

## Review

## Some important peptides and their role in obesity-current insights

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## ABSTRACT

**Background:** Different Signalling molecules, especially different peptides are the key modulators in various metabolic disorders, including obesity. Their expression at the cellular level changes the disease prognosis.**Aim:** The aim of present review is to enlist them all, and mention their significance in obesity, which helps researchers in drug discovery and future medicine.**Material and methods:** The last 20 years data has been searched and studied to mention their current role in obesity treatment and ailments of disease.**Results and conclusion:** This article stated the importance of various peptides, tissues and mast cells with their significance in relation to obesity. Authors also enlisted their role in other metabolic disorders because these complications are associated with obesity. This article will help researchers to explore the potential of mentioned peptides in drug discovery to cure metabolic disorders.

## 1. Introduction

Obesity is a complex, chronic disease, results in an imbalance of food intake, metabolism and energy expenditure (Flier, 2004). The pathological observation includes the enlargement of fat cells. These fat cells have increased production of various biomarkers like inflammatory Adipokines (TNF- $\alpha$ , Interleukins 6 & 18], Plasminogen activation inhibitor-1 (PAI-1), Angiopoietin like protein-2 (Angpt2), and vascular cell adhesion molecule (VCAM-1) that all of them could promote obesity (Angelopoulos et al., 2012; Ouchi et al., 2012; Prashar et al., 2017). This study is an updated review, explains the role of signalling molecules like Adiponectin, Cytokines, Leptin, (PPARS), Interleukin-6 (IL-6), Ghrelin, Cholecystokinin (CCK), Renin Angiotensin Aldosterone (RAAS), Insulin, Neuropeptide Y (NPY) in obesity. The previous reports published and other available data indicated the role of these molecules in obesity but a concise update needed, so we have taken the responsibility to explore their role in obesity.

## 2. Methods

PubMed, Scopus, Google's scholar and web of science were searched for studies reported in last 20 Years (1997–30/4/2019). The data were searched and archive by keywords like “Biomarkers” “obesity” and “role of Peptides or signalling molecules in obesity” without narrowing

or limiting search items. Only abstracts of searched publications were reviewed. Total 423 publications found in initial research, in which 92 publications were considered for study and remaining was excluded because of its specificity to the subject.

## 3. Role of adipose tissue &amp; adipokines

Adipose tissue exists as two forms in the human body, named as brown adipose tissue (BAT) and White adipose tissue (WAT) (Ahima and Flier, 2000; Kershaw and Flier, 2004). These ATs have stored amount of triglycerides by which they utilize energy, for example. WATs maintain the energy needed by organism and on the other side, BATs store fat for heat expenditure so both will maintain the store of energy and regulate the body temperature in hibernating or also in new-born mammals (Sartipy and Loskutoff, 2003) [Tables 1 and 2] (Figs. 1 and 2).

Adiponectin is one of the adipokine secreted by adipose tissue, which is helpful to perform different biological procedure of human body Adiponectin exert its action through receptors AdipoR1, AdipoR2, T-cadherin. In muscle AdipoR1 is exhibit, while in liver AdipoR2 is mainly exhibit. AMPK and PPAR $\alpha$  pathway in liver and skeletal muscle are magnified by adiponectin. Adiponectin show many function like expand fatty acids oxidation, control glucose level and manage receptor activity. Circulating level of adiponectin is lower in case of obesity,

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**Table 1**  
Examples of receptors expressed by Adipocytes.

Receptor type	receptors expressed by adipocytes.
Cytokine receptor's	Leptin, TNF- $\alpha$ , IL-6
Nuclear hormone Receptors	Androgen, oestrogen, glucocorticoid, progesterone, Thyroid hormone
Other endocrine Hormone receptors	Insulin, glucagon, growth hormone, Angiotensin 1 and 2, Adiponectin
Catecholamine Other receptors	$\alpha$ 1, 2; $\beta$ 1, 2, 3 PPAR- $\alpha$ , - $\gamma$ , - $\delta$ ; RXR (retinoid . receptor) prostaglandins

PPAR, peroxisome proliferators-activated receptor; TNF, tumor necrosis factor; IL, Interleukin.

insulin resistance and other metabolic disorder.

#### 4. Role of mast cells and its secretory substances

Mast cells are a type of immune cells, and produce by bone marrow. These cells located in most tissues like skin, mucosal membrane and respiratory tract, and it quickly pass through the blood wall to reach other tissues (Vague et al., 1965; Rodbell et al., 1965; Himms-Hagen, 1990; Shoelson et al., 2006). MCs contribute to obesity by affecting energy expenditure, adipose tissue angiogenesis, and preadipocyte differentiation. MCs are available at the micro vessels, and its populations were increased continuously in early phase of obesity (Bartelt et al., 2011). At cellular level, Mast cell's acts as reservoirs for inflammatory cytokines to stimulate vascular cells (Fredriksson et al., 2005) and adipocytes (Gurish and Boyce, 2002) to release cysteinyl cathepsins—an important proteases that can catabolize ECM protein fibronectin to promote adipogenesis, and degrade intracellular insulin receptor and glucose transporter (Glut)-4, leading to impaired insulin and glucose sensitivities may cause metabolic dysfunction (Metcalfe et al., 1997; Bais et al., 2017).

