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Regulation of Appetite for Treating Obesity: Lessons from the Rimonabant Debacle

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Abstract

Physiology of appetite regulation: Appetite functions to ensure sufficient food intake to provide energy for maintaining physiological and metabolic needs. The appetite, in turn, is regulated by a complex process and an intricate interplay of neural and hormonal mechanisms including several brain areas and their projections, various hormones, and gastrointestinal tract (GIT) and adipose tissue. In the brain, the hypothalamus, brain stem and autonomic nervous system (ANS) contribute to the central regulation of food intake and energy balance. A reservoir of nutrients is maintained in human body for metabolic needs and the accentuated evolutionary need to fill body stores for nutrients leads to weight gain, overweight and obesity.

Reward mechanisms and appetite suppression: The reward mechanisms play an important role in appetite and food intake. The reward pathways mainly relate to the mesolimbic system in the brain and utilize dopamine (DA), opioids, serotonin and noradrenalin neuronal fibres, connecting the midbrain and other brain areas to the hypothalamus. The desynchronization between the reward circuitry and inhibitory controls may be an important factor for genesis and perpetuation of obesity.

Endo cannabinoid signalling system: The ECS includes cannabinoid receptors CB1 and CB2, the ligands-endo-cannabinoids and enzymes for their synthesis and degradation. The CB1 receptors are densely present in hypothalamic areas and brain stem, which are concerned with control of appetite, food intake and feeding behaviour. Apparently, the ECS has a role in controlling appetite, food intake and feeding behaviour, and affects carbohydrate and lipid metabolism, and maintenance of energy balance and body weight. Further, the hypothalamic neurons have connexions with the reward pathways in the mesolimbic system. The CB1 antagonists, thus, inhibit the dopamine-mediated rewarding pathways in the mesolimbic region.

Rimonabant therapy and setback: Rimonabant, a CB1 antagonist, was discovered and developed as an anorectic antiobesity drug and approved in 2006. It was shown to improve various cardio-metabolic risk factors and to promote sustained weight loss. However, in October 2008, the use of rimonabant was suspended because the risks of the drug outweighed its benefits. Certain serious psychiatric symptoms, including suicide ideation were documented. By November 2008, the sale of the drug was suspended worldwide. It was shown that rimonabant inhibited the central processing of rewarding food stimuli which could be related to the increased risk of depressive symptoms.

Conclusion:

The current scenario: The history of anti obesity drugs is littered with approval, pitfalls and withdrawals. Considering the history of inventing an ideal anti-obesity drug promising an adequate weight loss, which is maintained with insignificant adverse effects, may seem as difficult as tracking the Holy Grail. Still, the pharmacological management of obesity shows a promise of new possibilities. The novel research strategies are being explored, the polytherapeutic strategies are being considered, the specific obese subpopulations are being identified to allow for tailor-made and personalised medication, and the potential anti-obesity targets are being investigated. The ongoing research has opened up a promise for new avenues and novel possibilities for identification better treatment modalities for obesity in near future.

Keywords: Regulation of appetite; Obesity; Anti-obesity treatment; Gut and brain axis; Reward circuitry; Feeding behaviours; Endo cannabinoid system; Rimonabant; Ideal anti-obesity drug; Future of obesity drugs

Physiology of Appetite Regulation

Complexity of appetite control

The appetite is desire to eat and exists in all higher life-forms including human beings, and functions to ensure food ingestion to fulfil nutritional and physiological needs. The appetite, in turn, is controlled by a complex mechanism involving brain, gastrointestinal system and body's nutrient stores. It is also influenced by gender and in general, females experience more satisfaction from food intake as compared to males. Further, the appetite declines in advancing years [1]. Glucose and fatty acids are the primary fuels for the cells and tissues, and a reservoir of the nutrients is maintained in human body for metabolic needs. There are two kinds of nutrient stores: glycogen stores

for storing carbohydrates for a short term, and fat stores which are for long-term. A depletion of nutrients in the body's stores leads to hunger, which is a variable for appetite. An accentuated evolutionary need to fill body stores for nutrients leads to weight gain, overweight and obesity [2].

