Physiological Factor in Obesity

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Abstract: Obesity is the most common nutritional disorder in the developed world and it is considered to be a risk factor associated with the development of the major human diseases, including cardiovascular disease, diabetes and cancer. Understanding the mechanisms underlying the regulation of obesity is important in obesity research. In this we reveal the factors involved in obesity and mechanism involved for obesity.

Key words: Obesity · Adipose tissue · Receptor · Enzyme · Hormone

INTRODUCTION

Obesity is simply fatness in a degree higher than overweight, which may even have a worse impact on a person's mental health. The energy intake coming from food that the body does not use is stored as fat. Obesity may be genetic but more often it is simply because of poor diet and lack of exercise in the child. To be more active is the best way to burn more calories and lose weight [1].

In a country like India, obesity is in association with modernization and urbanization. As the people are moving to urban centers and wealth is increasing, the obesity is becoming epidemic. In Northern India obesity was most prevalent in urban populations (male = 5.5%, female = 12.6%), followed by the urban slums (male = 1.9%, female = 7.2%), when compared to rural populations (male = 1.6%, female = 3.8%). Socioeconomic class also had an effect on the rate of obesity, with women of high socioeconomic class having greater rates (10.4%) than that of low socioeconomic class women (0.9%) [2].

Obesity is a medical condition, defined by body mass index (BMI) and further evaluated in terms of fat distribution via the waist–hip ratio and total cardiovascular risk factors in which excess body fat has accumulated to the extent that it may have an adverse effect on health. BMI is calculated by dividing the subject's mass by the square of his or her height, typically expressed either in metric or US "customary" units [3]. Metric: BMI = kilograms / meters. BMI is closely related to both percentage body fat and total body fat. Too much weight may increase the risk of developing many health problems which include Type diabetes, Heart disease, Stroke, High blood pressure (hypertension), High cholesterol (hypercholesterolemia), Certain cancers, Sleep apnea, Osteoarthritis, Gallbladder disease and gallstones, Fatty liver disease (also called nonalcoholic steatohepatitis or NASH), Gastroesophageal reflux disease (GERD), Gout and Psychological and emotional effect [4]. Understanding the neural mechanisms underlying the regulation of appetite and the control of energy expenditure by the CNS is becoming increasingly important in obesity research, by this review we reveal the factors involved in obesity. Many factors have been attributed to an epidemic of obesity including sedentary lifestyle, high-fat (HF) diets and consumption of large amount of modern fast foods. Fat not only increases the palatability of food but also is converted into body fat far more efficiently than carbohydrates. In scientific terms, obesity occurs when a person's calorie intake exceeds the amount of energy he or she burns though the cause for this imbalance is unclear. Evidence suggests that obesity often has more than one cause of which genetic, environmental, psychological, physiological play an important apart from other factors.

Genetic Factors: Obesity which tends to run in families, suggests having a genetic cause. However, separating the lifestyle factors from genetic ones is often difficult as family members share not only genes but also diet and lifestyle habits that may contribute to obesity. In a study on adults who were adopted as children, researchers found that the subjects' adult weights were close to those of their biological parents' than their adoptive parents' concluding that the environment provided by the adoptive family apparently had less influence on the development of obesity than the person's genetic makeup [4].

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Environmental Factors: Environment includes lifestyle behaviors such as what a person eats and how active he or she is. Americans' choice of meal tends to have high-fat, often for taste and convenience, ahead of nutritional content with imbalanced exercise, which may lead to obesity. Though people can't change their genetic makeup, they should be conscious of what they eat and how active they are.

Psychological Factors: Psychological factors also may influence eating habits. Many people eat in response to negative emotions such as boredom, sadness, or anger, which may count to obesity.

Other Causes of Obesity: Some rare illnesses which include hypothyroidism, Cushing's syndrome, depression and certain neurologic problems leads to overeating and certain drugs, such as steroids and some antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), may cause excessive weight gain and thus obesity.

Physiological Factors

Plasma Lipoproteins: Plasma lipoproteins are spherical particles with varied amounts of cholesterol, triglycerides, phospholipids and proteins. The phospholipids, free cholesterol and protein constitute the outer surface of the lipoprotein particles while the inner core contains mostly esterified cholesterol and triglycerides which serve to solubilize and transport cholesterol and triglycerides in the bloodstream. The density of the plasma proteins was determined by relative proportions of protein and lipid [5]. Lipoproteins are divided into 6 major classes based on the relative proportion of lipids and proteins: chylomicrons, chylomicron remnants, VLDL (very low density lipoproteins), IDL (intermediate density lipoproteins), LDL (low density lipoproteins) and HDL (high density lipoproteins) which have varied effects [6, 7]. From the various studies it can be observed that the high levels of VLDL and LDL cholesterol is pro-atherogenic and is the key factor in the pathogenesis of atherosclerosis and coronary artery disease (CAD), while HDL which is anti-atherogenic promotes the removal of cholesterol from peripheral cells and facilitates its delivery back to the liver, often showing protective effect makes its higher levels desirable. Monocytes attach to arterial wall, penetrate through subendothelium and get converted to tissue macrophages which via scavenger mechanism take up LDL. Though the total cholesterol concentrations are normal, an increase in LDL cholesterol can occur with an associated increased risk for CAD [8] i.e., with every 1%

increase in cholesterol there is 2% increase in Coronary Heart Disease risk. The LDL particles under conditions of high serum levels migrate into the subendothelial space where oxidation of LDL can occur. The actual oxidation process is believed to begin with lipid peroxidation, followed by fragmentation to result in short chain aldehydes which can form adducts with the lysine residues of apo B, creating a new epitope that is recognized by the scavenger receptor of macrophages. The conversion of lecithin to lysolecithin, a selective chemotactic agent for monocytes even occurs during the same process. The uptake of oxidized LDL continues until the macrophage is engorged with cholesteryl esters ultimately forming a foam cell. Groups of these foam cells constitute a fatty streak.

