesterol from the central nervous system in the form of 24-hydroxycholesterol.[60] Furthermore, ABC transporters (ABCA1, ABCG1, and ABCG4) promote the efflux of cholesterol from neurons into AroA1 and HDL-C particles, which are released into the cerebrospinal fluid or circulation.[61]

MetS is associated with aging of the body, an increase in the concentration of cholesterol in plasma, and a violation of the structure/function of HDL-C. In addition, a decrease in cholesterol synthesis and an increase in 24-hydroxycholesterol levels in obesity have been observed in the brain (of rodents).[62] Apolipoprotein E transports cholesterol from astrocytes to neurons. The link of systemic cholesterol metabolism is 27-hydroxycholesterol, which permeates the BBB.[63] 27-Hydroxycholesterol promotes cholesterol efflux through liver X receptors and suppresses *de novo* cholesterol production by insulin-induced genes.[64] However, in animals fed a HFD, 27-hydroxycholesterol induced hypercholesterolemia in the brain and a neurotoxic effect, violating the integrity of the BBB.[65]

The important role of BDNF in glucose homeostasis and cholesterol biosynthesis has been demonstrated. Exogenous cholesterol has been shown to restore the impaired signaling of BDNF-TrkB,[66] and activation of BDNF-TrkB induced genes for cholesterol biosynthesis.[67] MetS is also associated with the development of Alzheimer's disease, which is characterized by high cholesterol levels and low expression of BDNF and TrkB in the brain.[68]

Mechanistically, the interaction of BDNF with TrkB enhances

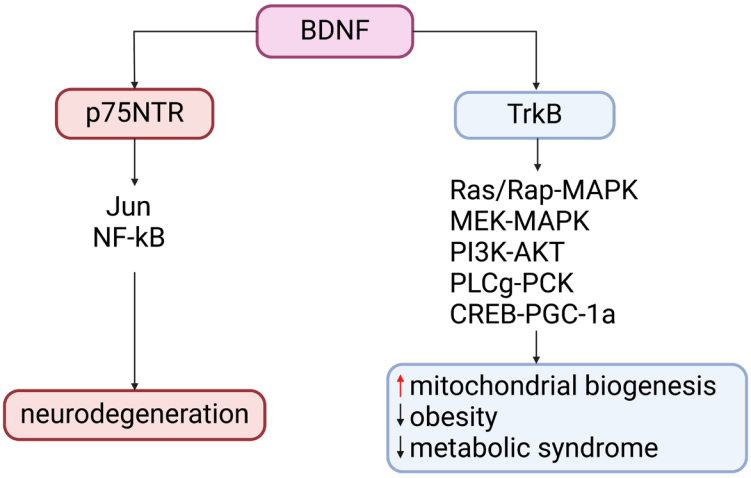

Fig. 1. Signaling pathways regulated by BDNF in the brain. AKT, protein kinase B; BDNF, brain-derived neurotrophic factor; CREB, cyclic adenosine monophosphate response element-binding protein; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; NF-kB, nuclear factor kappa B; PCK, phosphoenolpyruvate carboxykinase; PGC-1a, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; PLCg, phospholipase C gamma; TrkB, tropomyosin B kinase receptor.

the regulation of the key enzyme of cholesterol biosynthesis of the 3β-hydroxy-3β-methylglutaryl-coenzyme A reductase gene in neurons and neuron-like cells of the SH-SY5Y line, enriching lipid rafts with cholesterol and increasing the expression of presynaptic proteins. BDNF increases the expression of the leucine-rich repeat beta receptor (a regulator of cholesterol homeostasis), suppressing the absorption of cholesterol by neurons and preventing cellular apoptosis. Activation of the BDNF-TrkB-Erk1/2 signaling pathway regulates apoE and ABCA1 biosynthesis, regulating the transport of cholesterol from astrocytes to neurons.[69] p75NTR also regulates the metabolism of enzymes involved in the biosynthesis of cholesterol in the brain through the activation of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, farnesyl diphosphate synthase, and 7-dehydrocholesterol reductase. In addition, p75NTR regulates cholesterol biosynthesis genes via the neurotrophin receptor interacting factor receptor *in vitro* and *in vivo*.

