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Neurochemical regulators of food behavior for pharmacological treatment of obesity: current status and future prospects

Gayane Sargis Vardanyan^{*,1} , Hasmik Samvel Harutyunyan¹ , Michail Iosif Aghajanov¹
& Ruben Sargis Vardanyan²

¹Department of Biochemistry, Yerevan State Medical University, 2 Koryun str., Yerevan, 0025, Armenia

²Department of Chemistry & Biochemistry, University of Arizona, 1306 East University Boulevard, PO Box 210041, Tucson, AZ 85721, USA

*Author for correspondence: vgs.ysmu@gmail.com

In recent decades, obesity has become a pandemic disease and appears to be an ultimate medical and social problem. Existing antiobesity drugs show low efficiency and a wide variety of side effects. In this review, we discuss possible mechanisms underlying brain–gut–adipose tissue axis, as well as molecular biochemical characteristics of various neurochemical regulators of body weight and appetite. Multiple brain regions are responsible for eating behavior, hedonic eating and food addiction. The existing pharmacological targets for treatment of obesity were reviewed as well.

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Mechanisms of hunger and satiety regulatory circuits are a key area to overcome and treat obesity. Discovery of new molecular targets affecting different levels of regulatory circuits of appetite, energy metabolism and food behavior will contribute to the development of brand-new drugs for pharmacotherapy of obesity. Obesity is a chronic multifactorial heterogeneous disease, manifested by excessive formation of adipose tissue, progressing in its natural course. It is often accompanied by severe concomitant pathology: Type 2 diabetes, hypertension, dyslipidemia, atherosclerosis, coronary heart disease, cardiovascular failure, some forms of cancer, impaired reproductive function and diseases of the musculoskeletal system.

Central and peripheral systems regulating energy metabolism bidirectionally control appetite, feeding behavior and satiety. Various disturbances in these circuits may induce fluctuations in appetite and body weight. Typically, food is consumed in order to maintain energy homeostasis. Hence, the brain ‘likes’ palatable food independently of the energetic status of the organism, causing overeating – which is a primary reason for obesity.

The upcoming review focuses on the full pathway of hunger and satiety including gut–brain–adipose tissue axis, immersing into hormonal regulation, cascade mechanisms, signal processing, receptor systems and the role of various systems of organism in etiology of obesity and food behavior. Various levels of these mechanisms have therapeutic potential in preventing and/or treating obesity. The existing antiobesity drugs are reviewed as well.

Energy metabolism: hypothalamus is the key

The hypothalamus is a small area of the brain where endocrine and nervous systems intersect. Hypothalamic nuclei exchange projections with all brain centers, regulating almost all vital functions of organism. Among them regulation of energy metabolism, hunger and satiety circuits are crucial for the well-being of organism. Abnormal activation or inhibition of various groups of neurons will disturb homeostasis, commonly leading to overeating and, thus, overweight and obesity. Understanding the biochemical mechanisms underlying central energy metabolism regulation will provide a fertile ground to develop highly effective pharmacological agents to prevent and treat obesity.

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Figure 1. Functional interconnections of feeding behavior and energy metabolism regulatory pathways.

ARC: Arcuate nucleus of hypothalamus; BBB: Blood–brain barrier; LHA: Lateral hypothalamic area; PBN: Parabrachial nuclei; NTS: Nucleus of solitary tract; PVN: Paraventricular nucleus; VMH: Ventromedial hypothalamus.

The hypothalamus has a net of interconnected nuclei, including arcuate nucleus (ARC) paraventricular nucleus (PVN), lateral hypothalamic area (LHA), ventromedial nucleus (VMN), regulating various aspects of energy metabolism [1].

ARC involves two distinct groups of neurons: orexigenic, expressing NPY and AgRP and anorexigenic neurons coexpressing proopiomelanocortin and CART [2]. Posttranscriptional processing of POMC produces proACTH and β -LPH. Cleavage of 31 amino acid fragment (γ -LPH) from C-terminus of β -LPH produces β -endorphine. Further γ -LPH gives rise to β -MSH. ProACTH processing produces ACTH, α - and γ -MSH and CLIP and joining peptide (JP) (Figure 1).

ARC sends projections into multiple hypothalamic and extrahypothalamic areas, including LHA, PVN, VMH and so on [3]. LHA is a hypothalamic region considered as the feeding center [4]. Two distinct neuronal populations receiving projections from ARC express orexigenic peptides. MCH, a cyclic 19-amino acid peptide available as anabolic signal for food intake [5]. MCHR1 were found to be largely expressed in nucleus accumbens shell. This possibly mediates motivational aspects of eating behavior. Binding of MCH to MCHR1 [6] activates phospholipase C and inhibits adenylate cyclase pathway. Binding of MCH to MCHR2 activates only phospholipase C. Monoamines, such as norepinephrine, serotonin, gamma-aminobutyric acid (GABA) have inhibitory effect on MCH-producing neurons [7]. Another hormone expressed in LHA is orexin (hypocretin) [8], a neuropeptide responsible for in glucose sensing, sleep-awake and appetite stimulation (In Greek *orexis* means appetite) [9]. Two types of receptors have been reported for orexin – OX₁R and OX₂R.

PVN predominantly has an inhibitory effect on food intake [10], regulated by the synthesis of a set of hormones, including CRH, which has a great importance in mediating leptin effects [11], TRH reducing food intake, predominantly activated by α -MSH and exerting inhibitory effect on orexin and MCH via MC3-R and MC4-R [12], SST, binding to SST2 receptors and exerting orexigenic effect via downstream signaling of orexin-1, NPY (NPY1) and μ -opiate receptor [13], vasopressin exerting anorexigenic effect via V(1A) receptor, suppressing orexigenic effect of NPY, oxytocin exerting anorexigenic effect and activated by α -MSH hormone produced from POMC in ARC and nesfatin, a posttranslational processing product of NUCB2, targeting oxytocin neurons and exerting anorexigenic effect through oxytocin release. An evidence is accumulated that intraparaventricular injection of nesfatin induces c-Fos expression both in NTS and PVN oxytocin neurons [14]. Furthermore, nesfatin binds to G_s/G_i receptors [15] and appears to suppress feeding via leptin-independent melanocortin signaling [14]. These hormones activate catabolism and stimulate energy expenditure, exerting inhibitory effect on food intake and weight gain [16].

