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Can We Selectively Reduce Appetite for Energy-Dense Foods? An Overview of Pharmacological Strategies for Modification of Food Preference Behavior

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Abstract: Excessive intake of food, especially palatable and energy-dense carbohydrates and fats, is largely responsible for the growing incidence of obesity worldwide. Although there are a number of candidate antiobesity drugs, only a few of them have been proven able to inhibit appetite for palatable foods without the concurrent reduction in regular food consumption. In this review, we discuss the interrelationships between homeostatic and hedonic food intake control mechanisms in promoting overeating with palatable foods and assess the potential usefulness of systemically administered pharmaceuticals that impinge on the endogenous cannabinoid, opioid, aminergic, cholinergic, and peptidergic systems in the modification of food preference behavior. Also, certain dietary supplements with the potency to reduce specifically palatable food intake are presented. Based on human and animal studies, we indicate the most promising therapies and agents that influence the effectiveness of appetite-modifying drugs. It should be stressed, however, that most of the data included in our review come from preclinical studies; therefore, further investigations aimed at confirming the effectiveness and safety of the aforementioned medications in the treatment of obese humans are necessary.

Keywords: Antiobesity therapy, cannabinoids, food preferences, neuropeptides, neurotransmitters, opioids.

INTRODUCTION

Numerous theories have attempted to explain a socio-medical phenomenon dubbed the "obesity epidemic" in the context of human evolution (for review, see [1]). The rapid increase in the worldwide obesity prevalence over the last decades suggests, however, that changes in lifestyle, especially dietary habits, can be implicated for this trend. Nowadays, a growing number of modern communities live in an obesogenic environment characterized by an extremely easy access to cheap and palatable but high-calorie foods. Additionally, food products are advertized in a suggestive manner using neuromarketing techniques [2], and this, along with the natural attractiveness of sweets and fats, has led to the increased consumption of palatable, energy-dense foods [3]. There is a clear direct relationship between the rising body mass index (BMI) and preference for fatty foods in both genders, sweet foods in women [4], and fat and sweet foods in children [5]. Moreover, a free-choice cafeteria diet similar to the western diet style in humans has been shown to be the most efficient way to induce obesity in laboratory animals [6, 7]. Thus, increased consumption of high-calorie food combined with low physical activity has greatly facilitated the development of the obesity epidemic. This phenomenon is not only characterized by a growing number of obese individuals in general [8, 9] but also by an increasing number of morbidly obese people with the BMI greater than 40 kg/m^2 [10, 11] and, in particular, rapidly increasing percentage of obese children [9, 12]. Since excessive body weight is considered to be a serious public health problem resulting in a variety of medical disorders [13], unbeneficial psychological consequences [14], and even in a lower socioeconomic status [15], various strategies are used to counteract these negative trends. Indisputably, the best way to lose weight and maintain normal body weight is to change to a healthier lifestyle. Unfortunately, living in the modern world is not conducive to regularly eating healthy food products and exercising. Furthermore, follow-up studies have indicated that most dieting individuals who managed to lose weight successfully experienced the so-called "yo-yo" effect related to a fast weight regain after the end of a diet [16, 17]. Therefore, other strategies ensuring the maintenance of a reduced body weight have been developed. Currently, operations on the gastrointestinal tract, known as "bariatric" or "metabolic" surgery are considered to be the most effective anti-obesity treatment methods, and are especially recommended for patients with severe obesity with BMI ≥ 40 kg/m^2, for those with BMI ≥ 35 kg/m^{2}and significant comorbidities, for those with "diabesity" (*i.e.*, diabetes mellitus coexisting with obesity), or possibly for patients with metabolic syndrome [18, 19]. Although a variety of beneficial effects including fast weight loss and improvement in metabolic parameters have been found in patients after bariatric surgery [20, 21], this operation may cause long-term clinical complications such as nutritional (mainly mineral) deficiencies and difficult

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to predict changes in drug absorption [22, 23]. Also, despite this radical intervention on the digestive system, some patients who underwent this surgery failed to lose weight [24] or regained weight lost shortly after the operation [25]. These patients may be subjected, therefore, to the revisional bariatric surgery that increases the risk of postoperative complications [26, 27] and mortality [28]. Other patients with excessive weight, in turn, cannot be qualified for weight-loss operations because of medical contraindications or simply because of their reluctance to take on the risk of surgery. Hence, pharmacological treatment would be another option for them and for those who experienced cyclic weight loss and weight gain after dieting.

HOMEOSTATIC AND HEDONIC HUNGER – THE TWO FACES OF FOOD INTAKE CONTROL

It is generally accepted that the amount of food consumed is determined by two control mechanisms [29]. The first one is related to the regulation of energy balance homeostasis and is driven mainly by the hypothalamic feeding centers (*i.e.*, arcuate nucleus, lateral hypothalamic area, mediobasal hypothalamic area, paraventricular nucleus) [30]. They receive either direct or the brainstem dorsal vagal complex-mediated information from the periphery about the nutritional status [31]. Chemical signals such as absorbed nutrients and gastrointestinal (ghrelin, cholecystokinin – CCK, glucagon-like peptide-1 – GLP-1, and peptide YY - PYY), adipose tissue (leptin) and pancreatic (insulin) hormones are the carriers of this information [32-34]. This metabolic mechanism operates through the sensation of "homeostatic" hunger or satiety. The second mechanism regulating food intake is related to the brain reward system and consists of the corticolimbic (*e.g.*, the hippocampus, amygdala, prefrontal and insular cortex) and mesolimbic (*e.g.*, the ventrotegmental area, nucleus accumbens, and striatum) structures. They use dopamine, opioids, and endocannabinoids as neurotransmitters [35]. The corticolimbic system is responsible for "liking" food (*i.e.*, pleasure related to palatable food consumption reflected by characteristic behavior such as licking), and the mesolimbic system is related to "wanting" food (*i.e.*, appetite and motivation to eat reflected by a desire to work for food) [35, 36].

Brain areas involved in the homeostatic and hedonic regulatory mechanisms interact closely with each other to establish energy homeostasis in the body. This is possible due to numerous neural and functional connections between these two systems [2, 37] and prompts the view that they actually act as a single integrated system [38, 39]. In support of this hypothesis is the fact that brain structures involved in the reward-related mechanism express genes that encode similar feeding-related peptides [38] and respond to the same peripheral signals as those involved in homeostatic regulation, *e.g.*, portal blood glucose [40] and hormones such as leptin, insulin, ghrelin, GLP-1, PYY, and CCK [41, 42] (Fig. **1**). Interestingly, brain regions involved in both metabolic- (*i.e.*, hypothalamic nuclei) and reward-related (*i.e.*, the nucleus accumbens) food intake control were shown to be activated concurrently when rats pressed the lever to obtain sucrose [43]. Apparently, the changes in the nutritional status and energy balance in the body evoke a simultaneous response of the homeostatic and hedonic centers that, in turn, act in concert to affect feeding behavior through specific, aforementioned mechanisms. Indeed, the feeling of hunger, which is considered to be rather unpleasant, strongly activates food-seeking behavior and leads to consumption of food portions suitable for restoration of energy balance. On the one hand, consumption of an adequate amount of food is associated with both the sensation of pleasure and satiety that cause cessation of eating. Hence, the hedonic food intake control supports the homeostatic regulation. In addition, changes in the nutritional status may reinforce or attenuate the rewarding properties of food. A hungry individual would eat food that may not be palatable, whilst the satiated one would refuse to eat even highly palatable food [35]. Often, however, the hedonic mechanism especially triggered by unlimited access to palatable though high-calorie foods overcomes the metabolic cues, a phenomenon referred to as "hedonic hunger" in contrast to "homeostatic hunger". While the latter leads to restoration of energy homeostasis, overstimulation of the former results in overeating and gaining excessive weight. Food craving may be an evolutionarily-favored behavior [44] especially in populations that have experienced long-term periods of starvation in the past [1]. This genetically fixed behavior may be potentiated by learned environmental cues acting as conditioned stimuli that encourage people to reach for food even when they do not feel hungry [45]. At the individual level, storing up energy as fat leads to obesity that, in turn, has been found to enhance appetite for more energy-dense foods in rats and humans [46-48]. Moreover, when obesity-prone rats were prevented from access to the palatable, high-fat and high-sugar diet, they exhibited the withdrawal symptoms similar to those seen in drug-addicted animals [49]. Interestingly, research done on humans also indicated a positive correlation between the BMI and craving for palatable foods [50]. Hence, obesity in both humans and animals likely drives a positive feedback mechanism that finally leads to (possibly) permanent functional changes in neural circuits responsible for the food intake regulation (for review, see [51]). These changes manifest as an increased orexigenic drive to consume palatable, high-energy foods (Fig. **1**). In addition to the dysregulated consummatory behavior, obese individuals present with enhanced appetitive behavior that is directed towards food acquisition [52]. The altered function of brain areas responsible for the appetitive phase of ingestive behavior, as revealed in neuroimaging studies of overweight individuals, may result from repeated consumption of palatable foods [36, 41, 53, 54]. In this way, overconsumption becomes a fixed habit that shares some similarities with drug or alcohol addiction [51, 55-57], and which is driven by different brain areas than those responsible for satisfying hunger [58].

