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TARGETS TO COMBAT OBESITY – AN REVIEW

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ABSTRACT

Obesity is a multifactorial, chronic disorder in most of the countries and becoming a global epidemic. In this review, various approaches namely increased thermogenesis, decreased or reduced fat absorption, modification of fat metabolism and reduction of food intake and their mechanism of action to combat obesity is discussed. The recent developments on these approaches are briefly given.

KEYWORDS: Thermogenesis, food intake, fat metabolism, absorption of fat, obesity



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INTRODUCTION

Obesity is increasing tremendously as a consequence of easily available fat-rich food and an increasingly sedentary lifestyle. Obesity is a multigenic disorder.¹ The major health burden of obesity is the increased risk of Type 2 diabetes, cardiovascular morbidity and cancer.² The obvious recourse to diet and exercise in the treatment of obesity is successful in just a small minority. When these efforts fail, many morbidly obese patients resort to surgical intervention, which, although effective, is not without risk in itself. There is a clear need for effective pharmaceutical intervention, but this appears to be an area in

medicine. In this review, the various approaches and potential new drug targets derived as the result of research to control obesity has been discussed.¹

FIVE APPROACHES TO COMBAT OBESITY

As the obesity is due to improper balance in the energy expenditure, the approaches which reduce the food/energy intake, increase the energy expenditure, prevent/reduce the fat absorption, modify the fat and protein metabolism and reduce food intake can be targeted to combat the obesity.¹

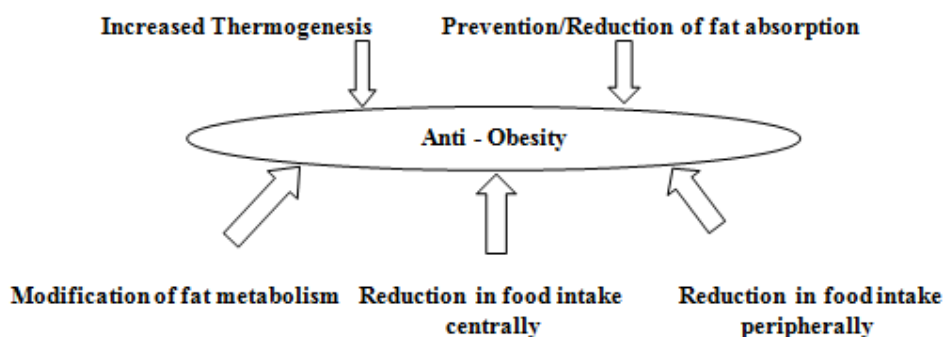


Figure 1
Five approaches to combat obesity¹

1.0. APPROACH I - THERMOGENESIS

As discussed, it is one of the methods to combat obesity. Thus the usage of drugs which stimulates the thermogenesis will reduce the obesity.^{2,3} In order to handle obesity, the drug should either affect energy intake or expenditure or both. As per the First law of thermodynamics, which states that amount of stored energy (fat) is equal to difference between the energy intake and work. In this context, the work is conversion of excess energy into heat. Such a conversion is achieved by various physical activities like exercises, food supplements and by the drugs. The drug which transforms the excess energy into heat are classified into different subdivisions depending upon their mode of action, site of action, stimulation, etc., The subdivisions are thyroid hormone and their

agonists, β -adrenergic receptors and UCP (Uncoupled Proteins).

1.1. Thyroid hormone and their agonists

Thyroid hormone induces high fatty acid utilization and raise in metabolic rate⁴⁻⁶ which contributes to its anti-obesity activity.⁷⁻¹¹ Thus increasing the thyroid hormone concentration decreases the obesity. However it is found satisfactory only in hypothyroid patients.¹² In case of euthyroid subjects suffering from obesity and hyperlipidemia, treating with naturally occurring T₃ and T₄ hormones resulted in undesirable cardiac side effects like tachycardia, arrhythmias^{5,13} bone and muscle loss, fatigue, psychological effect,^{14,15} heart failure^{5,13} and excessive increase in the metabolic rate.^{5,13} These undesirable side effects can be prevented if the obesity is

treated by using agonists which are specific to selective thyroid hormone receptors.