Fat Metabolism: Utilization of dietary lipids requires that they first be absorbed through the intestine but being oils they would be essentially insoluble in the aqueous intestinal environment [9]. Solubilization (emulsification) of dietary lipid is accomplished via bile salts that are synthesized in the liver and secreted from the gallbladder. The emulsified fats can then be degraded generating free fatty acids and a mixture of mono- and diacylglycerols from dietary triacylglycerols by pancreatic lipases (lipase and phospholipase A_2) which are secreted into the intestine from the pancreas. Pancreatic lipase degrades triacylglycerols at the 1 and 3 positions sequentially to generate 1, 2-diacylglycerols and 2-acylglycerols. Phospholipids are degraded at the 2 position by pancreatic phospholipase A_2 releasing a free fatty acid and the lysophospholipid. The resynthesis of triacylglycerols occurs after the products of pancreatic lipase are absorbed by the intestinal mucosal cells which are then solubilized in lipoprotein complexes (complexes of lipid and protein) called chylomicrons containing lipid droplets surrounded by the more polar lipids and finally a layer of proteins. Triacylglycerols synthesized in the liver are packed into VLDLs (very low density lipoproteins) and released into the blood directly. Chylomicrons from the intestine are then released into the blood via the lymph system for delivery to the various tissues for storage or production of energy through oxidation. The lipoprotein lipase hydrolyses triacylglycerol components of VLDLs and chylomicrons to free fatty acids and glycerol in the capillaries of adipose tissue and skeletal muscle, of which the free fatty acids are absorbed by the cells and the glycerol is returned via the blood to the liver (and kidneys) and converted to the glycolytic intermediate DHAP. Mobilization of long-chain fatty acids across the plasma membrane of mammalian

cells is facilitated by fatty acid transport protein (FATP) [10]. Activation of adenylate cyclase is by epinephrine binding to its receptor. The resultant increase in cAMP activates PKA which then phosphorylates and activates hormone-sensitive lipase. Hormone-sensitive lipase hydrolyzes fatty acids from triacylglycerols and diacylglycerols. The final fatty acid is released from monoacylglycerols through the action of monoacylglycerol lipase, an enzyme active in the absence of hormonal stimulation. In contrast to the hormonal activation of adenylate cyclase and (subsequently) hormone-sensitive lipase in adipocytes, the mobilization of fat from adipose tissue is inhibited by numerous stimuli and the most significant inhibition being that exerted upon adenylate cyclase by insulin.

Reactions of Oxidation: Fatty acids before being oxidized in the mitochondria must be activated in the cytoplasm that is catalyzed by fatty acyl-CoA ligase (also called acyl-CoA synthetase or thiokinase) and the net result of the process being consumption of 2 molar equivalents of ATP.

$$Fatty\ acid + ATP + CoA \longrightarrow Acyl\text{-}CoA + PP_i + AMP$$

The site of oxidation of fatty acids being mitochondria, the transport of fatty acyl-CoA is via an acyl-carnitine intermediate, which itself is generated by the action of carnitine palmitoyltransferase I (CPT I, also called carnitine acyltransferase I, CA I) an enzyme that resides in the outer mitochondrial membrane and transported into the mitochondria where carnitine palmitoyltransferase II (CPT II, also called carnitine acyltransferase II, CA II) catalyzes the regeneration of the fatty acyl-CoA molecule. After this activation, the CoA is exchanged for carnitine by CPT I and the resultant, the fatty-carnitine is then transported to the inside of the mitochondrion where a reversal exchange takes place through the action of CPT II. Due to the sequential removal of 2-carbon units by oxidation at the β-carbon position of the fatty acyl-CoA molecule the process is termed β-oxidation. Each round of β-oxidation produces one mole of NADH, one mole of $FADH_2$ and one mole of acetyl-CoA. The acetyl-CoA which is the end product of each round of β-oxidation then enters the TCA cycle, where it is further oxidized to CO_2 with the concomitant generation of three moles of NADH, one mole of $FADH_2$ and one mole of ATP. The NADH and $FADH_2$ generated during the fat oxidation and acetyl-CoA oxidation in the TCA cycle then can enter the respiratory pathway for the production of ATP.

Pathway of β-Oxidation: The oxidation of carbohydrates yields less energy per carbon atom than that of fattyacids. The net result of the oxidation of one mole of oleic acid (an 18-carbon fatty acid) will be 146 moles of ATP (2 mole equivalents are used during the activation of the fatty acid), as compared with 114 moles from an equivalent number of glucose carbon atoms [11].

Alternative Oxidation Pathways: The majority of natural lipids contain an even number of carbon atoms except a small proportion of plant derived lipids which contains odd number and upon complete β-oxidation these yield acetyl-CoA units plus a single mole of propionyl-CoA. The propionyl-CoA is converted, in an ATP-dependent pathway, to succinyl-CoA. The succinyl-CoA can then enter the TCA cycle for further oxidation.