SATIETY-ANOTHER PLAYER IN A CO-OP GAME OF SURVIVAL

Satiety is commonly considered as a term opposite to hunger. From the physiological point of view, satiety may be defined as the lack of hunger and feeling of fullness after eating the amount of food sufficient to restore energy balance. Although closely related to appetitive behavior, satiety is driven by brain centers and neurotransmitters

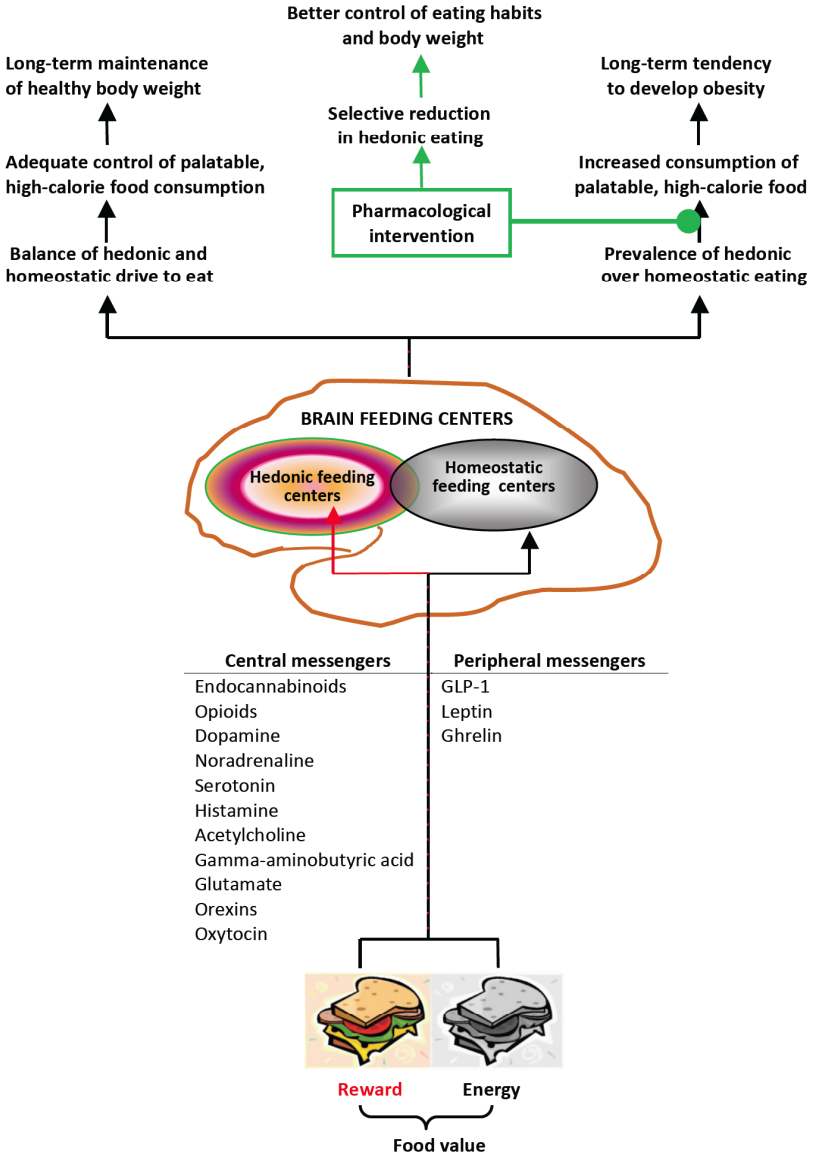

Fig. (1). Central and peripheral messengers conveying information about food value to the brain feeding centers, and the relationship between body weight changes and balanced or imbalanced hedonic and homeostatic drive to eat.

different from those responsible for hunger control. Also, the same peripheral stimuli differentially affect the activity of hunger and satiety centers. For example, the hypothalamic arcuate nucleus, one of the best-known feeding centers consists of both "anorexigenic" (*i.e.*, satiety-stimulating) and "orexigenic" (*i.e.*, hunger-stimulating) neurons. They use, respectively, the alpha-melanocyte stimulating hormone (α-MSH) and neuropeptide Y to communicate with neurons in other feeding centers. Hormonal (insulin, leptin) and metabolic (glucose, amino acids, and fatty acids) factors released after food intake stimulate the former and inhibit the latter group of neurons that is associated with increased satiety rates. The feeling of satiety is, however, largely subjective and may be affected by the individual's convictions and experiences as to the nutritional value of the just-eaten meal [59]. Moreover, evidence has accumulated that obese people are less sensitive to internal satiety signals [60], where leptin resistance is the most striking example of such dysregulated feedback mechanism. An important issue for the present review is that the feeling of satiety not only depends on the caloric content but also on the type and proportions of macronutrients in a meal with proteins having the highest satiating power and, hence, potential to support weigh loss [59]. It should be also noted that fat- and sugar- but not protein-rich foods are believed to have addictive properties [61]. Furthermore, according to the protein leverage hypothesis [62], too little protein intake might result in a "compensatory" overconsumption of carbohydrates and fats that thus contribute to obesity [63]. Consequently, a high-protein breakfast was demonstrated to reduce evening snacking; this indicates that increased protein intake may help with beneficial alteration in eating habits [64]. However, the latest reports suggest that excessive intake of some animal proteins may be an important risk factor for obesity [65], especially when associated with the consumption of carbohydrate-rich foods [66].

Table 1. Peripherally-applied pharmaceutical drugs found to selectively inhibit hedonic eating.

Physiological Messengers	Pharmacological Intervention	Drug	Species	References
Endocannabinoids	CB_1 receptor inhibition	Rimonabant (SR 141716)	Marmosets	[73]
		AM 251, rimonabant	♀ Rats	[77, 78]
Opioids	MOR receptor inhibition	Naltrexone	Rats	[93]
		Naltrexone	Humans	[104, 105]
Dopamine	D2/D3 receptor stimulation	Quinpirole	Rats	[127]
	Reuptake inhibition	Methylphenidate	Rats	[148]
Gamma-aminobutyric acid	$GABA_B$ receptor stimulation	Baclofen	Rats	[253, 257]
Glutamate	$mGluR_5$ receptor inhibition	MTEP	Baboons	[267]
	NMDA receptor inhibition	Memantine	Rats	[183]
Glucagon-like peptide-1	GLP-1 receptor stimulation	Exendin-4	Rats	[82]
		Liraglutide	Rats	[182]
		Liraglutide	Humans	[307]
Oxytocin	Oxytocin receptor stimulation	Oxytocin	Humans	[366]

CB_1 receptor – cannabinoid 1 receptor; MOR receptor – mu opioid receptor; D receptor – dopamine receptor; $GABA_B$ receptor – gamma-aminobutyric acid B receptor; $mGluR_5$ receptor – metabotropic glutamate receptor 5; NMDA receptor - *N-methyl-D-aspartate* receptor; GLP-1 receptor – glucagon-like peptide-1 receptor.

PHARMACOLOGICAL MODIFICATION OF HUNGER AND APPETITE

Many pharmaceuticals used for scientific purposes have been known to affect food consumption. However, considering the homeostatic and hedonic faces of food intake control discussed above as well as the role of excessive consumption of palatable, high-calorie foods in the obesity development and maintenance, it seems that the drug that impinges on both mechanisms would be the most promising solution. Ideally, the anti-obesity medication should not only be safe and decrease food consumption and body weight but also change eating habits without affecting other functions related to the activity of the reward system, such as mood and emotions. Such a drug would also be expected to decrease primarily the appetite for palatable, high-calorie foods (*i.e.*, fat and sweets) and to a much lesser extent reduce the intake of foods considered "healthy" (*i.e.*, containing all nutrients that are necessary for life but not as caloric and often not as attractive as sweet and fatty foods). Hence, the purpose of this study is to review pharmaceuticals that have been found to selectively reduce appetite for palatable, obesogenic foods when administered peripherally in humans and animals (Table **1**).

