CHAPTER 1

1. Introduction

Metabolic syndrome involves obesity, blood pressure elevation, increased triglyceride (TG), cholesterol, and blood glucose levels along with low HDL levels [1]. The terms "overweight" and "obesity" refer to bodyweight that is greater than normal or healthy weight considered for a certain height. Overweight is generally due to the deposition of extra body fat or due to extra muscle, bone density, or water content. Overweight people are considered obese when excessive accumulation of body fat takes place. Obesity has been established as a chronic ailment associated with social and psychological disorders as well as an increased rate of mortality [2].Obesity is indicated by a measure called body mass index (BMI) which is a calculation based on the ratio of one's height and weight. BMI provides a good correlation between "fatness" and health outcomes such as heart disease, diabetes, hypertension, coronary heart disease, hyperlipidemia, fatty liver, arteriosclerosis, tumor, cancer and overall mortality [3,4]. If BMI is greater than 25, the individual is considered overweight whereas if it is greater than or equal to 30 is considered as an obese individual. However, BMI does not capture "abdominal obesity". Abdominal obesity can be represented in terms of WHR (waist-hip ratio) or waist circumference. The WHO states that abdominal obesity is defined as a WHR above 0.90 for males and above 0.85 for females [5].

In the past 20 years, obesity has significantly increased among the adult population. Previously, obesity was just a problem of wealthy nations, but now its impact is widespread over the countries of all economic levels bringing with it a wave of ill-health and loss of productivity. According to the WHO, in 2014 there was a worldwide increase in proportion of overweight and obesity in children and adults leading to an increased prevalence of the disease in both developed and developing countries. According to the National Center for Health Statistics, United States, it was observed that about 39.8% of adults (aged above 20 years) are obese. Among the children and the teenage group (aged 2-19 years), 18.5 %, were found to be overweight in 2015[6]. In India, the increasing prevalence of overweight and obesity has coincided with the demographic and epidemiological transitions, in which declination of mortality and fertility was observed with an increase in lifestyle-related diseases. For instance, the prevalence of overweight and obesity amongst women has increased from 8.4% to 15.5% and 2.2% to 5.1% between 1998 and 2015, respectively. According to the ICMR-INDIAB study in 2015, the prevalence rate of obesity in India varied from 11.8 - 31.3% [7].

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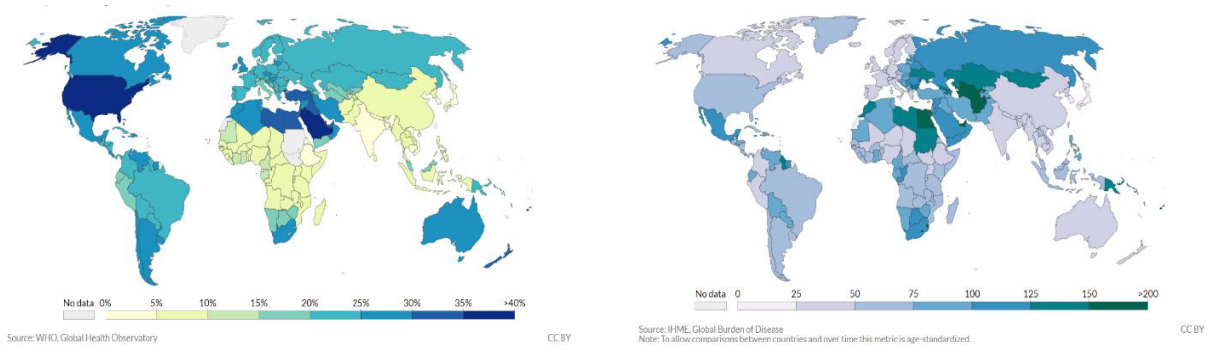
As per WHO's recent report (2016), around 1.9 billion people were overweight across the world. Of these, around 650 million people were obese (**Figure 1A**). In 2020, 39 million children (under 5 years of age) were found overweight or obese. Globally, 8% of deaths in 2017 were the result of obesity. Death rates tend to be higher in those countries where more people are obese (**Figure 1B**). It was also noticed that for a given prevalence of obesity, death rates can vary by various risk factors such as alcohol, drugs, smoking, and other lifestyle factors [8].



(A) **(B)**

Figure 1: Global prevalence of obesity worldwide; (A) Occurrence of obesity in 2016; (B) Global death rate in 2017

Obesity involves genetic factors, prenatal and early life influences, fatty diet, lack of physical activity, and sleep that causes impaired homeostasis. In modern days, obesity has greatly increased due to dietary problems and lack of physical activity in the urban lifestyle. Obesity not only deteriorates the quality of life of an individual but also threatens the health system that is already burdened with issues such as malnutrition, starvation, and many other infectious diseases. Obesity severely affects the economy of a nation. Thus, there is a lot of diversified research emerging in this domain to curb the epidemic before it reaches catastrophic proportions.

Present therapy includes a change in lifestyle with a proper balanced-diet and an increase in physical activity to reduce significant body weight. Secondary treatments are considered as add on treatment when BMI is more than 27 for any individual. Drug therapies are given to such individuals who are unable to follow strict diet and regular physical activities. Currently marketed drugs (1-11) in the obesity domain mostly include metabolic enzyme inhibitors (orlistat), appetite suppressors (sibutramine and fenfluramine formulations) and lipogenesis inhibitors (ephedrine). However, these drugs have major side effects and addiction problems that call for the discovery of novel anti-obesity drugs (**Table 1**) [9].

