Obesity Complications and Challenges

Chapter 1

Neurochemical Mechanisms of Brain Reward System in Obesity

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1. Introduction

Once upon a time there was a girl whose food intake and energy expenditure was in absolute balance, so she had an ideal body mass index. The girl lived in a country where food was taken only for its homeostatic properties. Everyone in the country was fit and some kind of incomplete.

Food sounds very exciting to us. It is consumed not only for homeostatic properties but for its hedonic properties as well. The calorie dense, palatable food is consumed even if the state of the satiety is reached. Palatable food looks attractive for its hedonic properties.

An ordinary cycle to maintain energy homeostasis looks like feeling of a hunger - eating – satiation and the same cycle repeats multiple times. Some organisms request less repetition of the cycle and some request more. The simple mechanism of hunger and satiety includes several levels of regulation and multiple active compounds in it. The simplified hunger and satiety cycle looks like hypothalamus senses the decrease of nutrients in the blood, sends signals to higher brain centers and to digestive tract, thus forming the sense of hunger and motivation to eat, the eating follows, digestive tract sends signals to release insulin and to form a feeling of satiety, insulin induces fat synthesis in adipose tissue and simultaneously activating leptin production, which is the main hormone to inform higher brain centers that satiation is reached and it is time to stop eating.

So two mechanisms are involved in regulation of hunger and satiety: a direct one, including generally hypothalamus and periphery, and indirect one, including brain reward system. The first mediates homeostatic feeding, and the second one is responsible for motivational and hedonic eating. Generally both systems are mutually interconnected and affect each other in various ways, but one thing still remains unclear: what is cue to eat more when a homeostatic amount of energy is taken.

Sometimes hunger-satiety cycle may repeat much more times, than organism really requires. Satiation is reached but you still eat, you feel full, another portion of food makes you to feel uncomfortable but you still eat. Afterwards it is difficult to understand what is driving you. The solution is hidden in brain reward system: a set of interconnected brain structures responsible for feeling of pleasure from daily activity. If simplified, every action we do is an anticipation for reward. We worked hard all the day, so it is a good idea to reward ourselves with a good film or some beer, or you carefully kept a diet and lost some weight, so it is time for compensation with a piece of tasty chocolate cake etc.

Disturbances in various levels of homeostatic and hedonic feeding regulation systems may cause two critical opposite states-anorexia and obesity. Nowadays obesity is one of the most frequent pathological states in the world. Recent research indicates that the cause of obesity is hidden in neural circuits and caused by abnormal regulation of hunger-satiety cycle and/or disturbances in reward system.

In the upcoming chapter the various levels of hunger-satiety regulation, involvement of brain reward circuits in food-oriented behavior and disturbances of the abovementioned mechanisms causing obesity are discussed.

2. Homeostatic Regulation of Hunger and Satiety

Hunger and satiety are the two important aspects of feeding to maintain homeostasis and to provide energy and structural blocks for normal metabolic processes in organism. The key structure for hunger and satiety regulation is hypothalamus, particularly, arcuate nucleus of hypothalamus [1]. It contains two distinct populations of neurons exerting orexigenic (induce food intake) and anorexigenic (stop feeding and induce satiety) effects. The anorexigenic region of arcuate nucleus involves proopiomelanocortin (POMC)/and cocaine- and amphetamine regulated transcript (CART). Orexigenic region neurons coexpress Agouti-related peptide (AgRP) and neuropeptide Y (NPY) [2]. Since multiple hormones and functional and anatomical interconnections are involved in hunger and satiety cycles, two hormones are the key: ghrelin-the hunger and appetite stimulator and leptin – satiety signal, corresponding to the level of energy stores in organism [3].

The primary structure sensing glucose and nutrient fluctuations in the blood is the arcuate nucleus of hypothalamus. It is surrounded by semipermeable blood-brain barrier, so even the slight changes of blood components are immediately sensed by hypothalamic neurons and response is formed [4]. Glucose, insulin, leptin, a number of gut-derived factors including glucagon-like peptide-1 (GLP-1), peptide YY (PYY), oxyntomodulin and ghrelin peripheral signals indicating energy balance, directly interact with hypothalamic neurons, regulating feeding behavior. There is a rich neuronal net between hypothalamus and various regions of the brain, as well as digestive tract [5].