PHARMACOLOGICAL INHIBITION OF THE ENDOCANNABINOID SYSTEM AND PALATABLE FOOD INTAKE

The two major endocannabinoids anandamide (N-arachidonoylethanolamide, AEA) and 2-arachidonoylglycerol (2-AG) are produced both centrally and peripherally and affect feeding mainly *via* the cannabinoid 1 (CB1) receptor. The role of cannabinoids and their antagonists as modulators of metabolic and hedonic food intake has been reviewed extensively by Kirkham [44], Di Marzo [67], and Silvestri [68] and has been updated recently by Cristino [69] and Jager [70] in terms of the involvement of the endocannabinoid system in the reward-motivated feeding. The most important conclusions arising from the studies cited in these review articles emphasize a role for endocannabinoids as orexigenic factors that primarily increase motivation to eat through activation of the nucleus accumbens neurons and interaction with dopaminergic, opioidergic and ghrelin signaling pathways. Stimulation of the CB1 receptor by its synthetic agonist, ACEA (N-(2-Chloroethyl)-5Z,8Z,11Z,14Z-eicosatetraenamide) injected intraperitoneally to rats given free access to a 3-component diet containing protein, fat, and carbohydrates resulted exclusively in an increase in carbohydrate consumption indicating that endocannabinoids may specifically influence the appetite for macronutrients [71]. Moreover, in the periphery, endocannabinoids were found to enhance specifically the taste cell response to sweeteners [72]. For the present review, however, the most important issue is that the pharmacological blockade of the CB1 receptor was found to reduce appetite for palatable foods in laboratory animals maintained on a free-choice diet that best reflects natural conditions conducive to overeating in humans. Indeed, SR 141716 (rimonabant), a CB1 receptor antagonist, given orally to primate monkeys (*i.e.*, marmosets) reduced intake of sweet food and increased intake of standard chow [73]. On the contrary, rimonabant injected intramuscularly to baboons representing another primate species reduced evenly intake of candies and normal food thus suggesting that the blockade of the CB1 receptor did not affect appetite for specific foods in these animals [74]. Similar results were obtained in obese diabetic humans treated with rimonabant for six months. Although the drug significantly reduced overall calorie intake and body weight in these patients, it did not change the relative proportion of macronutrients consumed, including sugar [75]. Rimonabant was found, however, to attenuate the neural response to the sight and flavor of chocolate in healthy volunteers treated with the drug for seven days, as observed with functional magnetic resonance imaging (fMRI) [76].

The data obtained in experiments performed on rodents that were allowed free choice between normal and palatable foods were also conflicting. The CB1 receptor antagonists

AM 251 and rimonabant injected intraperitoneally to female rats with optional access to standard chow and sweet foods reduced the intake of the latter only [77]. Similarly, rimonabant reduced selectively sucrose feeding and drinking in male Wistar rats [78]. Consistently with these findings, AM 251 markedly diminished motivation to obtain chocolate-flavored pellets in female rats that were taught to work (*i.e.*, press the lever) for food, while it did not change their responding to standard pellets [79]. Also, rimonabant attenuated the rewarding value of a palatable drink [80] and addictive-like eating behavior In mice [81]. Thus, blocking the CB1 receptor has the potential to reduce not only consummatory but also appetitive (*i.e.*, food-seeking) behavior. On the other hand, the results obtained in our laboratory indicated that AM 251 was not able to reduce selectively food consumption in male Wistar rats that were offered a choice between sweet and normal rat chow [82, 83]. This discrepancy may result from different experimental conditions (*e.g.*, restricted vs. non-restricted access to sucrose-rich food in the study by Arnone *et al*. [78] and Radziszewska *et al*. [82], respectively) as well as from different sensitivity of male and female rats to the CB1 receptor antagonists, an event found originally in mice [84]. Moreover, AM 251 used at doses comparable to those that specifically decreased sweet food intake in female rats in the aforementioned study by Mathes *et al*. [77] equally reduced the consumption of standard and sweet food in female mice [85]. Hence, animals, even within similar taxonomic groups, differ as to their response to the CB1 receptor inhibitors. Although it is not known exactly what the cause of these differences is, the work by Brand *et al*. [86] seems to provide possible explanation. They reported that two strains of rats commonly used in laboratories, *i.e.*, Wistar and Fischer344 rats, exhibited significant differences in the intake and motivation to obtain sweetened milk and in the sensitivity to rimonabant as a drug inhibiting palatable food intake. These variations could be likely attributed to congenital differences in expression of certain proteins (*e.g.*, CB1 receptor protein) that are pivotal for the endocannabinoid system function found in brains of both rat strains. It seems therefore that similar yet still hypothetical alterations in the endocannabinoid system activity occurring between various animal species/ strains/genders might account for the above-described differences in the CB1 receptor antagonists' efficacy to specifically inhibit appetite for sweet foods. It should be noted that rimonabant was initially approved in Europe for treating obesity but was withdrawn from sale due to adverse psychiatric side effects. Nevertheless, CB1 receptor antagonists could be considered as candidate medications with the potency to selectively reduce appetite for sweets in individuals susceptible to these drugs provided that safe and free of side effects CB1 antagonists will be developed.

PHARMACOLOGICAL INHIBITION OF THE OPIOID SYSTEM AND PALATABLE FOOD INTAKE

Opioid peptides (*e.g.*, endorphins, enkephalins, dynorphins) and their receptors (mu [MOR], kappa [KOR] and delta [DOR] opioid receptors) were detected in various brain structures including those involved in homeostatic and hedonic food intake control (for review, see [87, 88]). It is of particular importance for the present study to note that opioids principally influence intake of sweet and fatty foods [89]. In a review on the role of opioids in the food reward system, Peciña and Smith [90] indicated that MOR stimulation by opioid agonists increased both pleasure related to consumption of palatable foods ("liking") and motivation to obtaining them ("wanting") and suggested that inhibition of MOR activity by opioid antagonists would be a potential treatment method for eating disorders resulting from dysregulation of the brain reward system. Consistently, the MOR (*i.e.*, naloxone and naltrexone) but not KOR and DOR antagonists injected intraperitoneally were shown to decrease saccharin [91] and sweet-fat mixture [92] consumption in the rat. Naltrexone was also found to selectively decrease the consumption of sweet food under a free-choice (*i.e.*, chocolate cookies versus chow) paradigm in rats [93]. These findings were extended by Olszewski *et al*. [94] who demonstrated that naloxone, when used at low doses, selectively reduced intake of sweet chow in rats with scheduled access to either sweet or standard chow. Subsequent studies indicated, however, that naloxone decreased similarly consumption of chocolate cookies and standard diet or a sucrose and starch diet when they were presented simultaneously to the rat [95]. Moreover, Glass *et al*. [96] demonstrated that naloxone injected into rats offered a choice between a high-carbohydrate or high-fat diet decreased intake of the diet they preferred initially. In contrast, another report [97] showed that naltrexone injected subcutaneously within rats given a choice between sucrose and starch solutions increased the percentage of sucrose intake by reduction in starch intake independently of the basal sucrose/starch preference. Furthermore, a recent study [98] did not show any differences in food preferences in naloxone-treated rats maintained on a cafeteria diet containing ingredients found in typical snacks. Also, naloxone facilitated the extinction of the learned operant behavior of rats to obtain standard and sweet pellets in a similar way [99]. Hence, animal studies do not show clear evidence for efficacy of the MOR blockade in the selective suppression of palatable foods consumption. The above-described discrepancies might be explained, at least in part, by large differences in the susceptibility to naltrexone found between inbred mice strains in terms of the drug's ability to suppress sucrose intake [100]. Similar differences in the saccharin consumption were reported between the Lewis and Fischer rat strains treated with naloxone under two different experimental regimes [101]. Collectively, these data indicate that unidentified genetic variations may determine effectiveness of opioid antagonists as drugs that modify appetite for palatable foods in laboratory animals and, likely, humans.

Recent human studies demonstrated that MOR antagonists attenuated the response of certain brain structures, such as the amygdale, dorsal anterior cingulate cortex, and caudate, to the sight and taste of palatable foods,as reflected by fMRI [102, 103]. Consistently, naltrexone-treated individuals reported diminished pleasantness related to the consumption of sweet, fatty, and high-protein foods and consumed less fat and proteins as compared with placebo [104, 105]. Importantly, taste preferences and ingestion of cookies and chocolate was mostly reduced by naloxone in binge eaters [106, 107]. Based on results obtained in numerous studies, Lee and Fujioka [108] suggested, however, that this drug failed to reduce body weight in obese humans when administered as

monotherapy. Hence, considering the above-described inconsistencies in the experimental data obtained from animal and human studies, usefulness of opioid antagonists in reducing selectively consumption of tasty, high-calorie foods seems to be disputable.

PHARMACOLOGICAL INTERVENTION IN THE NEUROTRANSMITTER SYSTEMS AND PALATABLE FOOD INTAKE

Neurotransmitters known to be involved in food intake regulation include monoamines, such as dopamine, noradrenaline, serotonin, histamine, acetylcholine, gamma-aminobutyric acid, and glutamate. They all have been shown to affect food intake by interaction with the reward-related mechanisms [109], and at least some of them are now considered as targets for anti-obesity therapy [110].