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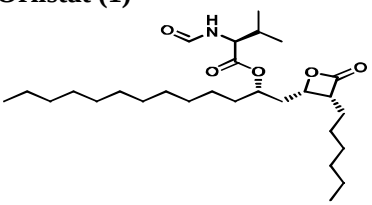
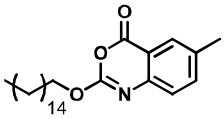
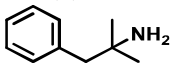
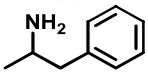
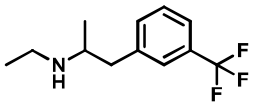
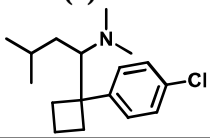
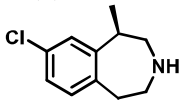
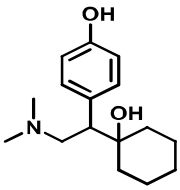
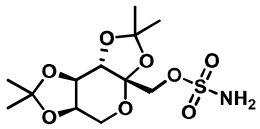
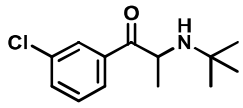
Table 1: Mechanism of action of the marketed anti-obesity drugs and their adverse effects

Name of the drug	Mechanism of Action	Adverse effects
Orlistat (1) 	Suppresses the lipase secreted from the pancreas and the digestive system	When administered for a year gives rise to side-effects such as diarrhea, fatty stool, vomiting, depression, leg pain, swollen feet, fecal incontinence, etc.
Cetilistat (2) 	A novel, orally active PL inhibitor	Mild to moderate adverse events, predominantly of gastrointestinal nature (steatorrhea)
Phentermine (3) 	Changes the serotonin levels in the brain to suppress appetite	Increases the blood pressure, heart rate and stimulates CNS
Amphetamine (4) 	Appetite-suppressant Stimulates anorexic signaling in the hypothalamus or dopamine receptor in the hippocampus	Nervousness, restlessness, excitability, dizziness, headache, fear, anxiety, and tremor. Increases blood pressure and heart rate. Chronic use may lead to dependence.
Fenfluramine (5) 	Increases serotonin levels in the brain synapses and inhibits serotonin reuptake, thus, decreasing the in take of calories	Causes heart valve disease, pulmonary hypertension and cardiac fibrosis
Sibutramine (6) 	Suppresses the reabsorption of norepinephrine and serotonin	Causes an increase in blood pressure, vertigo, anxiety, depression, stomach ache, insomnia, etc.
Lorcaserin (7) 	Selective 5-HT_{2C} receptor agonist	Cause cognitive impairment, psychiatric disorders, priapism, bradycardia, hematological changes, prolactin elevation, pulmonary hypertension and increase risk of breast cancer
Desvenlafaxine (8) 	Serotonin, dopamine, and norepinephrine reuptake inhibitor (SNRI) and potentiates neurotransmitters in CNS	Vision problem, headache, low libido, dry mouth, dizziness, insomnia, taste problems, vomiting, anxiety, sexual dysfunction, depression, high blood pressure, stomachache, numbness and tingling, fatigue, and involuntary quivering

Name of the drug	Mechanism of Action	Adverse effects
Topiramate (9) 	Enhances GABA signaling to promote anorexigenic signaling. Inhibiting voltage-gated channels and AMPA receptor in the orexigenic neurons	Tiredness, drowsiness, loss of coordination, tingling of the hands/feet, bad taste in the mouth, diarrhea, confusion, trouble concentrating or paying attention, memory problems may also occur. Rare side effects include kidney stones, depression, suicidal thoughts/attempts, and vision loss
Bupropione (10) 	Inhibits the neuronal uptake of dopamine, norepinephrine, serotonin	Nausea, vomiting, dry mouth, headache, constipation, increased sweating, joint aches, sore throat, blurred vision, strange taste in the mouth etc may occur. Rare side effects include cardiovascular effects, hearing problems, severe headache etc
Liraglutide (11) H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys(g-Glu-palmitoyl)-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly-OH	GLP-1 agonist that increases insulin release from the pancreas and decreases excessive glucagon release	Adverse effect includes thyroid cancer and pancreatitis

1.1 Pathogenesis and pathophysiology of obesity

There are various factors involving pathogenesis and pathophysiology of obesity. Polymorphism in genes, hormonal disbalance and change in environmental conditions are the key factors involved in obesity. Adipose tissue, the main energy storage site, is receptive to both central and peripheral metabolic signals for regulating lipid storage and mobilization. Dietary fat is absorbed in the gastrointestinal tract by the formation of circulating chylomicrons and very low-density lipoproteins (VLDL). One part of this is metabolized to provide energy and the rest of the part enters the liver and adipose tissues for short- and long-term storage. This process results in the secretion of several adipokines by adipose tissue **(Figure 2)**.

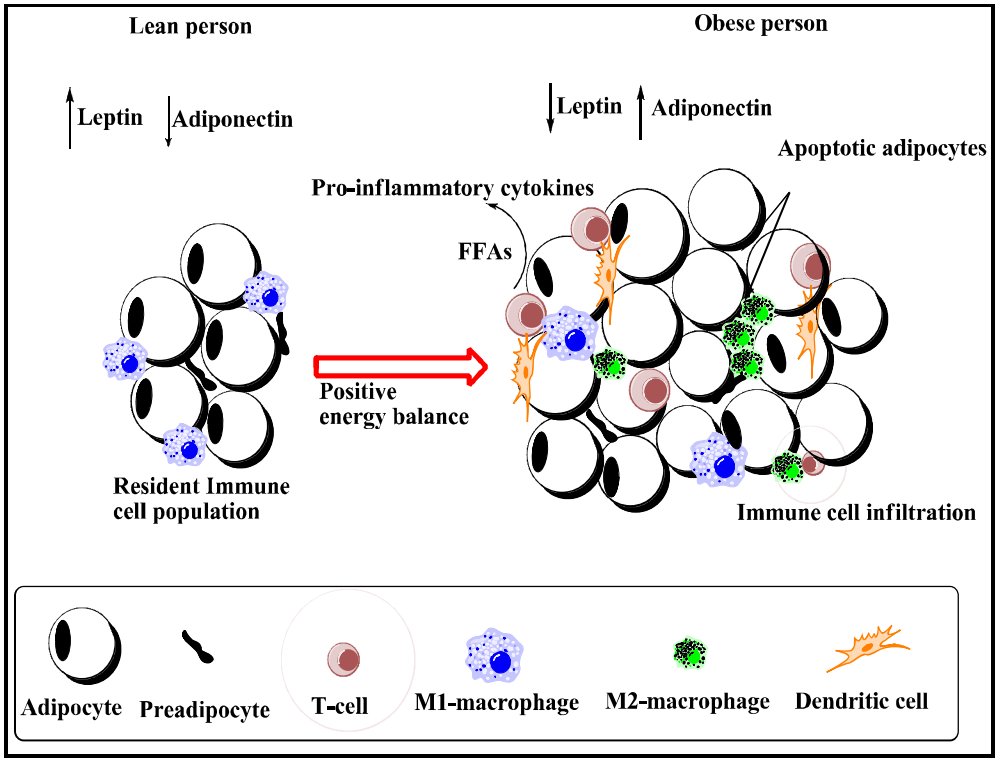


Figure 2: Changes in adipose tissues in an obese individual

Liver plays an important role as a homeostasis for transient energy fluctuation. It protects other tissues from postprandial triglyceridaemia by temporarily storing fatty acids (FAs) from the circulation as a benign derivative, triacylglycerol (TAG), and secreting them as VLDL when the period of maximum lipid load has passed. The liver is also an important site for energy conversion, exchanging energy sources from one form to another, such as glycogen to glucose, FA to TAG, and saturated FA to unsaturated FA **(Figure 3)**[10].

