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Therapeutics Effects of Drugs on Appetite and Food Intake- a Comprehensive Review

REVIEW ARTICLE

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ABSTRACT

A growing global desire for an effective treatment for hunger problems with maximal efficacy and minimal adverse effects has led to an increasing interest in appetite-related research.
Energy balance and food intake are essential components of existence for all organisms, including humans. Considerable increases or decreases in weight may be reason for alarm since they can lead to a number of physical and psychological problems. For example, obesity is a global issue affecting millions of people›s lives and is becoming worse. Anorexia is a dangerous and sometimes fatal illness that can also lead to malnutrition, organ damage, and other health problems.
The pharmacology and appetite regulation during the last five years are covered in this review.
Appetite regulation is a multifaceted process with several interrelated systems. This article reviews all the hormones, neuropeptides, and neurotransmitters—such as ghrelin, insulin, leptin, amylin, neuropeptide Y (NPY), agati-related peptide (AgRP), proopiomelanocortin (POMC), cocaine-amphetamine regulated transcript (CART), and glucagon-like peptide-1—that are involved in appetite regulation (GLP). -1
The majority of the drugs covered in this review are those that either directly affect how much food is eaten and how much appetite is regulated, such as beta 3-agonists, GLP-1 agonists, and amylin analogs, or indirectly affect these processes, such as antipsychotics, antidepressants, oxytocin receptor agonists, antiepileptic drugs, opioids, cannabinoids, corticosteroids, diabetes medications, and opioids.

Keywords: Appetite, orexigenic, anorexigenic, food intake, weight gain, weight loss

Abbreviations

AAPs: Atypical Antipsychotics
ABA: Activity-Based Anorexia
AED: antiepileptic drug
AgRP: Agouti-related peptide
AN: Anorexia Nervosa
ARC: Arcuate Nucleus
Asn: aspargine
BAT: brown adipose tissue
BMI: body mass index
CART: cocaine-and amphetamine-regulated transcript
CBD: Cannabidiol
CCK:cholecystokinin
Cys: Cysteine
ECS: Endocannabinoid System
EE: ethinyl estradiol
ERα, ERβ: estrogen receptor alpha / estrogen receptor beta
FDA: Food and Drug Administration
GABA: Gamma Aminobutyric Acid
GlyNH2: Glycine
Gln: Glutamine
GLP-1: Glucagon-Like Peptide-1
GR: Glucocorticoid Receptor
HPA: Hypothalamic-Pituitary-Adrenal Axis
Ile: Isoleucine
IGF-1: (insulin like growth factor)

Leu: Leucine
LMT: Lamotrigine
LNG: levongesterel
MET/MIR: metaformin/mirabegron
MORs: Mu-Opioid Receptors
MSH: Melanin-Stimulating Hormone
MS: Morphine
NPY: Neuropeptide Y
NTS: Nucleus Tractus Solitaries
OC: oral contraceptive
POMC: Proopiomelanocortin
PPAR: Peroxisome Proliferator-Activated Receptor
Pro: Proline
PVN: Paraventricular Nucleus
SGA: Second generation antipsychotics
SGLT2: Sodium-Glucose Co-Transporter-2
SON: Supraoptic Nuclei
THC: Delta-9-Tetrahydrocannabinol
TPM: Topiramate
Tyr: Tyrosine
TZDs: Thiazolidinediones
UCP1: uncoupling protein 1
VPA: Valproate
WAT:white adipose tissue
ZNS: Zonisamide

1. INTRODUCTION

Understanding the complex interactions between different drugs and hormones and their effects on hunger, weight management, and metabolic balance is becoming more and more important due to the multidimensional issues of obesity and its implications for general health. A line of inquiry focuses on the selective beta-3 receptor agonist mirabegron and its possible application to the treatment of obesity (Bel et al., 2021). In addition, scientists have moved into the field of combination therapy, focusing on the interactions between metformin (anti-diabetic) and mirabegron. Combination therapy is a novel approach to treating obesity and its associated conditions since it targets energy intake as well as energy expenditure (Zhao et al., 2023).

On the other hand, and no less concerning, women are increasingly turning to oral contraceptives to treat a range of illnesses, including endometriosis, dysmenorrhea, heavy bleeding, and menstrual abnormalities (Hirschberg, 2012). The reported weight gain in some women, however, is a noteworthy side effect that cannot be disregarded (Roberts et al., 2022). This has led to extensive research to better understand the complex interaction between the phenomena of weight gain and hormonal contraceptives, whether they are progestin-only or mixed.

In a different investigation, the opioid crisis has raised serious concerns about public health, with morphine and opioids' impact on appetite regulation drawing more attention (Sikora et al., 2019).

Furthermore, the connection between cannabis's cannabinoids and appetite control is another research concern. The regulation of hunger is mostly dependent on the endocannabinoid system (ECS), which is made up of receptors (CB1 and CB2), enzymes, and endocannabinoids(Lu et al., 2021). For diabetic individuals, managing their weight effectively presents a complex problem because some medications decrease hunger while others increase it. Notably, some drugs, such Saxenda and Ozempic, have received FDA approval to aid in weight loss, but insulin, a necessary component of diabetes treatment, can cause weight gain or loss depending on the kind taken (Dowarah et al., 2020), (Woods et al., 2006). Antiepileptic medications add a new level of complexity to the intricate picture of appetite regulation. While topiramate and zonisamide may cause weight loss, medications like carbamazepine and valproate have been linked to weight gain. On the other hand, lamotrigine and phenytoin seem to be weight-neutral (Hamed, 2015), (Antel et al., 2012).

This review expands on previous analysis to include hormonal influences on appetite control. Amylin is a hormone released by beta cells in the pancreas that is essential for blood sugar regulation and nutrient flow maintenance (Lutz, 2009), (Young et al., 1998). It controls the rate at which food is absorbed in the small intestine and the emptying of the stomach, working in tandem with glucagon and insulin to control blood sugar levels (Boyle et al., 2022) , (Dehestani et al., 2021) , (Mathiesen et al., 2021). Research into the possible advantages of oxytocin in managing obesity has been spurred by the hormone's ability to impact food consumption and weight regulation. Oxytocin is primarily recognized for its involvement in physiological processes such as lactation and childbearing(Hong et al., 2021). Additionally, the function of GLP-1, an endogenous hormone that reacts to food consumption, is being investigated. GLP-1 centrally inhibits hunger and glucagon while acting peripherally to increase insulin secretion (Grill, 2020). Without appreciably changing calorie expenditure, these intricate relationships present viable ways to control appetite (Hinnen, 2017), (Ard et al., 2021).