When blood glucose level decreases, hypothalamus informs stomach that organism needs nutrients. In response to the neural signal, ghrelin is synthesized in the stomach X/A cells. The synthesized ghrelin has two ways to exert its effects- via vagus nerve, initiated in digestive tract and sending afferents to the nucleus of solitary tract in brainstem and as hormone by blood [6,7]. Ghrelin receptors (Growth hormone secretagogue receptor-GHSR) are widely expressed in orexigenic regions of arcuate nucleus and ventromedial nucleus (VMN) of hypothalamus. Binding to the receptor, it exerts orexigenic effects and induces feeding behavior [8]. Among important effects in NTS is transfer of noradrenaline information via direct noradrenergic projections to hypothalamus [9]. The resulting effect of two ghrelin signals from the brainstem and as hormone by blood the feeding is stimulated.

Interestingly ghrelin has a key role in both homeostatic and hedonic feeding. Besides food intake stimulation, ghrelin has role of appetite maintenance while eating. Hedonic component of eating mediated by ghrelin includes motivational behavior and incentive salience applied to food rewards, as well as inherent palatability of eating [10]. This considers transfer of ghrelin information to higher brain centers, particularly to reward circuits. On this context ghrelin is responsible for the motivation to eat palatable food even if the homeostatic level of food consumption is met [11].

Circulating levels of ghrelin in fasting periods contribute to appetite and hunger, as well as increase in "liking" and "wanting" of food [12]. Ghrelin levels appear to be associated with increased dopamine output in neural circuits. Moreover, ghrelin administration increases reward circuits activity in response to palatable food exposure [13,14].

Another important hormone responsible for regulation of feeding behavior is leptin [15]. It informs hypothalamus about the level of long-term energy stores of organism. Leptin levels are in direct relationship with the body mass index: so people with lower body mass index correspondingly have lower leptin levels and higher body mass index considers higher leptin levels [16].

There is a long way from food intake until leptin signal reaches hypothalamus. Following food intake various cells of digestive tract synthesize multiple hormones, i.e. glucagon-like peptide (GLP), gastrointestinal peptide (GIP), vasointestinal peptide (VIP), cholecystokininie (CCK), etc [17]. All the hormones mostly exert anorexigenic properties sending signals via vagal afferents to brainstem. Among abovementioned hormones, the GLP-1 responsible for glucose dependent release of insulin from pancreas [18]. Insulin exerts multiple effects on carbohydrate and fat metabolism, stimulating synthesis of glycogen and fat in adipose tissue. When the fat synthesis rather took place, insulin stimulates leptin production [19]. The newly synthesized leptin stops insulin effects, is released from adipose tissue and moves to hypothalamus [20]. In hypothalamus it exerts its effects by binding to Ob receptors expressed in various regions of hypothalamus, exerting anorexigenic effect [21]. Formation of hormone-receptor complex activates signaling pathways with subsequent Stat3 protein activation. In arcuate nucleus it decreases NPY synthesis and release, thus increasing corticotropin-releasing hormone synthesis in arcuate nucleus and paraventricular nucleus [22]. Leptin also suppresses ghrelin effects via SOCS3 stimulation pathway [23].

3. Reward Circuits in Brain

Human organism is not just a biological machinery with energy input and output. We eat not only to maintain the energy balance in organism. A caloric dense, palatable food is consumed even if the state of satiety is already reached. Palatability of food can be described as the hedonic evaluation of oro-sensory food cues under standardized conditions" [24]. Multiple characteristics of food, including taste, odor, appearance, texture, temperature, trigeminal senses constitute palatability. The palatability of a food, especially its taste pleasantness, is the most important factor that determines food selection or preference. Another important marker of palatability is macronutrient composition: it is considered that higher fat and sugar content food has higher palatability as it is a better source of energy [25].

One of the key systems of the brain responsible for the wide variety of functions is the limbic system. It is responsible for maintenance of homeostasis, mediates learning and memory, emotional aspects of cognitions. In the heart of limbic system the brain pleasure center-mesolimbic dopaminergic system is located. It interconnects various structures involved in pleasure and motivation, particularly, ventral tegmental area and Nucleus accumbens of ventral striatum (**Figure 1**). Mesocortical pathway is another important dopaminergic pathway, interconnecting ventral tegmental area with prefrontal cortex [26].

Multiple brain structures are involved in reward processing, including ventral tegmental area (VTA), ventral striatum (Nucleus Accumbens (NAc), bulbus olfactorius), dorsal striatum (caudate nucleus and putamen), Substantia nigra, prefrontal cortex, anterior cingulate cortex, insular cortex, hippocampus, lateral hypothalamic area, multiple nuclei of thalamus, subthalamic

nucleus, globus pallidus, ventral pallidum, parabrachial nucleus, amygdala etc [27].