Genetic alterations of BDNF

The structure of the BDNF gene is complex and is regulated by nine functional promoters, which control the formation of different transcripts, depending on the stress signal.[51] Severe obesity in childhood has been associated with a chromosomal rearrangement (violation of one copy (allele) of the *BDNF* gene) and the BDNF missense mutations p.Thr2I1e and p.Arg209Gly. Deletion of *Bdnf/TrkB* in the hypothalamus of mice and polymorphism of *Bdnf/TrkB* in humans have been associated with metabolic dysfunction, obesity, and blocked anorexigenic signaling.[70] In hypothalamic astrocytes, the BDNF-TrkB.T1 signaling cascade regulates the activation of glutamatergic anorectic neurons by altering the synaptic tone of neurons. Additionally, elimination of BDNF in the hypothalamus blocked activation of the ventromedial nucleus of the hypothalamus neurons by altering the density of synaptic contacts,[47] which is part of a comprehensive molecular cellular mechanism.

Several genome-wide association studies have identified approximately 14 single nucleotide polymorphisms in the *BDNF* region that are associated with BMI,[71] some of which have been linked to compulsive overeating in patients undergoing bariatric surgery. Moreover, microdeletions at the *BDNF* gene locus are associated with obesity and developmental delay.[72] Furthermore, mutations (deletions) of the *NTRK2* gene in the hypothalamus mediate hyperphagic eating disorder and obesity. BDNF-TrkB activation is also an important regulator of a new population of hypothalamic neurons in the PVH that control eating behavior.[73]

Chromosomal inversion suppressing one *BDNF* allele and haplo-sufficiency of the retinoic acid gene leading to low BDNF expression in humans is associated with cognitive impairment, abnormal weight gain, and the development of MetS.[74] The effect of glutamate on the hypothalamus and adipose tissue in mice has been associated with a decrease in BDNF expression, hyperphagia, weight gain, cholesterol, and triglycerides. In addition, a HFD has been found to disrupt glycerol-3-phosphate acyltransferase 4/adenosine monophosphate/cyclic adenosine monophosphate response element-binding protein/BDNF signaling and contribute to the development of major depressive disorder in obesity (Fig. 2).[75]

At the same time, in carriers of single nucleotide polymorphisms of the *BDNF* gene (*rs10835211*), obesity parameters depend on fiber and macronutrient consumption.[76] The myokine apelin reduces the activity of the hypothalamic-pituitary-adrenal system and increases the expression of BDNF in the hippocampus, thereby reducing stress-induced depression in rats. Apelin also plays a protective role in the development of neurological/psychiatric disorders, obesity, and MetS.[77]

It has been demonstrated that the pathways that regulate energy balance consistently bind to melanocortin-4 receptor and BDNF in the hypothalamus. Autoregulatory gene therapy with the *BDNF* vector in heterozygous Mc4r mice suppressed hyperphagia, obesity, and MetS.[78] Genetic changes in *BDNF*, therefore, have a direct effect on the function of brain neurons and the body's metabolism via signaling cascades that are involved in the development of MetS.

Epigenetic changes of BDNF in the brain

The key role of BDNF in growth, development, central/peripheral nervous system nutrition, follicle formation, implantation/placentation, and maternal and fetal health has been established.[79] Epi-