Except when a double bond is encountered, the oxidation of unsaturated fatty acids is similar to that of saturated fats. In such a case, the bond is isomerized by a specific enoyl-CoA isomerase and oxidation continues. In the case of linoleate, the presence of the Δ^{12} unsaturation results in the formation of a dienoyl-CoA during oxidation which acts as substrate for an additional oxidizing enzyme, the NADPH requiring 2, 4-dienoyl-CoA reductase.

Phytanic Oxidation Pathway: Phytanic acid is a fatty acid present in the tissues of ruminants and in dairy products and is, therefore, an important dietary component of fatty acid intake. Methylated phytanic acid makes it inappropriate to act as a substrate for the first enzyme of the mitochondrial β-oxidation pathway (acyl-CoA dehydrogenase). Phytanic acid is first converted to its CoA-ester and then phytanoyl-CoA serves as a substrate in α-oxidation process. The peroxisomes acts as the center for the α-oxidation reaction (as well as the remainder of the reactions of phytanic acid oxidation) and requires a specific α-hydroxylase (specifically phytanoyl-CoA hydroxylase, PhyH), which adds a hydroxyl group to the α-carbon of phytanic acid generating the 19-carbon homologue, pristanic acid serving as a substrate for the remainder of the normal process of β-oxidation. As the first step in phytanic acid oxidation involves a α-oxidation step, the process is termed as α-oxidation.

Endogenous Cholesterol Synthesis: The two sources of cholesterol involve absorption from the gut and endogenous de novo synthesis. The steps involved in endogenous cholesterol synthesis are as follows: Acetyl- CoA and acetoacetyl-CoA forms hydroxymethylglutaryl-CoA (HMG-CoA)

using HMG-CoA synthase. Mevalonic acid converted to HMG-CoA by HMG-CoA reductase which is inturn converted to 5-phospho-mevalonic acid by Mevalonate kinase. Phospho mevalonate kinase and Pyrophospho-mevalonate decarboxylase produce 5-pyrophospho-mevalonic acid and 3-isopentyl-pyrophosphate respectively from 5-phospho-mevalonic acid. The 3-isopentyl-pyrophosphate is converted to 3,3- dimethyl-pyrophosphate by isopentyl-pyrophosphate isomerase. The use of Dimethylallyl-transferase is in two steps: geranyl pyrophosphate from 3,3-dimethyl- pyrophosphate and Farnesyl pyrophosphate from geranyl pyrophosphate. Squalene synthetase is used for the conversion of farnesyl pyrophosphate in to squalene up on which squalene epoxide acts and forms squalene, 2,3-oxidosqualene which inturn converted to lanosterol by 2,3-Oxidosqualene cyclase. Following this process, a series of enzyme reactions are required to produce cholesterol [12]. In final step of this cholesterol biosynthesis, 7-dehydrocholesterol reductase is essential to produce cholesterol. Deficiency of 7-dehydrocholesterol reductase causes severe developmental disorders with multiple congenital and morphogenic abnormalities, the Smith-Lemli-Opitz syndrome. Cholesterol converted to bile acids enhances hepatic LDL clearance by LDL receptor upregulation in the liver. Inhibition of cholesterol resorption results in a decrease of hepatic cholesterol and a compensatory increase of hepatic HMG-CoA reductase activity resulting from de novo cholesterol synthesis and an increase of hepatic LDL receptor levels. Cholesterol 7α hydroxylation occurs in liver microsomes utilizing cholesterol as substrate. 7α Hydroxycholesterol is converted into 7α-hydro-4 cholesten-3-one by cholesterol oxidase. The metabolism of cholesterol is by oxidation in liver to bile acids which undergo enterohepatic circulation. In the untreated state, approximately 95% of the bile acids that are secreted are reabsorbed and returned to the liver, while the small loss is replaced by de novo biosynthesis from cholesterol. Increased excretion of bile acids with the feces increases the rate of oxidation of cholesterol in the liver leading to a partial depletion of the hepatic cholesterol pool. A compensatory increase in uptake via the LDL receptors results in lower serum LDL levels. This can be achieved by addition of a bile acid binding resin, e. g., cholestyramine, to the food.

Role of Organs

Adipose Tissue: In humans, adipose tissue derived from lipoblasts is located beneath the skin (subcutaneous fat), around internal organs (visceral fat) and in the bone marrow (yellow bone marrow) and in breasts, also around kidneys. Adipose tissue is found in specific locations, which are referred to as 'adipose depots' technically composed of 80% fat. Adipose tissue contains many small blood vessels. In the skin, it accumulates in the deepest level, the subcutaneous layer, providing insulation from heat and cold. Around organs, it provides protective padding. Adipose tissue is also an important endocrine organ producing hormones such as leptin, resistin and the cytokine TNFα. Two types of adipose tissue exist: white adipose tissue (WAT) and brown adipose tissue (BAT).