In addition to discussing the aforementioned topics, this review looks at the effects of glucocorticoids, antidepressants, and antipsychotics on weight management(Gill et al., 2020), (Mukherjee et al., 2022), (Geer et al., 2014), (Ferris et al., 2012).

On the other hand, and no less concerning, women are increasingly turning to oral contraceptives to treat a range of illnesses, including endometriosis, dysmenorrhea, heavy bleeding, and menstrual abnormalities (Hirschberg, 2012). The reported weight gain in some women, however, is a noteworthy side effect that cannot be disregarded (Roberts et al., 2022). This has led to extensive research to better understand the complex interaction between the phenomena of weight gain and hormonal contraceptives, whether they are progestin-only or mixed.

In a different investigation, the opioid crisis has raised serious concerns about public health, with morphine and opioids' impact on appetite regulation drawing more attention (Sikora et al., 2019).

2. METHOD

Literature electronic search was conducted using the most popular search engines: Google Scholar, PubMed, Scopus, and Science Direct.

3. RESULTS AND DISCUSSION

Medications with impact on appetite

3.1 Beta- 3 Selective Receptor Agonists

Mirabegron (Figure 1), which is used for the treatment of overactive bladder (Bel et al., 2021) have been recently investigated for its metabolic and anti-obesity abilities.

There is continuing study into the "beiging" procedure that converts white adipose tissue (WAT) into brown adipose tissue (BAT). Increased BAT activity has several metabolic benefits, including protection against insulin resistance and a decrease in adiposity(Bel et al., 2021) , (Hao et al., 2019). There is also an inverse connection between active BAT and obesity (Cero et al., 2021), (van Marken Lichtenbelt et al., 2009) , (Orava et al., 2013), (Green et al., (2017).

Adrenergic receptor B3 is highly expressed in both the rodent BAT and WAT (Y. O. Pinto et al., 2022).

When beta-3 receptors are active in a cell, several secondary messengers are released. Finally, these messengers promote uncoupling protein 1 (UCP1), a protein that is typically associated with BAT and that decouples energy production from the electron transport chain and generates heat from stored fatty acids.

Mirabegron was observed to boost UCP1 protein expression, decrease body weight gain and adiposity, lipid droplet size, the development of beige adipocytes in WAT, and increase glucose tolerance and insulin sensitivity in a study conducted on obese male mice (Bel et al., 2021), (Loh et al., 2019).

Mirabegron has been proven to increase BAT metabolic activity as well as metabolic parameters including glucose absorption and insulin sensitivity in human trials at a dose of 100 mg/day (Bel et al., 2021), (O'Mara et al., 2020), (Kosteli et al., 2010).

Mirabegron enhances BAT after acute or chronic dosages and results in browning when administered for at least 10 weeks. It's important to note that BAT activity improvements were only apparent at dosages greater than those FDA-approved for use (Y. O. Pinto et al., 2022). Mirabegron may be regarded as the most promising drug to initiate WAT beiging because of its selectivity at beta-3 receptors (Bel et al., 2021).

It should be noted that no beta-3 agonist has yet received approval for use in the stimulation of beging, and research is still being done to determine whether mirabegron's potential for off-target binding to the heart and blood vessels may result in increased blood pressure and plaque development.

Furthermore, when given to healthy people, mirabegron does not appear to have a substantial impact on human body weight (Bel et al., 2021) , (Kosteli et al., 2010).

It has been made more challenging to comprehend the situation due to the smaller number of beta-3 receptors, the different ligand affinities (Cero et al., 2021) compared with mice, and that rodent beta-3 receptor is only 81% identical to that of humans (Bel et al., 2021). A systematic method to identify activated brown adipocytes is also still lacking 29. Additionally, it is questionable if these effects on obesity and diabetes are caused by UCP1 (Y. O. Pinto et al., 2022) , (Kazak et al., 2015), (Ikeda et al., 2017). Therefore, more research on a larger human sample is necessary .to determine the efficacy and safety of this medicine

Treatment for obesity and its comorbid problems may be improved with combination therapy, particularly one that tackles both energy intake and output.

They discovered that the combination therapy of metformin (Figure 1) and mirabegron (Met/Mir) results in a greater loss of body weight compared to either drug taken alone. The results show that Met/Mir therapy additively increases lipolysis to provide energy to mitochondria, promoting fatty acid oxidation and thermogenesis, improves glucose homeostasis and insulin sensitivity.

The Met/Mir therapy also caused WATs to brown more quickly, which improved energy expenditure and reduced body adiposity in the treatment model. These results suggest that Met/Mir may synergistically promote weight loss in diet-induced obese mice (Zhao et al., 2023).

It has been discovered that the thermogenic effects of mirabegron depend on adiposity or metabolic context, since there was no browning in healthy individuals (Zhao et al., 2023). These results demonstrate the enormous potential of Met/Mir as a cutting-edge pharmacological approach for the treatment of obesity (Zhao et al., 2023). Given this, this merely serves as a foundation for planned Met/Mir therapy clinical trials and upcoming investigations utilizing combination drug therapy as an obesity treatment method.

3.2 Glucagon like peptide-1 receptor Agonists

Glucagon-like peptide, an incretin hormone, is produced by L-enteroendocrine cells in the intestinal mucosa in response to the consumption of foods containing nutrients that increase insulin production induced by glucose while lowering blood glucose levels.

GLP-1 receptors are present in the CNS and are mostly found in the hypothalamus, where they are thought to have a role in regulating hunger and calorie intake (Ard et al., 2021), (Farr, Sofopoulos, et al., 2016), (Farr, Li, et al., 2016). Additionally, it was necessary to stimulate (POMC / CART) neurons, inhibit NPY and AgRP, and increase the activity of pre-synaptic GABAergic neurons (Z. He et al., 2019), to increase satiety, lessen hunger, decrease food intake, and change food preferences (Ard et al., 2021), (Drucker, 2022), (Secher et al., 2014).

Numerous studies have shown that the GLP-1 hormone decreases blood sugar through boosting insulin output and sensitivity, promoting beta cell growth, and lowering beta cell apoptosis. Additionally, it suppresses the synthesis of glucagon from pancreatic alpha cells (Drucker, 2018).