The appetite regulation is an immensely complex process and operates through an interplay of hormonal signals including those from gastrointestinal tract (GIT) and neural mechanisms and involving the central and autonomic nervous systems [3]. The GI hormones act through various pathways to stimulate or suppress appetite [4]. Thus, ghrelin stimulates appetite, leptin leads to feelings of satiety, whereas cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1) decrease the appetite. Ghrelin is secreted by gastric cells and leptin is secreted by adipose tissue [5]. Lowering food intake lowers the leptin levels and vice versa. Also, abnormal alteration in secretion of ghrelin and leptin favors weight gain. With obesity and increase in adipose tissue, more leptin is produced. With the increased levels of leptin causes the hypothalamus becomes resistant to leptin and leads to a perpetual cycle [6].

The CNS appetite regulating circuitry

Centrally, both the hypothalamus and brain stem control the appetite, food ingestion and energy balance. The main hypothalamic nucleus for the regulation of appetite is arcuate nucleus (ARC). The blood-brain barrier around the ARC is partially deficient, allowing it to be able to sense and integrate the peripheral signals related to food intake. It accesses signals from the periphery through two specialized neuronal groups. The orexigenic group expresses agouti-related peptide (AgRP) and neuropeptide Y (NPY), whereas the an or exigenic one, expresses cocaine and amphetamine regulated transcript (CART) and proopiomelanocortin (POMC) (Figure 1). There are neuronal projections from both of the groups to paraventricular nucleus (PVN) and other related nuclei [7]. In addition, several other hypothalamic nuclei apart from the ARC and the brain stem are involved in appetite regulation and energy homeostasis. Further, there are various neuropeptides including melanin concentrating hormone (MCH) and the orexins, which are related to appetite regulation. As to complicate the issue further, the rewarding stimulus related to food also facilitates feeding, despite surplus storage in nutrient reservoirs. The reward signals and circuitry involve interactions between dopaminergic, opioid, endo cannabinoid and serotonin systems [8]. Further, various neurotransmitters stimulate appetite, especially dopamine (DA) through the reward centers of the brain and serotonin through influencing neuropeptide Y(NPY) and agouti-related peptide (AgRP), and proopiomelanocortin (POMC) by inducing satiety. Both the hormones leptin and insulin suppress appetite through AgRP and POMC neurons. The hypothalamo-cortical and hypothalamo-limbic projections influence to the awareness of hunger. In addition, the hypothalamus controls the activity of the parasympathetic nervous system through vagal tone, regulates the metabolic rate through thyroid stimulation, and hypothalamic-pituitary-adrenal axis and other mechanisms. The opioid receptors in nucleus accumbens (NAc) and ventral pallidum influence food palatability. In addition, the NAc also coordinates opioid and endocannabinoid signals to regulate there ward-related feeding behaviour. Further, in NAC, signalling molecules like DA, acetylcholine, opioids and cannabinoids and their receptors influence eating behaviour and modulate affective reactions to food.

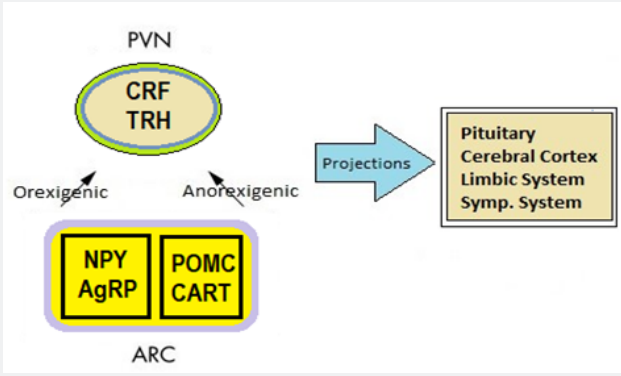

Figure 1: Map of study area West Shoa, Holeta town.

Appetite modulation by hypothalamus and brainstem

The hypothalamus is the 'gate keeper' for appetite signalling [9]. Apart from, the stimuli from higher centres, the hypothalamus is able to sense directly the peripheral inputs influencing appetite like the circulating hormones and other factors due to an incomplete blood-brain barrier. At other brainstem structures such as the area postrema also, the peripheral satiety signals are enabled to act directly due to a deficient blood-brain barrier. Further, there exist an extensive reciprocal neuronal nexus between brainstem and hypothalamic or exigenic and an or exigenic neurons providing the alternative pathway via which the circulating hormones are able to influence hypothalamus. The hypothalamus, is, thus, able to directly sense the factors and nutrients and adjust food ingestion. Also, in ARC the activation of AMPK, leads to increased food ingestion. In addition, by having glucose-sensing neurons, on sensing hypoglycemia, hypothalamus can directly increase hypothalamic NPY and AgRP, reduce POMC expression, and stimulate food intake.