The VMN is a satiety center and considered as main region to maintain glucose homeostasis. VMN expresses specific to this region SF1, pituitary adenylate cyclase-activating peptide, recognized by VPAC1, VPAC2 and PAC1 receptors. The first two receptor subtypes exert similar affinity also to VIP, which was reported not having a specific receptor. Brain-derived neurotrophic factor is also expressed in VMN [1].

The ARC is of primary importance as initial sensor of hormonal and nutritional signal variations, receiving information from gut, adipose tissue, pancreas as well as afferent input from lower brain centers. Simultaneously it receives afferent projections from brainstem, containing information from periphery. Blood vessels surrounding ARC develop incomplete blood–brain barrier, permitting nutrient and hormonal signals from blood to reach ARC. Plenty of receptors are expressed in ARC. Among them the ObR is of great importance. Circulating level of leptin is directly proportional to body fat amount, reflecting the status of long-term energy stores. After the release from white adipose tissue, it is transported to hypothalamus and binds to the ObR [17]. Leptin receptors are widely distributed in various central and peripheral tissues, hence highest density of ObR is found in hypothalamus. Binding of leptin to the receptors activates a number of signaling pathways, including JAK2/STAT3, IRS/PI3K, SHP2/MAPK, AMPK/ACC and many more. Thus, leptin inhibits expression of various orexigenic peptides, including NPY, MCH, AgRP, orexin and so on. Leptin positively affects expression of anorexigenic peptide, including POMC, CART, CRH and brain-derived neurotrophic factor. Anorexigens and orexigens are involved in dynamic regulation of hunger and satiety and complex effect obtained arranges the energy homeostasis [18].

In hypothalamic neurons, a concurrent expression of leptin and ghrelin receptors is revealed. Ghrelin is a peptide, synthesized by gastric mucosa and acting as an orexigenic hormone to induce feeding behavior and secretion of growth hormone. It acts binding to GHS-R and activates signaling pathways with final SOCS3 expression, which terminates the leptin signal. Ghrelin level is increased in fasting. Feeding studies suggest that ghrelin and leptin act by way of vagal afferent pathways to modulate satiety, whereas their receptors in the hypothalamus and other central non hypothalamic sites are more likely to be involved in regulating long-term feeding behavior and energy metabolism [19].

The response is mediated by production of multiple orexigenic and anorexigenic peptides directly in the ARC and other hypothalamic nuclei.

In recent years, growing body of literature demonstrated inclusion of various exogenous and endogenous opioids in neurobiological and behavioral relationships between food intake, drug addiction and withdrawal syndrome. Opioid receptors are widely distributed in nervous and other tissues and mediate the sense of pleasure, homeostatic and hedonic mechanisms underlying food behavior. Sense of pleasure overlaps with reward circuits, indicating the crucial role of opioids in food addiction. Likely, lack of positive emotions or disruptions in reward circuits may be compensated via hedonic overeating, inducing weight gain and thus obesity [20].

POMC-derived endogenous opioid, β -endorphin has wide variety of functions peripherally and centrally. It expresses orexigenic effect and positively affects mood and eating, food motivation, food seeking, more appropriate as food craving. β -endorphin exerts effects binding Gi protein-coupled MOR [21]. MORs are highly expressed in various regions of reward system, mediating dopamine level to increase, suppressing GABA production in presynaptic nerve terminals. Dopamine is the main mediator of reward system, which is initiated in ventral tegmental area and also includes nucleus accumbens. The mesolimbic dopaminergic system mediates rewarding effects of food, sense of pleasure, food motivation and goal-directed behavior. It is also responsible for development of food addiction. The stress circuitry mediated by CRH in cerebrospinal fluid is also under control of β -endorphin via endothelin system and inhibition of CRH release, thus, inducing a well-being or even euphoria. However, β -endorphin administration increases food intake. β -endorphin serves as a modulatory 'bridge' between primary and secondary effects of various neurotransmitters and peptides. The orexigenic effect obtained is due to inhibition of anorexigenic α -MSH effects. Elevated plasma concentrations of β -endorphin in patients suffering from obesity have been demonstrated. In experimental studies opiate receptor antagonists prevented development of obesity in genetically obese animals [22].

In recent years, a growing body of literature provides data about the role of the endocannabinoid (EC) system in obesity for its significant role in lipid metabolism, energy balance control and regulation of food reward. Endogenous cannabinoid ligands bind to specific CB1 and CB2 $G_{i/o}$ -protein coupled receptors. Activation of the receptor inhibits adenylyl cyclase, reducing cAMP level. A G_q and G_s coupled pathways are also reported for ECs, activating K^+ channels, MAPK pathway and inhibiting Ca^{2+} channels. Based on ligand type, selectivity to signaling pathway is revealed. Binding of different ligands results different conformational changes of receptor [23].

CB1 is highly expressed centrally in hypothalamus and mesolimbic pathways and peripherally as well, CB2 is expressed peripherally: in adipose tissue, liver, muscles and pancreas. For its crucial role in energy metabolism and pathological overactivation in obesity, CB1 antagonism may be considered as effective pharmacological target. Rimonabant is an antagonist of CB1 receptor and is widely used to regulate body weight. However, antagonizing CB1 receptor linked with serious psychiatric side effects development, including anxiety, depression and suicidal thoughts [24]. The development of compounds with limited brain penetration to minimize the side effects while retaining the therapeutic efficacies seems very promising. Moreover, enzymes of cannabinoid metabolism, particularly, cannabinoid hydrolases (monoacylglycerol lipase and fatty acid amide hydrolase) also may be considered as pharmacological target to decrease EC level, thus reducing body weight.

EC system in periphery is involved in a wide variety of functions, normalizing lipid and carbohydrate metabolism. Application of antagonists of CB1 results in body weight reduction and activation of thermogenesis. Activation of CB1 receptor is responsible for expression and activation of PPAR- γ in white adipocytes, responsible for expression of genes involved in adipogenesis and TAG synthesis on transcriptional level [25]. Simultaneously, CB1 activation suppresses expression of mitochondrial UCP-1, which is involved in 'fat browning' – transformation of white adipocytes into beige and brown. Activation of CB2 receptor shows increase of transformation of white adipose tissue into brown and increases UCP-1 expression. Interestingly in fat browning pathway a PRDM transcriptional factor is expressed which suppresses expression of genes responsible for white adipocytes, including CCAAT/C/EBP, Krox20, KLFs and EBFs [26].