1.1.a. Selectivity of thyroid hormone receptors⁵

Thyroid hormone acts through two distinct receptors TR α and TR β . These receptors are members of the nuclear receptor (NR) super family, which contains 48 individual genes that also encode receptors for fatty acids and cholesterol derivatives, retinoids, vitamin D, steroids, bile acids and xenobiotics and molecules for which ligands are not known (orphans).^[4,8,16-19] The predominant action of ligand subtype TR α , α 1 is on heart rate,^{4,14,20} whereas the predominant action of ligand subtype TR β , β 1 is on cholesterol lowering through liver.^{4,14,20} Thus attempt was made to develop thyroid hormone receptors (TR) agonists with high selectivity, which targets only on metabolic rate (energy expenditure / thermogenic) with minimal impact on heart. The development of TR agonist with high selectivity was found to be difficult due to structure activity relationship (SAR) around diphenyl ether scaffold which allowed limited chemical modification.⁸ With the above said constraints, recent discoveries led to the development of new compounds like KB141, GC-1 and MB07811 which are selective in nature.^{8,13,21} These new TR β selective compounds acts specifically on tissue and liver

uptake to reduce the cholesterol and increase the metabolic rate without tachycardia.^{5,22-24}

1.1.b. KB141

The TR β effect of KB141 was tested on zucker fa/fa rats. These rats were fed with high cholesterol diet for two weeks prior to drug therapy (KB141 was given P.O. once daily for 3 weeks by oral gavages) which resulted in significant reduction in weight, adiposity and with other bio chemical data namely blood urea nitrogen, liver function were normal with no tachycardia.²⁵ However the metabolic rate was not measured but suggested that decrease in obesity was due to increase in metabolic rate. In another study, the effect of KB141 on increase in metabolic rate was correlated.⁵ KB141 caused reduction in serum levels of total cholesterol and triglycerides. It also reduced the body weight in ob/ob mice.²⁵

1.1.c. GC-1

It is a halogen free agonist scaffold compound which was synthesized efficiently.²⁶⁻²⁸ It binds with TR β with four to tenfold higher affinity than it did with TR α .²⁹ Studies in rat, mice and monkey showed that it lowers cholesterol with 600 to 1400 fold more potentially.^{23,24&30} There is either no or minimal effect on heart rate.^{23,24} The GC-1 has increased the oxygen consumption thus increasing the metabolic rate in cholesterol fed rats.⁵

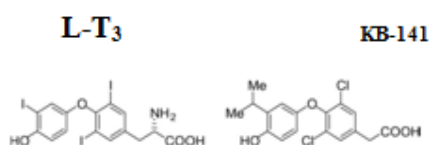


Figure 2
Structures of T₃, KB141²⁵

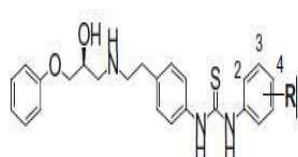
1.2. β -adrenergic receptors

β -adrenergic agents have been generally classified into β 1, β 2 and β 3 receptor-specific subtypes. Agonists of β -receptors promote the activation of adenylyl cyclase1. β 1-receptors predominate in the β -adrenergic agents have been generally classified into β 1, β 2 and β 3 receptor-specific subtypes. Agonists of β -receptors promote the activation of adenylyl cyclase1. β 1-receptors predominate in heart

and their stimulation causes an increase in the rate and force of contraction. β 2-receptors are found in vascular, bronchial and uterine smooth muscles. Their stimulation causes muscular relaxation. β 3-Receptors are found in intestinal and adipose tissues.³¹ The β 3-adrenergic receptors (β 3-AR), belonging to G-protein coupled receptor (GPCR) family. Activation of these receptor produces lipolysis in white adipocytes and thermogenesis