DOPAMINE

Dopamine is of particular interest for this review because it is the principle neurotransmitter of the brain reward system involved in the hedonic control of food intake [111]. Dopamine-producing neurons in the brain arise from the substantia nigra in the brainstem and the ventral tegmental area in the midbrain, and project to various brain areas related to the reward system [112, 113] where dopamine receptors are also located [114]. Here, dopamine interacts with peripheral satiety signals (*e.g.*, leptin and GLP-1) [115-117] to affect palatable food intake. Mesolimbic [118-121] and corticolimbic [122] dopamine signaling pathways were demonstrated to affect sucrose solution preference in rodents through enhancement of motivation ("wanting") to obtain it [123-125]. Dopamine-dependent modulation of the rewarding value of food is mediated presumably through the dopamine D2 receptor [126]. Nonetheless, a D1 receptor agonist, SKF 38393, injected subcutaneously was shown to significantly increase palatable food (chocolate biscuits) and decrease normal rat chow ingestion, while quinpirole, a D2/D3 receptor agonist, caused the opposite effects, *i.e.*, decreased intake of chocolate biscuits but increased normal chow consumption in rats maintained on a free-choice diet [127]. Hence, dopamine may differentially affect food intake; this has been confirmed by other studies demonstrating that dopamine might either stimulate or inhibit food intake depending on the brain area [128] and, possibly, receptor subtype. Although it has not been confirmed by all studies [129-131], a number of studies suggest that abnormal dopamine signaling related to decreased D2 receptor availability [132-134] and/or dopamine secretion [135, 136] found in the brain reward system (especially the striatal regions) of obese humans and animals might result in attenuated reinforcing properties of food. Whether this is a primary (*i.e.*, genetically determined) or secondary (*i.e.*, resulting from overeating and obesity) disorder remains a matter of debate. Nevertheless, to compensate for decreased pleasure from eating, subjects with that deficit will eat more food than is necessary for energy balance maintenance [132, 137] and thus continuously gain weight, creating a vicious cycle. Therefore, pharmacological intervention in the D2 receptor-dependent dopamine signaling might be a potential tool for breaking that cycle.

Studies on the effects of drugs/narcotics that impinge on the dopaminergic system provided further Interesting data about the potential usefulness of these substances in modifying appetite for palatable foods. Amphetamine has been long known for its anti-obesity effect but, because of its addictive properties and serious adverse effects, it cannot be used to treat obesity. Amphetamine affects food intake likely by increasing release of catecholamines including dopamine in the brain [138], particularly in the mesolimbic, mesocortical, and nigrostriatal pathways [139]. In humans, oral amphetamine decreased consumption of all basic nutrients (*i.e.*, fat, carbohydrates and protein) when subjects were allowed to self-select lunch but did not affect sweet food intake when they could choose between foods categorized by nonsweet/sweet taste [140, 141]. Similar results were obtained in non-human primates (*i.e.*, baboons) treated with intramuscular amphetamine [74]. Also, the drug did not affect appetitive behavior in these animals [142]. Methylphenidate, another psychostimulant that acts primarily as a dopamine reuptake inhibitor, is used to treat the attention-deficit hyperactivity disorder (ADHD) but may have potency to reduce selectively appetite for high-calorie foods. A single dose of methylphenidate given to obese adolescents [143], young adults [144], and obese males [145] reduced food intake during a subsequent meal especially due to the diminished energy intake from fat and carbohydrates. On the other hand, chronic methylphenidate treatment resulted in a reduced intake of all nutrients in ADHD individuals [146]. Importantly, this therapy resulted in a significant weight loss [146, 147]. Using a rat model of binge eating disorder to determine the methylphenidate effect on feeding behavior, it was shown that the drug concurrently increased the normal chow intake and decreased sugar intake thus indicating that methylphenidate might be targeted therapy for the aforementioned disorder in humans [148]. A separate category of drugs that, apart from treating psychiatric disorders, may affect appetite are antipsychotic medications (neuroleptics). Chronic treatment with haloperidol, a dopamine receptor antagonist, did not modify food selection [149], although a single haloperidol dose decreased the "sham" intake of sucrose solution [150] and changed reward-related behavior by increasing percent choice of smaller but immediately available to larger but delayed sucrose portions in rats [151]. Risperidone, a D2 receptor antagonist injected chronically to rats, reduced fat and increased protein intake without affecting body weight [152]. Raclopride, another D2 receptor antagonist, showed different (*i.e.*, stimulatory or inhibitory) effects on sweet-fat mixture consumption in rats depending on sucrose content and availability (daily versus intermittent) [92]. Interestingly, a recent report demonstrated that blocking the D1 and D2 receptor with ecopipam and haloperidol, respectively, reduced willingness to work for sucrose while leaving sucrose intake, preference, and hedonic impact intact in rats [153]. Hence, these pharmaceutical drugs are a viable candidate for reducing human appetitive response to palatable foods. Clozapine and quetiapine, second generation antipsychotic drugs that interact with a variety of monoamine receptors including dopaminergic receptors, have been found, however, to enhance preferences for a high-fat high-sugar diet in rats [154] and dietary saturated fat in humans [155]. Thus, determination of

whether or not pharmacological intervention in the dopaminergic system activity is a promising approach to selectively reduce calorie intake from palatable foods requires further investigations, likely due to the ambiguous impact of dopamine itself on food intake.

NORADRENALINE

Noradrenaline is involved principally in learning and cognition. These processes also underlie the control of food intake by the brain's reward system [156]. Noradrenergic pathways in the prefrontal cortex, which is responsible for planning and decision making, were demonstrated to affect dopamine release induced by palatable food intake in the nucleus accumbens in mice [157], thus indicating that these two transmitter systems interact to control food consumption. Also, noradrenaline affects food consumption through the effect on the hypothalamus, which receives noradrenergic inputs from the brainstem. Acting through different receptors, noradrenaline either enhances or inhibits food consumption [158]. Palatable food ingestion is associated with an increase in noradrenaline content in various hypothalamic nuclei and in the amygdale [159], indicating that this neurotransmitter may be involved in the regulation of rewarding food consumption. This was supported by studies demonstrating that infusion of noradrenaline into the paraventricular nucleus of the hypothalamus resulted in a profound increase in carbohydrate intake compared with other macronutrients [160]. Similar results were obtained in rats injected peripherally with clonidine, an alpha-2 adrenergic receptor agonist [161], whilst LY368975, a selective inhibitor of noradrenaline reuptake, was demonstrated to inhibit sweetened milk ingestion in rats [162]. Bupropion, a noradrenaline/dopamine reuptake inhibitor, currently approved for the treatment of depression and reduction of the withdrawal symptoms after smoking cessation, is now investigated as a component of the combined bupropion/naltrexone therapy for obesity. Unfortunately, the data on possible effects of bupropion on food preferences are scarce. In one study, the effect of bupropion on the macronutrient choice in abstinent women after smoking cessation was examined and no differences in macronutrient intake were found [163]. On the other hand, the results of another study performed on individuals who quit smoking and were treated with bupropion indicated that this medication decreased food reward [164]. Interestingly, the bupropion-dependent decrease in food intake likely occurred due to the effect on both the hypothalamic feeding centers and the reward system and was enhanced by the concurrent administration of naltrexone [165]. A recent study [166] using fMRI demonstrated that the combined bupropion/naltrexone therapy attenuated the activation of the hypothalamus and stimulated the regions involved in the inhibitory self-control in response to food cues, thus supporting the view that administration of drugs impinging on both the metabolic and hedonic control of food intake would be the most promising anti-obesity therapy. There is no data, however, on the effects of this combination therapy on food preferences in humans and animals.

SEROTONIN (5-HYDROXYTRYPTAMINE, 5-HT)

Like dopamine, serotonin is a key neurotransmitter of the brain reward system. It acts *via* different receptors categorized into 7 receptor families (5-HT_{1-7}) that are further subdivided into numerous receptor subtypes located in various brain areas responsible for both homeostatic and hedonic food intake control (for review, see [167, 168]). Serotonin effects on eating behavior depend on the receptor type and receptor localization. It has been demonstrated that central 5-Ht_{1A}, 5-Ht_{1B} (whose human counterpart is the 5-HT_{1D} receptor), 5-$Ht_{2C,}$ 5-HT_4 and 5-Ht_6 receptors are involved in food intake control and, at least some of them, may be potential targets for obesity treatment [169, 170]. It should be noted, however, that there are significant discrepancies as to the effects of stimulation and blockade/genetic knockout of these receptors on energy balance [167].