Some ECs (i.e., anandamide and 2-arachidonylglycerol) involved in regulation of energy homeostasis are agonists of TRPV1. Binding of exogenous ligands and activation of the receptor produces sensation of heat. Modulation via PKA, PKC and PIP2 cascade mechanism is reported [27].

The external ligand for TRPV1 is capsaicin, a pungent component of chili pepper. It was widely used as a flavoring spice since ancient times and was also known as a medication. Recently the effect of capsaicin on feeding behavior was outlined. Capsaicin exerts some effects on receptor-independent manner. It is involved in inactivation of NF- κ B and activation of PPAR- γ and PGC-1 α . This results in inhibition of adipogenesis in white adipose tissue and fat browning, thus, thermogenesis increasing UCP-1. In gastrointestinal (GI) tract capsaicin increases secretion of GLP-1. On the hypothalamic level, it induces expression of STAT3, so modulates leptin effects, reducing appetite and inducing feeling of satiety. In this context capsaicin exerts EC like effect. In obese patients, dysfunction of TRPV1 receptors is observed, indicating their involvement in energy metabolism. Overall it was found that capsaicin suppresses energy intake regulating appetite and satiety. It affects the brown adipose tissue as in cold exposure and increases energy expenditure and thermogenesis. Moreover, it suppresses immediate weight gain after weight loss. These properties make capsaicin an effective novel therapeutic target for body weight regulation [28,29].

Hypothalamic monoaminergic systems are involved in regulation of feeding behavior. Being the main neurotransmitter involved in mesolimbic reward and motivation circuit, dopamine is involved in food motivation and sense of pleasure. Dopamine deficient mice have shown to be hypoactive, not motivated in food and water intake. This shows the role of dopamine in compulsive intake of food and drugs, leading to obesity. Reward circuits initiate in ventral tegmental area (VTA), sending projections to nucleus accumbens, amygdala and prefrontal cortex [30].

Dopaminergic projections from amygdala and prefrontal cortex expand to lateral hypothalamus, directly involved in food and energy regulation. It affects expression of primary hormones included in hunger and satiety regulation – ghrelin, leptin and insulin. Dopamine binds to G-protein coupled DR1 and DR2 receptors. Food intake induces dopamine release and binding of dopamine to DR1 stimulates $G_{s/olf}$ receptor-mediated cAMP/PKA signaling pathway and increases food intake correlated with palatability of food, while binding to D2R reduces it. High levels of dopamine exert anorexigenic effect [31].

Another monoamine involved in regulation of feeding behavior is serotonin (5-hydroxytryptamine). It has various effects on energy metabolism. Serotonin exerts anorexigenic effect, suppressing appetite and reducing body weight. In ARC it increases expression of POMC, expression of MC4 receptors and inhibit orexigenic NPY expression. Serotonin mediates feeding behavior via 5-HT1B, 5-HT2C and 5-HT6 receptors [32].

Norepinephrine participates in mediating the GI tract input by vagal nerve into higher brain centers. Increased norepinephrine signaling leads to weight loss. Brainstem NTS projects to ARC and LHA stimulating noradrenaline release. Lesions of NTS-hypothalamus pathway induces weight gain. Furthermore, norepinephrine attenuates amphetamine anorectic effect [33].

Targeting monoamine neurotransmitters, such as dopamine, norepinephrine, and serotonin, as well as monoamine reuptake inhibitors may be effective driving weight loss in obese patients [34].

Substance P has effect on various physiological pathways regulating food behavior and energy metabolism. It acts through G-protein-coupled NK-1 receptor, which is widely expressed peripherally and centrally including hypothalamic ARC. Substance P decreases body weight and increases glucose utilization and sensitivity to insulin [35].

Gut processes hypothalamic signals about hunger

The primary feeling of satiety is developed in the GI tract in response to a meal. Gastric distension is important but insufficient signal of satiety. Being the largest endocrine gland, gut synthesizes multiple hormones, responsible for regulation of hunger and satiety [36]. These hormones have two ways to exert an effect: by gut–brain bidirectional axis, in which a primary role is given to vagal nerve and by blood, concentrating on brain regions with incomplete blood–brain barrier, particularly, brainstem and hypothalamus [37]. In the vagal nerve terminals into GI tract receptors for a number of satiety hormones are expressed, including CCK, peptide Y, GLP-1, secretin, VIP and pancreatic polypeptide (PP) and so on [38,39]. These hormones inhibit gastric emptying (CCK, amylin, GIP and GLP-1), gastric acid secretion (somatostatin, GIP, GLP-1 and CCK), inhibit (CCK, gastrin, secretin, GLP-1, VIP and NPY) or activate (PP, gastrin, ghrelin and motilin) gastric motility, stimulate insulin and suppress glucagon secretion, enhance glucose sensitivity of β cells and stimulate differentiation and development of β cells (GLP-1 and GIP) [40–43]. Agonists or antagonists of these peptides have already been used or may be used as effective therapeutic targets to treat obesity and diabetes.

The gut is the largest endocrine gland producing various hormones and biologically active peptides regulating hunger and satiety. When blood sugar level decreases, ghrelin is synthesized by gastric mucosa X/A cells [44] and other parts of digestive tract, such as duodenum, jejunum, ileum, colon and other tissues, such as lung, heart, pancreas, kidney, testis and pituitary as well [45]. Ghrelin is produced by cleavage of the precursor prepropeptide ghrelin/obestatin. Immediately after the synthesis in the form of preproghrelin, it loses pre-part and turns into proghrelin, subsequently producing ghrelin. An important step in producing the active ‘working’ variant of ghrelin is its post-translational octanoylation of serin in the third position via GOAT [46]. Acetylated ghrelin is transported by blood, passes blood–brain barrier and binds to growth hormone secretagogue receptor (GHS-R1- α) [47]. GOAT inhibition and restriction of ghrelin to interact with its receptor may open new perspectives to prevent and treat obesity [48]. GHS-R1- α is highly expressed in hypothalamic ARC, as well as in dopaminergic neurons in ventral tegmental area. The GHS-Rs were shown to amplify dopamine signaling inducing conformational changes in dopamine D1 receptor [49].