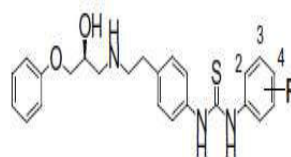
(energy expenditure) in brown tissue adipocytes,³¹ Hence β 3-AR has been an important target for anti-obesity and exploration of molecules with β 3-AR agonistic activity may provide potential anti-obesity agents.³² On the other hand, the simultaneous activation of β 1- or β 2-ARs would lead to undesirable side effects such as increased heart rate and/or muscle tremors. Therefore, the development of novel therapeutic agents with β 3-AR selectivity over β 1-AR and β 2-AR has been required.³³ The various therapeutic agents with specificity for β 3 receptors are in the line of discovery some of them are stated as below;

(S)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl) amino]ethyl}-phenyl)-3-(4-nitrophenyl) thiourea hydrochloride



R- 4 NO₂

(S)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl) amino]ethyl}-phenyl)-3-(3-methoxyphenyl) thiourea hydrochloride



R-3 OCH₃

Figure 3

Structures of phenoxypropanolamine derivatives³⁴

1.2.b. Acetanilide derivatives

A novel series of acetanilide-based analogues were prepared and their biological activities were evaluated at the human β 3-, β 2- and β 1-ARs. Among these compounds, 2-pyridylacetanilide, pyrimidin-2-ylacetanilide and pyrazin-2-ylacetanilide derivatives

exhibited potent agonistic activity at the β 3-AR with functional selectivity over the β 1- and β 2-ARs. In particular, compound pyrimidin-2-ylacetanilide was found to be the most potent and selective β 3-AR agonist with an EC₅₀ value of 0.11 mM and no agonistic activity for either the β 1- or β 2-AR.³⁵

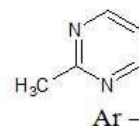
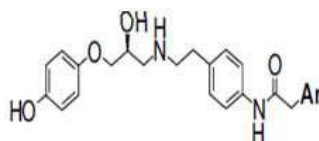


Figure 4

Structure of pyrimidin-2-ylacetanilide³⁵

1.2.c. Phenoxypropanolamine derivatives with acetanilides

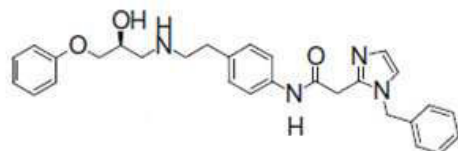
A novel series of phenoxypropanolamine derivatives containing acetanilides were

prepared and their biological activities were evaluated at the human β 3-, β 2-, and β 1-ARs. Most of the analogues namely, 1-benzylimidazol-2-ylacetanilide derivatives

exhibited a 53-fold increase in potency at the β 3-AR with good intrinsic activity ($EC_{50} = 0.18$ IM, $IA = 0.77$). Among the compounds described herein, the N-methyl-1-benzylimidazol-2-ylacetanilide derivative was

found to be the most potent and selective β 3-AR agonist, with an EC_{50} value of 0.28 IM and no agonistic activity for either the β 1- or β 2-AR.³⁶

1-benzylimidazol-2-ylacetanilide



N-methyl-1-benzylimidazol-2-ylacetanilide

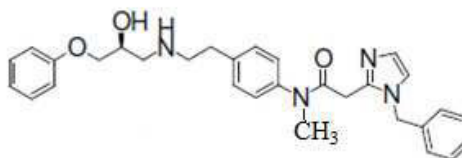


Figure 5

Structures of phenoxypropanolamine derivatives with acetanilides³⁶

2.0. APPROACH II - FAT ABSORPTION

Ingested dietary triglycerides are hydrolyzed by gastric and pancreatic lipases. The resulting fatty acids are taken up by enterocytes, (lining of the small intestine) where they are re-esterified to triglycerides and then transported into the blood. The obesity can be controlled by blocking the absorption of dietary fat either by preventing the hydrolysis of triglycerides by lipases or by blocking the absorption of fatty acids by the small intestine.³⁷