The listed structures have multiple functions in reward processing, including the evaluation of reward and hedonic value of food, motivational and incentive properties of food, food-seeking behaviors. All these functions are mediated and regulated through a complex neuroendocrine axis with hypothalamus as a central hub.

Here it is very important to understand how organism defines what produces pleasure and what is not. We can observe that mostly similar things produce pleasure and addiction in most of people, so it is cigarettes, alcohol, drugs, palatable food etc. Let's compare a piece of chocolate cake and a punch of greens. From nutritional aspect both have vitamins, structural blocks and fresh greens is also very good for digestion as provides dietary fiber. But just a simple pronunciation of chocolate cake already has a mouthwatering effects to anyone who has tried it just once. The same effect is not applicable for a fresh greens. So what is there in chocolate cake that greens lack.

Excluding the hedonic aspects of food it maintains the energetic balance in our organism and provides structural blocks for the renewal of the cells. Food intake and energy expenditure systems are carefully regulated by multiple systems of the organism, including digestive tract, endocrine system, adipose tissue.
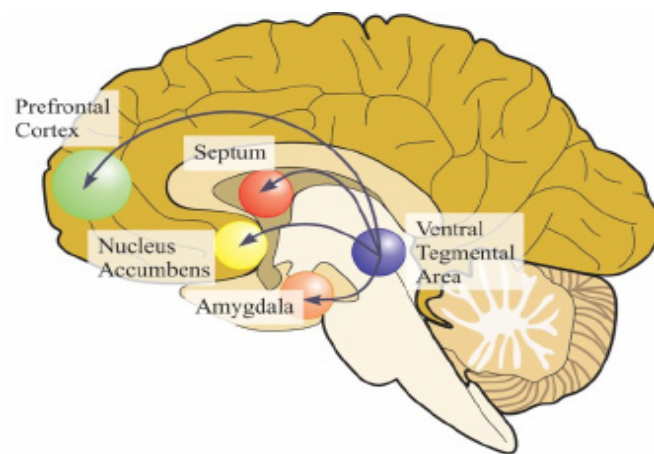
Figure 1: Schematic representation of structural organization of brain reward system.

A primary center regulating food intake and energy expenditure is hypothalamus. It has multiple anorexigenic and orexigenic neurons, regulating hunger and satiety. Hypothalamus cares primarily about homeostatic aspect of the food. The area surrounding arcuate nucleus has defective blood brain barrier, so even slight changes of glucose and nutrients are immediately sensed by the hypothalamus with a corresponding response. At the same time, hypothalamus receives vagal afferents from digestive tract via brainstem, so is informed about the real time situation in digestive tract. Simultaneously hypothalamic neurons are in direct association with higher brain centers, particularly reward circuits of the brain [28].

The neurons that connect the brain regions involved in reward behavior are related to many neurotransmitter systems. In this context hypothalamus is in mutual interconnection

with dopaminergic, opioidergic and serotoninergic signaling from various brain regions. Moreover, studies have shown that dopamine, endogenous opioids, and serotonin are highly related to drug and food addiction [29]. Known as hormone of happiness serotonin is involved in modulation of feeding behavior and satiety, regulation of the amount as well as the motor processes associated with eating, rewarding and aversive processing, hedonic experience, mood and higher cognitive functions,. In the brain, 5HT is synthesized in neurons of the brainstem Raphe nuclei, where most of the forebrain serotoninergic innervation originates and released into synapse to act as a neuromodulator of many brain circuits [30]. Serotonin may modulate incentive motivation through interactions with the mesolimbic dopamine (DA) system, originating in the ventral tegmental area (VTA) and predominantly terminating in the Nucleus accumbens [31]. Overall, serotonin decreases food consumption, thus exerting anorexigenic effect via three receptor subtypes: 5-HT1B, 5-HT2C and 5-HT6. Posttranslational processing of POMC produces α-melanocyte-stimulating hormone (α-MSH), an endogenous ligand that acts at melanocortin receptor (MC4) level. Recent data indicate the first two receptor subtypes exert anorexigenic properties via MC4 receptors. In the hypothalamic arcuate nucleus serotonin inhibits the activity of neurons expressing NPY and AgRP and activates POMC/a-MSH producing neurons, thus exerting anorexigenic effect and reducing food intake. [32]. In the periphery, serotonin is produced mostly by intestinal mucosa and released into circulation.