An early study [171] demonstrated that peripherally injected serotonin selectively inhibited fat consumption in the rat. Further reports using systemically administered pharmaceuticals modifying the serotonergic system activity provided further evidence that these drugs may change macronutrient selection in rodents and humans. Diabetic individuals reduced fat and carbohydrate consumption after oral administration of 5-hydroxy-tryptophan, the precursor of serotonin [172]. Similarly, stimulation of 5-HT receptors by mCPP, a nonselective serotonin receptor agonist, decreased carbohydrate intake [173]. In contrast, fluoxetine (Prosac), a selective serotonin uptake inhibitor, which is used to treat depression and eating disorders such as bulimia, was shown to decrease fat and protein consumption while leaving carbohydrate intake unchanged in male and female rats [174, 175]. Fluoxetine was shown, however, to decrease preference to carbohydrates and diminish intake of fats and protein in starved Zucker rats [176]. When rats were allowed to choose between the standard chow and a carbohydrate supplement, fluoxetine and 2,5-dimethoxy-4-iodoamphetamine (DOI; a 5-$HT_{2A/B/C}$ receptor agonist) but not fenfluramine, mCPP, RU24969 (a 5-HT_{1A}/5-HT_{1B} receptor agonist), and MK212 (a 5-HT_{1C} receptor agonist) reduced intake of carbohydrates more than the consumption of standard diet [177]. Another selective serotonin reuptake inhibitor, paroxetine, was found, however, to diminish the appetitive response to both palatable (sucrose-containing) and non-palatable (quinine-containing) fluids in rats [178]; this suggests that enhanced serotonergic transmission attenuated both positive and negative reward system-related reactions. In humans, fluoxetine decreased intake of all macronutrients [179, 180], thus indicating a nonselective action of this drug on nutrient intake. Similarly, sibutramine, a serotonin/noradrenalin uptake inhibitor, was demonstrated to reduce comparably intake of fat, carbohydrate and protein diets in male and female rats [181]. These results are consistent with the subsequent study where sibutramine was found to decrease the consumption of both palatable, high-sugar high-fat food and standard chow in rats offered a two-choice diet [182], but they are in contrast to other results that demonstrated the suppressory effect of sibutramine on lard consumption and, interestingly, the concurrent stimulation of standard chow consumption in rats allowed to chose between both feeds [183]. Importantly, these effects were achieved at drug doses similar to those administered in a previous study [179] (7.5 vs. 5 mg/kg, respectively). Sibutramine was also shown to reduce motivation to obtain sweet pellets as well as decrease the amount of sweet pellets or sweetened high fat chow eaten

under a free-feeding paradigm in rats [184, 185]. Despite the above-described discrepancies regarding this drug's ability to preferentially inhibit palatable food consumption, sibutramine seemed to have a potency to modify appetite and to significantly reduce body weight. Unfortunately, sibutramine was demonstrated to produce serious adverse cardiovascular effects and had to be withdrawn from the pharmaceutical market. Since other abovementioned selective serotonin reuptake inhibitors (*i.e.*, fluoxetine and paroxetine) significantly increased body weight when used for a long period of time [186], they cannot be applied as appetite-reducing drugs.

Fenfluramine, yet another pharmaceutical that activates the serotonergic system by stimulation serotonin release and inhibition of its uptake, was found to decrease primarily fat consumption in the rat [176, 187, 188]. On the other hand, dexfenfluramine, a fenfluramine isomer, selectively reduced the intake of carbohydrates and fat in one human study [189] but did not affect macronutrient selection [190] or sweet food intake [140] in the others. Other clinical studies suggested that dexfenfluramine like fenfluramine reduced mostly fat intake (for review, see [191]). Also, dexfenfluramine decreased liking of sucrose solution in female rats during estrous [192], demonstrating that sex hormones might modify the reward system response to this drug, and reduced sweet candy consumption in both male and female baboons [193]. This effect, however, was associated with the parallel reduction in standard food intake and did not alter food-seeking behavior in these animals, indicating that the drug did not affect motivation to obtain palatable food. Hence, the selective effect of fenfluramine/dexfenfluramine on palatable food consumption has not been proven conclusively. Importantly, both fenfluramine and dexfenfluramine turned out to be very effective in weight reduction both in humans and animals, and, therefore, there were high hopes for their use as antiobesity medications. Unfortunately, clinical studies revealed that they caused numerous severe side effects [194], which resulted in the withdrawal of approval to use these drugs. For the same reason, they cannot be used as appetite modifying drugs. Nevertheless, fenfluramine was shown to cause appetite inhibition *via* the 5-HT_{1B} and 5-Ht_{2C} receptors [146], and further studies demonstrated that pharmacological agents targeting these receptors may diminish the rewarding value of palatable foods. mCPP, which causes hypophagia specifically *via* the 5-HT_{2C} receptors [195], was demonstrated to reduce motivation ("wanting") for palatable food in mice [80]. Similar results were obtained in rats treated with another selective 5-HT_{2C} receptor agonist, WAY 163909 [196]. Lorcaserin, a 5-HT_2 receptor agonist with high affinity to the 5-HT_{2C} receptor, is devoid of adverse effects characteristic of other drugs impinging on the serotonergic system and has been approved currently for marketing by the U.S. Food and Drug Administration (FDA) as one of few antiobesity drugs. Lorcaserin affects eating behavior possibly by attenuation of the rewarding value of food [197]. Since there are no other data on the effect of this drug on food preferences in humans and animals, the possible impact of lorcaserin on highly palatable versus normal diet consumption remains to be investigated. This problem is of special interest, due to the high efficacy of the drug on body weight reduction. The data on the effects of pharmacological modification of the activity of other 5-HT receptors on food choice behavior are also scarce. DOI, the aforementioned 5-$HT2_{A/B/C}$ receptor agonist, and 8-OH-DPAT, a 5-Ht_{1A} receptor agonist, were demonstrated to enhance preference to glucose and saccharin (a non-caloric sweetener) containing solution over "pure" glucose solution [198]. Hence, the modification of food choice behavior mediated by the above-mentioned serotonin receptors involves a strong motivational component. In the other study, 8-OH-DPAT was found to increase the intake of a high-fat diet over a low-fat diet in Osborne-Mendel rats, *i.e.*, enhanced consumption of food that was initially preferred by these rats whilst the same drug increased intake of a low-fat diet in S5B/P1 rats that initially showed no preference for any of these foods [199]. Thus, unidentified genetic differences between the animals prone (*i.e.*, Osborne-Mendel) and resistant (*i.e.*, S5B/P1) to diet-induced obesity may affect the response of to the 5-HT_{1A} receptor agonist in respect with food choice behavior. Interestingly, mCPP, the aforementioned serotonin agonist influencing food intake primarily vie the 5-HT_{2C} receptor, decreased intake of both diets in Osborne-Mendel and S5B/P1 rats under the same experimental conditions [200], further supporting the view that particular serotonin receptors may differently affect food intake and food preferences. In conclusion, it seems that serotonin signaling *via* the 5-Ht_{1A} receptor increases appetite for palatable foods through strengthening motivation and, therefore, blockade of this receptor might result in decreased consumption of such foods. This statement, however, is only hypothetical because to date no studies have been performed on the effect of the 5-HT_{1A} receptor antagonists on food preferences. It is known, nevertheless, that those pharmaceuticals reduce food intake without causing adverse effects in mice [201], indicating that they could be potential candidates for medications modifying food-choice behavior. A review of previously published experimental data suggests that pharmacological blockade of the 5-HT_6 receptor is effective in appetite and body weight reduction [202], but, to our best knowledge, there are no full paper studies on the possible effects of 5-HT_6 receptor antagonists on food choice in animals or humans.

HISTAMINE

Histamine, a histidine-derived monoamine, is known to reduce food intake through the central H_1 receptor in the ventromedial hypothalamus [203, 204]. The knowledge about the possible impact of this amine on food choice and appetite for palatable foods is poor. Animal studies demonstrated that the hypothalamic histaminergic system responds differentially to various tastants including saccharin [205], indicating that histamine may be involved in taste perception. Histamine could affect palatable food consumption indirectly by inhibiting the mesolimbic dopamine pathways [203]. A single dose of betahistine (an H1 receptor agonist and H3 receptor antagonist) was not found, however, to affect hunger and satiety in obese women [206]. Considering that histamine was demonstrated to be released from the tuberomammillary nucleus where histamine-producing neurons are located during the appetitive but not consumatory phase of feeding in the rat, this neurotransmitter seems to cause transient anorexia associated with food-seeking behavior rather than satiety [207]. Consistently, histamine

might be involved in the control of food anticipatory behavior [204] and, therefore, participate in motivation to obtain palatable food. Interestingly, a significant increase in palatable, high-calorie fat emulsion intake was achieved due to the concurrent blockade of H_1, 5-$HT_{2A/2C}$ and muscarinic receptors, while the respective antagonists administered individually had no effect on food intake in rats [208]. This proves that the histaminergic, serotonergic, and cholinergic systems act in concert to regulate appetite for palatable foods, and, therefore, the simultaneous pharmacological intervention in these systems would result in changes in appetite that are more pronounced than appetite modifications by individual neurotransmitter systems. Therefore, modulation of histaminergic transmission might be a promising tool for appetite modification, but further studies are needed to check whether such modulation would result in the selective suppression of palatable food consumption.