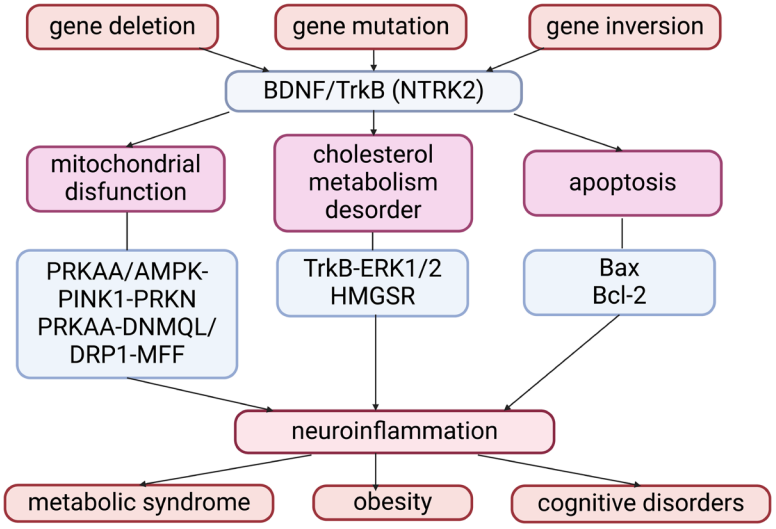

Fig. 2. The relationship between BDNF and the development of metabolic diseases. AMPK, 5′-adenosine monophosphate-activated protein kinase; Bax, B-cell lymphoma 2-like protein 4; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; DRP1, dynamin-related protein 1; ERK, extracellular signal-regulated kinase; MFF, mitochondrial fission factor; NTRK2, neurotrophic receptor tyrosine kinase 2; PINK1, phosphatase and tensin homolog-induced kinase 1; PRKAA, protein kinase adenosine monophosphate-activated catalytic subunit alpha; PRKN, parkin; TrkB, tropomyosin B kinase receptor; HMGSR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase.

genetic modulations such as DNA methylation, histone modifications, and the regulation of noncoding RNAs play an important role in BDNF expression.

Methylation

BDNF gene transcripts are regulated by DNA methylation. Prenatal stress-induced methylation of the *BDNF* gene (in rats) is associated with a decrease in BDNF protein expression in the brain of male offspring.[80] Prenatal stress decreased the expression of BDNF transcripts III, IV, VI, and IX in the adult rat brain. This occurred against a background of increased DNA methyltransferase 1/ten-eleven translocation methylcytosine dioxygenase 1 and high 5-methylcytosine/5hmC levels in the promoter regions of BDNF in mice.[81]

A HFD contributes to oxidative stress and a reduction in BDNF expression that mediates damage to neurogenesis and synaptic plasticity, alterations in the formation of projections of melanocortin neurons in the hypothalamus, and the maintenance of disorders in subsequent generations in the postnatal period.[82] A mechanism for transgenerational inheritance of disease in the offspring of obese mothers fed a HFD has been proposed through suppression of the insulin pathway, which promotes abnormal methylation/acetylation of BDNF in the ovaries of mothers.[83] Moreover, stress induces abnormal methylation of BDNF promoters in human blood samples.[84] Methylation of the *BDNF* gene also has been detected in the placenta, umbilical cord, and venous blood of women who had suffered traumatic events during pregnancy and in buccal mucosa samples from newborns at 2 months of age (exposed to intrauterine stress).[85]

Methyl-CpG-binding protein 2 (MeCP2) interacts with methylated DNA in the brain and inhibits/activates gene transcription. Mutations of MeCP2 and knockout in hypothalamic neurons (e.g., *POMC ARC* and *Sim1*) lead to hyperphagia and obesity.[86] The *MECP2* gene is involved in the development of MetS, and the MECP2 protein controls body weight through post-translational modifications.[85] It has been found that mice with a *MeCP2* mutation/deletion have lower levels of BDNF in the brain. At the same time, BDNF is involved in the phosphorylation of MeCP2 (antidepressant effect).[87]

Hypomethylation of the promoter (p) I BDNF has been shown to alter the expression of BDNF and to lead to abnormal eating behavior. Three CpG sites associated with obesity are located in two BDNF promoters. High methylation of pII BDNF and low methylation in pIV BDNF have been observed in carriers of the rs10767664 allele.[88]

Histone modifications

Fasting stress has been revealed to cause increased methylation of the tumor necrosis factor promoter histone H3 on lysine 27, which is associated with suppression of BDNF expression in the hypothalamus of chickens.[89] Histone acetyltransferases and deacetylases mediate the acetylation of histones by N-terminal lysine. The stress response induces acetylation of histone 3 at lysine 9, histone 3 at lysine 14, and histone 4 at lysine 12; histone deacetylase-mediated deacetylation; and suppression of BDNF expression in some areas of the brain.[90] Furthermore, gestational stress (in animals) has been shown to increase the expression of histone deacetylase 1/2 and decrease the expression of acylated-histone 3 at lysine 14, which is associated with a decrease in the expression of the *BDNF* gene in the offspring.[91]

