



Review Article

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



Natalia Todosenko¹, Kristina Yurova¹, Olga Khaziakhmatova^{1*} , Maria Vulf¹, Maria Bograya¹, Pavel Ivanov¹ and Larisa Litvinova^{1,2}

¹Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russia; ²Laboratory of Cellular and Microfluidic Technologies, Siberian State Medical University, Tomsk, Russia

Received: December 27, 2023 | Revised: January 03, 2024 | Accepted: February 28, 2024 | Published online: May 08, 2024

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-κB, nuclear factor kappa B; NTRK2, neurotrophic receptor tyrosine kinase 2; p75NTR, p75 neurotrophin receptor; PCK, phosphoenolpyruvate carboxykinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; PI3K, phosphoinositide 3-kinase; PINK1, phosphatase and tensin homolog-induced kinase 1; PLCγ, phospholipase C gamma; POMC, pro-opiomelanocortin; PRKAA, protein kinase adenosine monophosphate-activated catalytic subunit alpha; PRKN, parkin; PVH, paraventricular nucleus; TrkB, tropomyosin B kinase receptor.

*Correspondence to: Olga Khaziakhmatova, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Gaidara 6, Kaliningrad 236001, Russia. ORCID: <https://orcid.org/0000-0002-5525-3529>. Tel: +79-062157372, E-mail: olga_khaziakhmatova@mail.ru

How to cite this article: Todosenko N, Yurova K, Khaziakhmatova O, Vulf M, Bograya M, Ivanov P, et al. (Epi)genetic Aspects of Metabolic Syndrome Pathogenesis in Relation to Brain-derived Neurotrophic Factor Expression: A Review. *Gene Expr* 2024;000(000):000–000. doi: 10.14218/GE.2023.00202.

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 Ca²⁺ 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 45 α , 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 synaptic 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 tanyocytes—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 miRNAs 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 Ca²⁺ 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/intraventricular 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 ApoA1 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

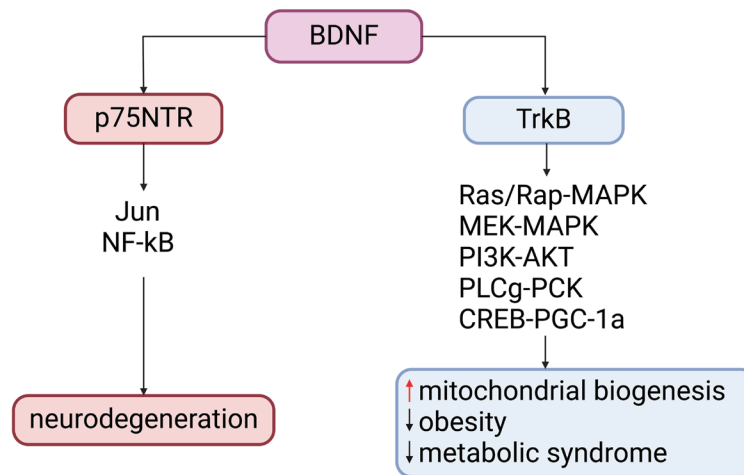


Fig. 1. Signaling pathways regulated by BDNF in the brain. AKT, protein kinase B; BDNF, brain-derived neurotrophic factor; CREB, cyclic adenosine monophosphate response element-binding protein; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; NF-kB, nuclear factor 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.Thr211e 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/placental, and maternal and fetal health has been established.⁷⁹ Epi-

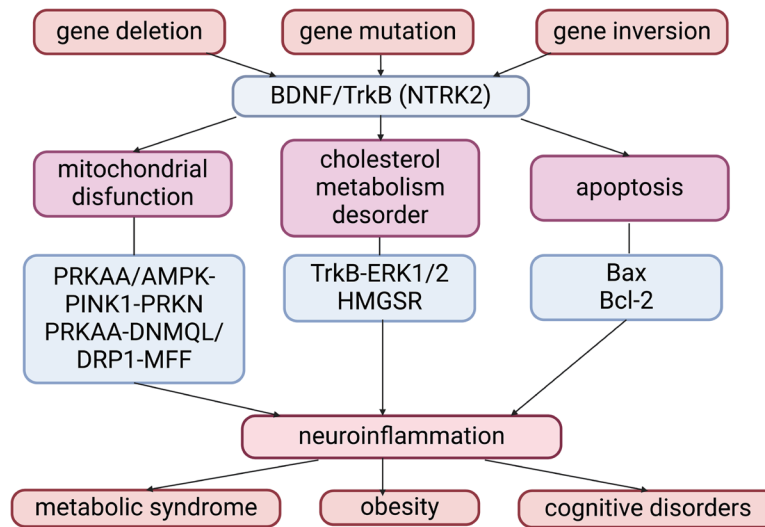


Fig. 2. The relationship between BDNF and the development of metabolic diseases. AMPK, 5'-adenosine monophosphate-activated protein kinase; Bax, B-cell lymphoma 2-like protein 4; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; DRP1, dynamin-related protein 1; ERK, extracellular signal-regulated 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* muta-

tion/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 acetylated-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, diacerein, 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 1 β 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 me-

dicinal potential (antidepressants). Phyto glycosides 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 proaedeutics. An undeniable limitation of this re-