CHOLINERGIC TRANSMISSION, NICOTINE, AND TOBACCO SMOKING

Acetylcholine has been proven to affect feeding through muscarinic M3, nicotinic β4, and, likely, α7 receptors in the hypothalamic neurons where this neurotransmitter is co localized with POMC [209-212]. Specifically, acetylcholine decreases food intake due to activation of the POMC neurons through α3β4 nicotinic receptors [210]. It should be noted, however, that different subtypes of nicotinic receptors have been identified in a variety of brain areas involved in the control of energy balance (for review, see [213]). Hence, acetylcholine may participate in food intake control at multiple levels of organization of feeding centers. For example, acetylcholine is considered to be a satiety signal when secreted within the nucleus accumbens, and its imbalanced release in this area may be linked with food addiction withdrawal symptoms [214]. In general, acetylcholine alters the reward system-related food intake using muscarinic receptors [215-218]. Importantly, both the muscarinic (scopolamine) and nicotinic (mecamylamine) antagonists, when injected peripherally to rats, were able to disrupt the incentive motivation to obtain food reward [219, 220], indicating that systemically administered pharmaceuticals impinging on the cholinergic system might be used to modify the rewarding value of food. Previous studies demonstrated that acute and repeated intraperitoneal injections of 18-methoxycoronaridine, an α3β4 nicotinic antagonist, resulted in a selective inhibition of sucrose solution intake in female [221, 222] but not male [223] rats. The latter, however, in contrast to females, did not develop obesity when maintained on a high-sucrose diet, indicating that the blockade of the α3β4 nicotinic acetylcholine receptor was most efficient in the selective inhibition of appetite for sweets in subjects originally preferring this kind of food.

Most reports that address the effects of cholinergic transmission modification on appetite for palatable foods, however, concern the effect of nicotine, a psychoactive constituent of tobacco smoke, on food intake and food preferences in humans and animals. A relationship between cigarette smoking and body weight has long been known. Active smokers maintain lower body weight than non-smokers, and smoking cessation results in a fast weight gain in both men and women [224]. The body weight-reducing effect of smoking is attributed to the nicotine-induced potentiating effects on energy expenditure and inhibiting effects on appetite [224], while weight gain following smoking cessation may be related to the increased rewarding value of food [164]. Smoking and nicotine may also modify brain mechanisms that control food preferences. The hypothalamic response to sweet milkshake, as revealed by the fMRI, was greater in smokers than in the age-, sex-, and BMI-matched non-smokers, while the respective response to tasteless solution was similar between these two groups of individuals [225]. Women who were current smokers preferred sweet foods more than women who did not smoke [226]. Similarly, male smokers consumed more sucrose than nonsmokers [227]. Furthermore, smokers were found to be less sensitive to food-related stimuli [228] and to consume fewer sucrose-containing foods than nonsmokers [229]. Hence, the results of studies on effects of tobacco smoke on food preferences are inconsistent. Exposure to nicotine in utero and/or *via* maternal nursing resulted in an increased motivation to obtain sucrose [230] associated with the permanent changes in nicotinic receptor expression in the brain reward system in adolescent rats [231]. Exposure of adult rats to nicotine also increased food-cue reactivity as measured by sucrose self-administration [232]. In agreement with the above facts, humans whose mothers smoked during gestation showed the preference to carbohydrates over proteins [233] and increased fat intake [234]. In conclusion, most of the data indicate that continuous smoking and prenatal nicotine/tobacco smoke exposure increases attractiveness of palatable, high-calorie foods through the effect on the brain reward system in humans and animals. This might, to some extent, explain the observation based on a large cohort study that heavy smokers tended to gain more weight, adjusted for age and body weight at baseline, than light smokers or nonsmokers [235]. On the other hand, smoking cessation and resulting nicotine withdrawal also augments the rewarding value of food, especially sweets and fats [236-238]. Furthermore, women who quit smoking and received nicotine replacement therapy tended to eat more fats and carbohydrates but gained less weight than those who were not subjected to nicotine therapy [239]. Likely, in these cases, eating palatable foods became a substitute for a habit of reaching for a cigarette, but nicotine-induced enhancement of energy expenditure prevented the body weight increment. Currently, to our best knowledge, there are no reports on the possible effects of the use of electronic nicotine delivery systems, commonly known as e-cigarettes, on food intake and preferences. Considering the variety of cholinergic receptors and neurotransmitters that acetylcholine may interact with and an evident paucity of studies on pharmacological modification of appetite for palatable foods by peripherally administered cholinergic agonists/antagonists, it is difficult to determine whether it will be possible to change eating behavior using such pharmaceuticals.

GAMMA-AMINOBUTYRIC ACID (GABA)

GABA receptors, categorized into $GABA_A$ and $GABA_B$ classes that are widely distributed in the brain of mammals, are responsible for synaptic inhibition [240]. At the level of the lateral hypothalamus, separate subsets of GABA-ergic

neurons control appetitive and consummatory behavior [241]. In addition, GABA is involved in food intake control both in the arcuate nucleus of the hypothalamus and ventral tegmental dopamine system where it acts as a neuro-transmitter suppressing anorexigenic signaling pathways [242]. Similarly, GABA, acting *via* the $GABA_A$ receptor, is likely an orexigenic signal within the ventromedial hypothalamus [243], but $GABA_A$ receptor inhibition with bicuculline increased ingestion of sweet milk and selective intake of fat when infused into the anterolateral hypothalamus and the medial ventral pallidum, respectively [244, 245]. There are, however, no studies on the effects of peripherally-injected bicuculline on palatable food intake. Genetic ablation of $GABA_B$ receptors in the hypothalamic POMC neurons failed to influence food intake [246] while the peripherally administered $GABA_B$ agonist, baclofen, was able to influence food consumption both in humans and animals. Baclofen decreased food intake when administered to obese mice and humans [247, 248], and attenuated both appetitive and consummatory behavior in baboons [249] but increased the short-term food consumption in lean mice [250] and rats [251, 252]. Interestingly, the results of many animal studies suggest that baclofen may specifically decrease appetite for certain palatable, high-calorie foods. The drug reduced intake of fatty food and increased the consumption of standard food in rats subjected to a binge-eating protocol [253]. Baclofen also decreased motivation to obtain fat-reach food in rats after the history of binge eating [254]. Subsequent studies demonstrated that the drug clearly inhibited consumption of fat, but its effect on standard food intake was ambiguous, *i.e.*, baclofen either did not change, decreased, or increased concomitantly the consumption of normal chow [255-258]. Baclofen was not able, however, to suppress the consumption of sucrose solution, and, furthermore, it increased sweet-fat food consumption [256]. On the other hand, baclofen (administered at doses similar to those in the above studies) was shown to suppress intake of fat-sucrose mixtures regardless of whether they were available intermittently or daily [92]. Importantly, the effectiveness of this drug in suppressing palatable food intake could be abolished by the thickening agent added to the foodstuff [259]. The selective suppressory effect of baclofen on fat- and/or sugar-containing feed could be enhanced by naltrexone [260]. Taking into account the above facts, baclofen might be considered as a candidate drug to limit craving for palatable foods under the condition that its effectiveness will be confirmed in human studies.

GLUTAMATE

Glutamate is the most abundant excitatory neuro-transmitter in the central nervous system. Glutamate is involved in food intake control *via* the metabotropic glutamate receptor $mGlu_5$ [261]. Recently, variations in genes responsible for glutamate signaling have been demonstrated to be crucial for human obesity pathogenesis [262], and drugs impinging on glutamatergic neurons have gained attention as potential medications for treatment binge eating disorder [263]. The results of studies conducted so far indicated that glutamate released within the hypothalamus and pharmacological modification of NMDA and AMPA glutamatergic receptors' activity in the reward-system regions affected palatable food intake [264, 265] by increasing selectively carbohydrate consumption in rats allowed to choose between 3 diets, each of which contained one basic macronutrient [266]. Consistently, the blockade of NMDA and $mGluR_5$ receptors by systemically injected memantine and MTEP, respectively, decreased sweet pellet consumption in baboons maintained on a binge-eating protocol but only the latter drug showed the selective effect, *i.e.*, reduced candy but not regular chow intake [267]. Under similar experimental conditions, memantine used in a higher dose decreased the lard and, interestingly, increased regular chow consumption in rats [183]. Since no relevant side effects have been reported for this drug, it may be assumed as a candidate for selective appetite suppression especially in binge eaters. Interestingly, stimulation of the $mGlu_{2/3}$ receptor with its agonist LY379268 *via* intraperitoneal injection attenuated sucrose seeking in rats [268], indicating that alterations in glutamate receptor activity may change various aspects of feeding behavior.