Another product of ghrelin/obestatin prepropeptide cleavage is obestatin, an anorexigenic peptide, synthesized by gastric cells, exerting the opposite effect to orexigenic ghrelin. Obestatin injection decreases overall caloric intake, hence, water and specific food consumption in palatable diet was not affected [50]. Intrahypothalamic injection of

obestatin produces an inhibition of dopamine release, thus reversing ghrelin effects. A similar contradicting effect was observed also for serotonin – obestatin eliminates ghrelin-induced inhibition of serotonin release [51].

The arcuate nucleus of the hypothalamus receives input from gut indirectly via brainstem (vagal nerve) nuclei, taking part in short-term regulation of hunger and satiety, as well as directly by blood [52]. Anatomically, ARC communicates with third cerebroventricle. Such a localization and an incomplete blood–brain barrier let ARC to be the first in sensing of nutrient and hormonal changes in organism [1]. The vagus nerve appears to be an important hub to transfer information from digestive tract to higher brain centers. Peptides produced in the digestive tract bind to their receptors, which are synthesized in nodose ganglion and then transferred to the vagal nerve fiber terminals, which reach to the mucosa of digestive tract. The orexigenic information is converted into electrical signals and transferred to brainstem by vagus nerve, to noradrenaline neurons of nucleus of solitary tract (NTS) (Figure 1), with further noradrenaline secretion from the hypothalamus to enhance appetite [53]. NTS is highly heterogeneous region, responsible for transfer of orexigenic and anorexigenic information. Various cell types in NTS differently affect feeding behavior. NTS neurons send projections directly to hypothalamus and indirectly via communication with parabrachial nucleus (PBN) [54]. In PBN CGRP producing neurons are of importance. These neurons are activated in response to anorexigenic information. Among gastrointestinal hormones CCK is involved in PBN mediated appetite suppression. PBN is considered to be activated by signals from higher brain centers. Neurons of PBN are under direct control of AgRP synthesizing neurons of hypothalamic ARC. During homeostatic need of food a dynamic balance is established between orexigenic AgRP neurons and anorexigenic CGRP neurons of PBN [55].

In response to a meal the I cells of small intestine secrete cholecystokinin into the circulation [56].

Cholecystokinin effects are short-term and are mediated through CCK1 and CCK2 receptors. An evidence is accumulated that only CCK1 receptors are responsible for satiety signaling. As a mechanism of satiety is proposed the inhibitory effect of high amounts of CCK on motility of GI tract and particularly, gastric emptying [39]. At physiological doses the effect is mediated by vagus nerve and further, through brainstem. However, a gastric preload is also required for the CCK to express its effects [57]. Peripheral administration of cholecystokinin induces the c-Fos, a neural activation marker expression in brainstem. However, blocking of CCK1 receptors do not diminish the meal-induced c-Fos levels in brainstem, so put under question the role of CCK in satiety processing [58].

Another gut hormone responsible in satiety processing are incretins: GIP, GLP-1 and GLP-2 and oxyntomodulin with minimal incretin effect. Synthesized by K-cells of upper small intestine and L-mucosa cells of ileum and colon correspondingly in response of glucose and fatty acid concentration changes, they are secreted into the blood stream [40]. GLP-1 inhibits the ileal motility and contributes to gastric emptying and acid secretion. At the same time GLP-1 directly binds to the GLP-1R, a G-protein-coupled receptor, located at the surface of the pancreatic β cells to enhance glucose-induced insulin secretion [41]. GLP-1 receptors are also found in various tissues, including adipose tissue and higher brain centers, including hippocampus, hypothalamus, thalamus and brainstem [59]. In experimental studies GLP-1 induces satiety and weight loss both in humans and animals. It has short-term effect, as rapidly degraded by dipeptidyl peptidase IV [60]. However, in the last decade the DPP-4 inhibitors, so called gliptins were developed. Gliptins exert antihyperglycemic effect and are used for treatment of diabetes Type 2 [61]. Another agent used in prevention of Type 2 diabetes is a rare, naturally existing sugar, 3-C epimer of fructose, D-allulose (D-psicose). It is an agonist of GLP-1 and stimulates its release, thus, contributes to vagal afferent signaling. Moreover, in long-term perspective it corrects arrhythmic overeating, obesity and diabetes. D-allulose has large perspectives for wide use due to anti-obesity and antidiabetic activity and minimal side effects [62]. Antidiabetic (Type 2) gliptins class drugs also exert anti-obesity properties. They are antagonists of SGLT-2 proteins, responsible for glucose reabsorption in kidneys, thus, increase its excretion. Reduction of blood pressure is among other favorable effects of gliptins [63].

Oxyntomodulin, another anorexigenic peptide, product of preproglucagon alternative processing, is synthesized by L cells of the colon. As an agonist of GLP-1R, it expresses anorexigenic effect and is considered to be responsible for appetite regulation on brainstem and hypothalamus level, activating POMC neurons in ARC, suppressing food intake and increasing energy expenditure. OXM exerts partial agonism to β -arrestin and G protein-coupled receptor kinase 2 for GLP-1R. If modulated by OXM, GLP-1R can exert effects differing from those of GLP-1 [64]. Oxyntomodulin is widely used as therapeutic agent to treat obesity. Thus short lifespan decreases its efficiency. A reversible pegylation (attachment of polyethyleneglycol residue) technology is now applied to increase the half-life of oxyntomodulin and other short-living peptides [65].

In pancreas GIP binding to its receptor stimulates glucagon secretion; in adipose tissue it stimulates fatty acids synthesis with further insulin-dependent incorporation into TAGs, increase of lipoprotein lipase activity [66].

Adipose tissue acts as a major endocrine gland

Insulin is synthesized and secreted by pancreatic β cells in response to blood glucose level increase [66]. It serves as a short-term feedback regulator of glucose level and a long-term satiety controller working as an adiposity signal targeting hypothalamus [67]. As a regulator of satiety insulin receptors are found in hypothalamus (ARC, DMH and PVN). As anorexigenic factor insulin acts through NPY/AgRP and POMC/CART neurons, located in the arcuate nucleus. Insulin receptors are also found in brainstem, but no data is available about direct effects of insulin on brainstem [68]. Insulin receptors are widely distributed in higher brain centers responsible for physiological and hedonic aspects of eating. Activation of receptor mediates polymodal effects of insulin. At peripheral level insulin has a great importance as an adipogenic factor [69].