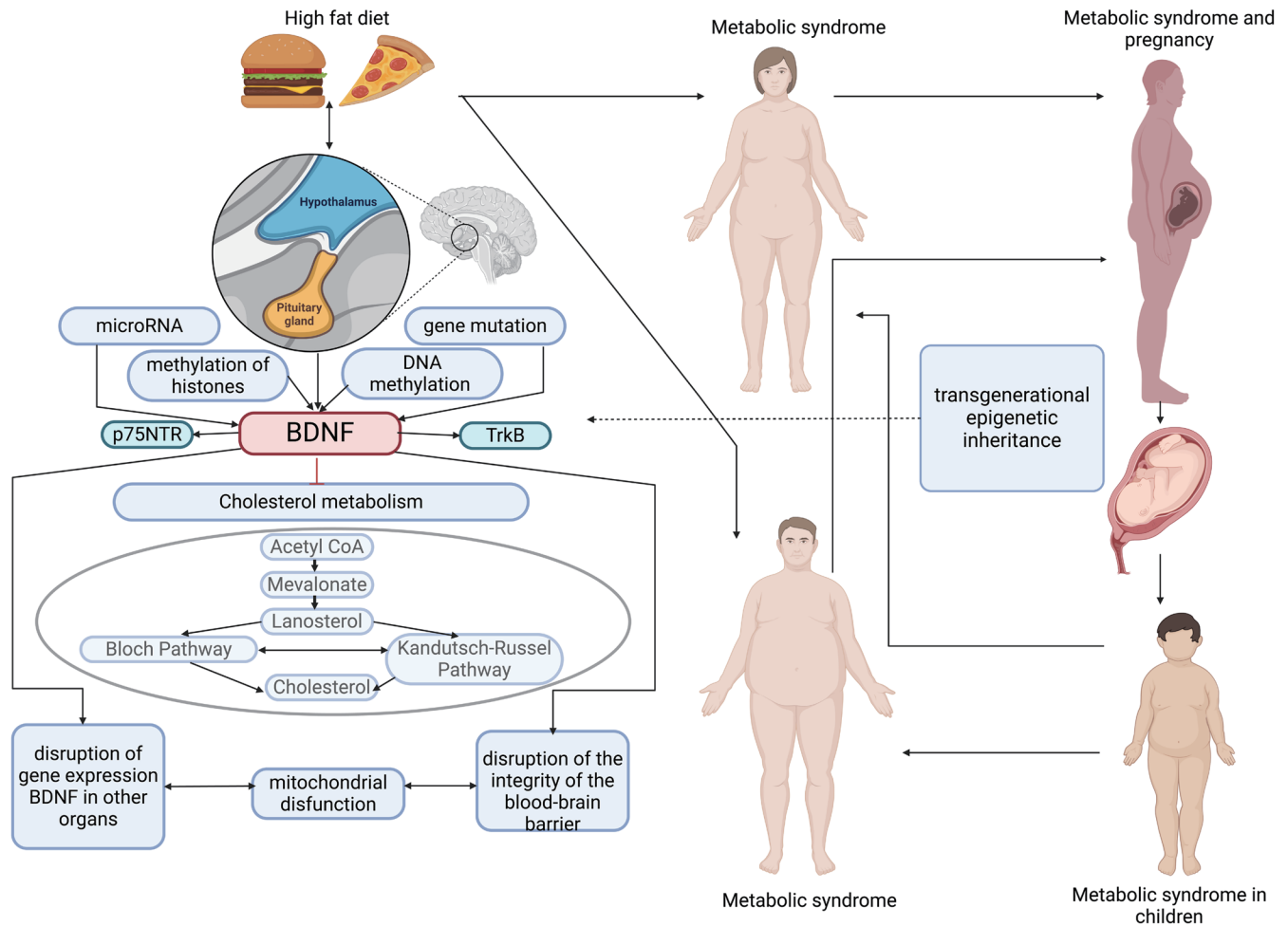


Fig. 3. On the one hand, a high-calorie diet is associated with structural and functional changes in brain structures, particularly in the hypothalamus. This is due to epigenetic components: microRNA, histone and DNA methylation, gene mutations that alter the expression and production of the neurotrophic 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.

Acknowledgments

None.

Funding

This work was supported by the Russian Science Foundation (project no. 23-15-00061).

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.