2.1. Orlistat

The orlistat (Xenical), the lipase inhibitor blocks fat absorption by inhibiting the hydrolysis of dietary fat in to fatty acids, however, the side effects of Xenical, i.e. faecal fat loss is a problem for some patients.¹

2.2. Fatty acid transport proteins

A family of proteins, termed fatty acid transport proteins (FATPs) that mediate the uptake of fatty acids into cells. Various studies provided the evidence that fatty acid transport protein 4 (FATP4) mediates the transport of fatty acids from the gut into enterocytes both *in vitro* and *in vivo*. The drugs which inhibit the FATP transporter can reduce the obesity. 4 aryl di

hydro pyrimidinones were identified as FATP4 inhibitors.³⁷

3.0. APPROACH III - FAT METABOLISM

Enzymes involved in fat metabolism are important obesity targets. Proteins involved in adipocyte differentiation, angiogenesis or apoptosis could also be targeted as a way to reduce fat mass. Various research studies on the effect of enzymes and hormones on fat metabolism are listed below.¹

3.1.1-acyl-glycerol-3-phosphate acyltransferase (AGPAT)³⁸

These enzymes catalyse the acylation of lysophosphatidic acid at the sn-2 position to form phosphatidic acid, which is an important intermediate in the biosynthesis of triacylglycerol (TAG) and glycerophospholipids.³⁹ Dephosphorylation of phosphatidic acid results in the formation of sn-1,2-diacylglycerol(DAG), which joins the MAG-acyltransferase(MGAT) pathway for TAG synthesis. The ligands which blocks the AGPAT is an active target for pharmacotherapies. CT32615⁴⁰ & CT32458⁴¹ are synthetic inhibitors of AGPAT.

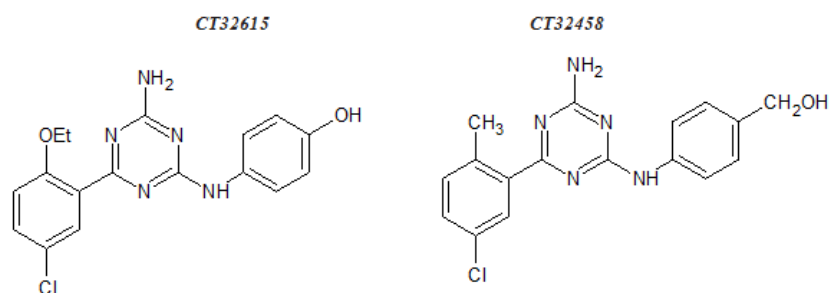


Figure 6
Structures of CT32615⁴⁰ and CT32458⁴¹

3.2. Diacylglycerol acyltransferase1(DGAT1)

Inhibition of triglyceride synthesis represents a potential therapeutic strategy for human obesity. Acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) is one of two DGAT enzymes that catalyze the final reaction in the known pathways of mammalian triglyceride synthesis. DGAT1 catalyzes the linkage of a sn-1,2-diacylglycerol with a fatty acyl CoA to form a triglyceride molecule. In cells, the reaction catalyzed by DGAT1 takes place primarily in the endoplasmic reticulum, thus ligand targeting the blocking of DGAT1 will be beneficial in reduction of obesity.⁴² Studies have been carried out on mice lacking DGAT1, which showed that DGAT1 deficient mice have ~50% less adipose mass and smaller adipocytes than wild type (WT) mice on a chow diet. Triglyceride levels in the adipose tissue and skeletal muscle of WT was decreased by ~30–40%. DGAT1 deficiency