The hypothalamic response is also modified by peripheral stimuli such as ghrelin, leptin, PYY 3-36, orexin and CCK, which are produced by GIT and adipose tissue. The hypothalamic appetite-stimulatory and appetite-inhibitory circuits are influenced by peripheral hormones such as leptin, insulin, ghrelin and peptide YY3-36, which can cross blood-brain barrier. Both, leptin and insulin stimulate appetite-inhibitory pathways through up-regulation of α-MSH and inhibit the appetite-stimulatory neurons by suppressing NPY and AgRP mRNA. Ghrelin, on the other hand, has the opposite effect. Following

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ingestion of food, the intestines release peptide YY3-36, which inhibits the hypothalamic NPY- and AgRP-expressing neurons, influences adjacent proopiomelanocortin-expressing neurons and decreases appetite. There have been demonstrated ghrelin and leptin receptors in brainstem nuclei also.

At the POMC neurons, prohormone convertases PC_1 and PC_2 cleave POMC and form melanocortins. The melanocortins, mainly α-melanocyte-stimulating hormone (MSH), thus produced, inhibit food intake by binding to G-protein-coupled melanocortin receptors (MC-Rs). The CART peptide also has anorectic effects. The majority of NPY expressing neurons are the ARC, and co-express AgRP. Because of its effects on food ingestion and calorie expenditure, NPY is considered a physiological regulator of bodyweight. The NPY pathways are also related to nor adrenergic and serotonergic regulation of appetite.

The PVN also influence the control of appetite and energy homeostasis. The NPY/AgRP and POMC neurons have connexions with PVN neurons, and through corticotrophin-releasing hormone (CRH) and thyrotrophin-releasing hormone (TRH), the PVN influences food intake, energy expenditure and energy balance. The projections from the limbic system and cerebral cortex on the hypothalamus also modify appetite through projections on hypothalamus. In addition, the biological clock controlled and tuned by hypothalamus, also modulates appetite and hunger [10].

Regulation of Appetite and Satiety

The gut and brain axis

The energy homeostasis need brain to sense about the nutrient reservoirs and adapt accordingly the nutritional uptake and calorie expenditure [11]. There are two main hypothesesput-forthabout the nutrient reservoirs and signals conveying the metabolic information to brain. As per the Mayer's glucostatic hypothesis, the decrease in blood glucose in the fasting state increases appetite, triggers hunger and feeding while an increase in blood glucose inhibits them [12]. Here, the glucose is acting as primary metabolic factor, which is inconsistent with the tight levels of blood glucose control, coupled with limited stores of glycogen in the liver and muscle. But, this hypothesis has gained favour in recent years as a low glycemic state has-been associated with prospective weight gain, also such state is the predictor of sum of weight regained following efforts at weight loss. Further, the state of relative hypoglycaemia leads to increased depressive symptoms following weight loss and a higher incidence of developing glucose intolerance and maturity onset diabetes. Furthermore, the glucostatic theory indicates that the glucose instability and recurrent hypoglycemia may lead to excess food ingestion, and the resultant weight gain may be favourable against relative hypoglycemia by compensating to blood sugar patterns brought about by the modern day dietary styles and fast food consumption [13].

The adipose tissue provides the major storage of energy. Kennedy [14] proposed the adipostatic hypothesis based on a simple fact that the body fat and weight are held a nearly constant level despite of day to day variation in type of food and nutrition. As per the 'adipostatic model', the factors secreted by adipose tissue influence brain to adapt feeding behaviour and homeostasis to avoid variation in body weight. The adipostatic theory is reinforced by findings in animal studies which document that depletion of energy stores by food deprivation resulted hyperphagia and vice versa until the energy stores and body weight were restored. The theory is further endorsed by parabiosis mouse experiments and 'centre model' which states that the satiety centre located in the ventromedial hypothalamus controls food intake and maintains weight [15].