References

- Cai X, Xue Z, Zeng FF, Tang J, Yue L, Wang B, *et al.* Population serum proteomics uncovers a prognostic protein classifier for metabolic syndrome. *Cell Rep Med* 2023;4(9):101172. doi:10.1016/j.xcrm.2023.101172, PMID:37652016.
- Więckowska-Gacek A, Mietelska-Porowska A, Chutorański D, Wydrych M, Długosz J, Wojda U. Western Diet Induces Impairment of Liver-Brain Axis Accelerating Neuroinflammation and Amyloid Pathology in Alzheimer's Disease. *Front Aging Neurosci* 2021;13:654509. doi:10.3389/fnagi.2021.654509, PMID:33867971.
- Choi M, Kim D, Youn YJ, Ryu J, Jeong YH. Effect of Obesity and High-Density Lipoprotein Concentration on the Pathological Characteristics of Alzheimer's Disease in High-Fat Diet-Fed Mice. *Int J Mol Sci* 2022;23(20):12296. doi:10.3390/ijms232012296, PMID:36293147.
- Belladelli F, Montorsi F, Martini A. Metabolic syndrome, obesity and cancer risk. *Curr Opin Urol* 2022;32(6):594–597. doi:10.1097/MOU.0000000000001041, PMID:36081396.
- Angoff R, Himali JJ, Maillard P, Aparicio HJ, Vasan RS, Seshadri S, *et al.* Relations of Metabolic Health and Obesity to Brain Aging in Young to Middle-Aged Adults. *J Am Heart Assoc* 2022;11(6):e022107. doi:10.1161/JAHA.121.022107, PMID:35229662.
- Rolls ET. The orbitofrontal cortex, food reward, body weight and obesity. *Soc Cogn Affect Neurosci* 2023;18(1):nsab044. doi:10.1093/scan/nsab044, PMID:33830272.
- Valdearcos M, Robblee MM, Benjamin DI, Nomura DK, Xu AW, Koliwad SK. Microglia dictate the impact of saturated fat consumption on hypothalamic inflammation and neuronal function. *Cell Rep* 2014;9(6):2124–2138. doi:10.1016/j.celrep.2014.11.018, PMID:25497089.
- Švorcová J. Transgenerational Epigenetic Inheritance of Traumatic Experience in Mammals. *Genes (Basel)* 2023;14(1):120. doi:10.3390/genes14010120, PMID:36672861.
- Lippert RN, Brüning JC. Maternal Metabolic Programming of the Developing Central Nervous System: Unified Pathways to Metabolic and Psychiatric Disorders. *Biol Psychiatry* 2022;91(10):898–906. doi:10.1016/j.biopsych.2021.06.002, PMID:34330407.
- Ullah R, Rauf N, Nabi G, Yi S, Yu-Dong Z, Fu J. Mechanistic insight into high-fat diet-induced metabolic inflammation in the arcuate nucleus of the hypothalamus. *Biomed Pharmacother* 2021;142:112012. doi:10.1016/j.biopha.2021.112012, PMID:34388531.
- Deem JD, Faber CL, Morton GJ. AgRP neurons: Regulators of feeding, energy expenditure, and behavior. *FEBS J* 2022;289(8):2362–2381. doi:10.1111/febs.16176, PMID:34469623.
- Paeger L, Pippow A, Hess S, Paehler M, Klein AC, Husch A, *et al.* Energy imbalance alters Ca(2+) handling and excitability of POMC neurons. *Elife* 2017;6:e25641. doi:10.7554/eLife.25641, PMID:28762947.
- Quarta C, Claret M, Zeltser LM, Williams KW, Yeo GSH, Tschöp MH, *et al.* POMC neuronal heterogeneity in energy balance and beyond: an integrated view. *Nat Metab* 2021;3(3):299–308. doi:10.1038/s42255-021-00345-3, PMID:33633406.
- Coppedè F. One-carbon epigenetics and redox biology of neurodegeneration. *Free Radic Biol Med* 2021;170:19–33. doi:10.1016/j.freeradbiomed.2020.12.002, PMID:33307166.
- van der Wijst MG, Venkiteswaran M, Chen H, Xu GL, Plösch T, Rots MG. Local chromatin microenvironment determines DNMT activity: from DNA methyltransferase to DNA demethylase or DNA dehydroxymethylase. *Epigenetics* 2015;10(8):671–676. doi:10.1080/15592294.2015.1062204, PMID:26098813.
- Stoccoro A, Coppedè F. Mitochondrial DNA Methylation and Human Diseases. *Int J Mol Sci* 2021;22(9):4594. doi:10.3390/ijms22094594, PMID:33925624.
- Hao Z, Wu T, Cui X, Zhu P, Tan C, Dou X, *et al.* N(6)-Deoxyadenosine Methylation in Mammalian Mitochondrial DNA. *Mol Cell* 2020;78(3):382–395.e8. doi:10.1016/j.molcel.2020.02.018, PMID:32183942.
- Mortillo M, Marsit CJ. Select Early-Life Environmental Exposures and DNA Methylation in the Placenta. *Curr Environ Health Rep* 2023;10(1):22–34. doi:10.1007/s40572-022-00385-1, PMID:36469294.
- Burton NO, Greer EL. Multigenerational epigenetic inheritance: Transmitting information across generations. *Semin Cell Dev Biol* 2022;127:121–132. doi:10.1016/j.semcdb.2021.08.006, PMID:34426067.
- Cheng Q, Trangucci R, Nelson KN, Fu W, Collender PA, Head JR, *et al.* Prenatal and early-life exposure to the Great Chinese Famine increased the risk of tuberculosis in adulthood across two generations. *Proc Natl Acad Sci USA* 2020;117(44):27549–27555. doi:10.1073/pnas.2008336117, PMID:33077583.
- A-L LG, C LP, A D, S M. Developmental, genetic and environmental variations of global DNA methylation in the first leaves emerging from the shoot apical meristem in poplar trees. *Plant Signal Behav* 2019;14(6):1596717. doi:10.1080/15592324.2019.1596717, PMID:30915897.
- Guillaumin MCC, Peleg-Raibstein D. Maternal Over- and Malnutrition and Increased Risk for Addictive and Eating Disorders in the Offspring. *Nutrients* 2023;15(5):1095. doi:10.3390/nu15051095, PMID:36904093.
- Mancini M, Andreassi A, Salvioni M, Pelliccione F, Mantellassi G, Banderali G. Myoinositol and D-Chiro Inositol in Improving Insulin Resistance in Obese Male Children: Preliminary Data. *Int J Endocrinol* 2016;2016:8720342. doi:10.1155/2016/8720342, PMID:27882052.
- Pecks U, Rath W, Bauerschlag DO, Maass N, Orlikowsky T, Mohaupt MG, *et al.* Serum cholesterol acceptor capacity in intrauterine growth restricted fetuses. *J Perinat Med* 2017;45(7):829–835. doi:10.1515/jpm-2016-0270, PMID:28195552.
- Fukunaga H. Mitochondrial DNA Copy Number and Developmental Origins of Health and Disease (DOHaD). *Int J Mol Sci* 2021;22(12):6634. doi:10.3390/ijms22126634, PMID:34205712.
- Furigo IC, Dearden L. Mechanisms mediating the impact of maternal obesity on offspring hypothalamic development and later function. *Front Endocrinol (Lausanne)* 2022;13:1078955. doi:10.3389/fendo.2022.1078955, PMID:36619540.
- Lee CH, Suk K, Yu R, Kim MS. Cellular Contributors to Hypothalamic Inflammation in Obesity. *Mol Cells* 2020;43(5):431–437. doi:10.14348/molcells.2020.0055, PMID:32392909.
- Wang X, Li H. Chronic high-fat diet induces overeating and impairs synaptic transmission in feeding-related brain regions. *Front Mol Neurosci* 2022;15:1019446. doi:10.3389/fnmol.2022.1019446, PMID:36226318.
- Page KA, Luo S, Wang X, Chow T, Alves J, Buchanan TA, *et al.* Children Exposed to Maternal Obesity or Gestational Diabetes Mellitus During Early Fetal Development Have Hypothalamic Alterations That Predict Future Weight Gain. *Diabetes Care* 2019;42(8):1473–1480. doi:10.2337/dc18-2581, PMID:31332028.
- Seong J, Kang JY, Sun JS, Kim KW. Hypothalamic inflammation and obesity: a mechanistic review. *Arch Pharm Res* 2019;42(5):383–392. doi:10.1007/s12272-019-01138-9, PMID:30835074.
- Dearden L, Buller S, Furigo IC, Fernandez-Twinn DS, Ozanne SE. Maternal obesity causes fetal hypothalamic insulin resistance and disrupts development of hypothalamic feeding pathways. *Mol Metab* 2020;42:101079. doi:10.1016/j.molmet.2020.101079,