The effectiveness of GLP-1 agonists in reducing body weight is thought to be caused by a decrease in caloric intake rather than an increase in energy expenditure. According to a thorough analysis of the literature, visceral malaise, greater satiation, and decreased hunger are thought to be responsible for this drug family's ability to inhibit eating. First off, visceral malaise, often known as nausea and vomiting, is the most common adverse reaction to GLP-1 agonists and is the primary effect of GLP-1R agonism on appetite and weight loss (Grill, 2020). The second is satiation, CNS GLP-1R-expressing sites release endogenous GLP-1. These GLP-1R signaling elements can be seen as necessary for the endogenous satiation control that results in meal termination (Grill, 2020). Finally, GLP-1R agonist significantly decreased the activation of appetitive behavior control brain regions upon viewing reward-predictive, energy-dense food pictures (Van Bloemendaal et al., 2014). In addition to the mentioned mechanisms involved, GLP-1 agonists increase gastric emptying time.

GLP-1A's involvement in maintaining weight following weight reduction has been suggested that preservation of free plasma leptin levels is involved in GLP-1RA-mediated maintenance of weight loss(Ard et al., 2021), (Iepsen et al., 2015).

GLP-1 receptor agonists contain warnings about the possibility of acute pancreatitis as well as thyroid C-cell tumors (Hinnen, 2017). GLP-1RA therapy for obesity seems to be well tolerated, and the proportion of clinical trial participants who discontinue treatment due to side effects is frequently low (5.4–9.9%). (Ard et al., 2021), (Wadden et al., 2021), (Garvey et al., 2020).

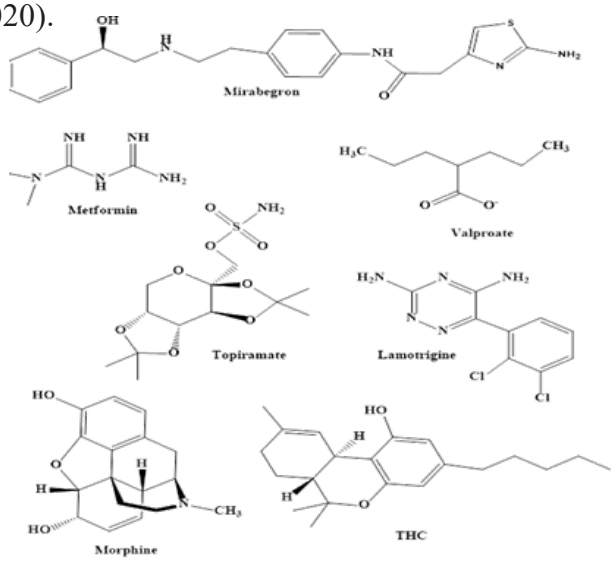

FIGURE 1

Chemical structures of Mirabegron, Metformin, Valproate, Topiramate, Lamotrigine, Morphine and THC,

3.3 Amylin analogs

Amylin is a peptide hormone containing 37 amino acids and is produced by pancreatic B-cells that plays a crucial role in regulating nutrient fluxes. Its functions include reducing food intake and appetite and controlling blood sugar levels (Lutz, 2009), (Young et al., 1998). Amylin is created from a precursor called Pro amylin (Betsholtz et al., 1989) and synthesizes into the biologically active monomeric form (Boyle et al., 2022).It is an insoluble protein with a molecular weight of only 3.9 kDa that forms long, stable fibers that cluster predictably. Amylin's ability to kill pancreatic beta cells is species-dependent (Adeghate et al., 2011), (Lorenzo et al., 1994). In humans, amylin has a disulfide bond that connects cysteine residues 2 and 7. To be biologically active, amylin or its analogs must have an intact amidated C-terminal and disulfide bond (Adeghate et al., 2011). The amino acid sequences of amylin and its analogue (pramlintide) are shown in Figures 2a and 2b.

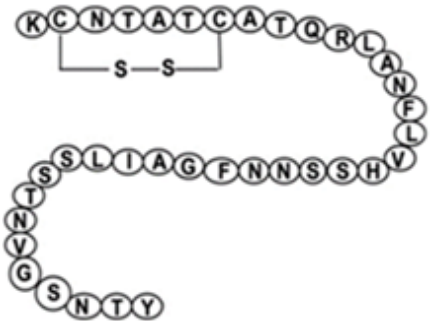

FIGURE 2a

An illustration of the amino acid sequence of amylin with cystine bond at position 2 and 7, the disulfide bond must be intact in order for amylin to be biologically active.

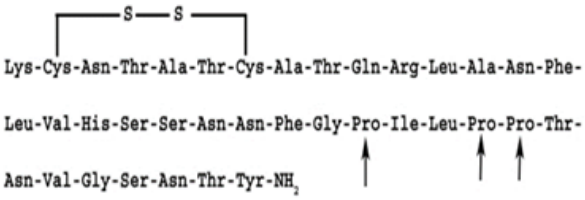

FIGURE 2b

An illustration of the amino acid sequence's homologue in pramlintides: There are cystine bonds at positions 2 and 7. Breaking the disulfide bond prevents amylin analogs from having biological activity. Positions 25, 28, and 29's amino acids have been replaced by proline (arrows).

Pramlintide and other amylin analogues work in tandem with insulin to manage blood sugar levels. In the treatment of type 1 diabetes, the soluble form of amylin, such as pramlintide, is combined with insulin. Amylin analogues have similar effects to insulin and can drastically lower body weight, HbA1c levels, and insulin dosage. They also reduce appetite by slowing gastric emptying and regulating hunger hormones, such as ghrelin (which stimulates hunger) and leptin (which promotes a feeling of fullness). Additionally, amylin acts on specific areas of the brain controlling appetite, signaling the brain to reduce the sensation of hunger and enhance the feeling of fullness, leading to a decrease in overall food intake. (Adeghate et al., (2011), (Heptulla et al., 2009), (Hassan et al., 2009 Amylin may be a good focus for a medicine that lowers body weight, especially when paired with other anorectic hormones (Lutz, 2009). Pramlintide acetate (an amylin analogue) has no reported adverse effects, but the most frequently reported side effects include mild-to-moderate nausea, vomiting, and reduced appetite. Obese people can lose a modest amount of body weight (Adeghate et al., 2011), (Dunican et al., 2010). but nausea and vomiting are significant side effects due to a potential stimulation of the postrema region in the medulla oblongata. (Adeghate et al., 2011), (Ryan et al., 2005).