Referred to reward system serotonin plays important role in self-administration process. Also it defines the number of actions to obtain the rewarding stimulus. Additionally it modulates dopamine levels. Based on the receptors involved serotonin appears to be inhibitory or excitatory on dopamine production. Basically serotoninergic neurons project to Nucleus accumbens and ventral tegmental area and regulate dopamine release [33].

The role of the "main player" in reward circuits belongs to dopamine-neurotransmitter responsible for goal-directed behavior, pleasure, addiction and memory consolidation.

Dopaminergic neurons are widely expressed along all the reward system. The mesolimbic dopaminergic system originates in VTA and sends projections to ventral striatum, particularly to Nucleus accumbens, olfactory tubercle, amygdala and hippocampus. The mesocortical dopaminergic system also originates in VTA, hence sends projections to prefrontal, cingulate and perirhinal cortex [34]. Dopamine acts through D1 and D2 receptors. The distribution of the receptor vary among dopaminergic pathways with a high density of D1 in prefrontal cortex [35].

Motivational stimulus induces dopamine release, which in turn, affects the behavioral response. At homeostatic level dopamine acts as a stimulus to seek food and water. At first stimulus will make dopamine to release as a motivational signal for homeostatic feeding, hence [36], if repeated several times, the same stimulus may gain rewarding properties. Once

the stimulus is evaluated as rewarding, it becomes selectively preferable even if there is no drive for it [37]. A habit is established which gains unconditioned autonomous properties. This mechanism underlies the addiction, including drugs of abuse, food and other types of addiction. Interestingly, drugs that are not abused or the food that is not considered palatable have no significant effect on dopamine concentrations [38].

The point in abovementioned mechanism is how motivational stimulus is turned into rewarding. First, a theory is proposed that dopaminergic systems are involved in human cognition [39]. On behalf of this theory subjects are able to influence the environment and determine their rate of reward. Upon determination a consolidation and maintenance of information is required.

Memory is an essential element to adaptive behavior since it allows consolidation of past experience guiding the subject to consider them in future. Dopamine has a key role in the consolidation of memory, including the drug-seeking reward, considered as a form of learning. The dopaminergic projections into striatum and prefrontal cortex are of importance [40]. Moreover, dopamine modulates the activity of brain regions such as Nucleus accumbens, putamen, ventral tegmental area (VTA), and synchronizes the activity of these nuclei to establish the neurobiological mechanism to set the hedonic element of learning [41].

On this context the interconnection between hypothalamic regions and mesolimbic dopaminergic system plays an essential role. Such a link brings together both homeostatic and hedonic aspects of eating. On homeostatic level, when blood glucose level is decreased stomach cells synthesize ghrelin, which has receptors in various regions of hypothalamus. Ghrelin directly activates orexin expressing neurons in lateral hypothalamic area. This neurons send projections to ventral tegmental area and activate dopaminergic neurons. [42]. In this context, dopamine is associated with the food intake to survive, so for homeostatic aspect of feeding. Studies indicate that dopamine-deficient animals with inactivation of tyrosine hydroxylase gene in dopaminergic system neurons develop fatal hypophagia. If dopamine replacement therapy is applied to NAc or caudate nucleus and putamen, animals show interest only for sweet and palatable foods [43]. A similar pattern is observed in Parkinson's disease patients with midbrain dopaminergic neurons degeneration. If treated with dopamine receptor agonists, patients exhibit compulsive consumption of palatable food [44].

At the same time hypothalamus is interconnected with some decision-making centers involved in reward system, including prefrontal cortex, which creates emotional associations with rewards, amygdala, which is involved in processing of the emotions, memories, and motivation, hippocampus, responsible for reinforcement learning, reward-guided motivation, and value-based decision making. In These context the integration of homeostatic and hedonic feeding signals from hypothalamus and brain reward system form a complete, reasonable

response [45].

Dopaminergic reward system is mediated through gamma-aminobutyric acid (GABA). GABA mostly mediates the reward properties of drugs of abuse. Various drugs of abuse affect the GABAergic receptors and induce hyperpolarization of neurons. The hyperpolarized neuron is unable to release GABA [46]. Thus the inhibitory effect on dopaminergic neurons is disappeared and high concentrations of dopamine will be released into the reward system. This induces a strong sense of pleasure, well-being and euphoria. GABAergic neurotransmission has a very wide distribution in central nervous system and most structures of the limbic system linked with reward processing, are GABA mediated [47].