miRs

miRs alter transcription by post-transcriptional modulation of the mRNAs of the target genes (so-called RNA interference) when they bind to the 3′-untranslated regions. Maternal obesity increases the amount of miR-210, which targets *BDNF* mRNA, in the placenta of female fetuses and decreases pro-BDNF in the placenta of male fetuses.[92] The maternal BMI before pregnancy is also associated with the expression of miR-210, which inhibits the expression of the *BDNF* gene in the placenta and umbilical cord blood.[93] Additionally, increased expression of miR-30a-5p inhibits *BDNF*, which is associated with methylation of the *BDNF* gene promoter

and damage to neuronal connections.[94] miR-30a-5p is also associated with increased adipogenesis. Maternal obesity leads to a decrease in the plasma miR-22 levels, while miR-22 decreases the expression of *BDNF* at both the mRNA and protein levels.[95] In the blood cells of newborns of overweight mothers, the level of miR-155 decreased, while a specific link between miR-155-5p/miR-155 and BDNF has been confirmed.[96] GDM and type 2 diabetes mellitus (cardiomyopathy) are associated with overexpression of miR-195-5p, which targets BDNF.[97] miR-191 is involved in the development of IR and inhibits the expression of BDNF,[94] which has been confirmed by the association of elevated miR-191a-5p levels in cognitive disorders. The important role of miR-206 in preventing the development of hepatosteatosis and hyperglycemia and in the resolution of myogenic disorders has been established. Moreover, elevated miR-206-3p levels have been associated with anxiety and decreased blood levels of BDNF in rats.[94] Pregnancy complicated by preeclampsia is characterized by the overexpression of miR-202-3p, which targets BDNF in the pathogenesis of depression.[97] Meanwhile, miR-134 in the brain (hippocampus) of mice interacts with the 3′-untranslated region of BDNF and thus contributes to chronic depression.[98] At the same time, high levels of miR-134 have been detected in the peripheral blood of pregnant women with GDM.[99] In addition, the serum level of miR-497 is a prognostic factor for atherosclerosis and cerebral infarction, which are associated with high glucose levels.[100] The target gene for miR-497 is also BDNF. The direct functional target for miR-103 is BDNF in brain tissues (and cell lines) in gliomas. Furthermore, an increase in the miR-103 level in the blood plasma of obese mothers has been found.[101]

Studying the epigenetic changes of BDNF in brain cells, peripheral blood, and various body tissues to identify the most important and significant changes targeting BDNF will allow us to understand the pathophysiological features of MetS and its components as well as to develop molecular structures capable of preventing the development of pathologies transmitted from parents to offspring.

Drug designs and perspectives for targeted therapy against BDNF

Herbal preparations

Natural anthraquinones (e.g., emodin, diacerin, and catenarin) are considered potential therapeutic agents with antidiabetic effects.[102]

Emodin

Emodin restores cognitive function by reducing inflammation and apoptosis through activation of BDNF/TrkB signaling. In obese C57BL/6J mice, emodin normalized glucose sensitivity by reducing adipose tissue dysfunction. Emodin regulates lipid metabolism and adenosine monophosphate-activated protein kinase, peroxisome proliferator-activated receptors, and nuclear factor kappa B signaling pathways, preventing the development of obesity, hyperlipidemia, nonalcoholic fatty liver disease, diabetes, atherosclerosis, and osteoporosis.[103] Emodin also has anticancer, anti-inflammatory, and anti-oxidant potential.[102]

Diacerein

Diacerein induces BDNF expression by inhibiting an increase in interleukin 1β levels, thus preventing depressive behavior in animals and the development of MetS. Catenarin has an antidiabetic effect.[102] Glycosides are secondary metabolites of plants with medicinal potential (antidepressants). Phytoglycosides modulate the activity of BDNF in the hippocampus, and anthocyanins of plant origin have a positive effect on the body's inflammatory status in obesity.[104]

Chemical preparations

Metformin

Metformin is used in the treatment of MetS and diabetes mellitus and improves the plastic properties of neurons. Metformin post-transcriptionally induces the MECP2E1/E2-BDNF signaling cascade in the brain. A study on childhood obesity has shown that the *BDNF* gene is a target of metformin.[105] At the same time, long-term metformin use may alter biochemical processes in the transcription of BDNF without affecting the protein levels, which requires further investigation.