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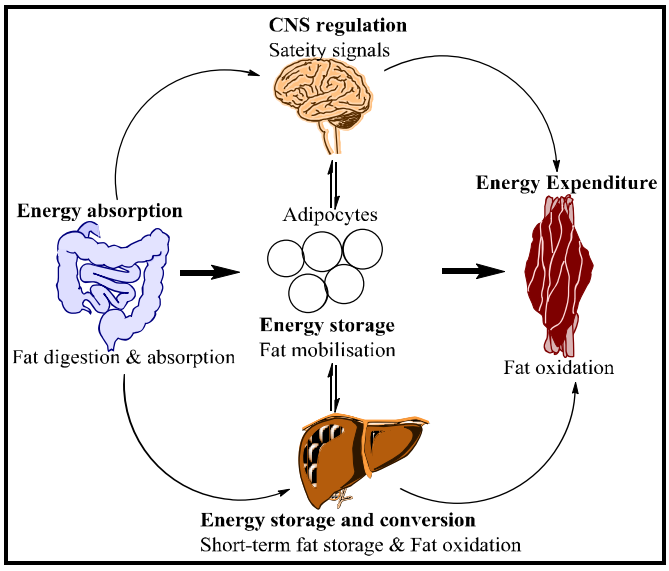


Figure 3: Maintenance of homeostasis by adipocytes

Leptin is the major adipokines that regulates energy homeostasis by signaling to the brain and other peripheral tissues. Adipose tissues, through the lipolysis and re-esterification process, are also the main sites for FA cycling, thereby securing the energy supply to oxidative tissues, such as skeletal muscle and the heart. Adipose tissue not only stores fat but is also capable of expanding to accommodate increased lipids through hypertrophy of existing adipocytes. It also capable of initiating the differentiation of pre-adipocytes [11]**.** Two types of adipose tissue that essentially have antagonistic functions can be distinguished as white adipose tissue (WAT) that stores excess energy as triglycerides (TG), and brown adipose tissue (BAT), that is specialized in the dissipation of energy through the production of heat (**Table 2**). There are numerous receptors expressed on the adipose tissues such as β_3 adrenergic receptor (β_3 AR), Peroxisome- proliferator-activated receptor-γ2 (PPAR-γ2), and interleukin 6 (IL-6). Polymorphism in these receptor genes can lead to obesity. The adrenergic system plays a key role in the regulation of energy balance by stimulation of both thermogenesis and lipid mobilization in adipose tissue. Polymorphisms in the ARs have been extensively studied since 1995 for association with obesity-related phenotypes [12]. The β_3 AR Trp64Arg polymorphism, a missense mutation in the first transmembrane domain of the β_3-AR, has drawn considerable attention from many researchers [13]. This mutation results in stimulation of lipolysis of WAT and thermogenesis of BAT [14].

Table 2: Characteristics of different adipose tissues

	White fat	Brown fat
Function	Energy storage	Heat production
Morphology	Single lipid droplet	Multiple small vacuoles & Abundant mitochondria
Characteristic proteins	Leptin	UCP1
Development	From Myf5-negative progenitor cells	From Myf5-positive progenitor cells (but there are also Myf5-negative brown fat cells which are derived from other lineages)

PPARs are members of the nuclear hormone receptor subfamily of ligand-dependent transcription factors. The isoform of PPAR-γ2 genes are expressed on adipose tissue and are involved in adipose differentiation, conversion of WAT to BAT, insulin sensitivity and inflammatory processes [15]. In some studies, a role for the common *Pro12Ala* polymorphism occurring in the PPARγ2 exon B has been indicated in the pathogenesis of obesity and obesity-associated insulin resistance (IR) [16,17]. It has also been further found that circulating levels of the IL-6 play a determinant role in the development of obesity and obesity-related complications such as IR and type 2 diabetes mellitus (T2DM). A role of genetic variants of the IL-6 gene, *C-174G* polymorphism, within the IL-6 promoter region determines the susceptibility to obesity and altered levels of insulin sensitivity [18,19], that also influences the transcription rate of IL-6. The interaction between the two variants of IL-6 and PPAR-γ genes have been evaluated to determine whether subjects carrying variants in both are at different risk for obesity based on the additive effects associated with each individual variant. It has been concluded that polymorphism of gene expression of the above receptors associated with adipose tissue can lead to develop obesity and other obesity related factors.

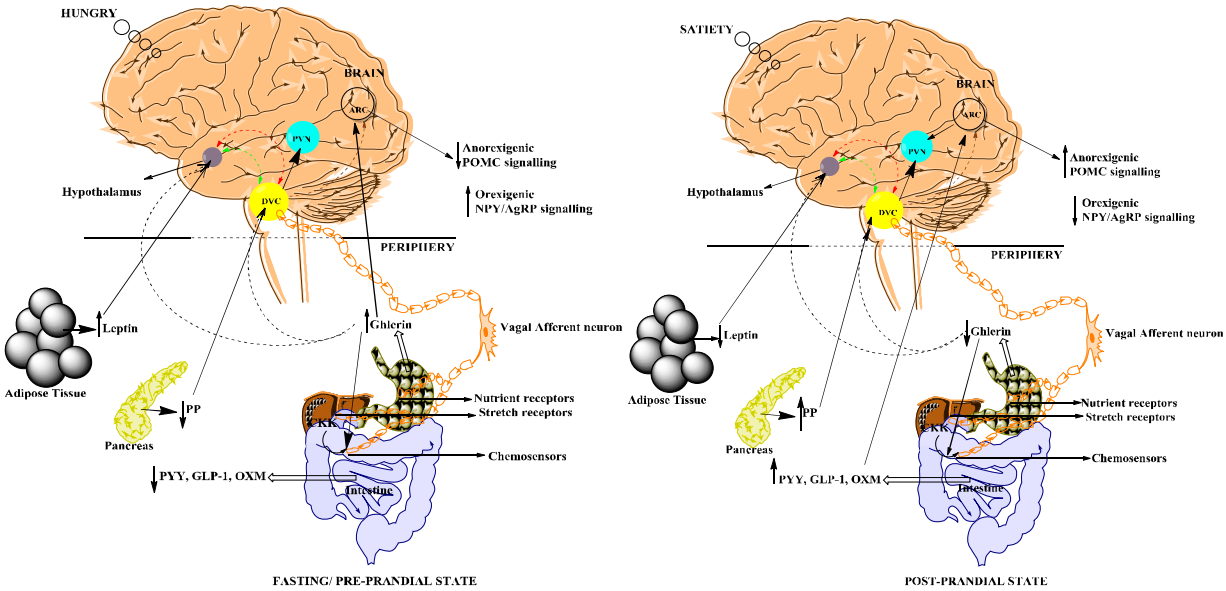
The hypothalamus and the dorsal vagal complex in CNS are important regions that are directly concerned with appetite regulation [20]. Recently, some of the main neural circuits involved in the obesity pathway have been identified. The nucleus of the hypothalamus plays an integrative role in