To maintain energy homeostasis organisms have developed a multicomponent system for peripheral regulation of hunger and satiety. In line with GI tract white adipose tissue synthesizes several adipokines, cytokines and hormones responsible for maintenance of homeostasis, particularly, energy and caloric level regulation [69].

Below we discuss the adiposity signals and their bidirectional regulation by digestive tract and central nervous system. White adipose tissue stores triglycerides in order to meet long-term energy requirements of organism. Moreover, adipose tissue was found to be an important endocrine organ, regulating hunger and satiety [70,71]. Along with GI tract it synthesizes multiple hormones and biologically active peptides which affect higher brain circuits of energy metabolism [67].

Postprandial glucose level increase and gut-derived peptides stimulate insulin synthesis by pancreatic β -cells. Insulin receptors are widespread in organism. Latest research suggests also expression of insulin receptor in higher brain centers with possible synthesis of it inside blood–brain barrier [72]. An important target for insulin regulatory effect is adipose tissue. Insulin regulates growth and differentiation, metabolism of adipocytes via direct activation and inhibition of various signaling cascades, including inositolphosphate, MAPK, ERK, protein kinase A pathways [73]. On transcriptional level it induces expression of SREBP1, CCAAT/C/EBP β and PPAR γ thus, stimulating adipogenesis [74].

Adipose tissue synthesizes multiple anti-inflammatory (adiponectin, TGF- β , IL-10, IL-4, IL-13, IL-1Ra and apelin) more specific to low body weight and proinflammatory (TNF- α , IL-6, leptin, visfatin, resistin, angiotensin II and plasminogen activator inhibitor 1), more specific to obesity [75].

Adiponectin is derived from adipose tissue and has great importance to improve insulin sensitivity [76]. Adiponectin receptors are distributed in various regions of brain, but adiponectin was found not to cross the blood–brain barrier. Nevertheless, continuous administration of adiponectin revealed possible mechanisms of transport from blood to brain [77].

On the central level, adiponectin induces neuronal activation (c-Fos) in PVN and stimulates synthesis of CRH. Adiponectin exerts its effect via melanocortin signaling pathway [78]. Peripherally adiponectin decreases glucose and lipid level via positive effect on energy expenditure [79].

Adipocyte-derived resistin induces insulin resistance, thus increasing glucose production. No receptor is found for resistin, though data available indicate the resistin mediates insulin resistance via TLR-4 activation, finally producing proinflammatory cytokines [80]. Centrally it has shown to exert effects on hypothalamic level via upregulation of POMC and downregulation of NPY-mediated mechanism, inhibit hypothalamic release of dopamine and norepinephrine but not serotonin [81]. Peripherally it is synthesized by macrophages and contributes to TNF- α , IL-6, and SOCS-3 increased production [82]. The interconnection between gut and adipose tissue is mediated through GIP in a positive correlation manner. Under the effect of GIP, resistin exerts its effects on adipose tissue inhibiting lipoprotein lipase and AMPK. Resistin and other resistin-like adipokines reach insulin resistance effect by phosphorylation of IRS or by inflammatory effects including JNK and IKK β /NF κ B pathway [75].

By activating the mTOR (mammalian target of rapamycin) pathway insulin stimulates the leptin biosynthesis. PKA, AMP-activated protein kinase pathways and nutritional signals are of great importance in biosynthesis of leptin [83]. Leptin is an adipose tissue derived hormone and is of great importance to inform higher brain centers about the energy status of organism [84]. Leptin mRNA expression and synthesis in adipocytes is activated in absorptive period with high level of energetic substrates and reversely, it is decreased in fasting. In obese patients, plasma levels of leptin are found to be high [85]. Leptin acts through LepR (Ob) receptors, which are widely distributed in organism, with highest density found in hypothalamic arcuate nucleus.

Similar to gut-derived hormones, leptin works as mediator, transferring information via vagal afferents to brainstem and as hormone. After synthesis in adipocytes, it is released to the blood, crosses the blood–brain barrier and reaches hypothalamus [86]. Binding to the receptors activates number of signaling pathways leading to expression of various orexigenic and anorexigenic peptides, including NPY, melaninconcentrating hormone, AgRP, galanin, orexin and GALP. Anorexigenic peptides, which expressions seem to be modulated by leptin, include POMC, cocaine- and amphetamine-regulated transcript, neurotensin, CRH and brain-derived neurotrophic factor [87].

Leptin and ghrelin are considered to modulate satiety while transferring information via vagal afferents, whereas as hormones in the hypothalamus and other central nonhypothalamic sites are more likely to be involved in regulating long-term feeding behavior and energy metabolism [38].

More recently discovered adipokine-chemerin was found to be involved in the regulation of adipogenesis, as well as in adipocyte differentiation and energy metabolism. Moreover, chemerin regulates inflammatory processes. On the peripheral level, it has a minor role in appetite regulation exerting anorexigenic effect in long-term perspective [88]. Chemerin producing glial cells are localized in the third ventricle and send tanycyte mediated projections [89] to the ARC. On central level chemerin exerts dual effect on up- and downregulation of various groups of orexigenic and anorexigenic peptides in dose-dependent manner. It has modulatory effect on serotonin release, thus exerting serotonin-mediated anorexigenic effect, but does not affect dopamine and noradrenaline release [88]. Blood circulating chemerin is found to be in a direct relation with body mass index and is considered as obesity marker [90].

Chemerin exerts both central and peripheral effects via ChemR23 (CMKLR1) receptor. It is expressed in multiple brain areas suggesting chemerin involvement in various brain functions. Long-term effects on food intake is one of the possible functions of chemerin.

Visfatin, also known as pre-B-colony enhancing factor [91], is expressed in multiple tissues (muscles, bones, liver and kidneys). Hence, the visceral adipose tissue is crucial for its production [92]. In obesity high levels of serum visfatin were identified [93]. Recently, visfatin has been found in cerebrospinal fluid, suggesting its ability to cross blood–brain barrier and/or to be expressed in the brain.