Another important neurotransmitter system with central role in reward, addiction, and eating behavior is expressed by endogenous opiates, such as β-endorphin, enkephalins and dynorphins [48].

Opioid receptors are widely distributed within central nervous system, comprising areas responsible for energy homeostasis and reward processing. Three different types of G protein coupled receptors-kappa (KOR), mu (MOR) and delta- (DOR) are involved in opioidergic neurotransmission. Generally, opiates increase food intake, thus exerting orexigenic properties [49]. The most widespread endogenous opiate-beta endorphin exerting orexigenic properties is derived from anorexigenic POMC in hypothalamic arcuate nucleus and acts via MOR. The arcuate nucleus is a hub for multiple interconnections between opiates and various orexigenic and anorexigenic peptides. The NPY and AgRP orexigenic effect is shown to be mediated by opioid system via MOR. Blockade of MOR and KOR suppresses anorexogenic effect of NPY and AgRP [50]. A link between opioid and melanocortin system is reported as well, with melanocortin suppressing beta-endorphin orexigenic effect via MC3 and MC4 receptors [51].

Opiates exert excitatory effect on dopaminergic neurons, thus inducing pleasure. Morphin, acting via MOR, enhances mesolimbic dopaminergic neurons firing frequency [52]. Opioids have found to be associated with states of pleasure, which are derived by laughter, love, sex and appetizing food.

The information above shows opioids to be involved in both homeostatic and hedonic feeding. Opioids are implicated in the modulation of highly palatable foods, and opioid antagonists attenuate both addictive drug taking and appetite for palatable food. Thus, craving for palatable food could be considered as a form of opioid-related addiction [53].

Another set of compounds acting through G protein coupled receptors and having impact in homeostatic and hedonic feeding, are endocannabinoids.

The endocannabinoid system (ECS) comprises neuromodulators expressed by endogenously produced lipid cannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG), enzymes responsible for their production and metabolism as well as specific receptors CB1 and CB2 [54].

The role of the endocannabinoid system is crucial in regulating the rewarding properties of food, in controlling energy balance by acting at the hypothalamic circuitries involved in food intake, The ECS controls energy balance and lipid metabolism centrally (in the hypothalamus and mesolimbic pathways) and peripherally (in adipocytes, liver, skeletal muscle and pancreatic islet cells), acting through numerous anorexigenic and orexigenic pathways [55].

Endocannabinoids are associated with the same reward circuits for both drugs of abuse and hedonic food intake. They exert modulatory, both inhibitory and excitatory effects on dopaminergic neurons in VTA. Several works report marijuana and other cannabinoids act upon the central drug reward circuitry in the mammalian brain [56].

CB1 receptors are found in multiple brain structures related to reward pathways, such as amygdala, hippocampus, hypothalamus, cingular cortex, showing the importance of endocannabinoid system in reward circuits. Endocannabinoids also have modulatory effect on GABAergic and glutamatergic neurons in various areas of brain reward system [57].

Leptin reduces endocannabinoid levels in the hypothalamus, which suggests that hypothalamic endocannabinoids might act via CB1 to increase food intake through a leptin-regulated mechanism [58].

4. Brain Reward System and Obesity

Obesity is considered the body mass index more than 30. It may be resulted on overeating, as a symptom of various diseases due to low metabolic rate or other specific changes. Obesity is a serious challenge for today's society and is associated with various medical conditions such as type 2 diabetes, cardiovascular diseases, stroke [59]. Freely available, calorie dense palatable food, low physical activity motivates people to overeat, thus to become overweight [60]. A new picture of obesity is being developed representing it not as just a simple overeating or metabolic problem, but a nervous system disorder [61]. Two basic systems are involved in pathogenesis of obesity: hypothalamus as homeostatic feeding center and reward circuit as hedonic eating center. Hence, these two systems are anatomically and functionally interconnected, a single disorder in one of the systems leads to disruptions in whole well-coordinated machinery [62].