3.4 Antipsychotics

Schizophrenia, a severe neurodevelopmental illness, presents both positive and negative cognitive symptoms. Therapeutic strategies, including antipsychotics, aim to address these symptoms and improve cognitive function, addressing both psychotic symptoms like hallucinations and delusions. (Lis et al., 2020), (Kaar et al., 2020), (Carli et al., 2021), (Mukherjee et al., 2022). Typical or First-generation antipsychotics (FGA) have been linked to side effects like tardive dyskinesia and parkinsonism (Kaar et al., 2020), (Mukherjee et al., 2022). Second-generation antipsychotics (SGA) have decreased this motor impairment risk; however, clozapine and olanzapine are found to cause metabolic effects like weight gain and dyslipidemia (Mukherjee et al., 2022). These drugs stimulate central nervous system receptors as histaminergic, serotonergic, dopaminergic, and muscarinic M1 and M3 receptors, leading to metabolic disturbances (Reynolds et al., 2010), (Mukherjee et al., 2022).

The H1 histaminic receptor, a target of atypical antipsychotics (AAPs), is linked to weight gain and metabolic changes (Carli et al., 2021). AAPs with high affinity to this receptor, like clozapine and olanzapine, effectively block this receptor, causing weight gain (Carli et al., 2021). Olanzapine blocks H1 postsynaptic receptors (Davoodi et al., 2008), causing hyperphagia, while clozapine blocks acetylcholine and noradrenaline release, causing hunger dysregulation (Schlicker et al., 1996).

The arcuate nucleus (ARC) of the hypothalamus contains pro-opiomelanocortin (POMC) centers which project to the serotonergic neurons and both modulate calorie intake and expenditure and when activated, POMC neurons secrete more -MSH, decreasing appetite (Carli et al., 2021). Clozapine and olanzapine have potent 5-HT2A/2C receptor antagonistic activity, affecting lipid and glucose metabolism and weight gain (Carli et al., 2021). A recent study using mice lacking the 5HT2c receptors demonstrated the influence of olanzapine-induced weight gain and hyperphagia (Lord et al., 2017).

Dopamine regulates food intake by modulating orexin and -MSH synthesis (Beaulieu et al., 2011). Blockage of D2 receptors in the arcuate (ARC) region can increase appetite and cause weight gain (Carli et al., 2021). D2 receptor antagonists like APD sulpiride and risperidone can increase calorie consumption and reduce energy expenditure, potentially leading to weight gain (Mukherjee et al., 2022).

Muscarinic acetylcholine receptors, particularly the M3 receptor, regulate metabolic hormones and are linked to APD-related risks (Mukherjee et al., 2022), (Nakajima et al., 2013). Olanzapine and clozapine are M3 antagonists that happens to increase M3 binding density in the hypothalamus, leading to increased weight gain and food intake (Weston-Green et al., 2012).

Weight reduction, decreased appetite, and concern over gaining weight are the hallmarks of anorexia nervosa (AN), a severe eating disorder (Fraga et al., 2021). According to a study, ABA develops in mice with limited food access and rotating wheels, which causes hypophagia, weight loss, and restlessness (Fraga et al., 2021). Antipsychotic medication amisulpride, acting as a D2/3R receptor antagonist, prevents hypophagia and weight loss when used with ABA (Mukherjee et al., 2022), (Lian et al., 2014). This suggests that ABA levels can be decreased by targeting D2 and/or D3 receptors (Mukherjee et al., 2022).

Obesity can be reduced by taking specific medications along with atypical antipsychotic medications (APDs) (Mukherjee et al., 2022). Combining atypical antipsychotic medicines with betahistine, a potent agonist of H1 and H3 receptors, has shown potential in reducing food intake and preventing obesity in mice and people (Lian et al., 2014), (Barak et al., 2016). Lorcaserin, a specific agonist targeting the 5HT2c receptor, has also been found to reduce hyperphagia and weight gain caused by olanzapine (Mukherjee et al., 2022), (Lord et al., 2017) Studies also have shown that patients taking clozapine can experience significant weight loss if they are accompanied with metformin, potentially lowering their risk of metabolic syndrome (Siskind et al., 2016).

3.5 Antidepressants

Antidepressants are advised as a first line for treating major depressive disorders (MDD) (Kennedy et al., 2016). About 65.3% of antidepressant users reported weight gain as a major side effect (Cartwright et al., 2016).

Antidepressant patients were also shown to have a slight increase in sedentary behavior and a significantly greater daily caloric consumption of more than 200 kcal. Their results suggest that an increase in calorie intake and sedentary behavior may be the cause of weight gain associated with antidepressants (Gill et al., 2020), (Jensen-Otsu et al., 2015). Due to pharmacological variations, weight gain may be susceptible to distinct kinds of antidepressant classes.

Serotonin is an essential target in depressive disorders. SSRIs improve the antidepressant effects by raising serotonin's extracellular synaptic concentration (Artigas et al., 2002). The acute serotonin reuptake inhibition controls hunger and has anorexigenic effects, by activating (POMC) neurons and causing anorexia (G. W. Kim et al., 2011), (Yu et al., 2012) , and decreasing NPY/RP neurons and their inhibitory projections (Carvalho et al., 2016). However, weight gain happens when extracellular synaptic serotonin concentration rises as a result of decreased serotonin reuptake, blocking serotonin receptors and causing an increase in weight (Schwartz et al., 2007). The hypothalamic melanocortin system is modulated by dopamine neurotransmission, which results in reduced calorie intake and higher energy expenditure (J. D. Kim et al., 2014).In addition, some users of MAOI drugs, such as phenelzine, may experience hypoglycemia effects (Gill et al., 2020), that may trigger feelings of hunger, which would increase calorie intake (Cooper et al., 1966).

Amitriptyline and nortriptyline are the TCAs that cause the most weight gain, due to high histaminic H1blocking affinity (Serretti et al., 2010), (Wang et al., 2018). Mirtazapine exhibits H1 blockage and 5-hydroxytryptamine (5HT3) antagonistic activities (Gill et al., 2020). There is a significant relationship between the H1 receptor affinity of antidepressants and weight gain (p value: 0.001) (Salvi et al., 2016). The well-known feeding regulator AMP-activated protein kinase (AMPK) is triggered by antagonists of hypothalamic H1 receptors. Additionally, H1 receptor antagonism may lessen sympathetic fluxes to the brainstem's rostral raphe pallidus and rostral ventrolateral medulla, hence reducing the thermogenesis of brown adipose tissue, and may cause fat to accumulate by causing white adipose tissue's lipogenesis to outpace its lipolysis (M. He et al., 2013).