The metabolic hormones including leptin and insulin help to regulate body weight through their long-term effects on feeding behaviour and homeostasis. The gut–brain axis is thought to control both appetite and satiety through hormonal and neural signals. With food intake, nutrients enter stomach and intestine, and lead to secretion of peptides which have negative feedback signals on hypothalamic and brainstem neurons related to regulation of feeding and homeostasis. Thus, the neuronal and hormonal signals from the GIT influence appetite, food intake and satiety. Apart from this, the reward and motivational aspects of food ingestion is dealt by neuronal circuits in the limbic system.

The meal size and termination is largely determined by satiety. It also responds to signals from mechano- and chemo receptors from the GIT. Also, gut peptides are released in response to a meal. The main GI hormones related to appetite regulation are CCK, peptide YY (PYY), glucagon-like peptide 1 (GLP1), glucagon-like peptide 2 (GLP2), oxyntomodulin (Oxm), pancreatic polypeptide (PP), adiponectin and resist in apart from ghrelin [16]. Ghrelin, synthesized and secreted by gastric cells. The human studies end or set the role of ghrelin in feeding behaviour.

Reward Mechanisms and Appetite Suppression

Reward mechanisms and appetite regulation

The reward mechanisms involve the mesolimbic system. The orbit frontal cortex, amygdala, olfactory cortex and cingulate gyrus are involved in experiencing the food and food odours. These areas have projections to the hypothalamus. The CB_1 receptors are expressed in NAc, hippocampus and medial forebrain bundle. They are also densely expressed in hypothalamic areas including PVN, which regulate appetite. In the CNS, endocannabinoids act as orexigenic signals via cannabinoid CB_1 receptors and inhibit excitatory inputs to neurons in NAc. In animal experiments, blocking CB_1 receptors inhibits food intake, leading to weight loss. Further, the endocannabinoid levels in hypothalamus increase during fasting and decrease subsequently on feeding. The endocannabinoids increase appetite via CB_1

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receptors by altering secretion of anorexigenic and orexigenic neuropeptides. The animal experiments, especially in obese animals, have documented an accentuated weight-reducing effect of CB_1 antagonists (e.g., rimonabant). Further, there has been documented a close interaction between endocannabinoids and opioids. Furthermore, naloxone, an opioid antagonist, attenuates the orexigenic effects of an endocannabinoid. The reward pathways appear to utilize DA, opioids, serotonin and nor adrenaline fibres, connecting midbrain and hindbrain to hypothalamus. In addition, orexigenic NPY and anorexigenic POMC neurons in ARC, have projections to various the brain areas, including serotonergic system in raphe nuclei and areas such as amygdala involved in reward circuitry. The sight of food, thus, activates reward circuitry and simultaneously the frontal cortical control circuit also becomes activate for appetite inhibition, but it is often difficult to inhibit the urge following visual food signals. Whereas, inhibition following the imaginary food intake activates precunei, anterior cingulate, parietal and frontal areas. As compared to a normal person, an obese person during inhibitory appetite control shows less response in medial frontal, middle cingulate and dorsal caudate nuclei. Thus, functional control circuitry is abnormal during appetite control, in those obese, reflecting an impaired integrative and executive function in obesity [17]. This altered balance between reward and inhibitory circuits may be the underlying cause of weight gain and obesity.

Further, to control an urge to eat is required a balanced functioning of neural pathways responsible controlling opposing two stimuli, on one hand, the conditioned response from the reward circuitry potentiating desire to eat and eating the food, and on the other hand, inhibitory control through the higher centres. The studies have shown that obese persons have impaired dopaminergic circuitry that regulates reward mechanisms [18]. There is an intricate and multichannel nexus between reward circuitry and neuronal circuits for regulating food intake. Based on various imaging studies, in aproposed model of obesity, the overeating reflects an asynchrony between circuits that motivate feeding, and streamline reward conditioning. This model assumes three reward related pathways: reward-saliency, motivation–drive and learning-conditioning; and an inhibitory pathway: eating regulation-executive function. Various neurotransmitters like DA and serotonin, cannabinoids and opioids; and hormones and neuropetides like leptin, ghrelin and orexin are involved in energy homeostasis and food intake, and influence and alter reward mechanisms [19]. From the evolutionary angle, the palatability of food guaranteed that available food was eaten, enabling nutrients energy to be stored as fatreservoir for future use in an ecosystem having food supply scanty and irregular. In present times, when food is readily available, this evolutionary adaptation is a homeostatic liability leading to weight gain and obesity.