Semaglutide

Semaglutide is an agonist of glucagon-like peptide-1, which is used in the treatment of obesity. Semaglutide activates the phosphoinositide 3-kinase/protein kinase B signaling pathway, blocks glycogen synthase kinase-3 beta, and triggers the process of remyelination of nerve fibers via the cyclic adenosine monophosphate response element-binding protein/BDNF axis.[106]

Empagliflozin

Empagliflozin is an inhibitor of sodium-glucose transporter 2, which is used to treat type 2 diabetes mellitus and heart failure. Studies in mice have shown the efficacy of this drug against obesity, IR, and hepatic steatosis under HFD conditions. Empagliflozin has been shown to increase BDNF levels in the brain.[107]

Minocycline

Minocycline has been demonstrated to reduce inflammation and hyperphagia by regulating the activity of neurons in the hypothalamus of mice.[108] The ability of minocycline to increase BDNF expression also has been highlighted.[109]

Physical activity as therapy

Physical exercise can improve cognitive brain function in metabolic disorders via epigenetic mechanisms by altering the expression of BDNF.[110] Current research aims to develop lipidic nanomolecular antidiabetic agents based on recombinant BDNF to obtain a structure with low pharmacological restrictions for clinical trials.[111]

Attempts to summarize the current literature on the role of epigenetic transgenerational inheritance and hypothalamic dysfunction, with a focus on BDNF expression/production and functional potential in the pathogenesis of MetS, are complicated by several factors. In particular, there are insufficient clinical data to assess the expression of BDNF in the brain during the development of MetS (and its components) and its precise (detailed) role and molecular mechanisms of action on mitochondrial (and other organelle) biogenesis in different brain structures (as well as heterogeneous cell populations). We have attempted to link the pathogenesis of MetS at the molecular and epigenetic level to the transmission of pathology between generations, which is undoubtedly of great interest, but also raises the problem of studying specific factors (e.g., BDNF) in offspring (more than one generation) in order to collect detailed results and a possible application in propaedeutics. An undeniable limitation of this re-