On peripheral and central levels visfatin exerts opposite effects. It increases food intake, possibly via modulation of dopamine, CART, POMC, AgRP, NPY and CRH activity in hypothalamus. Hence, intracerebroventricular injection of visfatin has shown to express anorexigenic effects [94].

Peripherally, some evidence is accumulated about insulin receptor as a binding site for visfatin in hepatocytes, myocytes and adipocytes [95]. The wide expression may suggest also other binding sites. Cell proliferation, NAD⁺ synthesis (key-regulatory enzyme nicotinamide-phosphoribosyltransferase) and glucose level decrease (insulinomimetic) are the main effects of visfatin [94,96].

Anti-obesity drugs

The hope that medications might be useful in preventing and managing obesity was alive for nearly a century.

Different pharmacotherapy approaches have been used to reduce body weight and its complications for many years. These include herbal medicines such as green tea and black Chinese tea, *Nigella sativa*, *Camellia sinensis*, *Cissus quadrangularis*, *Sambucus nigra*, *Asparagus officinalis*, *Garcinia atroviridis*, ephedra and caffeine, smilax (extract of several plants, including *Zinger officinalis* and *bofutsushosan*).

Historically in the early 1930s, 2,4-dinitrophenol [97] was widely used as a treatment of obesity. But serious side effects of this drug, such as fatal hyperthermia, agranulocytosis and cataract, were recognized [98].

There is a gap of an ideal drug which is efficacious, safe, produces sustained weight reduction.

Most of the synthetic drugs for the treatment of obesity over the past years and described below have been withdrawn because of adverse reactions, which appears, likely, because of the structural similarity with amphetamine (**1**), which targets monoamine neurotransmitters managing obesity. Most central-acting appetite-reducing amphetamine-like drugs were discontinued due to side effects that often lead to the death of patients. These include a pronounced stimulating effect on the central nervous system, addiction as well as a ‘withdrawal syndrome’. The most dangerous was the development of severe pulmonary hypertension [99,100].

Amphetamine

Amphetamine (**1**), which was discovered over 100 years ago, and appears to be one of the most restricted controlled drugs, was approved as a weight loss drug, but its addictive properties soon became evident. Amphetamine exists as two enantiomers and has multiple mechanisms of action. It promotes the release of presynaptic nerve endings

Figure 2. Amphetamine structural analogs.

from the vesicular pool and inhibits the reuptake of dopamine and norepinephrine, and inhibits MAO. Indirectly stimulates the central dopamine and noradrenergic receptors (has a psychostimulating and anorexigenic effect), has peripheral α - and β -adrenomimetic activity, causes narrowing of peripheral vessels, increased heart rate, increased blood pressure, relaxation of the bronchi muscles, mydriasis.

Additionally, it reduces the feeling of fatigue, causes a feeling of strength and vigor, increases mental and physical performance, reduces the need for sleep, improves mood, weakens and shortens sleep caused by sleeping pills and narcotic analgesics, Exerts a psychotomimetic effect and is a drug of abuse. It was previously used for a large variety of conditions, but now amphetamine is generally indicated for the treatment of attention-deficit/hyperactivity disorders and central nervous system disorders such as narcolepsy [101,102].

The L-form of amphetamine – levoamphetamine (**1a**) has less central nervous system activity but stronger cardiovascular effects. The D-form – dextroamphetamine (**1b**) exhibits more pronounced effects on the central nervous system than levoamphetamine (Figure 2) [103].

Phentermine

Sympathomimetic amine phentermine (**2**) is the first FDA-approved prescription anti-obesity drug, which was approved in 1959. It is commonly referred to as an atypical amphetamine. Phentermine has low abuse potential and was approved for short-term weight management (Figure 2) [101,102,104].

Chlorphentermine

Chlorphentermine (**3**) is also an analog of phentermine, with central nervous system stimulating motor activity, mental alertness and excitement, which causes euphoria, and suppresses appetite (Figure 2) [105,106].

Benzphetamine

Benzphetamine (**4**) is a sympathomimetic agent with properties similar to dextroamphetamine. It was used in the treatment of obesity (Figure 2) [107].

Fenfluramine

Another derivative of phenylethylamine, fenfluramine (**5**) was approved in 1973. Fenfluramine has a serotonergic mechanism of action. It is proved that the drug affects the center of saturation more than the center of hunger. It does not have psychostimulating activity.

It reduces food intake without suppressing salivation at the sight of food as an indicator of appetite (in contrast to amphetamine and its derivatives). Long-term treatment with the drug leads to a decrease in the content of

Figure 3. More complicated amphetamine structural analogs.

catecholamines in the circulating blood, which is clinically manifested in the form of moderate bradycardia and a slight decrease in blood pressure.

But unlike other drugs with fenfluramine-like structure, is a depressant rather than a stimulant, and its metabolite nordexfenfluramine acts as an agonist of serotonin receptors. Fenfluramine has been available on the market for 20 years for the treatment of obesity. Dexfenfluramine (**6a**) reduces appetite by increasing the amount of extracellular serotonin in the brain. For a short time during the middle of the nineties, it was approved for use in managing weight loss. In 1997, the FDA withdrew dexfenfluramine and fenfluramine from the market because of a high incidence of cardiac valvular abnormalities found in patients who were taking the drugs.

In 1992, there was a trial that demonstrated additive effects on weight loss when fenfluramine was used in combination with phentermine (**2**) in the ‘fen-phen’ combination [106]. Since fenfluramine was a depressant and phentermine was a stimulant, the side effects canceled each other and improved tolerability (Figure 2) [108,109].

Sibutramine

Sibutramine (**6**) – another amphetamine structural analog. The mechanism of action is due to selective inhibition of serotonin and norepinephrine reuptake, to a lesser extent – dopamine. Accelerates the onset and prolongs the feeling of satiety, which leads to a decrease in food consumption. Sibutramine was withdrawn from the market because of concerns over increased rates of cardiovascular events (Figure 2) [110–112].

Phendimetrazine

Phendimetrazine (**7**) is also a sympathomimetic amine and has with similar side effects, but less frequent, to those associated with amphetamine. Being chemically related to amphetamines and is a drug under the Convention on Psychotropic Substances. But it is considered to be the safest among amphetamine analogs (Figure 3) [113].