Motivational and hedonic feeding behaviours

The hippocampus is associated with appetite and regulation of food intake, apart from several other functions including memory. The reward systems related to food ingestion identifies separately the motivation to desire for food, termed as 'wanting', from another associated with hedonic character of food, termed as 'liking'. The dopamine striatal system is related to 'wanting', where as the opioid and cannabinoid systems are mainly associated with food 'liking' stimuli [20]. It has been documented that obese compared to lean persons, experience greater activation of reward pathways when they anticipate, rather than from the actual food ingestion. The imaging studies verify the increase dreward sensitivity to conditioned stimuli in obese persons vis-a-vis a decreased sensitivity to the actual food ingestion in dopaminergic pathways. Here, the imaging studies highlight a consistent decrease in the hypothalamic reactivity to satiety signals. Further, the ability to control urge for desirable food is a physiological variation among individuals, and one of the factors that may contribute to atendency for overeating. It may be inferred that a large proportion of obese persons have a significant imbalance between an increased sensitivity to the reward pathways to conditioned stimuli related to palatable and high-calorie food and impaired executive control on feeding behaviour.

Appetite suppressants

The appetite controlling mechanisms appear to be the effective and likely objective for weight loss drug therapy. Thus, fenfluramine and phentermine were the earlier anorectics to be used therapeutically. A more recent one was sibutramine, which is a serotonin and nor adrenaline reuptake inhibitor and increases serotonin and nor adrenaline concentration in the CNS. Sibutramine was withdrawn from clinical use when the post-marketing studies repeatedly endorsed its adverse and potentially serious cardiovascular risk profile. The same fate led to discontinuance of another appetite suppressant, rimonabant, a CB_1 receptor antagonist, which that acted on several central pathways to reduce appetite and weight. Rimonabant was withdrawn when it was documented to lead to a morbid depression and a significantly higher risk of suicide in the patient on rimonabant therapy. Both these drugs, sibutramine and rimonabant were found to be capable for a moderate weight loss in clinical practice amounting from 4% to 8% of the body weight.

Endocannabinoid signalling system and cannabinoid receptor antagonists

The endogenous cannabinoid system or endocannabinoid signalling system (ECS) has cannabinoid receptors, the ligands-endo-cannabinoids and the enzymes for their synthesis and degradation. The receptors associated with the ECS are

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cannabinoid receptor 1 (CB_1) and 2 (CB_2). The CB_1 receptors are present in a high concentration in the CNS and in a low concentration in the adipose tissue, liver, GIT and muscles; whereas CB_2 receptors are mostly located in the immune and haematopoietic systems.

Having derived their name from their affinity to the major ingredient of Cannabis sativa, Δ9-tetrahydrocannabinol (THC), the CB_1 and CB_2 receptors are responsible for the effects of THC [21]. In its various preparations, the cannabinoid agonist, THC, through its effect on CB_1 receptors enhances appetite. Therefore, as was rationally concluded, blocking of the CB_1 receptors proved effective in decreasing appetite and food intake. The circumstantial evidence and animal studies verified it. The CB_1 receptor blockade, thus, presented itself as a new therapeutic option available for the weight loss therapy, and led to the development of rimonabant, the first specific CB_1 receptor antagonist or inverse agonist rimonabant, in the year 1994.

The endocannabinoids are basically eicosanoids, which act as agonists for ECS and are present in the CNS as well as certain peripheral tissues. The ECS and related mechanisms and pathways are associated with memory, cognition and anxiety; appetite regulation, feeding behaviour and emesis; motor, sensory, autonomic and neuroendocrine responses; and immune system and inflammatory response. Some of the naturally occurring endocannabinoids are anandamide (arachidonoyl ethanolamide), 2-AG (2-arachidonoyl glycerol), virodhamine (O-arachidonoyl ethanolamine), noladin ether (2-arachidonoyl glyceryl ether) and NADA (N-arachidonoyl dopamine).