appetite regulation; for example, by receiving signals from the periphery *via* the brainstem (**Table 3**)[21].

Table 3: Role of gut-hormones in control of appetite

Sl no	Gut hormones	Site of synthesis	Food intake-regulating receptor	Peripheral effect on food intake
1	CCK	Intestinal L-cells	CCK_A	Decrease
2	Ghrelin	Stomach	GHS	Increase
3	PP	Pancreas/ colon	Y4R	Decrease
4	PYY	Intestinal L-cells	Y2R	Decrease
5	GLP-1	Intestinal L-cells	GLP1R	Decrease
6	OXM	Intestinal L-cells	GLP1R	Decrease

Receptors for the gut hormones are found on these neuronal populations within the nucleus. Leptin and insulin are involved in the long-term regulation of energy balance whereas ghrelin, cholecystokinin (CCK), peptide YY (PYY) PYY, and glucagon-like peptide-1 (GLP-1) are the sensors related to meal initiation and termination that affect appetite and body weight more acutely. Ghrelin stimulates while GLP-1, oxyntomodulin (OXM), PYY, CKK, and pancreatic polypeptide inhibits appetite **(Figure 4)**.



(A) **(B)**

Figure 4: Signaling of the Gut hormone to the brain under fasted and fed states. (A) During the fasting/ pre-prandial state, (B) In the postprandial state

The arcuate nucleus (ARC) of the hypothalamus can also be directly influenced by circulating factors because it is partially outside the blood-brain barrier. There are two well-characterized neuronal populations involved in this pathway, namely, appetite inhibiting and appetite-stimulating neurons. The appetite inhibiting neurons further include proopiomelanocortin (POMC), cocaine & amphetamine-regulated transcript (CART) co-expressing neurons. Appetite-stimulating neurons includes neuropeptide Y (NPY) and agouti-related peptide co-expressing neurons [21-23]. Both neuronal populations project to the paraventricular nucleus (PVN) and other important nuclei involved in the regulation of food intake. The PVN also receives important inputs from other hypothalamic nuclei. Melanocortin receptor genes (*MC2R*, *MC3R*, and *MC4R*) stimulates melanocortin stimulating hormone (MSH) and melanin-concentrating hormone (MCH) for anorexigenic signals [24]. In the hypothalamus, the neurotransmitter α-melanocyte stimulating hormone (α-MSH) is produced which acts on the melanocortin receptor in another part of the hypothalamus to reduce food intake. Lack of leptin on the leptin receptor, in both animals and humans, leads to obesity. Another possible reason for obesity is the lack of genes for α-MSH or melanocortin receptors. Therefore, it is a very potent and important pathway for controlling body weight **(Figure 5)**. Indeed, of all the genes that are associated with human obesity, the largest number appears to be associated with this network. For example, mutations of the MC4R have

been identified in up to 4% of obese human populations, and at the same time mutations have also been found for genes encoding leptin, the leptin receptor, and POMC (melanocortin precursor).

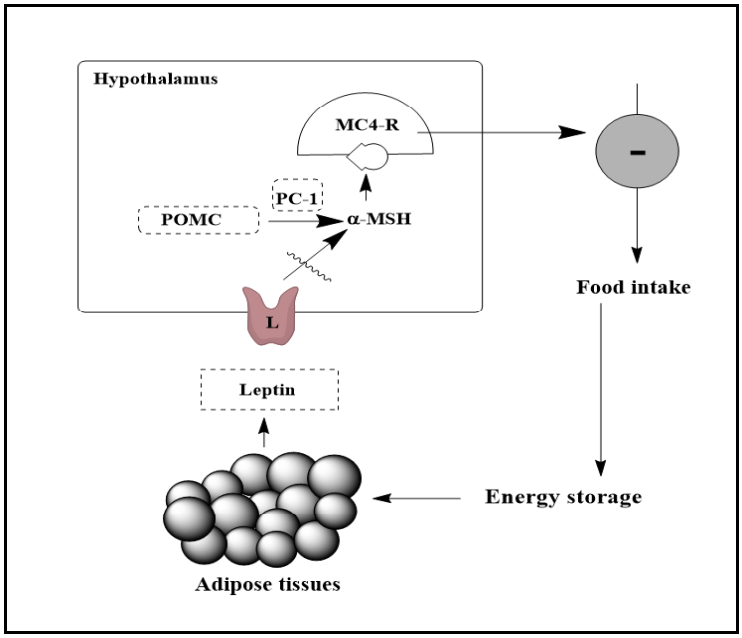


Figure 5: Schematic representation of the leptin regulation of food intake and proteins mutated in obesity

Another major reason for the development of obesity includes lifestyle changes. Over the years, the transition from paleolithic nutrition to western diets, along with a lack of corresponding genetic adaptations, has caused significant distortion of the metabolism that has evolved over millions of years in humans. Paleolithic diets are higher in protein (19 - 35% of energy) and low in carbohydrate (22 - 40% of energy) by normal western standards, whereas the fat intake is higher (28 - 58% of energy) in the case of the Western diet. Thus, the "Western diet" invariably leads to a dramatic increase in IR and hyperinsulinemia that further leads to progression in obesity, T2DM, hypertension, cancer, and other metabolic syndromes **(Figure 6)**[25].