- PMID:32919096.
- [32] Mas-Parés B, Xargay-Torrent S, Gómez-Vilarrubla A, Carreras-Badosa G, Prats-Puig A, De Zegher F, *et al.* Gestational Weight Gain Relates to DNA Methylation in Umbilical Cord, Which, In Turn, Associates with Offspring Obesity-Related Parameters. *Nutrients* 2023;15(14):3175. doi:10.3390/nu15143175, PMID:37513594.
- [33] Gao Y, Layritz C, Legutko B, Eichmann TO, Laperrousaz E, Moullé VS, *et al.* Disruption of Lipid Uptake in Astroglia Exacerbates Diet-Induced Obesity. *Diabetes* 2017;66(10):2555–2563. doi:10.2337/db16-1278, PMID:28710138.
- [34] Marschallinger J, Iram T, Zardeneta M, Lee SE, Lehallier B, Haney MS, *et al.* Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. *Nat Neurosci* 2020;23(2):194–208. doi:10.1038/s41593-019-0566-1, PMID:31959936.
- [35] Ogrodnik M, Zhu Y, Langhi LGP, Tchkonja T, Krüger P, Fielder E, *et al.* Obesity-Induced Cellular Senescence Drives Anxiety and Impairs Neurogenesis. *Cell Metab* 2019;29(5):1061–1077.e8. doi:10.1016/j.cmet.2018.12.008, PMID:30612898.
- [36] Lee CH, Shin SH, Kang GM, Kim J, Yu R, *et al.* Cellular source of hypothalamic macrophage accumulation in diet-induced obesity. *J Neuroinflammation* 2019;16(1):221. doi:10.1186/s12974-019-1607-0, PMID:31727092.
- [37] Rivera P, Guerra-Cantera S, Vargas A, Díaz F, García-Úbeda R, Tovar R, *et al.* Maternal hypercaloric diet affects factors involved in lipid metabolism and the endogenous cannabinoid systems in the hypothalamus of adult offspring: sex-specific response of astrocytes to palmitic acid and anandamide. *Nutr Neurosci* 2022;25(5):931–944. doi:10.1080/1028415X.2020.1821519, PMID:32954972.
- [38] Chandrasekaran S, Melhorn S, Olerich K, Angelo B, Chow T, Xiang A, *et al.* Exposure to Gestational Diabetes Mellitus Prior to 26 Weeks Is Related to the Presence of Mediobasal Hypothalamic Gliosis in Children. *Diabetes* 2022;71(12):2552–2556. doi:10.2337/db22-0448, PMID:36095276.
- [39] Martins MG, Silver Z, Ayoub K, Hyland L, Woodside B, Kiss ACI, *et al.* Maternal glucose intolerance during pregnancy affects offspring POMC expression and results in adult metabolic alterations in a sex-dependent manner. *Front Endocrinol (Lausanne)* 2023;14:1189207. doi:10.3389/fendo.2023.1189207, PMID:37396180.
- [40] MacKay H, Gunasekara CJ, Yam KY, Srisai D, Yalamanchili HK, Li Y, *et al.* Sex-specific epigenetic development in the mouse hypothalamic arcuate nucleus pinpoints human genomic regions associated with body mass index. *Sci Adv* 2022;8(39):eabo3991. doi:10.1126/sciadv.abo3991, PMID:36170368.
- [41] Doubi-Kadmiri S, Benoit C, Benigni X, Beaumont G, Vacher CM, Taouis M, *et al.* Substantial and robust changes in microRNA transcriptome support postnatal development of the hypothalamus in rat. *Sci Rep* 2016;6:24896. doi:10.1038/srep24896, PMID:27118433.
- [42] Croizier S, Park S, Maillard J, Bouret SG. Central Dicer-miR-103/107 controls developmental switch of POMC progenitors into NPY neurons and impacts glucose homeostasis. *Elife* 2018;7:e40429. doi:10.7554/eLife.40429, PMID:30311908.
- [43] van der Klaauw AA, Croizier S, Mendes de Oliveira E, Stadler LKJ, Park S, Kong Y, *et al.* Human Semaphorin 3 Variants Link Melanocortin Circuit Development and Energy Balance. *Cell* 2019;176(4):729–742.e18. doi:10.1016/j.cell.2018.12.009, PMID:30661757.
- [44] Haddad-Tóvolli R, Morari J, Barbizan R, Bóbo VC, Carraro RS, Solon C, *et al.* Maternal obesity damages the median eminence blood-brain barrier structure and function in the progeny: the beneficial impact of cross-fostering by lean mothers. *Am J Physiol Endocrinol Metab* 2023;324(2):E154–E166. doi:10.1152/ajpendo.00268.2022, PMID:36598900.
- [45] Billah MM, Khatiwada S, Morris MJ, Maloney CA. Effects of paternal overnutrition and interventions on future generations. *Int J Obes (Lond)* 2022;46(5):901–917. doi:10.1038/s41366-021-01042-7, PMID:35022547.
- [46] Cao L, Ali S, Queen NJ. Hypothalamic gene transfer of BDNF promotes healthy aging. *Vitam Horm* 2021;115:39–66. doi:10.1016/bs.vh.2020.12.003, PMID:33706955.
- [47] Arévalo JC, Deogracias R. Mechanisms Controlling the Expression and Secretion of BDNF. *Biomolecules* 2023;13(5):789. doi:10.3390/biom13050789, PMID:37238659.