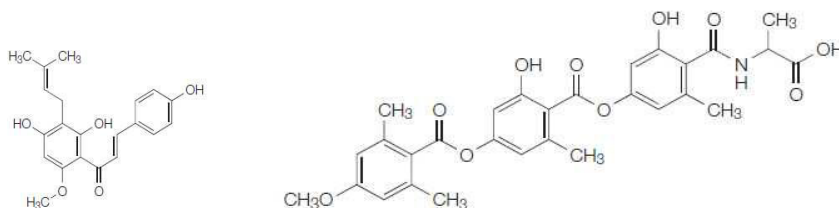
also resulted in altered fatty acid composition of triglycerides in the adipose tissue and skeletal muscle, resulting in a relative decrease in monounsaturated (16:1 and 18:1) fatty acids and a relative increase in saturated (16:0 and 18:0) fatty acids.⁴³

3.2.a. Xanthohumal

Xanthohumal is an inhibitor of DGAT enzyme. It is a natural product obtained from *Humulus lupulus*. It exhibited the biological activity of $IC_{50} = 50 \mu M$. However, the specificity for the xanthohumal was not been confirmed with recombinant DGAT enzymes.⁴⁴

3.2.b. Amidepsine A

Amidepsine A is an inhibitor of DGAT enzyme. Natural product obtained from *Humicola species*, having a biological activity of $IC_{50} = 10 \mu M$, although the specificity for the amidepsine was not been confirmed with recombinant DGAT enzymes.⁴⁴



Xanthohumal⁴⁴

Amidepsine⁴⁴

Figure 7

3.3. Hormone-sensitive lipase (HSL)

HSL is highly expressed in white and brown adipose tissues, where it is believed to

catalyse the release of fatty acids from stored TAGs, thereby providing energy and heat to peripheral tissues.⁴⁵ Transgenic expression of

human HSL in mice leads to an increase in hydrolytic activities against TAG, a reduction in fat mass and a decrease in body weight on calorie restriction.⁴⁶ By contrast, mice that are deficient in HSL manifest adipocyte hypertrophy, reduced fatty-acid release, decreased hepatic TAG storage and resistance to obesity caused by leptin deficiency.^{47,48} The main pathophysiological conditions that are associated with HSL deficiency are male sterility, fasting hyperglycaemia and hyperinsulinaemia.⁴⁹ No small-molecule effort has been reported so far in the development of HSL inhibitors or activators. The human HSL sequence is unrelated to any of the known mammalian lipases, which makes it difficult to predict its drug ability.

3.4. Fatty-acid synthase (FAS)

Mammalian FAS catalyses the *de novo* synthesis of saturated fatty acids, such as myristate, palmitate and stearate, using acetyl- and malonyl - CoA. The enzyme is abundantly expressed in lipogenic tissues, such as liver, adipose and lactating breast. FAS is believed to be important in coordination with CPT and ACC in maintaining energy homeostasis by converting excess food intake into lipids for storage and providing energy by up regulating the rate of β -oxidation. The inhibitor of FAS, the synthetic compound C75, on administration, caused a dose-dependent decrease in food intake in BALB/c mice, and blocked the fasting-induced up regulation of orexigenic neuropeptides and the down regulation of anorexigenic neuropeptides in the hypothalamus.³⁸

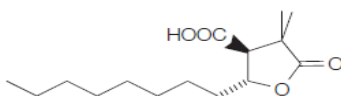


Figure 8
Structure of C75³⁸

The other enzymes which play major role in the fat metabolism are Carnitine palmitoyl transferase (CPT) and Acetyl-CoA carboxylase (ACC). The quizalofop and CP-610431 were the inhibitors of ACC and helps in prevention of obesity.³⁸

3.5. Hormones and Fat metabolism

The hormonal systems that modulate cellular metabolism can be targeted to combat obesity.¹ Both testosterone and growth hormone have been used to treat obesity.⁵⁰⁻⁵³ Growth hormone increases energy expenditure and increases the loss of fat,⁵⁴ whereas testosterone and anabolic steroids in males can lower visceral fat relative to total body fat, suggesting selective effects on different fat deposits.⁵⁰⁻⁵³ Growth hormone also reduces visceral fat more than total fat. Both testosterone and growth hormone have undesirable side effects — testosterone is related to the development of prostatic hypertrophy and prostatic cancer, whereas excess growth hormone has been associated with enhanced risk of cardiovascular diseases.