Contrave, which combines bupropion and naltrexone, for treating obesity Bupropion, a mild dopamine and norepinephrine reuptake inhibitor (Gill et al., 2020), works by increasing the production of (POMC) cells and the release of melanocyte-stimulating hormone (alpha-MSH), which activates the melanocortin-4 receptor (MC4R), reduces appetite, and raises energy expenditure.

An opioid antagonist naltrexone works by blocking the MOP-R, which prevents beta-endorphin from having its intended inhibitory effect on POMC cells (Sherman et al., 2016) When taken together, naltrexone and bupropion improve the effects of POMC signaling more than either drug alone does (Billes et al., 2016).

3.6 Oxytocin

The hypothalamic hormone oxytocin regulates a variety of physiological processes, including parturition, lactation, social behavior, and metabolism. Oxytocin is created in the brain directly and travels to the rest of the body via the posterior pituitary gland. Additionally, many studies have demonstrated that oxytocin boosts energy intake while decreasing food consumption and may aid in weight loss. The effects of oxytocin on metabolism and appetite suggest potential therapeutic applications for the medication in the treatment of obesity and overeating (Hong et al., 2021).

Nine amino acids make up the neuropeptide hormone oxytocin: Cys, Tyr, Ile, Gln, Asn, Cys, Pro, Leu, and GlyNH2. The G protein coupled receptor family includes the oxytocin receptor, which has a disulfide bridge connecting cysteines 1 and 6 (Kerem et al., 2021) , (DU VIGNEAUD et al., 1953). Parvocellular neurons and magnocellular neurosecretory cells in the hypothalamus' PVN and supraoptic (SON) nuclei generate oxytocin (Tuppy et al., 1953), (McCormack et al., 2020). The posterior pituitary gland is where the hormone is released into the bloodstream (Kerem et al., 2021) to control satiety, hunger, and energy balance. Particular hypothalamic nuclei, such as the arcuate nucleus (ARC), paraventricular nucleus (PVN), and ventromedial hypothalamic nucleus, integrate peripheral signals reflecting energy consumption and reserves with higher order neural input from sources like adipose tissue and the gastrointestinal tract (Tuppy et al., 1953) , (Lawson et al., 2020).

Oxytocin has been shown to decrease appetite in obese mice, affecting their cravings for sugar and carbs (Hong et al., 2021). It also reduced the expression of sugar in rats that had consumed sugar over an extended period (Hong et al., 2021) , (Sabatier et al., 2013). Oxytocin injections caused a dose-dependent reduction in eating and drinking in both sexes (Hong et al., 2021) , (Cornejo et al., 2016) , with intraventricular injections showing superior results. Chronic oxytocin injections reduced food intake, body weight, and visceral fat, but no weight recovery occurred (Hong et al., 2021). On the other hand, over the past 20 years, research on the relationship between endogenous oxytocin levels, metabolic health, and disease has grown due to animal studies showing oxytocin is an anorexigenic hormone with beneficial metabolic effects (Kerem et al., 2021) ,(Ludwig et al., 2006), (Lawson et al., 2015). It reduces reward-related eating motivation and is linked to satiety signals (Hong et al., 2021), (Mitra et al., 2010).

In a randomized controlled experiment, 40 IU of intranasal oxytocin reduced 24-hour calorie intake in bulimic patients, but the intake of women in the anorexia nervosa and control groups remained the same (Hong et al., 2021) , (Arletti et al., 1990) Studies have also examined how men's central oxytocin levels are affected by 24 IU of intranasal oxytocin (Hong et al., 2021) , (Kim et al., 2015). One-dose oxytocin administration has been shown to impact calorie and weight loss, with more weight loss in those who are fatter (Hong et al., 2021). Further research is needed to understand its adverse effects, particularly on cardiovascular patients.

3.7 Anti-epileptic drugs

Epilepsy is a prevalent chronic medical condition that can lead to weight changes due to the metabolic effects of long-term antiepileptic drug (AED) therapy (Hamed et al., 2015) , (Isojärvi et al., 2001) , (Hamed et al., 2009). Antiepileptic drugs like gabapentin, pregabalin, valproate (VPA), vigabatrin, and carbamazepine are linked to weight gain, while others, such as topiramate (TPM), felbamate, and zonisamide (ZNS), typically result in weight loss. Lamotrigine, levetiracetam, and phenytoin are weight-neutral antiepileptic drugs (Hamed et al., 2015) , (Antel et al., 2012). Weight changes can hinder growth, particularly in children and adolescents (Sheth et al., 2002).

The exact reasons for weight changes brought on by AEDs are unknown, but they may be connected to the metabolic or endocrinological effects of these drugs on peripheral and/or central processes that regulate glucose metabolism, weight homeostasis, or energy balance. Homeostasis is a complex process regulated at peripheral and central levels by multiple pathways and various neuromolecules, peptides, and hormones. Weight is the end-result of complex and redundant interactions between short- and long-term signals, neuronal circuits regulating food intake and energy expenditure, and endocrine secretions that change the activity of the neurons within those circuits (Hamed et al., 2015).

Valproate (Figure 1) raises body weight through gamma aminobutyric acid (GABA) agonists, which increase membrane depolarization and may directly stimulate the hypothalamus, leading to an increase in appetite, a desire for high-calorie beverages, and an increase in energy expenditure. This could be the mechanisms causing valproate-induced weight gain (Luef et al., 2003).

Topiramate (Figure 1) is a sulfamate-substituted fructose derivative associated with weight loss and used to treat epilepsy and prevent migraines (luef et al., 2002) , (Martin et al., 2009). It may impact metabolic functions in the body, changing how energy is consumed and stored, may lower blood sugar levels raise insulin levels, decrease in appetite and an increase in sensations of fullness may be brought on by these effects, which may aid in weight loss (Biton et al., 2003).

Lamotrigine (Figure 1) was initially categorized as an antiepileptic drug and has been found to help epileptic individuals maintain a constant weight in multiple studies (Rissardo et al., 2021). It is less likely than other antiepileptic drugs to cause significant weight gain or loss, and its tolerability, low frequency of prescription, low number of side events, and weight neutrality make it a viable option for those concerned about weight changes while controlling their epilepsy (Ebrahimi et al., 2012).