- [48] Abdulsada MM, Wilhelm ZR, Opekun AR, Devaraj S, Jalal PK, Mindikoglu AL. The effect of four-week intermittent fasting from dawn to sunset on circulating brain-derived neurotrophic factor levels in subjects with metabolic syndrome and healthy subjects. *Metabol Open* 2021;9:100070. doi:10.1016/j.metop.2020.100070, PMID:33376976.
- [49] Ameroso D, Meng A, Chen S, Felsted J, Dulla CG, Rios M. Astrocytic BDNF signaling within the ventromedial hypothalamus regulates energy homeostasis. *Nat Metab* 2022;4(5):627–643. doi:10.1038/s42255-022-00566-0, PMID:35501599.
- [50] Ateaque S, Merkouris S, Barde YA. Neurotrophin signalling in the human nervous system. *Front Mol Neurosci* 2023;16:1225373. doi:10.3389/fnmol.2023.1225373, PMID:37470055.
- [51] Miao Z, Wang Y, Sun Z. The Relationships Between Stress, Mental Disorders, and Epigenetic Regulation of BDNF. *Int J Mol Sci* 2020;21(4):1375. doi:10.3390/ijms21041375, PMID:32085670.
- [52] Nieves Torres D, Lee SH. Inter-neuronal signaling mediated by small extracellular vesicles: wireless communication? *Front Mol Neurosci* 2023;16:1187300. doi:10.3389/fnmol.2023.1187300, PMID:37181650.
- [53] Gao LL, Wang ZH, Mu YH, Liu ZL, Pang L. Emodin Promotes Autophagy and Prevents Apoptosis in Sepsis-Associated Encephalopathy through Activating BDNF/TrkB Signaling. *Pathobiology* 2022;89(3):135–145. doi:10.1159/000520281, PMID:34872094.
- [54] Sharma D, Barhwal KK, Biswal SN, Srivastava AK, Bhardwaj P, Kumar A, *et al.* Hypoxia-mediated alteration in cholesterol oxidation and raft dynamics regulates BDNF signalling and neurodegeneration in hippocampus. *J Neurochem* 2019;148(2):238–251. doi:10.1111/jnc.14609, PMID:30308090.
- [55] Di Rosa MC, Zimbone S, Saab MW, Tomasello MF. The Pleiotropic Potential of BDNF beyond Neurons: Implication for a Healthy Mind in a Healthy Body. *Life (Basel)* 2021;11(11):1256. doi:10.3390/life11111256, PMID:34833132.
- [56] Taha MA, Al-Maqati TN, Alnaam YA, Alharbi SS, Khaneen R, Almutairi H, *et al.* The Association between Brain-Derived Neurotrophic Factor (BDNF) Protein Level and Body Mass Index. *Medicina (Kaunas)* 2022;59(1):99. doi:10.3390/medicina59010099, PMID:36676721.
- [57] Bumb JM, Bach P, Grosshans M, Wagner X, Koopmann A, Vollstädt-Klein S, *et al.* BDNF influences neural cue-reactivity to food stimuli and food craving in obesity. *Eur Arch Psychiatry Clin Neurosci* 2021;271(5):963–974. doi:10.1007/s00406-020-01224-w, PMID:33367955.
- [58] Flöck A, Odainic A, Dolscheid-Pommerich R, Jaskolski MR, Diedrich AK, Puth MT, *et al.* High maternal BMI and low maternal blood BDNF may determine the limit of detection of amniotic fluid BDNF throughout gestation: Analysis of mother-fetus trios and literature review. *PLoS One* 2022;17(3):e0265186. doi:10.1371/journal.pone.0265186, PMID:35271679.
- [59] Bai X, Mai M, Yao K, Zhang M, Huang Y, Zhang W, *et al.* The role of DHCR24 in the pathogenesis of AD: re-cognition of the relationship between cholesterol and AD pathogenesis. *Acta Neuropathol Commun* 2022;10(1):35. doi:10.1186/s40478-022-01338-3, PMID:35296367.
- [60] Mast N, El-Darzi N, Li Y, Pikuleva IA. Quantitative characterizations of the cholesterol-related pathways in the retina and brain of hamsters. *J Lipid Res* 2023;64(7):100401. doi:10.1016/j.jlr.2023.100401, PMID:37330011.
- [61] Colardo M, Martella N, Pensabene D, Siteni S, Di Bartolomeo S, Pallottini V, *et al.* Neurotrophins as Key Regulators of Cell Metabolism: Implications for Cholesterol Homeostasis. *Int J Mol Sci* 2021;22(11):5692. doi:10.3390/ijms22115692, PMID:34073639.
- [62] Nunes VS, da Silva Ferreira G, Quintão ECR. Cholesterol metabolism in aging simultaneously altered in liver and nervous system. *Ageing (Albany NY)* 2022;14(3):1549–1561. doi:10.18632/aging.203880, PMID:35130181.
- [63] Kim D, Lee KM, Lee C, Jo YS, Kim JH, Yoon JH, *et al.* Pathophysiological role of 27-hydroxycholesterol in human diseases. *Adv Biol Regul* 2022;83:100837. doi:10.1016/j.jbior.2021.100837, PMID:34774482.
- [64] Abdalkareem Jasim S, Kzar HH, Haider Hamad M, Devaraj S, Jalal PK, Mindikoglu AL, *et al.* The emerging role of 27-hydroxycholesterol