These side effects made the targets questionable for the development of potential novel drug discovery.

4.0. APPROACH IV- REGULATE FOOD INTAKE PERIPHERALLY

Gastrointestinal peptides are studied as potential regulators of satiety. Cholecystokinin (CCK) was one of the first peptide shown to reduce food intake. Peptide analogues of CCK have been developed, but none has reached the clinical trial, suggesting that they may have undesirable side effects.⁵⁵ Gastrin-releasing peptide, neuromedin B and bombesin, the peptide derived from frog skin, reduces food intake in animals and human beings. If the duration of action of these peptides or an effective analogue could be developed, it would have a potential place in modulating intake at individual meals.⁵⁶ Pancreatic peptides modulate feeding. Enterostatin, the pentapeptide signal portion of pancreatic colipase, selectively reduces fat intake in experimental animals. This peptide increases satiety in humans.¹

4.1. Glucagon-like peptide – 1 (GLP-1)

The glucagon and glucagon-like peptide-1, a derived peptide, reduces food intake in animals and humans.⁵⁷ GLP-1 was originally identified as a gastrointestinal hormone synthesised by L-cells of the intestine as one of product of tissue-specific processing of pre-proglucagon. In the periphery, GLP-1 release is stimulated from the intestine following food intake. It then acts as an incretin, synergising with glucose to stimulate insulin secretion from pancreatic β -cells, inhibits gastric motility, and induce a state of satiety.⁵⁷ Analogues that might influence GLP-1 receptors, GLP-1 release or the duration of action were developed. Few example are exenatide, liraglutide, CJC-1131, ZP10, albugon, BIM51077,⁵⁸ etc.

4.1.a. Exenatide⁵⁹

Exendin-4, originally isolated from the saliva of the Gila monster, has 53% sequence homology with human GLP-1 in its first 30 amino acids. Synthetic exendin-4, referred to as exenatide, is resistant to DPP-4 cleavage. The injectable glucagon-like peptide-1 (GLP-1) receptor agonist exenatide significantly improves glycaemic control, with average reductions in HbA1c of about 1.0%, fasting plasma glucose of about 1.4 mmol per L, and causes a weight loss of approximately 2–3 kg after 30 weeks of treatment. The adverse effects are transient nausea and vomiting.⁵⁹

4.1.b. Liraglutide⁵⁹

Liraglutide is a once-daily human GLP-1 analogue offering 24-h exposure, is administered as an isotonic solution for injection by the subcutaneous route. Liraglutide is both intrinsically (because it may form micellar-like aggregates) and as a consequence of binding to albumin, relatively stable towards DPP-4 degradation. Liraglutide reduces HbA1c by about 1.0–2.0%, weight by 1–3 kg and seems to have fewer gastrointestinal side effects than exenatide.⁵⁹

5.0. APPROACH V - REGULATE FOOD INTAKE CENTRALLY

The centrally acting appetite suppressants are broadly classified into biogenic amines, neuropeptides, melanin-concentrating hormone (MCH), galanin, orexin, corticotropine releasing hormone and leptin.⁶⁰

5.1. Biogenic amines

The biogenic amines include noradrenergic agents, serotonergic agents and histaminergic agents.

5.1.1. Noradrenergic agents⁵⁷

These agents act by increasing catecholamine release from nerve endings terminating in the paraventricular nucleus of the hypothalamus, a brain area central to feeding behaviour. As a consequence of noradrenaline release, activation of postsynaptic α 1- and β 1-adrenoceptors reduces appetite. The noradrenergic agents include phentermine, diethylpropion, mazindol, and phenylpropanolamine.