It's vital to understand that not all antiepileptic drugs will affect appetite in the same way, and that influence might differ significantly from person to person. Some people might have an increased hunger and put on weight, while others might have a decreased appetite and lose weight.

3.8 Opioids

Opioids are potent analgesic drugs commonly used to manage pain, but there is growing concern about their effects on appetite, which can have implications for metabolic functions and overall health (Mysels et al., 2014).
Opioids exert their effects by binding to specific receptors in the central nervous system, with mu-opioid receptors (MORs) playing a significant role in hunger regulation.
Activation of MORs, particularly in the hypothalamus, has been linked to increased hunger and food intake. AgRP (agouti-related peptide) and neuropeptide Y (NPY), which increase hunger, are released in response to this effect Pasternak et al., 2013). Conversely, opioids can also influence the reward system, impacting the hedonic aspects of eating behavior. Activation of MORs in certain brain areas, such as the nucleus tractus solitaries (NTS), can trigger the release of peptides that promote satiety, like proopiomelanocortin (POMC). Additionally, opioids can alter the release of hormones like leptin, ghrelin, insulin, and cortisol, which are essential for appetite control (Le Merrer et al., 2009). Chronic opioid use may lead to dependence and tolerance, making it even more challenging to manage appetite. Mixed results have been found in clinical trials examining the association between morphine (Figure 1) and hunger; some indicate increased food intake after opioid administration, while others report decreased appetite or weight loss. Variations in patient characteristics, opioid dosages, and research designs could be the .(cause of these disparities (Mysels et al., 2010
Healthcare professionals need to consider the potential impact of opioids on appetite when treating pain in patients with pre-existing metabolic disorders or those at risk of obesity. Future research should focus on understanding how opioids, particularly morphine, affect appetite, considering various confounding factors like opioid dosage, pain severity, and underlying medical conditions (Wiffen et al., 2014).

3.9 Cannabinoids

Cannabis constituents called cannabinoids are drawing notice for how they affect hunger. This section examines at their connection to the endocannabinoid system (ECS), hunger, and possible medical uses (Pacher et al., 2006). The ECS, which is made up of CB1 and CB2 receptors, enzymes, and endocannabinoids, is essential for controlling hunger. Hunger is influenced by central nervous system CB1 receptors. The hypothalamus's CB1 receptors are activated by delta-9-tetrahydrocannabinol (THC, Figure 1), which increases food intake and modifies neurotransmitters that control hunger (Gamage et al., 2012), (Bourdy et al., 2023).

Eating becomes more enjoyable due to the impact of cannabinoids on the brain's reward system. Additionally, they may heighten flavor preferences by altering taste perception—a phenomenon known as the "munchies" (Bourdy et al., 2023).

A complex role for cannabidiol (CBD) in appetite regulation exists. While CBD doesn't directly activate CB1 receptors like THC does, it can moderate their activity, which may lessen THC's effects on hunger stimulation.

Through its effects on peripheral appetite systems, reduction of inflammation, and enhancement of insulin sensitivity, CBD exhibits promise in mitigating binge eating and promoting metabolic health (J. S. Pinto et al., 2022).

It's fascinating to investigate the complex connection between hunger management and cannabis. Endocannabinoids and their receptors, as well as the ECS, are essential for preserving physiological homeostasis. The manner that THC stimulates CB1 receptors provides insight into the way that cannabinoids interact with the reward pathways in the brain. In the meantime, CBD plays a complex role that may lessen the effects of THC while also showing promise for enhancing metabolic health. (Zou et al., 2018), (Coelho et al., 2023).

3.10 Glucocorticoids

Corticosteroid hormones, including glucocorticoids, are produced by the adrenal cortex under the hypothalamic-pituitary-adrenal (HPA) axis (Akalestou et al., 2020). Glucocorticoids are currently a strong treatment for cancer, autoimmune disorders, post-organ transplant rejection prevention, and inflammatory illnesses (Geer et al., 2014).These drugs can save many lives, but they are expensive and can cause diabetes, obesity, insulin resistance, and other metabolic syndrome symptoms (Ferris et al., 2012).

Patients worry mainly about weight gain from long-term glucocorticoid use (Ferris et al., 2012). Weight gain can be caused by glucocorticoid insulin resistance, dyslipidemia, increased food consumption, and appetite management by consuming calorie-dense meals (Geer et al., 2014), (Kuckuck et al., 2023).

It's interesting that the hypothalamic-pituitary-adrenal (HPA) axis and cortisol work closely with the gut-brain hormonal relationship (Kuckuck et al., 2023), (Maniam et al., 2012). The effects of glucocorticoids include peripheral gluconeogenic and anti-inflammatory actions, increased food consumption, and a preference for high-calorie meals. Thus, medicine or long-term stress can raise glucocorticoid levels, leading to weight gain and obesity (Kuckuck et al., 2023). The hypothalamus, mesolimbic areas, and ventral tegmental area are all directly impacted by glucocorticoids. This may exacerbate homeostatic regulation and enhance appetite by influencing appetite regulators (Maniam et al., 2012), (Adam et al., 2007), (Sominsky et al., 2014).
According to the research, using glucocorticoids excessively may lessen the effects of leptin on the brain (Kuckuck et al., 2023).When an animal's adrenal glands are destroyed, they become more sensitive to leptin and hence lose weight. However, this impact can be offset by supplementing with dexamethasone (Zakrzewska et al., 1997).

Another example is the use of prednisolone therapy, which has been shown to boost food intake in women even in the presence of elevated leptin levels (Kuckuck et al., 2023), (Uddén et al., 2003). Not to be overlooked, leptin-mediated IL-1β expression was suppressed by dexamethasone in both glia cell culture and the murine hypothalamus, despite the absence of any change in leptin receptor expression in the hypothalamus. This finding raises the possibility that intra-neuronal signaling is at play (Hosoi et al., 2003). Insulin resistance is a shared feature of obesity, the metabolic syndrome, and type 2 diabetes mellitus. Adiponectin, for example, is released from adipose tissue and can increase insulin sensitivity in tissues. However, glucocorticoid therapy reduces its efficiency, leading to insulin resistance (Ferris et al., 2012). Additionally, glucose levels can be raised by directly stimulating hepatic gluconeogenesis with glucocorticoids. Obesity may appear as a clinical characteristic in either the Cushing syndrome or the metabolic syndrome, which can both develop as a result of this hyperglycemia (Mazziotti et al., 2011).