Brown Fat: Brown Fat or brown adipose tissue located around the neck and large blood vessels of the thorax is specialized tissue generating heat by "uncoupling" the respiratory chain of oxidative phosphorylation which is a metabolic pathway that uses energy released by the oxidation of nutrients to produce adenosine triphosphate (ATP) within mitochondria through a large enzyme called ATP synthase. On a whole, this reaction is driven by the proton flow, which forces the rotation of a part of the enzyme; the ATP synthase is a rotary mechanical motor. Uncoupling is the process where when protons transit down the electrochemical gradient across the inner mitochondrial membrane, the energy is released as heat rather being used to generate ATP. This thermogenic process may be vital in neonates exposed to the cold, who then require this thermogenesis to keep warm as they are unable to shiver, or take other actions to keep themselves warm. Uncoupling protein (UCP) is a family of inner mitochondrial membrane transporters upregulated by thyroid hormones of which UCP1 is expressed exclusively in brown adipose tissue; UCP2 widely and UCP3 in skeletal muscle and brown adipose tissue. Thermogenin [13] known as uncoupling protein 1, or UCP1 is an uncoupling protein found in the mitochondria of brown adipose tissue (BAT), used to generate heat by non-shivering thermogenesis which is the primary means of heat generation in hibernating mammals and in human infants. The cascade is initiated by binding of norepinephrine to the cells β_3-adrenoceptors.UCP1 is restricted to brown fat where it is activatedby fatty acids and inhibited by nucleotides, where it provides a mechanism for the enormous heat-generating capacity of the tissue. Fatty acids cause the following signaling cascade: Sympathetic nervous system terminals release Norepinephrine onto a Beta-3 adrenergic receptor on the plasma membrane. This activates adenylyl cyclase, which catalyses the conversion of ATP to cyclic AMP (cAMP). cAMP activates protein kinase A (PKA), causing its active C subunits to be freed from its regulatory R

subunits. Active protein kinase A in turn phosphorylates triacylglycerol lipase, thereby activating it. The lipase converts triacylglycerols into free fatty acids, which activate UCP1. At the termination of thermogenesis, the mitochondria oxidize away the residual fatty acids, UCP1 inactivates and the cell resumes its normal energy-conserving mode. The thermogenic activity of brown adipose tissue established the binding of the nucleotide guanosine diphosphate (GDP) to thermogenin. Thermogenetic activity of brown adipose tissue was measured by determined the binding of the nucleotide GDP to brown adipose tissue membrane protein, the uncoupling protein itself and the glucose transporter 4 (GLUT4).

White Adipose Tissue (WAT) or White Fat: White fat composes as much as 20% of the body weight in men and 25% of the body weight in women acts as thermal insulator, aiding in the maintenance of body temperature. Its cells contain a single large fat droplet, which forces the nucleus to be squeezed into a thin rim at the periphery. They have receptors for insulin, growth hormones, norepinephrine and glucocorticoids. The insulin receptors, upon release of insulin from the pancreas, cause a dephosphorylation cascade that lead to the inactivation of hormone-sensitive lipase and the release of glucagon from the pancreas, results in phosphorylation cascade that activates hormone-sensitive lipase by glucagon receptors, causing the breakdown of the stored fat to fatty acids, which are exported into the blood and bound to albumin and glycerol, which is exported into the blood freely. Muscle and cardiac tissue take up fatty acids as a fuel source and glycerol by the liver for gluconeogenesis.

Hypothalamus: The hypothalamus is well recognized for its importance in regulating sympathetic activity and energy balance [14]. A few discrete nuclei in the basal hypothalamus are crucial in the regulation of daily energy homeostasis, especially those sites connected with neural mechanisms affecting appetite. The inference that hypothalamic sites such as nuclei, contain neural mechanisms affecting ingestive behavior was based on the results of numerous studies employing either discrete lesion in the hypothalamus or surgical transection of neural pathways [15, 16]. NPY immunoreactivity was found mainly in cell bodies of the hypothalamic areas including the ARC and NPY-immunoreactive fibers can be seen in the periventricular hypothalamic nucleus, paraventricular thalamic nucleus, or the PVN, a major site of NPY release [17].

Liver: The liver is generally considered to be the primary organ responsible for maintaining cholesterol homeostasis by regulating plasma lipoprotein metabolism and the lipid output in the bile. In the liver, high FFA concentration contribute to resistance to the action of insulin by enhancing glucose output from liver [18]. The accumulation of TG in liver by high FAs also bring about non-alcoholic fatty liver disease (NAFLD). NAFLD does damage to liver, which is the main organ of glucose metabolism, such as steatosis, steatohepatitis and hepatocellular necrosis to fibrosis [19]. The balance between hepatic lipogenesis and lipolysis is important to improving insulin resistance and NAFLD.

Pancreas: In the pancreas, prolonged exposure to FFA might cause impairment of insulin release through the mechanism of lipotoxicity [20].

Role of Receptors
Beta-2 Adrenergic Receptor: The ADRB2 is an intronless gene. Different polymorphic forms, point mutations and/or downregulation of this gene are associated with nocturnal asthma, obesity and type 2 diabetes. The effects of the beta-2 adrenergic receptor include Smooth muscle relaxation, e.g. in bronchi [21], Lipolysis in adipose tissue [22], Anabolism in skeletal muscle [23, 24], Relax non-pregnant uterus, Relax detrusor urinae muscle ʃ of bladder wall, Dilate arteries to skeletal muscle, Glycogenolysis and gluconeogenesis, Contract sphincters of GI tract, Thickened secretions from salivary gland, Inhibit histamine-release from mast cells and Increase renin secretion from kidney. This receptor is directly associated with one of its ultimate effectors, the class C L-type calcium channel $Ca_V 1.2$. This receptor-channel complex is coupled to the G_s G protein, which activates adenylyl cyclase, protein kinase A and the counterbalancing phosphatase PP2A. The mechanism provided by the signaling complex assembly provides specific and rapid signaling. To check the pH and REDOX sensitivity of this and other GPCRs, a two-state biophysical and molecular model has been proposed [25]. Beta-2 Adrenergic Receptors have also been found to couple with G_i, possibly providing a mechanism by which response to ligand is highly localized within cells. In contrast, Beta-1 Adrenergic Receptors are coupled only to G_s and stimulation of these results in a more diffuse cellular response [26]. This appears to be mediated by cAMP induced PKA phosphorylation of the receptor [27]. Beta-3 Adrenergic Receptor:

Actions of the β_3 receptor located mainly in the adipose tissue, gallbladder and in brain adipose tissue includes enhancement of lipolysis in adipose tissue, thermogenesis in skeletal muscle and suppression of leptin gene expression and serum leptin levels, epinephrine- and norepinephrine-induced activation of adenylate cyclase through ngono the action of the G proteins of the type G_s, reduce the body fat apart from the regulation of lipolysis and thermogenesis. Some β_3 agonists have demonstrated antistress effects in animal studies, suggesting it also has a role in the CNS. Their role in gallbladder physiology is unknown [28].

Nuclear Receptors: The nuclear receptors that regulate systemic glucose and lipid metabolism are Peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs). They are expressed by macrophages in which they modulate cholesterol homeostasis and inflammation and even act as lipid sensors and bind with micromolar affinities to ligands derived from either intracellular metabolism or dietary lipids. These receptors are heterodimerize with retinoid X receptors (RXRs) to modulate transcription at the promoters of target genes. Endogenous ligands of PPARs include fatty acids and eicosanoids, whereas metabolites of oxidized cholesterol activate the LXRs.

Peroxisome Proliferator-activated Receptors (PPARs): The PPAR family consists of three proteins, α, β/δ and γ of which the experimental data suggest that PPAR-α and PPAR-γ activation corrects metabolic disorders. The recruitment of leukocytes to endothelial cells was modulated by PPARs along with the activities like control of the inflammatory response and lipid homeostasis of monocytes/macrophages and regulates inflammatory cytokine production by smooth muscle cells. PPARα induces a massive increase in peroxisomal fatty acid oxidation in hepatocytes thus providing a powerful action for the clearance of fat from the serum. PPARα is responsible for clofibrate-induced fatty acid oxidation by disrupting the PPARα gene in mice. Lee and Evans (2002) reviewed the role of the peroxisome proliferator-activated receptor-γ in macrophage lipid homeostasis [29]. Chinetti *et al.* (1998) reported that PPARα and PPARγ activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway[30]. PPARγ is a transcription factor required for the activation of many adipose-specific genes [31]. PPARγ essentially controls the accumulation of lipids in adipocytes and

many experiments have demonstrated the ability of the receptor to direct adipocyte stimulation [32]. Reginato *et al.* (1998) reported that prostaglandins can both promote and block adipogenesis through opposing effects on PPARγ [33]. PPARγ promotes lipid clearance in the liver of mice [34]. Direct activation of PPARγ leads to contribution of lowering TG and FFA levels and suppresses TNF-α gene expression, which is potential systemic mediators of insulin resistance [35].

Endocannabinoid Receptor: The endocannabinoid receptors which are appetite stimulatorhave been identified so far as two types that include the CB1-receptor present in brain and periphery and the CB2-receptor found in the periphery only. Both types of receptors are negatively coupled to Ca^{2+} channels through G proteins [36]. Endocannabinoids play important roles in the gastrointestinal tract [37] and in energy metabolism [38].

LDL-Receptor: The LDL-receptor is in charge of low density lipoprotein absorption in liver. Changes in hepatic LDL-receptor contribute to the elevation in blood cholesterol levels induced by high-cholesterol diets as well as to the reduction that follows hepatic cholesterol depletion [39].

Role of Enzymes
Lipase: Liapse is a lipid (fat) digesting enzyme from Aspergillus oryzae. Incomplete digestion of fat allows fat to coat food particles and therefore interferes with the hydrolysis of other food components such as protein and carbohydrates which may result in diarrhea and/or, more seriously, essential fatty acid deficiency [40]. Normal digestion of dietary fat is accomplished by lipases with the assistance of bile, which is produced by the liver and normally supplied by way of the gallbladder. The function of bile is to bring ingested fats into emulsion to facilitate the work of the lipases. Adequate absorption of essential fatty acids is necessary to maintain membrane structure in cells throughout the body and healthy skin and deficiency reduces the blood clotting time. Pancreatic lipase is the most important enzyme for the digestion of dietary fat. Pancreatic lipase (PL) is the important enzyme for the digestion of dietary triacylglycerols. Lipoprotein lipase (LPL) is an enzyme responsible for the hydrolysis of triglycerides from plasma lipoproteins, mainly chylomicra and very low density lipoproteins. Its activity is known to be influenced by nutritional and hormonal