The ECS is associated with appetite control and feeding behaviour (Figure 2). The CB_1 receptors are densely present in hypothalamic regions linked to central regulation of appetite and food intake, and feeding behaviour. Further, these hypothalamic are as have connexions with the mesolimbic dopamine pathway, which form the 'reward system'. The CB_1 antagonists, thus, inhibit the dopamine-mediated rewarding pathways related to food in CNS. The peripheral CB_1receptors are found in adipose tissue, GIT, liver and muscles. In the GIT, CB_1 receptors are present on the nerve terminals in intestines. The endocannabinoids act on the CB_1 receptors to increase hunger and promote food intake, at the same time retard intestinal peristalsis and gastric emptying. A CB_1 receptor antagonist or inverse agonist inverses these effects. In addition, at the peripheral level increases insulin sensitivity and oxidises fatty acids in liver and muscles [22]. In general, the ECS works to regulate glucose and lipid metabolism through modifying appetite, energy balance and body weight.

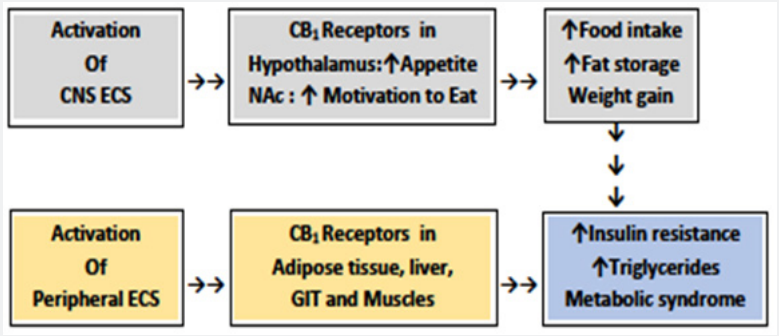

Figure 2: The metabolic effects of CB_1 receptor activation.

Rimonabant Therapy and Setback

Enter & exit rimonabant the selective CB_1 antagonist

The selective CB_1 receptor blocker, rimonabant is a 1,5-diarylpyrazole, having chemical name N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide-hcl. Pharmacologically, a selective CB_1 receptor antagonist, rimonabant is a potent ligand of the CB_1 receptor, can be given orally and antagonizes effects of the typical cannabinoid agonist, THC. Further, Rimonabantis an inverse agonist rather than a simple antagonist, acts by selectively blocking CB_1 receptors in the CNS and in peripheral tissues where it binds preferentially to the inactive state of the CB_1 to decreases activation of signalling pathways [23]. The CB_1 receptor blockade by rimonabant decreases the over-activity of the ECS [24]. It also influences the leptin-regulated endocannabinoids, associated with food intake and satiety [25]. Rimonabant (Acomplia) was developed by Sanofi-Aventisand was the first drug approved in the class for clinical use in Europe in June 2006, when the European Medicines Agency approved its sale as a prescription drug for use in conjunction with diet and exercise for patients with a body mass index (BMI) greater than 30kg/m^2, or patients with a BMI greater than 27kg/m^2 with associated risk factors, such as type 2 diabetes or dyslipidaemia [26]. In clinical studies, rimonabant was shown to improve various cardio-metabolic risk factors and promoted sustained weight loss [27]. There was also an improvement in HDL-cholesterol, triglycerides and HbA_1C. Soon after, the use of CB_1 receptor antagonist rimonabant for endocannabinoid antagonism as an appetite suppressant treatment for obesity

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and metabolic syndrome became a widely endorsed area of pharmaco therapeutics, with several trials showing weight loss benefits and improvements in other elements of the metabolic syndrome.

But, in a span of about two years during October 2008, the European Medicines Agency actively suspended the clinical use of rimonabant after the Committee for Medicinal Products for Human Use (CHMP) ruled that risks of the drug exceeded its advantages due to documented risk of serious psychiatric adverse effects, including suicide [28]. By November 2008, Sanofi-Aventis had suspended the sale of rimonabant in all countries. The EMA approval was soon withdrawn later in January 2009. In India the drug was banned in 2009 [29]. Rimonabant was never got approved by FDA in the United States of America.

Lessons from rimonabant failure

The basis of adverse effects: The clinical trials documented that rimonabant was associated with nausea and upper respiratory tract infections in about 10% of patients. Other frequent side effects (from 1% to 10% patients) were diarrhoea, vomiting, anxiety, irritability, increased risk of fall and sleep disorders including insomnia. There were reported hot flushes, dry or itchy skin, tendonitis, muscular pains, cramps and spasms, fatigue and flu-like symptoms. On the serious side, depressive disorders or mood alterations, leading to withdrawal of the drug, were documented in about 10% and suicidal ideation was documented in around 1% subjects. It was shown that rimonabant inhibited the central processing of rewarding food stimuli which apparently was responsible for the increased risk of depressive symptoms [30]. A declined experience of reward, perhaps precipitated symptoms of morbid depression. Rimonabant was withdrawn, in a short span, following the reports of significant adverse effects, notably severe depression and mood disorders [31].