Glucocorticoids regulate glucose metabolism in several tissues via the GR. This regulation involves manipulating essential enzyme expression (Akalestou et al., 2020), (Moraitis et al., 2017). Obesity maintains cortisol levels around normal, indicating intracellular regulation of glucocorticoid receptor (GR) function. This suggests that glucocorticoid receptor (GR) gene variations may cause diabetes and obesity (Akalestou et al., 2020), (Majer-Łobodzińska et al., 2017).

3.11 Oral contraceptives (OC

3.11.1 Progestin only contraceptives

Food consumption is known to be stimulated by progestins (Hirschberg, 2012), (Maltoni et al., 2001). For example, megestrol acetate at high dosages can be used to treat several types of malnutrition. This medication significantly raises blood levels of insulin and insulin-like growth factor (IGF)-I (Hirschberg, 2012), (Maltoni et al., 2001).

Additionally, androgenic OC may contribute to weight gain in some women by decreasing the secretion of the satiating peptide CCK and increasing body fat, interfering with the regulation of appetite (Hirschberg, 2012), (Lindén et al., 1992), (Lindén Hirschberg et al., 1996).

22,450 women participated in 22 clinical trials to examine this notion. No appreciable change in weight or other physical features was seen in 15 of them. Five studies found differences between the research groups, but the quality of their findings ranged from low to moderate (Lopez et al., 2016). These 22 clinical studies found only weak evidence that using progestin-only contraceptives altered body weight or composition. Most studies found that the mean weight gain at 6 or 12 months was less than 2 kg. The mean weight change was almost twice as much at two to four years than it was at one year, according to those having multiyear data, but overall, there were no appreciable differences between the research groups (Lopez et al., 2016).

3.11.2 Combined hormonal contraceptives

Combination oral contraceptives (OCs) usually contain either natural estradiol or the synthetic estrogen ethinyl estradiol, while the type of progestin utilized varies. Derivatives of 19-nortestosterone or 17-hydroxyprogesterone are the most important progestins.

Estradiol has a critical role in controlling food intake and energy balance in humans, as evidenced by the large increase in obesity incidence that occurs after menopause (Butera, 2010), (Garber et al., 2018).

The effects of estradiol on the brain circuits that regulate eating behavior may potentially contribute to the sex differences in food intake and eating disorders, which are significantly more common in young women (Butera, 2010), (Södersten et al., 2003).

It is clear that estradiol interacts with brain estrogen receptors to mediate its effects on food intake. Additionally, scientists have proposed that estradiol can enhance satiety signals by stimulating estrogen receptors (ERα, ERβ) in the parts of the brain that process the vagally mediated signal produced in the belly by the activity of CCK (Butera, 2010).

The results of the studies suggested that attenuating orexigenic signals could be one of estradiol's effects. Modulating the effects of peripheral ghrelin signaling on neuropeptides (NPY) in the hypothalamus that regulate food intake may be one way to achieve this (Butera, 2010).

A meta-analysis of 49 trials was conducted in 2011 by the Cochrane Collaboration. The authors concluded that not enough data was available to make a firm conclusion about the effect of combined oral contraceptives on weight gain, but they also suggested that the impact was not significant. (Mayeda et al., 2014),(Gallo et al., 2014).

Studies show that antiandrogenic oral contraceptives containing ethinylestradiol and drospirenone decrease testosterone levels as well as binge eating and hunger during meals (Hirschberg, 2012), (Naessén et al., 2007). Users of this specific OC also exhibit a slight loss of body weight (Hirschberg, 2012), (Sitruk-Ware, 2006).

In a 2016 study involving women of normal weight and obesity. Weight and body composition were generally not significantly affected by short-term oral combination contraceptive treatment with formulations of 20 μg ethinyl estradiol (EE) and 100 μg levonorgestrel (LNG) or 30 μg EE and 150 μg LNG. They did, however, raise the possibility that over a longer duration of follow-up, weight or changes in body composition would have become apparent (Mayeda et al., 2014).

There is a compelling argument for greater research on the effects of different oral contraceptives on appetite and body weight, even with the extensive clinical experience with their usage. There is still much to learn about this relationship.

3.12 Diabetes drugs

Diabetes medications, which either stimulate or inhibit appetite, are essential in controlling the amount of hunger experienced by people with the disease. Blood sugar levels rise as a result of inadequate insulin synthesis in type 1 diabetes. Conversely, type 2 diabetes is characterized by the body's inefficient use of insulin, which is frequently brought on by insulin resistance. Weight gain with insulin therapy, a frequent diabetes treatment, can have a detrimental effect on diabetes management and cardiovascular health (Woods et al., 2006).

Sulfonylureas, a traditional diabetes treatment, increases insulin secretion by pancreatic beta-cells and can lead to hypoglycemic effects (Costello et al., 2025).

Glinides, such as Repaglinide and Nateglinide, also enhance insulin production but may cause weight gain during the initial three months of treatment (Vaughan et al., 2020), (Sola et al., 2015), (Kalra et al., 2018). Thiazolidinediones (TZDs), like Pioglitazone and Lobeglitazone, activate PPAR gamma, reducing insulin resistance in peripheral tissues but often resulting in weight gain, primarily affecting subcutaneous fat [Ko et al., 2017), (Soccio et al., 2014), (Cariou et al., 2012), (Aronoff et al., 2000), (Lebovitz et al., 2001).

A diabetic-friendly diet and regular exercise are crucial lifestyle changes to prevent weight gain brought on by diabetes drugs. These modifications have been shown to be successful in lowering blood sugar levels and encouraging weight loss. Changes in lifestyle, however, might not always have the desired effect.

It's important to remember that Mounjaro and other GLP-1 agonists, which are diabetes medications, can help with weight loss. The double-agonist medication mounjaro releases hormones that control blood sugar, suppress appetite, and aid in weight loss by activating GLP-1 and GIP receptors. Mounjaro is presently being reviewed by the FDA for weight loss, and it could be a good choice for people with high BMIs who want to lose some weight.

Metformin, a common diabetes medication, may cause weight loss in certain people by changing the flora in the gut and perhaps decreasing hunger via influencing the leptin hormone. Its benefits on weight loss are mild, though, and not everyone loses a lot of weight. To fully reap the benefits of metformin, a balanced diet and regular exercise are advised.