- in cancer development and progression: An update. *Int Immunopharmacol* 2022;110:109074. doi:10.1016/j.intimp.2022.109074, PMID:35978522.
- [65] Alanko V, Gaminde-Blasco A, Quintela-López T, Loera-Valencia R, Solomon A, Björkhem I, *et al.* 27-hydroxycholesterol promotes oligodendrocyte maturation: Implications for hypercholesterolemia-associated brain white matter changes. *Glia* 2023;71(6):1414–1428. doi:10.1002/glia.24348, PMID:36779429.
- [66] Wang S-S, Lu A-X, Li W-H, Zhang H, Hu C-P, Liu J-X, *et al.* Effects of food-borne cholesterol supplementation on lead-induced neurodevelopmental impairments of rats based on BDNF signaling pathway and cholesterol metabolism. *Ecotoxicol Environ Saf* 2023;259:115026. doi:10.1016/j.ecoenv.2023.115026, PMID:37210997.
- [67] Wang S-S, Xu X, Lu A-X, Li W-H, Liu J-H, Liu C, *et al.* Amelioration of cholesterol sulfate for lead-induced CTX cell apoptosis based on BDNF signaling pathway mediated cholesterol metabolism. *Ecotoxicol Environ Saf* 2022;248:114307. doi:10.1016/j.ecoenv.2022.114307, PMID:36423370.
- [68] Amidfar M, de Oliveira J, Kucharska E, Budni J, Kim Y-K. The role of CREB and BDNF in neurobiology and treatment of Alzheimer’s disease. *Life Sci* 2020;257:118020. doi:10.1016/j.lfs.2020.118020, PMID:32603820.
- [69] Spagnuolo MS, Donizetti A, Iannotta L, Aliperti V, Cupidi C, Bruni AC, *et al.* Brain-derived neurotrophic factor modulates cholesterol homeostasis and Apolipoprotein E synthesis in human cell models of astrocytes and neurons. *J Cell Physiol* 2018;233(9):6925–6943. doi:10.1002/jcp.26480, PMID:29323721.
- [70] Iwase M, Matsuo K, Nakatochi M, Oze I, Ito H, Koyanagi Y, *et al.* Differential Effect of Polymorphisms on Body Mass Index Across the Life Course of Japanese: The Japan Multi-Institutional Collaborative Cohort Study. *J Epidemiol* 2021;31(3):172–179. doi:10.2188/jea.JE20190296, PMID:32147644.
- [71] Marcos-Pasero H, Aguilar-Aguilar E, Ikonopoulou MP, Loria-Kohen V. BDNF Gene as a Precision Skill of Obesity Management. *Adv Exp Med Biol* 2021;1331:233–248. doi:10.1007/978-3-030-74046-7_15, PMID:34453302.
- [72] Harcourt BE, Bullen DVR, Kao K-T, Tassoni D, Alexander EJ, Burgess T, *et al.* Maternal inheritance of BDNF deletion, with phenotype of obesity and developmental delay in mother and child. *Am J Med Genet A* 2018;176(1):194–200. doi:10.1002/ajmg.a.38539, PMID:29160031.
- [73] An JJ, Kinney CE, Tan JW, Liao GY, Kremer EJ, Xu B. TrkB-expressing paraventricular hypothalamic neurons suppress appetite through multiple neurocircuits. *Nat Commun* 2020;11(1):1729. doi:10.1038/s41467-020-15537-w, PMID:32265438.
- [74] Javed S, Chang YT, Cho Y, Lee YJ, Chang HC, Haque M, *et al.* Smith-Magenis syndrome protein RAI1 regulates body weight homeostasis through hypothalamic BDNF-producing neurons and neurotrophin downstream signalling. *Elife* 2023;12:RP90333. doi:10.7554/eLife.90333, PMID:37956053.
- [75] Maraziti D, Arone A, Palermo S, Annuzzi E, Cappellato G, Chiarantini I, *et al.* The Wicked Relationship between Depression and Metabolic Syndrome. *Clin Neuropsychiatry* 2023;20(2):100–108. doi:10.36131/cnfiortiditore20230202, PMID:37234360.
- [76] Miksza U, Adamska-Patruno E, Bauer W, Fiedorczuk J, Czajkowski P, Moroz M, *et al.* Obesity-related parameters in carriers of some BDNF genetic variants may depend on daily dietary macronutrients intake. *Sci Rep* 2023;13(1):6585. doi:10.1038/s41598-023-33842-4, PMID:37085692.
- [77] Li C, Cheng H, Adhikari BK, Wang S, Yang N, Liu W, *et al.* The Role of Apelin-APJ System in Diabetes and Obesity. *Front Endocrinol (Lausanne)* 2022;13:820002. doi:10.3389/fendo.2022.820002, PMID:35355561.
- [78] Siu JJ, Queen NJ, Liu X, Huang W, McMurphy T, Cao L. Molecular Therapy of Melanocortin-4-Receptor Obesity by an Autoregulatory BDNF Vector. *Mol Ther Methods Clin Dev* 2017;7:83–95. doi:10.1016/j.omtm.2017.09.005, PMID:29296625.
- [79] D’Angelo A, Ceccanti M, Petrella C, Greco A, Tirassa P, Rosso P, *et al.* Role of neurotrophins in pregnancy, delivery and postpartum. *Eur J Obstet Gynecol Reprod Biol* 2020;247:32–41. doi:10.1016/j.ejogrb.2020.01.046, PMID:32058187.