Conclusion- The Current Scenario of Pharmacological Anti-obesity Treatment

Obesity is already a huge health disorder in both the economically advanced and challenged countries due to high consumption of calorie-rich food and sedentary lifestyle. The overweight and obesity incapacitate the quality of life and alter the course of various chronic diseases, and on their own are risk factors for diabetes, hypertension, cardiovascular disease and stroke, neurological degenerative diseases and cancers. The today's health scenario can be summed up as 'The Obese-obese World' [32]. It has been proved time and again that diet control and an exercise plan are often not successful in controlling obesity. The bariatric surgical procedure may help in those morbidly obese. For others and those who do not prefer a surgical option, there is a need for a successful and satisfactory pharmacological therapy. But, the history of antiobesity drugs is littered with approval, pitfalls and withdrawals. Many anti-obesity drugs had to be withdrawn because of undesirable effects and serious concerns. Among recently withdrawn drugs, Ephedra was withdrawn over concerns that it raised blood pressure in 2004 [33].

The promising anti-obesity drug of the first decade of twenty-first century, rimonabant was withdrawn catastrophically in 2008. Due to serious psychiatric AEs. The drug was highly effective but the treatment was documented to have an increased risk of anxiety symptoms and depression, and major psychiatric disorders and suicidal behaviour [34]. Apart from being an effective anorexic anti-obesity drug, rimonabant showed therapeutic potential for disorders like metabolic syndrome as well as some psychiatric illnesses in which the ECS is involved. After various clinical adverse reports, rimonabant, was withdrawn from therapeutic use in October 2008 by the European Medicines Agency. Shortly thereafter, several pharmaceutical giants including Sanofi-Aventis, Merck, Pfizer and Solvay, declared to stop further development and clinical research on the CB_1 receptor antagonist drugs [35]. Another drug, sibutramine (Meridia in the USA, Reductil in Europe and other countries), pharmaceutically sibutramide hydrochloride monohydrate, a centrally acting appetite suppressant and chemically related to amphetamines, was withdrawn in 2010 due to cardiovascular concerns [36]. Both the drugs, rimonabant and sibutramine, mainly affected the central pathways, and were barred from therapeutic use and their sales banned due to serious adverse effects.

An ideal anti-obesity drug should cause a sustained weight loss without significant adverse effects. It is noteworthy that the mechanisms that influence and regulate energy homeo stasis carry a considerable built-in redundancy. Also, they overlap extensively with other physiological mechanisms and pathways, and are affected by several psychological, personal and social variants that may curtail the efficacy of a therapeutic intervention. It is, thus, not surprising to find the anti-obesity drug development research and programs plagued with aborted starts, uncompleted research, fiascos in clinical development, and therapeutic bans due to unwanted and serious side effects. Considering the history, inventing an ideal anti-obesity drug promising a significant and continued weight loss with nominal side effects may seem as difficult as tracking the Holy Grail [37]. Still, the drug treatment of obesity and weight management presents hopeful promises. The novel research strategies are being explored and new treatment modalities seem to be available in near future.

For one, it is being realized that the successful development of effective and safe anti-obesity regimens might require polypharmacy approach. Secondly, the specific obese subpopulations have to be identified so that tailor-made and personalised therapeutic interventions can be planned [38]. Further, the diversified and potential anti-obesity treatment targets need to be identified and categorised into certain broad categories. Thus, controlling appetite through central pathways,

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increasing somatic metabolic rate or influencing energy expenditure through peripheral mechanisms, modulating gastro-intestinal receptors, moderating targets to affect cardio-metabolic factors, and planning a set of combination therapies focussed against multiple targets might be envisioned as multi-pronged approaches [39]. Furthermore, knowledge gained from the recent research related to the peptidergic signalling of appetite and satiety mediated by hormones from gut and adipose tissue, ghrelin, CCK, P-YY, GLP-1 and leptin, the homeostatic mechanisms and central pathways and projections in hypothalamus, brainstem and higher centres show a promise for novel prospects leading to identification of successful treatment modalities for obesity in near future [40].

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