Diethylpropion

Diethylpropion (**8**) is the popular amphetamine-related anti-obesity drug in Brazil, but not in the USA. Central nervous system stimulation of diethylpropion has been reduced by a keto substitution on the beta carbon of the phenethylamine backbone which considered to produce less central nervous system disturbance than most drugs in this therapeutic category 22 (Figure 3).

Aminorex

Aminorex (**9**), an amphetamine-like anorectic agent, which was approved for treatment of obesity in Europe in 1965 but was never approved in the USA [101]. It may cause amphetamine like characteristic effects on central nervous system and pulmonary hypertension. This led to its withdrawal from the market in 1968 (Figure 3) [105–107].

Mefenorex

Mefenorex (**10**), is a well-tolerated antiobesity drug which was developed in the 1970s as an adjunctive therapy to diet, for the treatment of obesity. Mefenorex produces amphetamine as a metabolite, and for this reason has been withdrawn in many countries and is included in the list of centrally acting stimulants and/or hallucinogens despite the fact that it did not produce typical amphetamine-like psychostimulant profile and has only mild stimulant effects and relatively little abuse potential. Moreover, no health or social problems associated with mefenorex use are reported or registered. But despite having only mild stimulant effects and relatively little abuse potential, mefenorex has been withdrawn in many countries (Figure 4) [114,115].

Figure 4. N-Substituted amphetamine structural analogs.

Clobenzorex

Clobenzorex (**11**) is a relatively new anorectic drug and represents an N-substituted chemical analog of amphetamine. It has been cited in the literature in the last couple of years. It is not available in USA, but is available in other countries such as Mexico, Spain, Argentina and France.

Benfluorex

Benfluorex (**12**) is an anorectic and hypolipidemic drug structurally related to fenfluramine. It decreases the relative rate of hepatic triacylglycerol synthesis. Benfluorex was never approved for use in USA and was withdrawn in the European Union because of an increased risk of pulmonary hypertension and valvular disease (Figure 4) [116,117].

Fenfluramine/phentermine

In 1992 a trial demonstrated additive effects on weight loss when fenfluramine (**6**) was used in combination with phentermine (**4**) in the 'fen-phen' combination. The essence of combination therapy is that the two drugs show at least additivity: that is, their combined effects should be predictable knowing the action of each drug alone. Fenfluramine is a racemic mixture of two enantiomers levofenfluramine and dexfenfluramine. Whereas, levofenfluramine has been shown to exert antidopaminergic activity, phentermine has dopaminergic properties. Mixing phentermine with racemic fenfluramine would at least theoretically cancel out these dopaminergic effects, so as to minimize patient complaints and improve compliance [118,119].

Fenfluramine/dexfenfluramine

Concomitant administration of fenfluramine (**6**) and dexfenfluramine became widely used in 1960. This product was discontinued because of a high incidence of cardiac valvular abnormalities found in patients who were taking the drugs. In 1997, the FDA withdrew dexfenfluramine and fenfluramine from the market (Figure 6) [120,121].

Phenylpropanolamine

Phenylpropanolamine (**13**) is a nonselective adrenergic receptor agonist and norepinephrine reuptake inhibitor, phenylpropanolamine used as a decongestant and appetite suppressant caused intracranial bleeding and strokes is withdrawn from the market due to the risk for hemorrhagic strokes (Figure 5) [122–124].

Ecopipam

Ecopipam (**14**) is a dopamine receptor antagonist that was developed for the treatment of obesity, in the treatment of Tourette's syndrome, Lesch–Nyhan disease, pathological gambling and self-injurious behavior. However, the adverse effects on mood observed in the Phase III studies exclude its projected use in weight management (Figure 5) [125].

Rimonabant

Rimonabant (**15**) is an anorectic anti-obesity drug. It is the first selective CB1 receptor blocker to be approved for use anywhere in the world, which was approved by the FDA in 2006, but presently was rejected for approval in USA because it may increase suicidal thinking and depression in persons who are already suffering from mental disorders. The most common side effects were anxiety, depression, insomnia and dizziness. Nausea and diarrhea were also noted. Nonetheless, rimonabant is approved in 42 countries [126–132]. (Figure 5).

Figure 5. Anti-obesity compounds of miscellaneous structures.

Figure 6. Structure of orlistat and lorcaserin.

Tesofensine

Tesofensine (**16**) is a serotonin–noradrenaline–dopamine reuptake inhibitor, shown to be safe and effective in animal models and in humans. It is found to suppress feeding by stimulation of $\alpha 1$ adrenoceptor and D1 dopamine receptor pathways. As of 2019, tesofensine has been discontinued for the treatment of Alzheimer's and Parkinson's disease but is in Phase III clinical trial for obesity (Figure 5) [133,134]. The level and the rate of obesity is continuing to increase globally. At the same time safety concerns prompted the withdrawal of amphetamine structural analogs proposed as anti-obesity drugs from the pharmaceutical market [135]. At present, there are six major anti-obesity medications approved by the FDA (phentermine: 1959; orlistat: 1999; liraglutide: 2014; lorcaserin: 2012, phentermine/topiramate: 2012; naltrexone/bupropion: 2015).

Orlistat (xenical, alli)

Orlistat (**17**) as a drug used in the treatment of obesity, which was approved in 1999 and since 2007 it has been available as an over-the-counter (OTC) drug in the US orlistat works by inhibiting lipase – an enzyme that breaks triglycerides down into fatty acids. Thereby triglycerides from the diet are prevented from being hydrolyzed and are excreted undigested which results in a lower rate of fat absorption by 30%. Orlistat administration is also associated with a reduction of total cholesterol and low-density lipoprotein cholesterol. The most common side effects associated with orlistat therapy are gastrointestinal symptoms. It is the only agent approved in the European Union for weight loss. Numerous total syntheses of orlistat have been reported (Figure 6) [136–140].

Lorcaserin (belviq)

Lorcaserin (**18**) is a centrally acting serotonin agonist and acts as an anorectic. Lorcaserin (**18**), which is among the ten most prescribed drugs in the world, is a centrally acting serotonin agonist with high affinity and selectively activates the 5-HT_{2C} receptors on anorexigenic pro-opiomelanocortin neurons located in the hypothalamus, which control fat and caloric intake. It is believed that this causes the release of alpha-melanocortin-stimulating hormone, which acts on melanocortin-4 receptors in the paraventricular nucleus to suppress appetite, but the exact mechanism of action is unknown. Lorcaserin provides weight loss without possible side effects related to 5-HT_{2A} receptor

Figure 7. Liraglutide amino acid sequence.