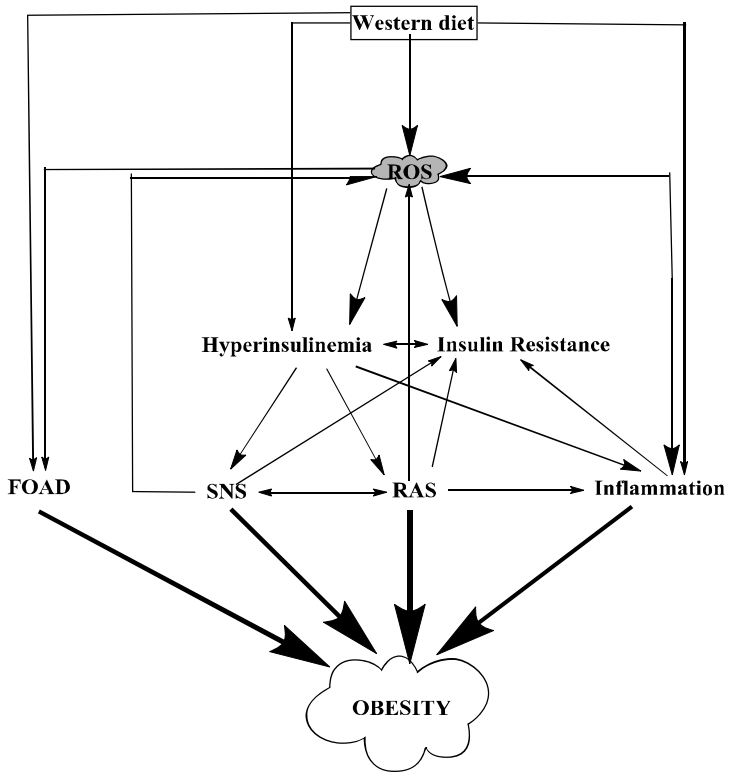


Figure 6: Pathophysiology of obesity due to the Western Diet

At present, carbohydrates play an important role in the human diet. WDs consist of large amounts of carbohydrates such as refined cereals, potatoes and sugars, dairy products, as well as high amounts of fat. Glucose is in large quantities derived from carbohydrate source, particularly from starchy foods and sugars, is currently the most important source of energy for the human body and accounts for about 40–75% of the energy intake [26,27]. Fats includes excessive amounts of omega-6 polyunsaturated fatty acids (PUFAs) and only small amounts of omega-3 PUFAs, resulting in an unhealthy omega-6/omega-3 ratio of 20: 1 as compared to a balanced ratio during the Paleolithic period. The consumption of the omega-6 PUFAs has noticeably increased in the western world primarily in the form of vegetable oils. A diet rich in omega-6 fatty acids is proinflammatory and prothrombotic and has been implicated in the development of various degenerative diseases, such as T2DM, CVD, cancer, obesity, inflammatory bowel disease, major depression, Alzheimer's disease, etc [28-30]. Therefore, WDs often are associated with excessive supraphysiological postprandial peaks in blood sugar and lipids **(Figure 7)**.

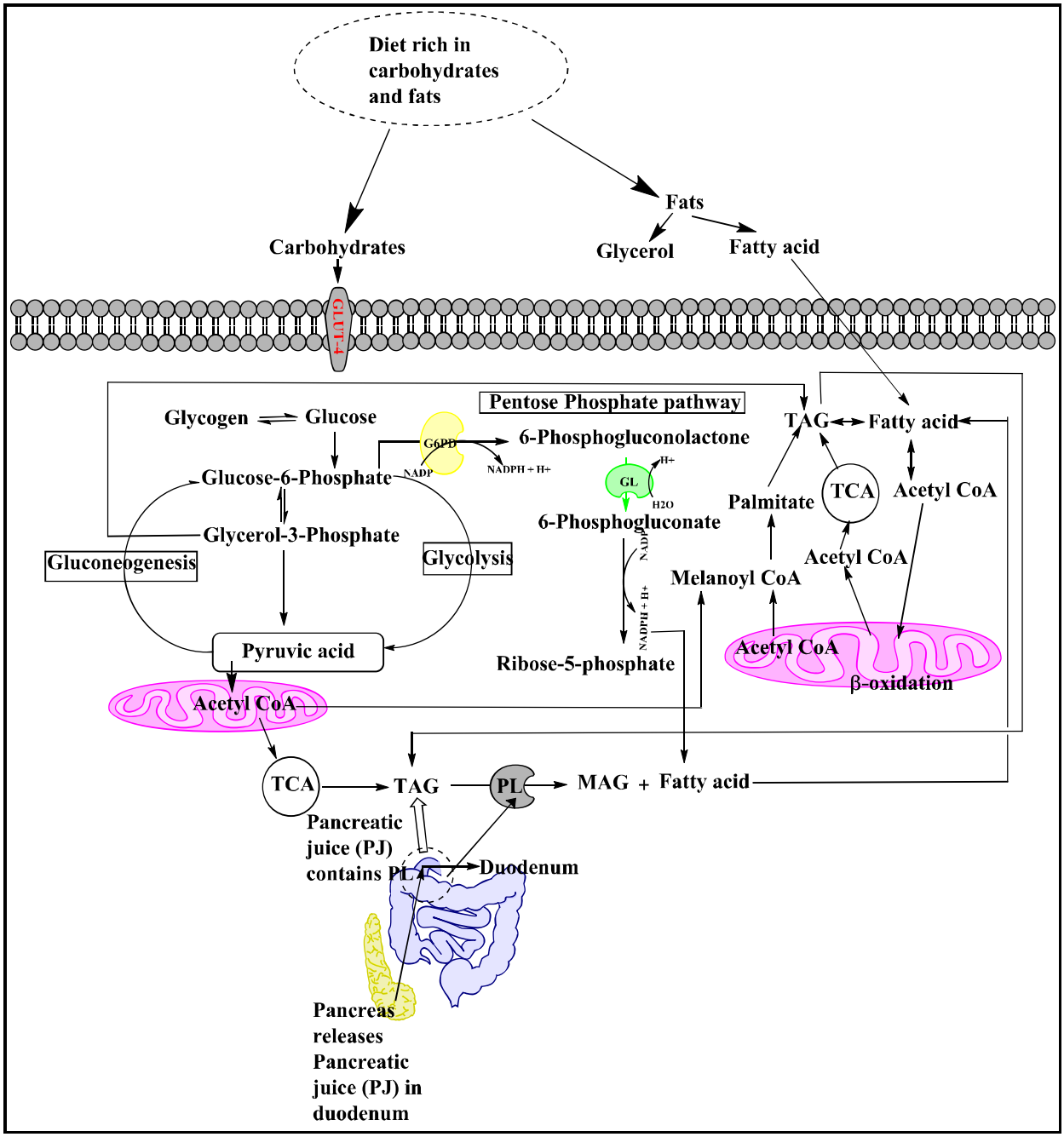


Figure 7: Carbohydrate and lipid cycle

1.2 Emerging Drug Targets for obesity

There are four general strategies by which obesity can be treated and/or prevented **(Figure 8)**. These four strategies are summarized into two broad target categories: central and peripheral