5.1.1.a. Phentermine

Phentermine, an analogue of amphetamine, but with reduced abuse liability, has been available as monotherapy for obesity since the early 1960s. It is restricted to short-term (maximum 3 months) treatment in conjunction with calorie restriction, one reason being that treatment is limited is due to intolerance to its CNS stimulatory activity.

5.1.1.b. Mazindol

Mazindol is an imidazoline derivative, structurally different from amphetamine. It elicits additional weight loss and improvement in insulin sensitivity in patients who have already lost weight on very low-calorie diets. It was found to be effective in the long-term management of weight loss.

5.1.1.c. Phenylpropanolamine

Phenylpropanolamine is chemically related to ephedrine, like ephedrine it has some thermogenic activity also.

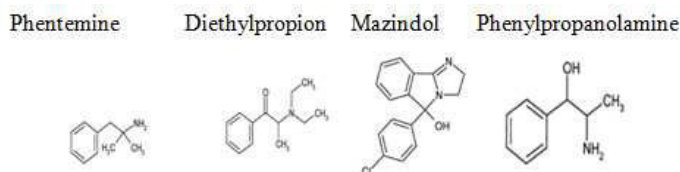


Figure 9
Structures of noradrenergic agents⁵⁷

5.1.2. Serotonergic agents⁵⁷

These agents act by causing release or by inhibiting reuptake of serotonin (5-HT, 5-hydroxytryptamine), and by stimulating hypothalamic 5-HT_{1B/D} and 5-HT_{2C} receptors. Serotonergic agents include fenfluramine, its dextrorotatory stereoisomer dexfenfluramine, fluoxetine and sertraline.

5.1.3. Histaminergic agents⁵⁷

Histamine is involved in the central processes, governing satiety and hunger perception. In common with other neurotransmitters involved in feeding behaviour, histaminergic nerves project axons to the paraventricular nucleus and the ventromedial hypothalamus. Three histamine receptor subtypes (H₁, H₂, and H₃) were originally distinguished by pharmacological means. The H₁ and H₂ receptors are located postsynaptically, and the H₃ receptor is located presynaptically. Feeding behaviour modification is predominantly mediated via H₁ and H₃ histamine receptors. The H₁ receptor agonist 2-(3-trifluoromethylphenyl) histamine, but not the H₂ agonist dimaprit, suppresses feeding behaviour in the rat.

5.2. Neuropeptides¹

Many neuropeptides affect food intake when injected into the hypothalamus, a lateral brain ventricle, or the third ventricle. Some neuropeptides (e.g., NPY) alter both food intake and metabolic rate, and the two effects synergise in their influence on body weight. Neuropeptide Y is among the most potent stimulators of feeding.⁶¹ Synthesis and release of neuropeptide Y is modulated by insulin, leptin and starvation. Antagonists to either the Y-5 or the Y-1 NPY receptor are being explored as potential agents for treatment of obesity. The various small molecule neuropeptide antagonists were reported, few among them are :

5.2.a. J-104870⁶²

J-104870 is the first reported potent, orally bio available, brain penetrant neuropeptide Y Y1 receptor antagonist. The compound has high affinity for cloned rat and human neuropeptide Y Y1 receptors (human Y1 Ki=0.26 nM, rat Y1 Ki=0.51 nM) and no significant affinity for human neuropeptide Y Y2, Y4, and Y5 receptors (Ki>1000 nM).

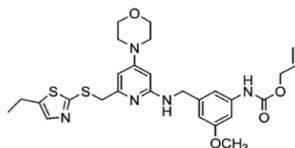
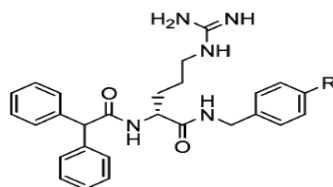


Figure 10
Structure of J-104870⁶²

5.2.b. BIBP3226⁶²

The first potent and selective non-peptidic neuropeptide Y Y1 receptor antagonist, BIBP3226 was designed to mimic the C-terminal region of neuropeptide Y. Since BIBP3226 does not penetrate the blood-brain

barrier, central administration of the compound was carried out, which was reported to block neuropeptide Y-induced food intake. However, it was resulted in CNS toxicity. A structurally related analogue, BIBO3304, is claimed to cause less CNS toxicity than BIBP3226.