Let's consider the factors responsible for overeating. As it is already mentioned in most areas of the Earth where obesity rate is high, the calorie dense, palatable food is freely available. Marketing and design of public places to eat predisposes to stay longer. This is just a very small

part of overeating problem. The next "culprit" is synthesized in the stomach. It is ghrelin. As it was mentioned above ghrelin is synthesized in response to low blood sugar. The hormone decreasing blood sugar level, is insulin. The food is considered palatable, when it is rich with sugar and fats. Insulin is released in response to high sugar and fatty acids. If sugar and fat rich food is consumed, more insulin is released and as a result blood sugar level drops. At this point a new cycle with participation of ghrelin originates, which again produces feeling of hunger. One this kind of cycle requires short period of time, as sugars and fats will reach blood quite more soon, than proteins. Hence, the main reason of overeating is hidden in reward circuits with dopamine and serotonin involvement. Once eating palatable food dopamine and serotonin are released. Serotonin produces feeling of happiness, dopamine produces satisfaction. These two neurotransmitters are involved in various circuits. Serotonin is involved in descending pain transmission systems with analgesic effect, dopamine is involved in memory processes and participates in memory consolidation. Once eating palatable food organism feels good and remembers the feeling, which will be stored in long-term memory. Next time if there is a choice organism will remember that specific food makes us happy and we will choose that food. As much we use the food making us happy as much it is required to evoke the same feeling of happiness.

Overweight patients are found to have higher demand for serotoninergic and dopaminergic signaling, so to get serotonin and dopamine to release more, they eat more [63]. This vicious cycle impairs the efforts to lose weight. A similar pattern is observed in substance abuse, which makes obesity and addiction to share common mechanisms [64].

Obese individuals show higher activity of brain regions responsible for reward processing while exposed to palatable food. However, obese patients are found to have anhedonia – inability to fell pleasure. Weight gain first increases then significantly decreases activity of reward circuits. That is as much you eat palatable food, as much you need it to provide the same level of pleasure [65].

To reveal specific distortions in reward circuits multiple animal studies were performed showing that rats are ready to expose themselves to extreme cold, heat or aversive stimuli to get access to palatable food such as peanut butter, shortcake, yogurt, chocolate, Coca Cola etc., even if standard chow is freely available [66]. Rapid weight gain shows progressively worsening brain reward deficit, which considers diminished responsiveness of lateral hypothalamus to rewarding stimulation [67]. A similar pattern is observed in human studies where human subjects gained weight over a six months period demonstrate decreased striatal activation when exposed to food reward [68]. Low responsiveness of various brain circuits has been observed in rats overconsuming cocaine or heroin [69].

Obesity and drug addiction share common mechanisms. The experiments presented above prove the neural character of obesity associated with loss of sensitivity of different components of brain reward circuits.

Multiple endogenous systems and peptides are involved in the pathogenesis of obesity.

In obese people reward deficits may develop while being exposed to palatable food. This pattern is greatly associated with dopaminergic signaling, as obese individuals show lower reaction ability of D2 receptor in striatum. When losing weight, obese individuals exert increased D2 receptor density. This findings highlight essential role of dopamine signaling in regulation of responsiveness to palatable food [70].

Obesity is closely related to alterations in opioidergic neurotransmission, thus, correlating with the changes in the number of opioid receptors in the brain. An opposite correlation has been shown regarding body mass index and density of opiate receptors in striatum and thalamus. As the body mass index is high, the opiate receptors number is low and vice versa. Elevated plasma levels of beta-endorphins appear to be high in obesity patients [71].

The deficiency or failure of opioid receptors appears to be a reason of overeating as an attempt to compensate the lack of positive emotions. In this regard, there is enough evidence, indicating the involvement of opioidergic neurotransmission in the regulation of nutritional practices and obesity.

Obesity has also an association with pathological over activation of the endocannabinoid system [72].

Consumption of rewards (e.g., palatable food, mating, cocaine) produces hedonic consequences which initiate learning processes that consolidate liking the rewarding goal. Motivational states such as hunger, sexual arousal, and perhaps early symptoms of drug withdrawal increase the incentive salience of reward-related cues and the reward itself. The greater the hunger, the greater the likelihood that behavioral sequences aimed at obtaining food will be initiated and carried to conclusion despite distractions and obstacles that may arise. Positive reinforcement involves an increase over time in the frequency of behaviors that lead to a reward [73].

Alterations in brain reward circuits prepare a background to understand neurochemical mechanisms underlying obesity, to develop effective methods for weight control. No doubt that brain reward system has essential and primary role in overeating and, hence, obesity. To overcome obesity pandemic multilevel research of neural circuits of homeostatic and hedonic eating are of greatest importance.

5. Acknowledgements

6. References

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