status and by environmental conditions. LPL is a factor that contributes to the development of the obesity [41, 42]. In adipose tissue, hormone-sensitive lipase (HSL) functions as the rate limiting enzyme catalyzing the lipolysis of triacylglycerol and diacylglycerol following the phosphorylation of the enzyme by protein kinase A [43]. Hormone Sensitive Lipase (HSL), controlled by several hormonal pathways [44], is vital enzyme in the regulation of lipid metabolism and its effect on glucose control and diabetes has received intense interest [45]. The HSL-controlled lipolysis may also play a central role in the development of insulin resistance and the onset of metabolic syndrome also known as Syndrome-X [46]. Thus, the inhibition of HSL may reduce levels of circulating free fatty acid (FFA) linked to insulin resistance in obese patients. Still, to date, it is not clear whether a pharmacologically induced reduction in the release of FFA from adipocytes would be beneficial in the reduction of obesity. Post-heparin plasma lipolytic activity is measured by at least two lipase activities, the hepatic lipase (HL) and lipoprotein lipase (LPL). Using glycerol tri[1-14C]oleate as substrate and selective blocking of hepatic lipase activity with antiserum to rat hepatic lipase, lipoprotein lipase activity in post-heparin plasma is measured. Hepatic triglyceride lipase activity in post-heparin plasma is obtained by subtracting lipoprotein lipase activity from total plasma lipase activity.

Amylase: The digestion of carbohydrates during their transit through the gastrointestinal tract is allowed by supplementation with amylase which can tolerate the low pH of the gastric juice and even hydrolyzes the starchy foods and liberates maltoses.

Protease: The protease blend consists of proteases that are active in a wide range of pH's, ensuring that protein digestion will begin in the stomach and includes alkaline, neutral and acid proteases plus peptidase apart from a wide range of specificities (i.e. both endo- and exo-peptidase) in order to ensure the highest degree of protein degradation.

HMG-CoA (3 Hydroxy-3-Methylglutaryl-Coenzyme A) Reductase: HMG-CoA reductase is the rate limiting enzyme governing cholesterol biosynthesis and the synthesis of other isoprenoids in mammalian cells[47], on which more than 70% of total production of body cholesterol in humans is derived from denovo synthesis. When inhibiting hepatic HMG-CoA reductase, the inhibitors trigger an increased production of LDL receptors in the liver. As LDL receptor activity increases, more LDL is extracted from the blood and thus the level of circulating LDL-cholesterol is reduced.

ACAT (Acyl Coenzyme A: Cholesterol Acyltransferase): ACAT activity in liver microsomes and intestinal cell homogenates is determined by measuring the incorporation of [14C]oleoyl-CoA into cholesteryl oleate. Acyl coenzyme A: cholesterol acyltransferase (ACAT), catalyses the intracellular formation of cholesteryl esters, plays an important role in the intestinal absorption of cholesterol, foam cell formation within the arterial wall and VLDL production in the liver. The two isoforms of the enzyme includes, ACAT1 expressed in macrophages and ACAT2 expressed in intestine and liver. Exclusively from the gut, the unesterified form of cholesterol is absorbed, but appears in the lymph esterified with various long-chain unsaturated fatty acids. ACAT inhibitors also have potential actions beyond inhibition of cholesterol absorption. Inhibition of hepatic ACAT could reduce the production of cholesteryl esters for packaging into lipoproteins, while inhibition of ACAT1 in macrophages could reduce the deposition of cholesteryl esters and prevent the formation of foam cells and atherosclerotic lesions. Nevertheless, from investigations in ACAT2 knockout mice it is known that ACAT2 is not the only rate limiting pathway for cholesterol absorption. The inhibition of ACAT as treatment for hypercholesterolemia and atherosclerosis is an attractive target.

The Cholesterol 7α Hydroxylase: The determination of the percentage conversion of [14C] cholesterol to 7α-hydroxy[14C]cholesterol is used in the quantification of cholesterol 7α hydroxylase activity in the microsomes.

Squalene synthase: Squalene synthase (farnesyl diphosphate:farnesyl diphosphate farnesyl-transferase), an enzyme vital for cholesterol biosynthesis, catalyzes the dimerization of two farnesyl pyrophosphate molecules to form squalene, a key cholesterol precursor. Unlike HMG-CoA reductase inhibitors, squalene synthase inhibitors do not lower the levels of ubiquinone and dolicol *in vivo.*

Squalene Epoxidase: Squalene epoxidase, a microsomal enzyme, catalyses the oxidation of squalene to 2,3-oxidosqalene, the last reaction of non-sterol metabolites in the cholesterol biosynthesis pathway [48].

The production of biologically important non-sterol products, such as isoprenyl adenine, dolichol, coenzyme Q, or heme A, is not inhibited by squalene epoxidase inhibitors in contrast with HMG-CoA reductase inhibitors.

Strearoyl-CoA Desaturase-1 (SCD-1) and Fatty Acid Synthase (FAS): The amount of fat mass is increased when the number and/or size of adipocytes are multiplied by proliferation and differentiation. Differentiated adipocyte stores fatty acids (FAs) in the form of triglycerides (TGs) in their cytoplasm, with an involvement of various enzymes such as strearoyl-CoA desaturase-1 (SCD-1) and fatty acid synthase (FAS). This overall lipid synthetic process is called lipogenesis.

CYP7A1: CYP7A1 is the rate-determining enzyme in the biosynthetic pathway of bile acids from cholesterol in the liver for its excretion into the bile [49] which accounts for about 50% of the daily cholesterol excretion[50]. Xu *et al.* demonstrated that feeding rats with cholic acid and cholesterol down-regulates the transcription of CYP7A1 through simulation of the nuclear farnesoid X receptors [51].