targets. Central targets include appetite suppression that stimulates the release of anorexigenic signals or block orexigenic signals. For example, Sibutramine an anti-obesity drug used for long-time treatment acts by suppressing the appetite.

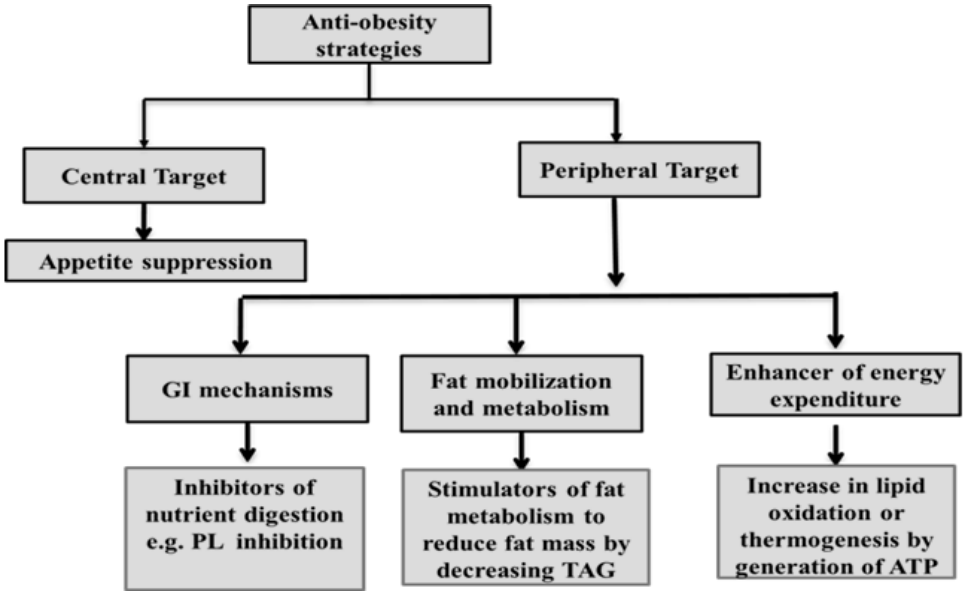


Figure 8: Strategies to control obesity

Peripheral targets are the basis of the other strategies. The first includes nutrients and digestion inhibitors that reduce energy intake through gastrointestinal mechanisms and do not directly alter the central system. Orlistat another long-term approved drug for anti-obesity is a gastrointestinal lipase inhibitor and it reduces the absorption of dietary fat. Another approach of anti-obesity therapy is the stimulation of fat mobilization and metabolism that reduces fat mass by decreasing triacylglycerol (TAG) synthesis and therefore decreases the deposition in adipose tissue. Next therapy is the enhancers of energy expenditure that act peripherally to increase lipid oxidation or thermogenesis by uncoupling fuel metabolism by the generation of ATP, thereby dissipating energy as heat [31].

1.2.1 Gastrointestinal mechanisms

Amongst all the peripheral targets, GI mechanisms are found to be most favorable target for treatment of obesity. They are as follow:

1.2.1.1 Pancreatic and gastric lipase

Pancreatic Lipase (PL) is the major lipolytic enzyme secreted in the small intestine, that functions *via* activation of pancreatic co-lipase in presence of bile acids [2,32]. Dietary fats are present as triacylglycerol (TAG) comprising one molecule of glycerol and three molecules of fatty acid. TAG undergoes a series of biochemical processes before entering the intestinal cavity and transportation

into circulation (**Figure 9**). The TAG is partially broken down to one molecule of *sn*-1,2-monocylglycerol (MAG) and two molecules of free fatty acid (FFA) [33]. This hydrolysis is completed in the duodenum using PL. The hydrolyzed product is FFA and MAG, that are absorbed into enterocytes lying on the brush border of the intestine [34].