Regardless of the fact that glutamate as a neuro-transmitter is synthesized in the brain, glutamic acid is ubiquitously present in dietary proteins [269]. Glutamate blood levels, however, increase only slightly after consumption of meals, even when enriched with this compound, because of a very efficient intestinal breakdown [270]. Furthermore, the blood-brain barrier protects the brain from the excessive influx of circulating glutamate [271]. Nevertheless, peripheral glutamate may directly affect feeding centers lacking this barrier such as the hypothalamic arcuate nucleus [272] or indirectly influence the brain feeding centers such as the lateral hypothalamus *via* stimulation of vagal afferents in the digestive system [273]. Of special relevance for this review is, however, the effect of monosodium glutamate, an important umami tastant that signals the presence of proteins in the digestive system, on appetite. Monosodium glutamate is commonly added to food to improve its taste. As such, this compound increases appetite and therefore food intake [274, 275], but its long-term use is not associated with higher energy intake or a significant body weight increase among nursing home elderly [276], in mice [277, 278], and rats [278, 279]. This might result from the simultaneous stimulating effect of glutamate on appetite and satiety, leading to the increased pleasantness of meals during ingestion and subsequent enhancement of satiety [274]. In agreement with this finding, addition of monosodium glutamate to nutritionally valuable foods increased their intake and reduced the subsequent consumption of sweet desserts and snacks [280, 281] but did not alter the consumption of the subsequent "main" meal [282]. Hence, a simple procedure of flavoring dishes with a popular tastant might help to change eating habits in the more desirable direction. Furthermore, monosodium glutamate was shown to decrease body weight in rats fed with high-fat high-sugar diets due to increased energy expenditure [273, 283], but this beneficial effect has not been reported in humans. Importantly, Luscombe-Marsh *et al.* [284] suggested that the addition of monosodium glutamate to a meal may contribute to increased energy intake at a second course. Although the use of monosodium glutamate in a diet is considered to be safe [285], it should be remembered that the excessive administration of this compound may be potentially dangerous for the central

nervous system neurons due to the known neurotoxicity of this amino acid neurotransmitter [272], and the parenteral injection of monosodium glutamate to neonatal rodents is one of methods used to induce obesity in animal studies.

PHARMACOLOGICAL INTERVENTION IN THE ADIPOSE TISSUE-GUT-BRAIN AXIS AND PALATABLE FOOD INTAKE

The adipose tissue and the alimentary tract synthesize and secrete hormones that influence feeding centers in the brain. Except ghrelin, all of these hormones (*e.g.*, GLP-1, galanin, CCK, and leptin) produce satiating effects and reduce food intake. Recently, a lot of evidence collected from preclinical studies indicated that some of these hormones may modify intake of rewarding foods, and, therefore, they have potential to diminish appetite for palatable foods.

GLUCAGON-LIKE PEPTIDE-1 (GLP-1)

GLP-1, one of the most studied peptides of the gut-brain axis, is a well-known anorectic and body weight reducing agent. GLP-1 analogs such as exenatide and liraglutide, which are more robust than the natural hormone, have been approved for diabetes treatment. The role of peripheral and central GLP-1 in the food intake control in humans and animals has been extensively reviewed recently [286-289]. An increasing number of reports suggest that GLP-1 analogs may be used as anti-obesity medications [287, 290-292] and, consequently, liraglutide has recently been approved by the FDA for obesity treatment. Furthermore, research on the central effects of GLP-1 indicate that this peptide decreases the rewarding value, palatability and appetitive responses to foods in animals [117, 293-296] and humans [288, 297]; therefore, this suggests that GLP-1 agonists might be useful as appetite suppressants that especially decrease appetite for palatable foods. Many studies reported that peripherally administered GLP-1 agonists inhibited high-fat and high-sugar food consumption [298-303] but few addressed the issue of whether these drugs may be useful in the selective inhibition of sugar and fat intake. An early study in this field indicated that exendin-4 (a potent GLP-1 agonist) injected intraperitoneally decreased high-protein diet consumption without changing intake of high-carbohydrate food in rats [304]. On the other hand, liraglutide did not modify intake of basic nutrients, although it did decrease overall calorie intake in humans [305]. Other studies demonstrated, however, that exenatide attenuated sweet taste reactivity in obese rats [306], and this might contribute to the decreased preference to high-fat/high-sugar diet seen in liraglutide-treated rats [182] and humans [307]. It is of special interest that apart from the decrease in palatable food consumption the drug was shown to increase the regular chow intake in rats [182] and to change the eating habit to a healthier pattern in humans [308]. Similar results, *i.e.*, a decrease in palatable food intake and simultaneous increase in regular food intake, were obtained in rats co-injected with GLP-1 and an inhibitor of dipeptidyl peptidase IV (an enzyme responsible for GLP-1 degradation, inagliptin) maintained on a two-choice diet consisting of standard chow and a high-fat/high-sugar chow [309]. Exendin-4 and AM 251 is another drug combination that involves the long-lasting GLP-1 analogue and has been demonstrated to inhibit selectively high-sucrose diet intake in rats [82]. Although the GLP-1 agonist used in that study was able, as such, to decrease sweet food consumption, the blockade of the CB1 receptor by AM 251 significantly enhanced this effect. Surprisingly, the effect of co-injection of exendin-4 and WIN 55, 212-2, a CB1 receptor agonist, on the selective inhibition of palatable food intake was even more spectacular and resulted not only in almost complete suppression of high-sucrose food consumption but also in an increase in the standard food consumption and reduction in body weight [82]. Hence, administration of GLP-1 agonists, regardless of whether alone or in combination with other drugs that potentiate their action, seems to be a promising approach aimed at specifically reducing appetite for palatable, high-calorie foods. It should be noted, however, that some distressing gastrointestinal side effects related to GLP-1 agonists may limit usefulness of such drugs [310].

LEPTIN

The role of leptin as a hormone, which inhibits hunger by impacting both homeostatic and hedonic feeding centers and therefore has the potential to be an antiobesity medication, has been investigated repeatedly in recent years [311-316]. Briefly, leptin, *via* the specific receptor LepRb (referred to as ObRb in animals) located in hypothalamic and brainstem feeding centers and mesolimbic reward circuits, was demonstrated to decrease food intake, food palatability, appetitive activities, and to induce satiety and reduce body weight in humans and animals. It is of special notice, however, that exogenous, peripherally administered leptin may influence food preferences. Leptin added to (and, presumably, naturally occurring in) maternal milk, which the pups were fed with, modified food preferences in adult rats by diminishing fat intake [317]. Leptin and its analog, metreleptin, decreased the reward value of visual food stimuli in subjects with the congenital and acquired leptin deficiency [318, 319]. This phenomenon might account for attenuated sweet cravings seen in metreleptin-treated women after Roux-en-Y gastric bypass [320] and in leptin-injected mice [321]. Consistently, leptin infused to Wistar rats with normal body weight decreased the consumption of sweet carbohydrates and proteins [322], while in obese leptin-deficient women, leptin treatment resulted in a proportional reduction in the intake of all basic macronutrient including sugar [323]. Leptin was not able to decrease the consumption of a three-choice (*i.e.*, standard, high-sugar and high-fat chow) diet, although it decreased the intake of two-choice (*i.e.*, chow and high-sugar or chow and high-fat) diets, thus indicating that the former feeding paradigm caused leptin resistance [324]. It is worth notice, however, that leptin-induced reduction in the total caloric intake in chow and high-sugar diet-fed rats found in that study resulted from the decreased chow but not sugar intake, which is in agreement with the observation made in a study by Wierucka-Rybak *et al*. [83]. Thus, the usefulness of leptin as a selective suppressant of high palatable food consumption seems to be ambiguous. What is more, due to leptin resistance, when administered as monotherapy, this hormone failed to reduce food intake and body weight in obese individuals, but further studies indicated that combined therapies involving leptin and other

anorectic hormones had greater potential for weight loss [325] and, possibly, for selective inhibition of palatable food consumption.