Role of Harmones: Food intake and fat deposition are regulated by neurotransmitters peptides, most of the located in the brain, particularly in the hypothalamus [52, 53] and in the gut. This includes peptides that are orexigenic (appetite-stimulating) signals and anorectic peptides. Neuropeptide Y (NPY), orexins A and B, galanin, melanin concentrating hormone (MCH) and agouti-related peptide (AgRP) all act to stimulate feeding, while alpha-melanocyte stimulating hormone (αMSH), corticotropin releasing hormone (CRH), cholecystokinin (CCK), cocaine and amphetamine regulated transcript (CART), neurotensin, glucagons like peptide 1 (GLP1), calcitonin gene related peptide (CGRP), bombesin and ciliary neurotropic factor [54] have anorectic actions [55].

Leptin: Leptin, one of the most important adipose derived hormone is a 167 amino acid protein that is synthesized and secreted primarily by white adipose tissue, circulates in the blood and acts on receptors in the hypothalamus to decrease food intake and increase energy expenditure [56, 57], thus used in the treatment of obesity. The clinical studies showed that most of obese humans have higher plasma levels of leptin than nonobese individuals [58], suggesting that obesity is associated with leptin resistance rather than leptin deficiency. The Ob(Lep) gene (Ob for obese, Lep for leptin) is located on chromosome 7 in humans. In addition of being a biomarker for body fat, serum leptin levels also reflect individual energy balance. Leptin levels do not rise extensively after overfeeding but the dynamics of leptin due to an acute change in energy balance are related to appetite and eventually to food intake. The interaction of leptin with the CNS is through leptin receptors in endothelial cells that function as transporters [59], which aid to cross the blood-brain barrier, by two effects: Repression of anabolic circuits, causing decreased food intake and increased energy expenditure. Leptin action in the hypothalamus causes down-regulation of Neuropeptide Y (NPY) and AgRP. These are both potent orexigenic (appetite-stimulating) molecules which stimulate increased energy intake. Whilst NPY is the more potent of the two when measured over several hours, AgRP has much longer-lasting effects. Leptin is known to act on the ARC-PVN (arcuato-paraventricular-nucleus) feeding regulatory pathway, inhibition of a signal that produces positive balance involving NPY arcuato-paraventricular projection by leptin. Leptin acts centrally to inhibit the effects of NPY by decreasing its synthesis in the ARC and its concentration in the paraventricular nucleus (PVN) Activation of catabolic circuits, also causing decreased food intake and energy expenditure [60]. Leptin is necessary for the cleavage of the pro-opiomelanocortin (POMC) precursor molecule. This allows the hormone alpha-melanocortin stimulating hormone (α-MSH) to be produced. Low α-MSH levels activate melanocortin anorexia pathways, stimulating energy intake; the increase in α-MSH therefore inhibits energy intake. Deficiency in leptin leads to a syndrome of intense hyperphagia and morbid obesity in humans [61] and rodents [62], which can be reversed by administration of recombinant leptin [63].

Leptin Resistance and Obesity: Although leptin is a circulating signal that reduces appetite, in general, obese people have an unusually high circulating concentration of leptin (Wang *et al.* 1996), the people are said to be resistant to the effects of leptin, in much the same way that people with type 2 diabetes are resistant to the effects of insulin. The high sustained concentrations of leptin from the enlarged adipose stores result in leptin desensitization. The pathway of leptin control in obese people might be flawed at some point so the body doesn't adequately receive the satiety feeling subsequent to eating.

Resistin: Adipocytes secrete a unique signalling molecule, which we have named resistin (for resistance to insulin). Circulating resistin levels are decreased by the anti-diabetic drug rosiglitazone and increased in diet-induced and genetic forms of obesity. Administration of anti-resistin antibody improves blood sugar and insulin action in mice with diet-induced obesity. Moreover, treatment of normal mice with recombinant resistin impairs glucose tolerance and insulin action. Insulin-stimulated glucose uptake by adipocytes is enhanced by neutralization of resistin and is reduced by resistin treatment. Resistin is thus a hormone that potentially links obesity to diabetes. Resistin-like molecules (RELMα) are a secreted protein that has a restricted tissue distribution with highest levels in adipose tissue. Another family member, RELMβ, is a secreted protein expressed [64].

Orexin: Orexin-A and orexin-B are 33-and 28- residue peptides, present in locus coerulus, are also called as hypocrites and are released by the hypothalamus. The oxerins control the feeding and energy metabolism. Food consumption is dose dependently increased after intracerebroventricular infusion of orexin A and B to rats. Oxerin antagonists are potential anti obesity drugs. The neuropeptides orexins/hypocretins are essential for normal wakefulness and energy balance and disruption of their function causes narcolepsy and obesity one of the main targets of orexinergic neurons is the arcuate nucleus (ARC) of the hypothalamus, which plays a key role in feeding and energy homeostasis. ARC neurons coexpress orexin receptors and glutamate decarboxylase-67 and are excited by orexin. Acting on postsynaptic orexin type 2 receptors, orexin activates a sodium-calcium exchange current, thereby depolarizing the cell and increasing its firing frequency. Because GABA is a potent stimulus for feeding, in both the ARC and its main projection site, these results suggest a mechanism for how orexin may control appetite [65].