Figure 8. Phentermine/topiramate combination.

activation (no hallucinating effect), as well as related to 5-HT_{2B} receptor activation (cardiovascular side effects and pulmonary hypertension). Lorcaserin may have peripheral effects resulting from interactions with gastrointestinal cholecystokinin and leptin signaling (Figure 6) [141–144].

Liraglutide

Liraglutide (19, victoza) is the only weight loss medication which is administered subcutaneously as an isotonic solution. This medication is a GLP-1 agonist that, in addition to stimulating insulin release and inhibiting glucagon secretion, slows gastric emptying and increases satiety after eating. Liraglutide is indicated as an adjunct to a low-calorie diet and physical activity for weight management in overweight or obese adults.

Liraglutide is a synthetic molecule, GLP-1 analog with a 97% homology to endogenous human GLP-1 produced using recombinant DNA technology. Compared with native GLP-1, it has an addition of a palmitic acid side-chain at Lys26 and substituting arginine for lysine at position 34 [145–147]. Liraglutide sequence (γ -E-palmitoyl at E21) HAEGTFTSDVSSYLEGQAAKEEFIAWLVRGRG (Figure 7).

In addition to the above single target agents, combination drug formulations multipathway approach described below, is another possibility to achieve weight loss without causing major adverse effects. Combination drug formulations multipathway approach is another possibility to achieve weight loss without causing major adverse effects.

Phentermine/topiramate

As mentioned above, phentermine (3), a centrally acting sympathomimetic agent is an appetite suppressant. Topiramate (2) – a sulphated monosaccharide with multiple targets such as blocking voltage-dependent sodium and calcium channels. It also inhibits the excitatory glutamate pathway while enhancing the inhibitory effect of GABA. Moreover, it inhibits carbonic anhydrase activity. The combination of phentermine and topiramate decreases energy intake and increases energy expenditure leading to weight loss (Figure 8) [148–150].

Figure 9. Naltrexone/bupropion combination.

Naltrexone/bupropion

Naltrexone/bupropion was approved in 2014. The mechanism of action of this combination medication assume various mechanisms and is not entirely understood. Naltrexone (21) is an opioid receptor antagonist and represents a synthetic congener of oxycodone with no opioid agonist properties. It is used for treatment of alcohol and narcotic addiction. Bupropion (22) is a selective dopamine and noradrenaline reuptake inhibitor. It is an antidepressant used to treat major depressive disorder and seasonal affective disorder. It is also beneficial to promoting tobacco cessation and weight loss. The effect of this combination is to reduce hunger and significantly reduces weight. It has no effect on energy metabolism [151–153].

The FDA has marked naltrexone–bupropion with a ‘black box’, warning for potential increased risk of suicidality (Figure 9).

The search for effective medications continues, and a number of new compounds have recently been examined in preclinical and early phase trials.

Understanding biochemical pathways underlying food behavior and energy metabolism is a milestone on the way to overcome and treat obesity. Each of the components included in peripheral and central mechanisms of energy metabolism may be considered as a potential target to regulate body weight and appetite. Targeting various combinations of adipokines, neurotransmitters, neuropeptides, hormones, regulating their synthesis on gene or posttranscriptional level, affecting extracellular and intracellular signaling events, complex approaches may be developed in treatment and prevention of obesity. The pharmaceutical industry is about to reach a qualitatively new level of drug development based on biochemical mechanisms of food behavior.

Conclusion

Many anti-obesity drugs have been developed over the past century but today only some of them are in demand in the pharmaceutical market. Obesity has a unique neurobiological base with central role for the reward system. Growing body of literature published in recent years, has shown both – neurological and behavioral relationships between food intake, drug abuse and withdrawal syndrome. For successful treatment of obesity, molecular mechanisms of abovementioned relationship have to be investigated and interpreted. Understanding the neurochemical basis of obesity may provide a fertile ground for pharmacological prevention and treatment of obesity.

Future perspective

Many anti-obesity drugs have been developed and many have to be. Central and peripheral mechanisms of various aspects of food intake and energy expenditure open promising perspectives for development of qualitatively new anti-obesity drugs. Anti-obesity drugs with novel multi-target mechanisms of actions based on complex effect, focusing centrally on neurotransmitters and neuropeptides and peripherally on adipokines are of particular interest. Focus on new molecular targets such as enzymes of synthesis and degradation of neuroregulators and modulators of particular signal transduction pathways seem to be attractive approach for development and design of new combined pharmaceutical compositions.

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Executive summary

- Obesity is widespread, polygenic state, primarily developed due to overeating and disturbed feeding rhythm and appears to be a risk factor for various pathological states. Prevention and treatment of obesity is one of the leading challenges of modern medicine and pharmacy.
- Nowadays, the available options for the pharmacotherapy of obesity are very limited due to poor efficacy and/or safety profiles of the majority of the anti-obesity drugs.
- To design effective anti-obesity drugs, lacking aversive side effects, neuroendocrine endogenous regulators of food behavior and energy metabolism are to be targeted.
- Effective regulation of body weight and appetite requires exploring of energy input/output balance system based on short-term signals in long-term perspective.
- Energy metabolism and body weight depends on the balance of orexigenic/anorexigenic neurons switch on/switch off state. Disturbances of homeostasis of this dynamic system may induce extremal body weight gain/reduction.
- Medications used to reduce body weight are subdivided into three main groups: drugs that suppress appetite, drugs that reduce the absorption of nutrients from the intestines (dietary correctors) and drugs that increase energy consumption.
- The combination medicines like phentermine/topiramate or naltrexone/bupropion seems to be the optimal treatment for obesity.
- The cross talk of biochemical mechanisms underlying feeding behavior and energy metabolism with molecular pharmacology opens exciting horizons for effective prevention and treatment of obesity.
- Despite new approaches in effective anti-obesity drug design and brand new data about biochemical aspects of energy homeostasis, the best way to maintain optimal body weight is to control food intake and increase energy expenditure.

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