GHRELIN

The gastric hormone ghrelin (its active form is acyl ghrelin, a product of acylation of the peptide by an enzyme ghrelin O-acyl transferase) [326] and ghrelin-related peptides such as desacyl ghrelin have recently gained much attention due to their ability to regulate glucose and energy homeostasis including reward-motivated feeding (see [327-330] for review). Accordingly, the growth hormone secretagogue (GHS) receptor, *i.e.*, the ghrelin receptor, was detected in the brain centers responsible for both homeostatic and hedonic feeding in humans and animals [331-333]. Genetic deletion of the GHS receptor resulted in resistance to diet-induced adiposity in mice, thus confirming a role for ghrelin in obesity pathogenesis [334]. A significant majority of studies on ghrelin action on eating behavior have been concerned with evaluating the effects of centrally applied hormone. They indicated that ghrelin increased motivation for palatable food and, importantly, regulated independently homeostatic and rewarding aspects of food intake, thus affecting differentially the consumption of palatable and bland food (for review, see [335, 336]). Consequently, the peptide increased motivation to obtain palatable food without affecting regular chow consumption. Thus, rats and mice with pharmacological or genetic ablation of the GHS receptor-reduced intake of rewarding food (*i.e.*, sugar pellets, peanut butter, or chocolate drink) but not of regular chow intake in a free choice or operant paradigm [337, 338]. Similarly, the ghrelin O-acyl transferase-null mice with subsequent acyl ghrelin deficiency decreased consumption of the high-fat chow presented after normal chow to previously fasted animals (a procedure referred to as a "dessert effect test") as compared with their wild-type littermates [339]. These findings suggest that manipulation in the peripheral ghrelin signaling system might be a potential tool for the selective inhibition of reward-motivated eating. On the other hand, the lack of ghrelin, acyl ghrelin, or GHS receptor did not result in body weight/food intake reduction when the mice were fed a no-choice high-fat diet [340]. Since the free-choice protocol employed in the study by Davis *et al*. [339] seems to better correspond to natural conditions leading to overeating than the non-choice diet in the study by Sun *et al*. [340], the pharmacological blockade of the ghrelin system may still be a promising method for suppression of excessive appetite for palatable foods. To be effective in the suppression of appetite, however, ghrelin antagonists should be able to cross the blood-brain barrier [341]. In favor of this approach, a GHS receptor antagonist, JMV2959, injected intraperitoneally to rats was shown to antagonize the changes in the activity of brain areas involved in both metabolic and hedonic food intake control induced by ghrelin revealed by fMRI [342]. This drug was also demonstrated to reduce intake of sweet-tasting solutions containing either sucrose or saccharine in rodents [343], whilst, consistently, intraperitoneally injected ghrelin increased saccharine but not bland food consumption in mice [344]. On the contrary, JMV 2959 injected intraperitoneally to the prairie vole did not affect either sucrose preference or consumption [345]. In summary, most studies indicate that ghrelin antagonists are worthy of further research as drugs to specifically inhibit appetite for palatable, especially sweet, foods. Since ghrelin was shown to interact with other orexigenic (*i.e.*, dopamine, endocannabinoids, and orexins) [330, 346-348] as well as anorexigenic (*i.e.*, leptin, GLP-1) [349, 350] substances to influence food intake, studies on combined treatment with the respective antagonists would be also of interest.

OTHER NEUROPEPTIDES, NUTRACEUTICS, AND DIETARY SUPPLEMENTS INHIBITING PALATABLE FOOD CONSUMPTION

OREXIN

Orexins A and B (hypocretins 1 and 2), peptide neurotransmitters produced in the lateral hypothalamus, promote hyperphagia and stimulate the reward seeking behavior [351]. Orexin knockout mice were shown to consume less sucrose solution than the wild-type mice [352], and, consistently, the orexin 1 receptor antagonist SB-334867 decreased sucrose self-administration in food restricted rats, although it did not affect sucrose-seeking behavior [353, 354]. Pharmacological blockade of the orexin 1 receptor by ACT-335827 resulted, however, in a significant increase in the standard and simultaneous decrease in high-fat high-sugar food consumption in rats. This effect was associated with weight gain, and no beneficial changes in the metabolic profile of ACT-335827-treated obese rats were found. Therefore, the authors concluded that the therapy based on inactivation of orexin 1 receptor would be of minor significance as an obesity treatment method [355].

OXYTOCIN

A hypothalamic neurohormone oxytocin has long been known to be involved in the regulation of reproductive functions and social behavior. Recently, however, oxytocin has been stressed as an anorexigenic agent limiting the intake of palatable foods [356]. Indeed, peripherally administered oxytocin reduced food intake in humans [357] and animals [358-361]. Rodent studies indicated that endogenous oxytocin was an inhibitor of carbohydrate (especially sucrose) but not fat intake [362-364] that decreased sweet taste sensitivity [365]. Importantly, these findings were confirmed by human studies reporting the suppressory effect of intranasal oxytocin on snack, *i.e.*, chocolate cookies intake without affecting hunger rating and consumption of the (basic) test meal [366]. Although further long-term studies are necessary to confirm the usefulness of oxytocin treatment for the selective inhibition of appetite for high-sugar foods, the results of studies published so far in this field seem to be very promising.

BROWN RICE

γ-Oryzanol is a mixture of ferulic acid esters present in the bran of brown rice that was recently found to have anti-diabetic and anti-obesity properties [367, 368]. Moreover, addition of brown rice to the laboratory chow decreased significantly not only body weight but also the preference for high-fat diet in mice maintained on a free-choice procedure [369], thus indicating that supplementation of meals with

brown rice (or, possibly, γ-oryzanol) has a potency to change appetite for palatable food. Nevertheless, more studies are needed to verify the usefulness of such therapy.

PLANT EXTRACTS

A series of recent studies indicate that plant extracts might be helpful in reducing appetite for palatable foods. A plant extract made of the common kidney bean *Phaseolus vulgaris* was shown to reduce motivation to obtain chocolate-flavored beverage in rats [370] and consumption of sweet, palatable cookies and beverages in mice [371]. The latter effect, however, was not specific because the *P. vulgaris* extract also reduced the regular chow intake [371]. On the other hand, morning, pre-meal consumption of spinach extract was found to decrease desire and, consequently, intake of sweet and fat snacks in overweight women, which is associated with body weight reduction [372, 373]. Hence, these preliminary studies suggest a new and simple method of supplementation a diet with natural compounds derived from the easily available plants that have a potential to reduce not only homeostatic but also hedonic hunger.

FATTY ACIDS

The jejunal infusion of linoleic acid, one of the long-chain fatty acids, resulted in a selective reduction of high-fat diet consumption in rats that could choose between a high-fat and high-carbohydrate diet [374]. Obese women whose diet was supplemented with oil rich in docosahexaenoic acid, an omega-3 fatty acid, decreased carbohydrate and fat intake and showed tendency to lower body weight [375]. Hence, these preliminary studies indicate that diet supplementation with (at least some) fatty acids may be another promising direction of research on appetite-modifying medications.

Despite the rapidly increasing number of studies on the effects of gut microbiota modifying agents (probiotics and prebiotics) on calorie intake and obesity development, we were not able to find any reports on their effects on food preferences in humans or animals.

SUMMARY AND PROSPECTS FOR FUTURE RESEARCH

In this review, we focused on the discussion of research studies investigating the possible usefulness of currently available pharmaceuticals in changing food preferences. Feeding behavior is controlled by homeostatic and hedonic centers that act in concert to induce hunger/satiety and "liking"/"wanting" of food, respectively. The non metabolic cues, however, that are driven mostly by food palatability may overhelm the homeostatic control and lead to overeating. Due to "additive-like" properties and high energy content, dietary sweet carbohydrates and fats are responsible primarily for increasing obesity rates worldwide. Therefore, we have searched especially for systemically active pharmaceuticals that selectively inhibited appetite for such rewarding high-calorie foods without reducing bland food consumption in a free-choice protocol when at least two dietary components (*i.e.*, sweet/fat and bland food) were available. Many of these drugs could inhibit not only the consummatory but also appetitive behavior. The review of results of animal and human studies revealed several drugs that satisfy the abovementioned conditions with varying degrees. The most promising treatments include CB1 receptor antagonists, methylphenidate, baclofen, GLP-1 agonists, and oxytocin. Additionally, lorcaserin and two combined therapies with bupropion/naltrexone and exendin-4/AM251 as well as dietary supplements sodium glutamate and fatty acids have been found to have potency to reduce rewarding food intake, but their effectiveness needs to be confirmed by further studies. The main problems we encountered when discussing the results of research studies were different (and sometimes difficult to compare) methodologies used to estimate the effects of a given treatment on food preferences and a relative paucity of animal studies enabling the estimation of drugs' effects under a free choice paradigm. Another important issue that may hinder an objective evaluation of results obtained is different individual sensitivity to pharmaceuticals caused by not completely identified factors, including sex hormones, genetic differences in enzyme activity, or receptor sensitivity to pharmaceuticals. It seems, therefore, that future studies aimed at finding successful therapeutic agents that modify food preference behavior must also take account of these issues.

CONFLICT OF INTEREST

There is no conflict of interest. None of the authors have any relationships with the pharmaceutical industry, including the current or past employment or grants or honoraria received.

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