Galanin: Galanin, a 29 amino acid C-terminally amidated peptide (30 amino acids in humans), is localized mainly in the mammalian CNS and also in other organs. The food intake increased by central administration of galanin and decreased by administration of galanin receptor antagonists [66, 67] through the interaction with at least three G protein coupled receptors, designated GAL1, GAL2 and GAL3 receptor, galanin mediates its physiological effects. The activity of galanin in the hypothalamus is modulated by metabolic hormones and by the ingestion of nutrients.

Agouti-Related Protein: Agouti-related protein affects pigmentation when its expression is limited to the skin, but ubiquitous expression causes obesity [68]. The hypothalamic expression of agouti related protein is regulated by leptin and overexpression of agouti related protein results in obesity and diabetes [69]. Agouti-related protein is a neuropeptide implicated in the normal control of body weigh downstream of leptin signaling.

Melanin Concentrating Hormone: Melanin concentrating hormone (MCH), a cyclic 19 amino acid neuropeptide was originally found to regulate pigmentation in fish and plays a role in the central feeding behavior increasing food consumption [70]. MCH may be a target of leptin signaling [71] and a functional melanocortin antagonist in the hypothalamus [72].

Neuropeptide Y: It is a 36 amino acid peptide that is widely distributed throughout both the central and peripheral nervous systems, which plays a key role in the control of body weight. Neuropeptide Y mediates its physiological effects via interaction with at least six distinct G protein coupled receptors, designated Y1, Y2, Y3, Y4, Y5 and Y6. NPY neurons in the hypothalamic PVN play a critical role in regulating energy homeostasis in the body [73]. NPY released from these neurons increases food intake[74], reduces thermogenic capacity [75] and reduces the oxidation of dietary fat. NPY also has inhibitory effect on sympathetic outflow to brown adipose tissue in rodents and thus decreases the metabolic rate [76]. It is one of the several orexigenic peptides that when given repeatedly results in the development of obesity, with all of the expected metabolic sequelae. Blockade of NPY action by antibodies or pharmacological antagonists decreased food intake. NPY in ARCPVN neurons may interact in a homeostatic loop to regulate body fat mass by leptin. Pharmacological studies have implicated the hypothalamic Y5 subtype as a mediator of the effects of NPY on food intake and energy homeostasis.

Cocaine- and Amphetamine-regulated Transcript: Cocaine- and amphetamine-regulated transcript (CART), a brain located peptide, has potent appetite suppressing activity and is closely associated with the actions of leptin and neuropeptide Y. A role of CART peptides in substance abuse and addiction is suggested by psychomotor-stimulant regulation of CART transcription in the striatum, as well as its localization within neural circuits that mediate reward and reinforcing behaviors [77].

Adipsin: Adipsin proteins of the alternative complement pathway are secreted by adipose tissue [78]. Adipsin (complement D) was the first to be cloned from an adipose tissue cell line and shown to be synthesized and secreted by adipose tissue. In contrast to rodents, adipsin increases with adiposity in humans and in response to feeding and is decreased during fasting, cachexia and lipatrophy [79]. Adipsin is required for the synthesis of acylation stimulating protein (ASP), a protein implicated in fat metabolism [80]. ASP is produced by the cleavage of C3a by carboxypeptidase and is highly expressed bymature adipocytes. The synthesis of C3a from C3 requires complement factor B and adipsin. Plasma ASP increases with meals and facilitates the synthesis and storage of triglycerides. Consistent with its role as a mediator of lipogenesis, ASP deficiency increases postprandial fatty acid levels and decreases weight gain and trigylceride synthesis in mice. Several other factors, such as adiponectin are involved in the function of adipose tissue acting as target as well as an endocrine organ.

Ghrelin: Small synthetic molecules called growth hormone secretagogues (GHSs) which act through the GHS-R, a G-protein-coupled receptor stimulate the release of growth hormone (GH) from the pituitary. The natural ligand of this receptor was discovered as a 28-aminoacid-containing peptide, called ghrelin[81], produced in the XA-like cells of the stomach; however, smaller amounts of ghrelin are also found in the small and large intestine. Ghrelin and the growth hormone secretagogue receptor were expressed in the rat adrenal cortex and also in human T cells, B cells and neutrophils. Ghrelin is the first peptide hormone with its third amino acid serine modified by a fatty acid which is essential for the peptide's biological activity. Beside ghrelin's GH releasing effect, it is a powerful appetite-simulating peptide. Plasma ghrelin concentration is increased in fasting conditions and reduced after habitual feeding, suggesting that ghrelin may act as an initiation signal for food intake. Chronic systemic or intracerebroventricular application to rats produced hyperphagia and obesity in rats. The appetite stimulatory signal of ghrelin is mediated through action on the hypothalamic neuropeptide Y (NPY) and the Y1 receptor. [125I-His 9]-ghrelin was recommended as a radioligand for localizing GHS and GH receptors in human and rat tissue. Various heterocyclic compounds acting as ghrelin receptor agonists have been developed, whichmight be useful for the treatment of anorexia nervosa. Multiple ghrelin-derived molecules produced by

post-translational processing were identified indicating structural divergence of human ghrelin. Until now, however, no specific ghrelin receptor antagonist has been described, although such a compound might be an attractive approach to reduce feed intake and to decrease obesity.

CONCLUSION

Among so many factors involved in obesity, physiological factors are very important to know about the exact mechanism involved in obesity.

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