- [80] Blaze J, Asok A, Borrelli K, Tulbert C, Bollinger J, Ronca AE, *et al.* Intrauterine exposure to maternal stress alters Bdnf IV DNA methylation and telomere length in the brain of adult rat offspring. *Int J Dev Neurosci* 2017;62:56–62. doi:10.1016/j.ijdevneu.2017.03.007, PMID:28330827.
- [81] Dong E, Dzitoyeva SG, Matrisciano F, Tueting P, Grayson DR, Guidotti A. Brain-derived neurotrophic factor epigenetic modifications associated with schizophrenia-like phenotype induced by prenatal stress in mice. *Biol Psychiatry* 2015;77(6):589–596. doi:10.1016/j.biopsych.2014.08.012, PMID:25444166.
- [82] Lippert RN, Hess S, Klemm P, Burgeno LM, Jahans-Price T, Walton ME, *et al.* Maternal high-fat diet during lactation reprograms the dopaminergic circuitry in mice. *J Clin Invest* 2020;130(7):3761–3776. doi:10.1172/JCI134412, PMID:32510473.
- [83] Urbonaite G, Knyzeliene A, Bunn FS, Smalskys A, Neniskyte U. The impact of maternal high-fat diet on offspring neurodevelopment. *Front Neurosci* 2022;16:909762. doi:10.3389/fnins.2022.909762, PMID:35937892.
- [84] Peng H, Zhu Y, Strachan E, Fowler E, Bacus T, Roy-Byrne P, *et al.* Childhood Trauma, DNA Methylation of Stress-Related Genes, and Depression: Findings From Two Monozygotic Twin Studies. *Psychosom Med* 2018;80(7):599–608. doi:10.1097/PSY.0000000000000604, PMID:29781947.
- [85] Stocco A, Nicoli V, Coppedè F, Grossi E, Fedrizzi G, Menotta S, *et al.* Prenatal Environmental Stressors and DNA Methylation Levels in Placenta and Peripheral Tissues of Mothers and Neonates Evaluated by Applying Artificial Neural Networks. *Genes (Basel)* 2023;14(4):836. doi:10.3390/genes14040836, PMID:37107594.
- [86] Frayre J, Frayre P, Wong I, Mithani A, Bishop S, Mani C, *et al.* Perinatal exposure to high fat diet alters expression of MeCP2 in the hypothalamus. *Behav Brain Res* 2021;415:113518. doi:10.1016/j.bbr.2021.113518, PMID:34391798.
- [87] Kim JW, Autry AE, Na ES, Adachi M, Björkholm C, Kavalali ET, *et al.* Sustained effects of rapidly acting antidepressants require BDNF-dependent MeCP2 phosphorylation. *Nat Neurosci* 2021;24(8):1100–1109. doi:10.1038/s41593-021-00868-8, PMID:34183865.
- [88] Keller S, Sarchiapone M, Zarrilli F, Videtic A, Ferraro A, Carli V, *et al.* Increased BDNF promoter methylation in the Wernicke area of suicide subjects. *Arch Gen Psychiatry* 2010;67(3):258–267. doi:10.1001/archgenpsychiatry.2010.9, PMID:20194826.
- [89] Jiang Y, Denbow C, Meiri N, Denbow DM. Epigenetic-Imprinting Changes Caused by Neonatal Fasting Stress Protect From Future Fasting Stress. *J Neuroendocrinol* 2016;28:1. doi:10.1111/jne.12333, PMID:26542089.
- [90] Viana Borges J, Souza de Freitas B, Antoniazzi V, de Souza Dos Santos C, Vedovelli K, Naziaseno Pires V, *et al.* Social isolation and social support at adulthood affect epigenetic mechanisms, brain-derived neurotrophic factor levels and behavior of chronically stressed rats. *Behav Brain Res* 2019;366:36–44. doi:10.1016/j.bbr.2019.03.025, PMID:30880220.
- [91] Zheng Y, Fan W, Zhang X, Dong E. Gestational stress induces depressive-like and anxiety-like phenotypes through epigenetic regulation of BDNF expression in offspring hippocampus. *Epigenetics* 2016;11(2):150–162. doi:10.1080/15592294.2016.1146850, PMID:26890656.
- [92] Prince CS, Maloyan A, Myatt L. Maternal obesity alters brain derived neurotrophic factor (BDNF) signaling in the placenta in a sexually dimorphic manner. *Placenta* 2017;49:55–63. doi:10.1016/j.placenta.2016.11.010, PMID:28012455.
- [93] Opsahl JO, Moen G-H, Qvigstad E, Böttcher Y, Birkeland K, Sommer C. Epigenetic signatures associated with maternal body mass index or gestational weight gain: A systematic review. *J Dev Orig Health Dis* 2021;12(3):373–383. doi:10.1017/S2040174420000811, PMID:32873364.
- [94] Ehinger Y, Phamluong K, Darevesky D, Welman M, Moffat JJ, Sakhai SA, *et al.* Differential correlation of serum BDNF and microRNA content in rats with rapid or late onset of heavy alcohol use. *Addict Biol* 2021;26(2):e12890. doi:10.1111/adb.12890, PMID:32135570.
- [95] Guo XX, He QZ, Li W, Long DX, Pan XY, Chen C, *et al.* Brain-Derived Neurotrophic Factor Mediated Perfluorooctane Sulfonate Induced-Neurotoxicity via Epigenetics Regulation in SK-N-SH Cells. *Int J Mol Sci* 2017;18(4):893. doi:10.3390/ijms18040893, PMID:28441774.
- [96] Gao J, Liang Z, Zhao F, Liu X, Ma N. Triptolide inhibits oxidative stress