#### 5. Role of gut hormones

- A. Role of glucagon-like peptide (GLP) 1:** the distribution of GLP-1 receptors are in most of the cells in human body, specially adipose tissue. The effect of GLP in adipose tissue to increase glucose uptake which results in reduced appetite, gastric emptying and food intake. GLP-1 receptor agonists preferred in therapy to treat T2DM, improve insulin sensitivity and b-cell functions (Drucker and Nauck, 2006; Nauck et al., 2011). At molecular level GLP is secreted by L cells in the intestinal wall and quickly broken down by dipeptidyl peptidase-4 (DPP-4) within 3–4 min and it affects postprandial insulin secretion and blood glucose level (Zander et al., 2002; Meier, 2012). The lipolytic activity of GLP-1 is reported as controversial with concentration, at lower dose it act as lipogenic and in higher dose it act as lipolytic (Meier, 2012). Furthermore, GLP-1 knockout mice did not show weight gain or increased fat mass from a high-fat diet compared with non knockout mice (Hansotia et al., 2007) [Table 3][Fig. 3].
- B. Role of Cholecystokinines (CCK) in Obesity:** CCK is one of the intestinal peptide (Gibbs et al., 1973), secreted by the, I cells in various locations like lower GIT, Brain cells, enteric nervous system (Rehfeld, 2004). It secreted in response to food intake, to stimulate pancreatic hormone secretion, bile secretion (Liddle et al., 1985) and delayed the gastric emptying (Moran and McHugh, 1982). CCK is the first known hormone to acts as a hunger suppressant (Gibbs et al., 1973). CCK peptides interact with two receptors expressed in the gut and brain. CCK receptor 1 (CCK1R, formerly known as CCK-

A, for “alimentary”) predominates in the GI system, whereas CCK2R (formerly known as CCK-B, for “brain”) predominates in the brain. Through endocrine and/or neural mechanisms, CCK regulates many GI functions, including satiation it interacts with two types of receptors CCK1 and CCK2, which are present in GUT and Brain (Gibbs et al., 1973). CCKA or CCK1 receptor plays an important role in food intake regulation due to its location in pancreas and in afferent neurons of vagus nerve (Mora et al., 1986; Moran et al., 1998). A study reported that the rats, lacking CCKA expression had high food intake, which may cause obesity and hyperglycemia (Moran et al., 1998).

- C. Role of Oxyntomodulin:** Oxyntomodulin (OXM) is a peptide hormone which released in gut area and acts on both GLP-1 receptor and glucagon. Their combined effect leads to weight loss when given with GLP1R agonist. It also reduce food intake and modulates energy expenditure in metabolic imbalance. The activation of glucagon receptor (GCGR) increases the hyperglycemic risk by increase in production of glucose which is further counteract by activation of GLP1R so basically, OXM modulates glucose tolerance and become a new dual agonist of GCGR and GLP1R to treat diabetes and obesity (Pocai, 2013).