The competitive SGLT2 inhibitor empagliflozin has been approved for the treatment of type 2 diabetes. It increases energy expenditure, improves glucose excretion, and decreases weight gain, insulin resistance, and hepatic steatosis (Ndefo et al., 2015), (Haddad et al., 2023).

4. SUMMARY AND CONCLUSION

Researchers have demonstrated that the selective beta-3 agonist mirabegron increases metabolic activity, which in turn promotes weight loss in people with pre-existing conditions and precludes diet-induced obesity.

Additionally, evidence suggests that antiandrogenic oral contraceptives reduce appetite and binge eating, but progestin-only and combined contraceptives only marginally change weight composition. Cannabinoids, like THC and CBD, also have a great deal of potential to influence appetite and food intake when paired with medications like Epidiolex, Nabilone, and Dronabinol. In contrast, people gain weight when using antidepressant drugs like mirtazapine, SSRIs, and TCAs. Antiepileptic drugs (AEDs) can vary in how they affect body weight in addition to antidepressants. For example, while topiramate and other drugs might cause weight loss, valproate and other medications may cause weight gain.

Antipsychotic medications, particularly those with a strong affinity for dopamine D2 receptors, serotonin 5HT2c, and histamine H1 receptors, might result in hyperphagia and weight gain. Long-term use of glucocorticoids interferes with hunger hormone signaling pathways, leading to hedonic overeating and weight increase, according to the previously mentioned study results. However, no scientific evidence supports its usage to treat hypophagia diseases. In the hormone domain, insulin therapy for diabetes often causes weight gain; however, weight gain may be reduced with the SGLT2 inhibitor empagliflozin. Additionally, the domain of appetite includes amylin hormone, which, when combined with other anorectic hormones like peptide YY and leptin, shows promise as a medication for weight loss in individuals with type 1 and type 2 diabetes. Mice treated with Oxytocin and male obese mice both lose weight. Furthermore, compared to placebos like semaglutide (2.4 mg), GLP-1 RAs are more effective in reducing weight, suggesting that they may be useful in the treatment of obesity.

There is evidence that opioids can both stimulate and reduce hunger, although their effects are nuanced and context-dependent. The article highlights that since the use of opioids is still an essential part of pain management, further research is required to completely understand how these drugs impact appetite and associated metabolic processes. Greater knowledge of the possible metabolic effects on long-term opioid users as well as better pain management techniques should result from a deeper comprehension of these intricate relationships.

We believe that further studies are necessary to elucidate and demonstrate the ways in which these medications and hormones impact appetite and regulation of body weight.

Table 1 provides a brief overview of the medications covered in this article along with their impact on appetite and food consumption.

Author contribution: Beta-3 agonists and contraceptives were written by BA; Glucagon Like Peptide-1 Receptor Agonists and Antidepressants were written by BB; Amylin Analogs and Anti-Epileptic Drugs were written by HY; Anti-Psychotics and Corticosteroids were written by NA; Oxytocin, Synopsis, and Conclusion were written by RM; Opioids and Cannabinoids were written by ZA; Editing and revisions were done by RK.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

Table 1. A summary of drugs affecting food intake and their therapeutic effects.

Classes of drugs	Therapeutic effects	Animal/Human Trials
Antiepileptic	Increased hunger can result from Valproate's direct stimulation of the hypothalamus. Rarely does Lamotrigine lead to noticeable weight changes. Assisting in weight loss, Topiramate decreases hunger and enhances feelings of fullness.	Human trails
Amylin analogs	Reduced appetite, blood sugar control, and reduced food intake can be achieved by slowing down the emptying of the stomach and controlling hunger hormones like leptin and ghrelin.	Human and animal trails
Atypical antipsychotics	Primarily inhibit dopaminergic, muscarinic, histamine, and serotonin receptors, which results in hyperphagia and weight gain. Research is being done on the use of several AAPs to treat activity-based anorexia (ABA).	Human and animal trails
Glucocorticoids	It has been demonstrated that glucocorticoids enhance hunger and contribute to weight gain by altering leptin levels, resulting in insulin resistance, and boosting the consumption of meals high in calories.	Human and animal trails
Anti-diabetics	Insulin production is stimulated when blood glucose levels fall due to the blockage of ATP-dependent potassium channels in the beta cells of the pancreas. As a result, weight gain is noticeable due to the medication's effects.	Human and animal trails
Beta- 3 receptor agonists	Mirabegron: It decreases body weight gain, adiposity, and lipid droplet size while increasing BAT metabolic activity, UCP1 protein expression, the development of beige adipocytes in WAT, glucose absorption, insulin sensitivity, and glucose tolerance.	Human and animal trails
Contraceptives	1) OCs on progestin alone: no appreciable change in weight or other physical attributes was seen. 2) Combined OCs: *EE/LNG short-term use had no effect on body composition or weight. *EE/drospirenone: studies have shown that this OC lowers hunger during meals and prevents binge eating. Individuals using this particular OC also show a small decrease in body weight.	Progestin only OCs: Human Trials EE/LNG: Human Trials *EE/drospirenone: Human trials
Oxytocin	Research indicates that intranasal or intravenous oxytocin administration led to a decrease in hunger (desiring carbohydrates and sweets), food consumption, body weight, and visceral fat, as well as no weight recovery.	Human and animal trails
GLP-1 Agonists	By activating (POMC/CART) neurons, which block NPY and AgRP, reduce food intake, and diminish appetite, weight can be reduced. enhances the sensitivity of insulin secretion, reduces the secretion of glucagon, and slows down stomach emptying.	Human and animal trails
Antidepressant	Bupropion decreases appetite, activates MC4R, releases alpha-MSH, and promotes the formation of POMC cells. The opioid antagonist naltrexone inhibits MOP-R and stops beta-endorphin from inhibiting POMC cells.	Mirtazapine: Human studies Bupropion and Naltrexone: Human and animal trails
Opioids	Promote hunger by activating the hypothalamic mu-opioid receptor (MOR), which releases neuropeptide Y (NPY) and agouti-related peptide (AgRP). possess an impact on the hedonic elements of eating behavior and the reward system. Modify the release of hormones necessary for controlling appetite, such as cortisol, insulin, ghrelin, and leptin.	Human trails
cannabinoids	Arouse appetite-regulating neurotransmitters, enhance food intake, and activate CB1 receptors in the hypothalamus. Impact the brain's reward system and enhance the pleasure of eating.	Specific trials are not mentioned

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