- and inflammation via the microRNA-155-5p/brain-derived neurotrophic factor to reduce podocyte injury in mice with diabetic nephropathy. *Bioengineered* 2022;13(5):12275–12288. doi:10.1080/21655979.2022.2067293, PMID:35603354.
- [97] Xin C, Xia J, Liu Y, Zhang Y. MicroRNA-202-3p Targets Brain-Derived Neurotrophic Factor and Is Involved in Depression-Like Behaviors. *Neuropsychiatr Dis Treat* 2020;16:1073–1083. doi:10.2147/NDT.S241136, PMID:32425535.
- [98] Wang G, An T, Lei C, Zhu X, Yang L, Zhang L, *et al.* Antidepressant-like effect of ginsenoside Rb1 on potentiating synaptic plasticity via the miR-134-mediated BDNF signaling pathway in a mouse model of chronic stress-induced depression. *J Ginseng Res* 2022;46(3):376–386. doi:10.1016/j.jgr.2021.03.005, PMID:35600767.
- [99] Sørensen AE, van Poppel MNM, Desoye G, Damm P, Simmons D, Jensen DM, *et al.* The Predictive Value of miR-16, -29a and -134 for Early Identification of Gestational Diabetes: A Nested Analysis of the DALI Cohort. *Cells* 2021;10(1):170. doi:10.3390/cells10010170, PMID:33467738.
- [100] Feng T, Li W, Li T, Jiao W, Chen S. Circular RNA_0037128 aggravates high glucose-induced damage in HK-2 cells via regulation of microRNA-497-5p/nuclear factor of activated T cells 5 axis. *Bioengineered* 2021;12(2):10959–10970. doi:10.1080/21655979.2021.2001912, PMID:34753398.
- [101] Carreras-Badosa G, Bonmatí A, Ortega F-J, Mercader J-M, Guindo-Martínez M, Torrents D, *et al.* Altered Circulating miRNA Expression Profile in Pregestational and Gestational Obesity. *J Clin Endocrinol Metab* 2015;100(11):E1446–1456. doi:10.1210/jc.2015-2872, PMID:26406295.
- [102] Martorell M, Castro N, Victoriano M, Capó X, Tejada S, Vitalini S, *et al.* An Update of Anthraquinone Derivatives Emodin, Diacerein, and Catenarin in Diabetes. *Evid Based Complement Alternat Med* 2021;2021:3313419. doi:10.1155/2021/3313419, PMID:34589130.
- [103] Yu L, Zhao Y, Zhao Y. Advances in the pharmacological effects and molecular mechanisms of emodin in the treatment of metabolic diseases. *Front Pharmacol* 2023;14:1240820. doi:10.3389/fphar.2023.1240820, PMID:38027005.
- [104] Lee YM, Yoon Y, Yoon H, Park HM, Song S, Yeum KJ. Dietary Anthocyanins against Obesity and Inflammation. *Nutrients* 2017;9(10):1089. doi:10.3390/nu9101089, PMID:28974032.
- [105] Anguita-Ruiz A, Pastor-Villaescusa B, Leis R, Bueno G, Hoyos R, Vázquez-Cobela R, *et al.* Common Variants in 22 Genes Regulate Response to Metformin Intervention in Children with Obesity: A Pharmacogenetic Study of a Randomized Controlled Trial. *J Clin Med* 2019;8(9):1471. doi:10.3390/jcm8091471, PMID:31527397.
- [106] Sadek MA, Kandil EA, El Sayed NS, Sayed HM, Rabie MA. Semaglutide, a novel glucagon-like peptide-1 agonist, amends experimental autoimmune encephalomyelitis-induced multiple sclerosis in mice: Involvement of the PI3K/Akt/GSK-3 β pathway. *Int Immunopharmacol* 2023;115:109647. doi:10.1016/j.intimp.2022.109647, PMID:36584570.
- [107] Mousa HH, Sharawy MH, Nader MA. Empagliflozin enhances neuroplasticity in rotenone-induced parkinsonism: Role of BDNF, CREB and Npas4. *Life Sci* 2023;312:121258. doi:10.1016/j.lfs.2022.121258, PMID:36462721.
- [108] Coker CR, White M, Singal A, Bingaman SS, Paul A, Arnold AC, *et al.* Minocycline Reduces Hypothalamic Microglia Activation and Improves Metabolic Dysfunction in High Fat Diet-Induced Obese Mice. *Front Physiol* 2022;13:933706. doi:10.3389/fphys.2022.933706, PMID:35784876.
- [109] Qaid EYA, Abdullah Z, Zakaria R, Long I. Minocycline Protects Against Lipopolysaccharide-Induced Cognitive Impairment and Oxidative Stress: Possible Role of the CREB-BDNF Signaling Pathway. *Neurochem Res* 2023;48(5):1480–1490. doi:10.1007/s11064-022-03842-3, PMID:36509985.
- [110] de Lima NS, De Sousa RAL, Amorim FT, Gripp F, Diniz E Magalhães CO, Henrique Pinto S, *et al.* Moderate-intensity continuous training and high-intensity interval training improve cognition, and BDNF levels of middle-aged overweight men. *Metab Brain Dis* 2022;37(2):463–471. doi:10.1007/s11011-021-00859-5, PMID:34762211.
- [111] Wu Y, Rakotoarisoa M, Angelov B, Deng Y, Angelova A. Self-Assembled Nanoscale Materials for Neuronal Regeneration: A Focus on BDNF Protein and Nucleic Acid Biotherapeutic Delivery. *Nanomaterials (Basel)* 2022;12(13):2267. doi:10.3390/nano12132267, PMID:35808102.