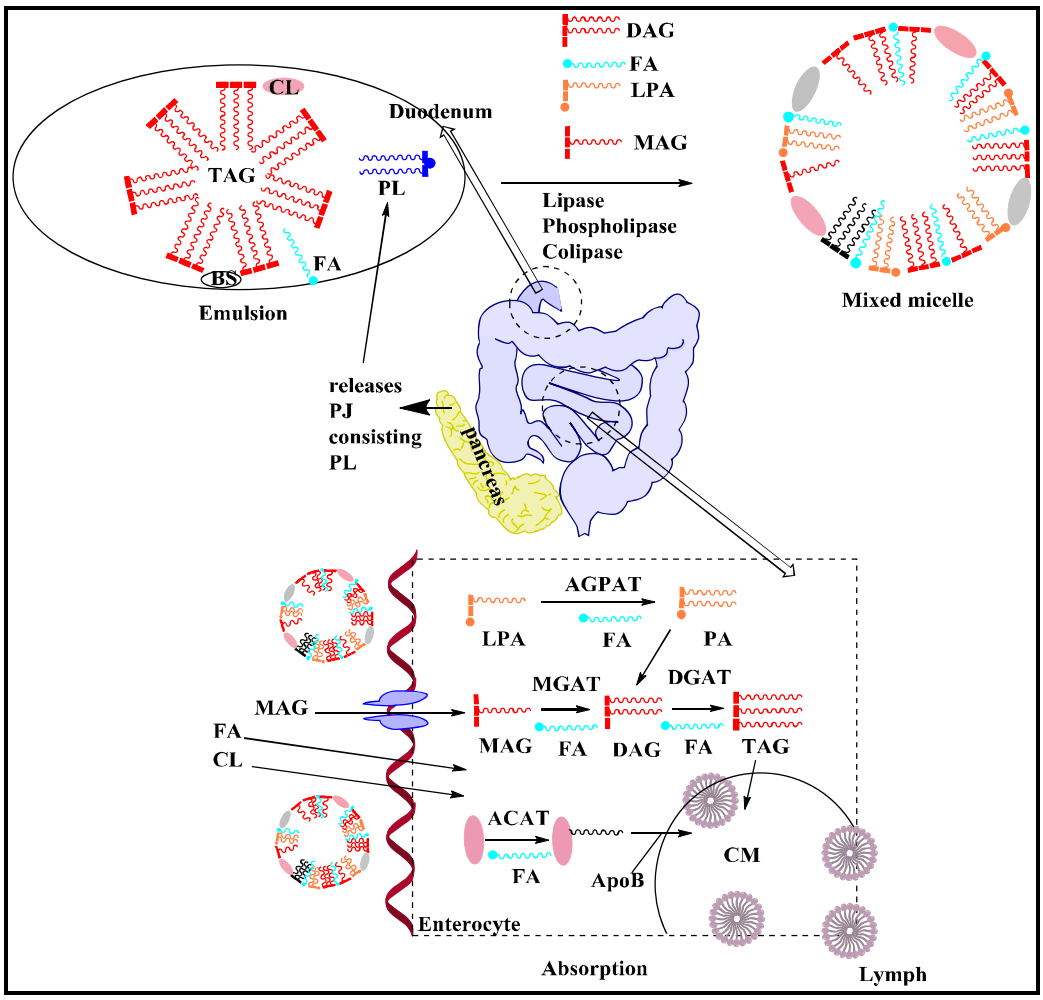


Figure 9: Fat digestion and absorption

Lingual lipase secreted from von Ebner's glands contributes very little to fat digestion in the stomach because of its optimal activity at pH 5.4 and low level of expression in humans [35]. On the other hand, gastric lipase is stable and active at acidic pH and is mainly responsible for lipase activity in the stomach, that accounts for 10–30% of dietary fat hydrolysis [36]. In the absence of PL, 5-40% of TAG is hydrolyzed by gastric and lingual lipases, whereas PL hydrolyzes 50-70% of TAG. Gastric lipase is found in children that is replaced with PL during adulthood.

Orlistat (tetrahydrolipstatin), a PL inhibitor, is the only drug approved for long-term treatment of

obesity. It is a chemically synthesized derivative of lipstatin, a natural product of *Streptomyces toxytricini* [37]. It reduces fat absorption by approximately 30% and is almost completely excreted with fatty stools. It forms a covalent bond with the active serine of the active site of gastric and pancreatic lipases in the lumen of the gastrointestinal tract and prevents the hydrolysis of dietary fat into absorbable FFAs and MAG [38]. However, long term usage of orlistat has been recently reported to cause pancreatic, liver, and kidney injuries [39].

1.2.1.2 Pancreatic Phospholipase A2 (pPLA2)

In response to food intake, pPLA2 is secreted from the pancreas. It catalyzes the hydrolysis of phospholipids at the *sn*-2 position to generate FFAs. Phospholipids are the second most abundant type of lipid present in the intestinal lumen [40] and 90% of them are derived from bile. The hydrolysis of the intestinal phospholipids leads to the formation of mixed micelles and efficient absorption of both TAG and cholesterol [41].

1.2.1.3 Fatty acid transport and binding proteins

After digestion of TAG, lipolytic products such as FFAs and MAG are dispersed in vesicles. These lipolytic products along with bile salt from the mixed micelles and are absorbed across the brush-border membrane of enterocytes of the small intestine [42,43].

1.2.1.4 Monoacylglycerol acyltransferase (MGAT)

MGAT is the key enzyme involved in dietary absorption in enterocytes where the re-synthesis of TAG takes place and represents one of the two main biochemical pathways in TAG synthesis [44]. The activity of these pathways is determined by the relative abundance of *sn*-2-MAG and FFAs relative to glycerol-3-phosphate. Under normal lipid-absorption conditions in the intestinal mucosa, the MAG pathway contributes 80% of the TAG that is incorporated into chylomicrons. The enzyme further inhibits the glycerol-3-phosphate pathway [45].

1.2.1.5 Microsomal triglyceride-transfer protein (MTP)

Chylomicrons are transportation vehicles for fat and fat-soluble vitamins that provide a possible target for the prevention of dietary fat absorption. MTP has an essential role in the assembly of chylomicrons in intestinal enterocytes and VLDL in the liver. It transports lipids and cholesterol esters from the endoplasmic reticulum lumen to lipoprotein particles [46]. Several of the MTP inhibitors (eg. Implitapide) are used for lowering cholesterol, TG, and VLDL levels in experimental animals and in humans [47].

1.2.2 Fat storage and mobilization:

1.2.2.1 1-acyl-glycerol-3-phosphate acyltransferase (AGPAT)

Acylation of lysophosphatidic acid (LPA) to form phosphatidic acid by these enzymes at the *sn*-2 position. This is an important intermediate in the *de novo* biosynthesis of TAG and glycerophospholipids. Further, dephosphorylation of phosphatidic acid results in the formation of *sn*-1,2-DAG, that enters the MGAT pathway for the synthesis of TAG that is catalyzed by diacylglycerol 1,2 acyltransferase (DGAT) **(Figure 10)** [48].

1.2.2.2 Diacylglycerol acyltransferase (DGAT):

DGAT is responsible for the synthesis of TAG from DAG and ultimately relates to the MGAT and glycerol-3-phosphate pathways **(Figure 10)**[49,50]. Several natural products from microorganisms have been reported to inhibit DGAT, however the specificity of these compounds has not been confirmed against cloned DGAT enzymes [51].