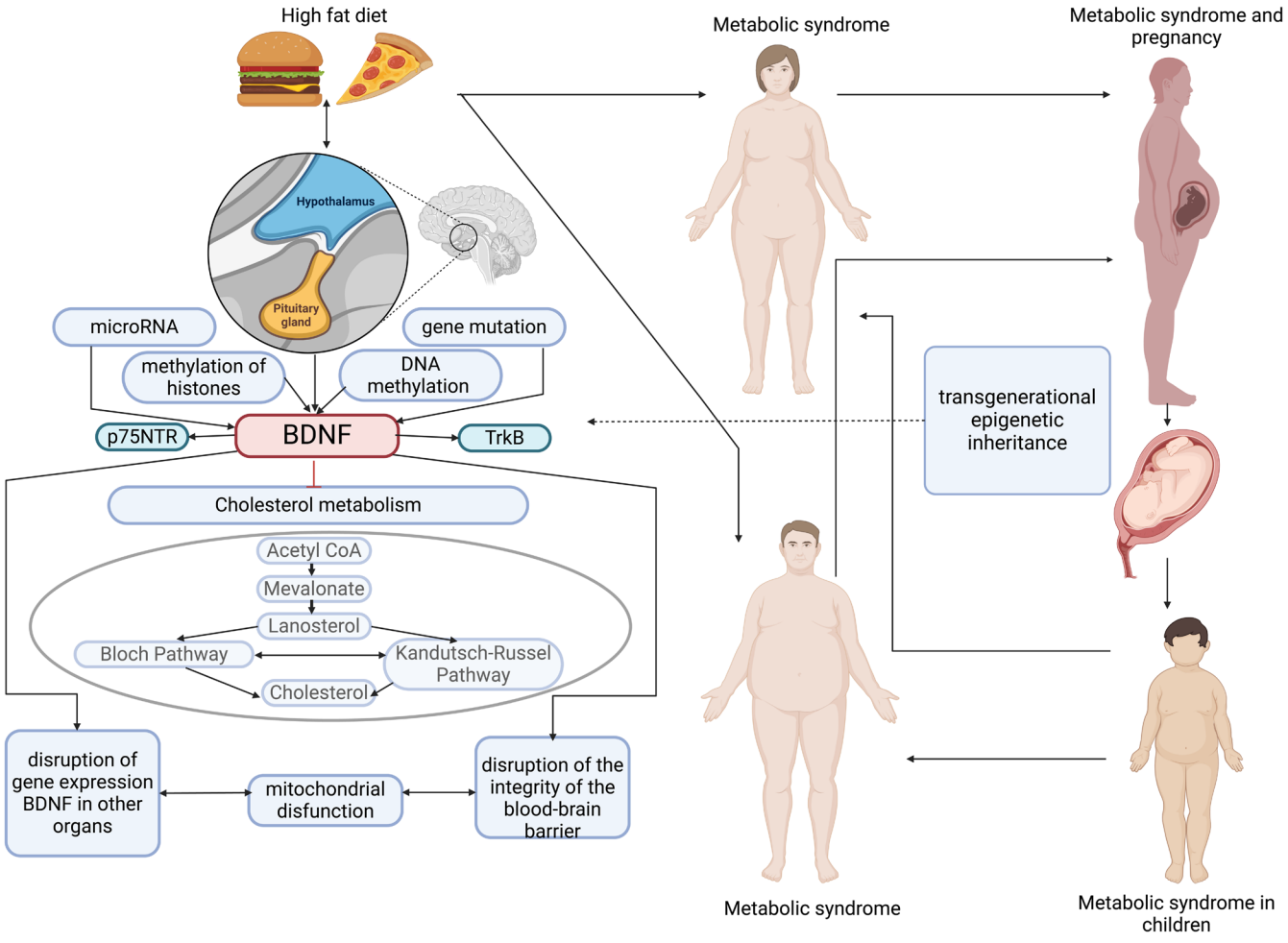

Fig. 3. On the one hand, a high-calorie diet is associated with structural and functional changes in brain structures, particularly in the hypothalamus. This is due to epigenetic components: microRNA, histone and DNA methylation, gene mutations that alter the expression and production of the neurotrophic factor BDNF, which interacts with the receptors p75NTR and TrkB. BDNF has a regulatory effect on cholesterol metabolism in the brain. At the same time, there is a link between a disruption of the integrity of the blood-brain barrier, BDNF expression (also in other organs and tissues) and mitochondrial dysfunction. On the other hand, a high-calorie diet and metabolic syndrome in mothers and fathers contribute to fetal developmental disorders and predispose offspring to the development of metabolic syndrome. This pattern is explained by the theory of transgenerational inheritance, which links changes in BDNF expression to the development of metabolic diseases.BDNF, brain-derived neurotrophic factor; p75NTR, p75 neurotrophin receptor; Acetyl-CoA, acetyl coenzyme; TrkB, tropomyosin B kinase receptor.

view is the insufficient coverage of the role of BDNF in the brain (in the hypothalamus) during obesity and MeS in animals and humans under *in vivo* conditions; therefore, conclusions about the role of BDNF can be drawn in most cases by reference to changes in BDNF in the peripheral blood. Another drawback is the lack of direct evidence (based on clinical studies) for the effect of drugs on changes in BDNF specifically in the brain in those with metabolic disease.

Conclusions

Studies on BDNF point to its role in metabolic processes, including glucose, insulin, and cholesterol homeostasis. Evidence-based studies show that a significant number of genes are involved in the development of MetS with regions in close proximity to BDNF. Studies aimed at analyzing BDNF in metabolic diseases using different biological samples will reveal clear pathophysiological links between processes in the brain and in the periphery. A broad spectrum of signaling pathways controlling MetS development is regulated by BDNF expression, and its modulation by nanostructural, molecular, plant, and chemical structures can radically change the understanding of MetS inheritance and development as well as stop development at the root (Fig. 3).

A more detailed understanding of the molecular and (epi)genetic mechanisms involved in the development of pathophysiological traits and disorders (in brain cells) associated with the development of MetS will allow us to identify potential gene/molecule/protein targets for the development of structures with therapeutic potential and to identify predictors of this pathology (and concomitant disorders) for future use in propaedeutics.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (NT, LL), acquisition of data (NT, KY, OK, MV, MB), analysis and interpretation of data (NT, LL), drafting of the manuscript (NT), critical revision of the manuscript for important intellectual content (MV, LL), administrative, technical, or material support (LL, PI), and study supervision (MV, OK, LL). All authors have made a significant contribution to this study and have approved the final manuscript.

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