BIBP3226 R = -OH
 BIBO3304 R = -CH₂NHCONH₂

Figure 11
Structure of BIBP3226 and BIBO3304⁶²

5.3. Melanin-concentrating hormone (MCH)
 Antagonists to melanin-concentrating hormone (MCH) receptor are another potential approach for drug development. MCH is produced by neurons in the lateral hypothalamus and microinjection of this peptide increases food intake. MCH-knockout mice are lean,⁶³ suggesting that the peptide has a physiological role in the control of food intake and body fat stores. The various small molecule MCHR1

antagonists were reported, few among them are :

5.3.a. T-226296⁶⁴

Compound T-226296, binds with high affinity (IC₅₀ 10 nM) to both human and rat receptors. It is a functional antagonist of MCH in cell-based assays. T-226296 is the first small molecule antagonist, which is orally-active and able to inhibit the effects of MCH on food intake.

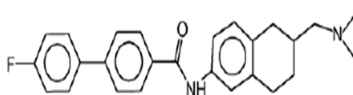


Figure 12
Structure of T-226296⁶⁴

5.3.b. SNAP-7941⁶⁴

SNAP-7941 potently blocks MCH-mediated phosphoinositide accumulation in cells expressing MCHR1 receptors. This compound was also tritiated and then utilized as a radioligand at MCHR1 receptors, binding to MCHR1 receptors with sub-nanomolar affinity. Again, no data was shown, but the compound has N1000× selective for MCHR1 versus other receptors, including other orexigenic receptors (e.g. 5HT_{2c}, NPY and galanin) and MCHR2

receptors. Systemic administration of SNAP-7941 (10 mg/kg ip) was able to effectively inhibit icv MCH-induced food intake. Additionally, SNAP-7941 has shown decreased weight gain in lean growing rats and produced dramatic weight loss in high-fat diet-induced obese male Long-Evans rats. SNAP-7941 has also significantly reduced sweetened milk ingestion, a model of palatable food consumption.

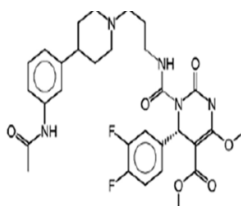


Figure 13
Structure SNAP-7941⁶⁴

5.4. Galanin, orexinA and corticotropin-releasing hormone

Several other peptides that stimulate food intake are of lesser interest to us because they have been associated with other significant biological events. Galanin is an endogenous peptide that will increase food intake when injected into the brain's ventricular system. Mice lacking galanin, however, are unable to maintain lactation, suggesting that modulation of milk-producing hormones may be the primary role for this peptide.⁶⁵ Orexin A was identified originally as a peptide that stimulates food intake⁶⁶, but defects in the orexin peptides and receptors causes narcolepsy in mice and dogs.^{67,68} Thus the orexin peptide, which is abundant in the lateral hypothalamus, serves an arousal function, and its effects on food intake may be secondary. Whether sleepiness is a good alternative to over-eating is debatable. Corticotropin-releasing hormone

(CRH) and the closely related urocortin affect food intake and body weight.⁶⁹ CRH receptors and CRH binding protein have therefore been considered as antiobesity targets. However, intervention with this pathway may have negative consequences on the stress axis and anxiety.⁷⁰

CONCLUSION

The wealth of information about various pathways/approaches to cure and prevent obesity has been discussed along with the current studies on the said approaches. Some of newly developed molecules has undesirable adverse effect on human body and kept the challenge open to scientists. There is a major need for more safe and effective medicinal products to control obesity.

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