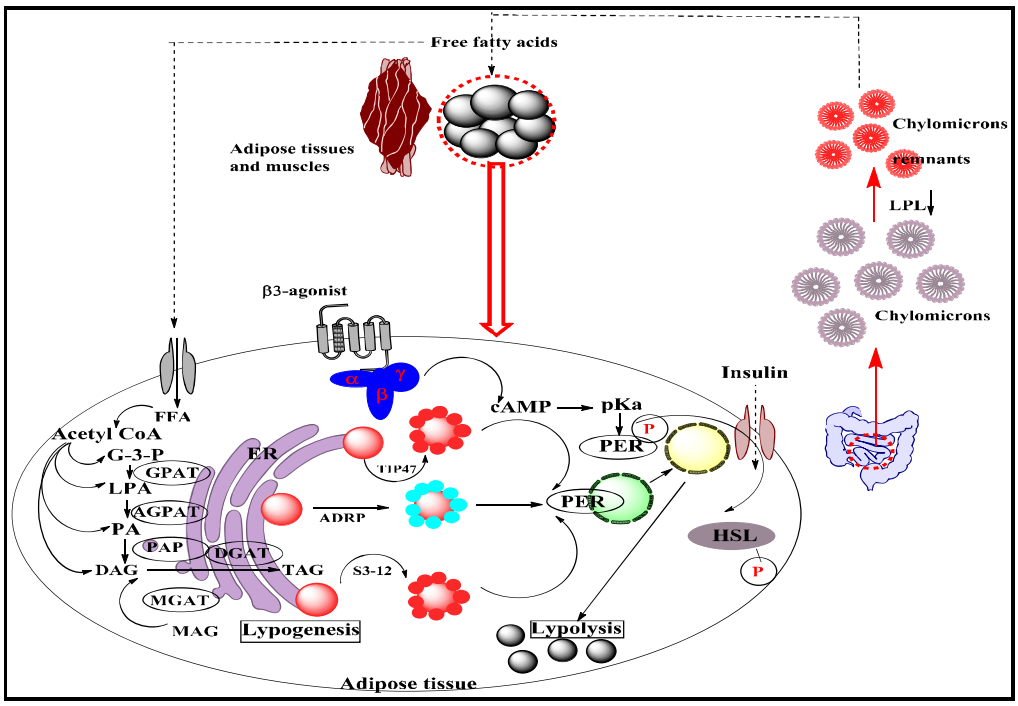


Figure 10: Lipid storage and mobilization in adipocytes

1.2.2.3 Hormone-sensitive lipase (HSL)

HSL is highly expressed in white and brown adipose tissues, where it releases fatty acids from stored TAGs, thereby providing energy and heat to peripheral tissues [52].

1.2.3 Fatty acid synthesis and oxidation:

1.2.3.1 Glycerol-3-phosphate acyltransferase (GPAT)

The enzyme is involved in the initial and committed step in the *de novo* synthesis of TAG by acylation of glycerol-3-phosphate at the *sn*-1 position to form *sn*-1-acylglycerol-3-phosphate **(Figure11)**.

1.2.3.2 Fatty acid synthase (FAS)

Mammalian FAS is associated with the *de novo* synthesis of saturated fatty acids such as myristate, palmitate and stearate, using acetyl- and malonyl CoA. It works as a homodimer of a multifunctional protein that contains seven catalytic domains and a site for the prosthetic group 4′-phosphopantetheine [53]. The enzyme is abundantly expressed in lipogenic tissues, such as the liver, adipose, and lactating breast.

1.2.3.3 Carnitine palmitoyl transferase (CPT)

This enzyme converts acetyl-CoA to acetylcarnitine, which is a rate-limiting step in the transfer of long-chain fatty acyl-CoAs from the cytosol to the mitochondria for oxidation; its activity is inhibited by malonyl-CoA, which is an allosteric inhibitor **(Figure 11).**

1.2.3.4 Acetyl-CoA carboxylase (ACC)

This enzyme is involved in the carboxylation of acetyl-CoA to malonyl-CoA, a crucial regulator of mitochondrial fatty acid β-oxidation through its inhibition of CPT1.

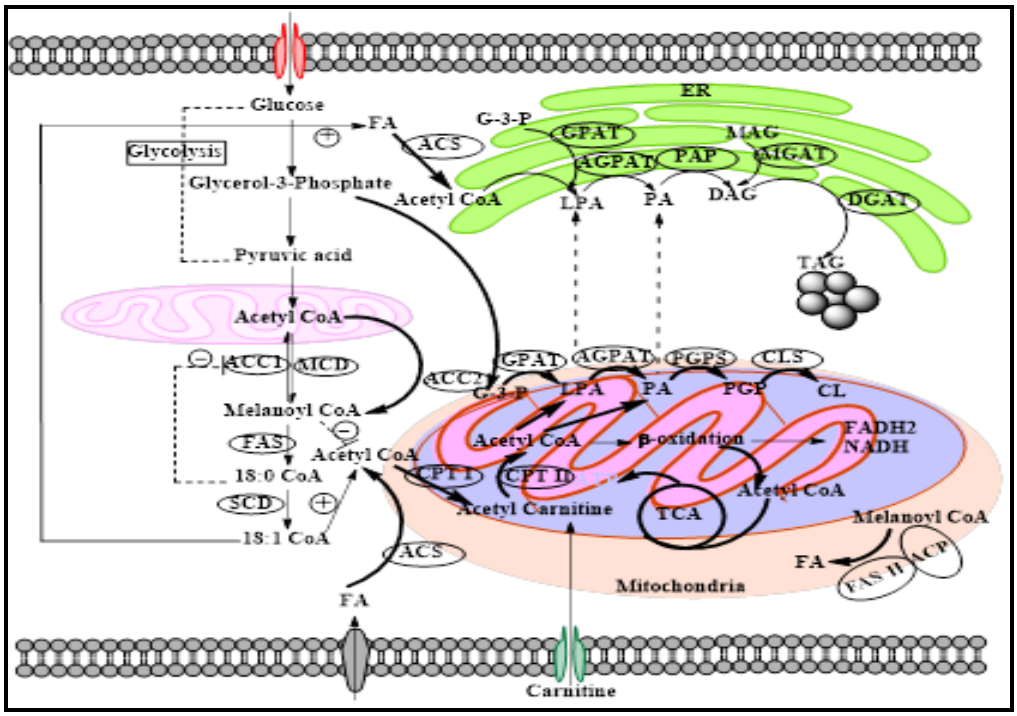


Figure 11: Common metabolic pathways involved in lipid synthesis in the endoplasmic reticulum and lipid oxidation in mitochondria of the liver and skeletal muscle

1.3 The rationale for exploring PL inhibitors

PL is the primary enzyme involved in the digestion of dietary lipids. Consequently, PL inhibition results in lipid indigestion and subsequent prevention of fat intake into the systemic circulation. After taking into account the pros and cons of all the targets mentioned in Section 1.2, inhibition of PL was considered as the safest and effective strategy for the treatment of obesity, since the target is peripheral, and the inhibitor does not require any systemic absorption [54].

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