#### 6. Role of gut proteins

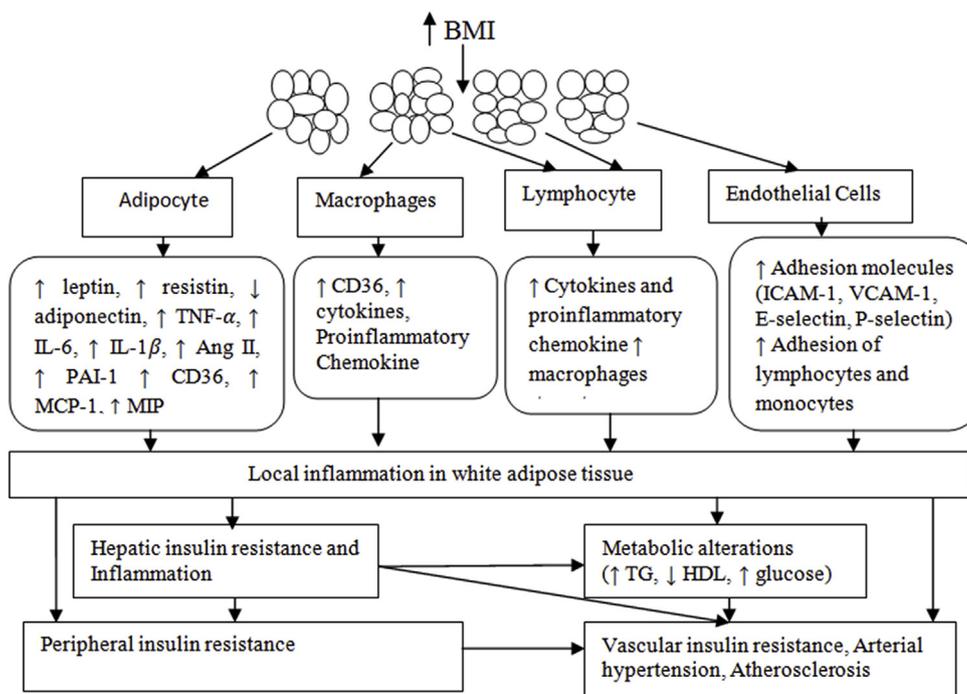
- A. Role of Ghrelin in Obesity:** Ghrelin level and their role in obesity are still controversial because on some extent, their level is decreased in obesity but in meantime it also causing weight gain by increasing food intake and reducing fat utilization. It binds to NPY/Agouti-related protein (AGRP) neurons and promote the GABA mediated appetite stimulation and release of corticotropin-releasing factors (CRF). Experimentally its administration also showed the initial rise in appetite, and its level was up regulated in fasting condition and pathologically tissue showed hyperphagia. The ghrelin level is also correlated with excessive food intake because, (i) if its level decreases the patient feel Hungry for the longer period of time. (ii) If its level increased by the consequences of first reason the feeling of satiety not elicited so again the person sifted to higher feed intake (Trujillo et al., 2004; Petersen et al., 2005; Sam et al., 2012; Heppner and Tong, 2014; Higgins et al., 2007).
- B. Role of NPY in Obesity:** Neuropeptide Y (NPY) is a member to the peptide family belongs to endocrine peptides like polypeptide (PP) and peptide (PYY) (Kimmel et al., 1968). It is present at higher concentration in various regions within the brain like Hypothalamus (Allen et al., 1983). It acts as an orexigenic hormone so its abnormal stimulation causes a more food intake (Edwards et al., 1999; Kalra and Kalra, 2004). This hormone was studied by several scientists in obesity because of their effects in feeding behavior, CVS complication and its release along with nor epinephrine (Pedrazzini, 2004). It acts on ARC sites of NPY receptors with neuronal binding and stimulates the food intake by central mechanism (Inui, 2000). NPY receptors belong to Five G-protein coupled NPY receptors subtypes identified as- Y1, Y2, Y4, Y5 and Y6 and act by decreasing adenyl cyclase & cAMP levels in hypothalamus and increase intracellular calcium (Gehlert, 2004; Wahlestedt and Reis, 1993).

Administration of exogenous neuropeptide Y in specific regions within the brain causes a significant increase in starvation or appetite through neuronal pathways, so it has an important role in energy homeostasis (Clark et al., 1984; Stanley et al., 1983, 2001). Hence, neuropeptide Y release in the hypothalamus is most critical in the regulation of energy homeostasis. Central administration of neuropeptide Y to rats also reduces energy expenditure by decreasing sympathetic nervous system activity; as a result, thermogenic activity in brown adipose tissue and a key regulator of energy expenditure in rodents, it also decreases the thermo-genics activity in BATs by decreasing the sympathetic activity (Egawa et al., 1993). NPY affects both food

**Table 2**  
List of adipokines and their endocrine functions.

Adipocyte derived Proteins	Metabolic regulation	Effects
TNF- $\alpha$	Increased	Promotes insulin resistance
IL-6	Increased	Promotes insulin resistance
IL-18	Increased in obesity	Proatherogenic
Leptin	Increased in obesity	Promotes insulin resistance Modulates immune response Suppresses appetite
Adiponectin	Decreased	Anti-inflammatory Promotes insulin sensitivity Stimulates fatty acid oxidation Antiatherogenic
Visfatin	Increased in obesity	Promotes insulin resistance
Resistin	Increased in obesity	Promotes insulin resistance
MCP-1	Increased in obesity	Encourages macrophage migration Proatherogenic
PAI-1	Increased in obesity	Promotes insulin resistance Promotes insulin resistance Proatherogenic
Adipsin	Increased in obesity	Modulates glucose, lipid metabolism
ASP	Increased in obesity	Modulates glucose, lipid metabolism
MIF	Increased in obesity	Inhibits macrophage migration
C-reactive Protein	Increased in obesity	Proinflammatory, atherogenic

Where MCP-1, macrophage chemo attractant protein 1; TNF, tumor necrosis factor; IL, interleukin; PAI, Plasminogen activator inhibitor; ASP, Acylation stimulating protein; MIF, macrophage Migration inhibitory factor.



**Fig. 1.** Figure showing the role of WAT in obesity and its related complications. Its showing the migration of Proinflammatory cytokines with increased in body mass index (BMI) that leads to hepatic insulin resistance and altered metabolism (Vague et al., 1965).

consumption and energy expenditure, which leads to imbalance body homeostasis and promotes a weight gain. A study, showed when the chronic dose of NPY is given to rats, its produces a sustained hyperphagia and increased body weight (Zarjevski et al., 1993).

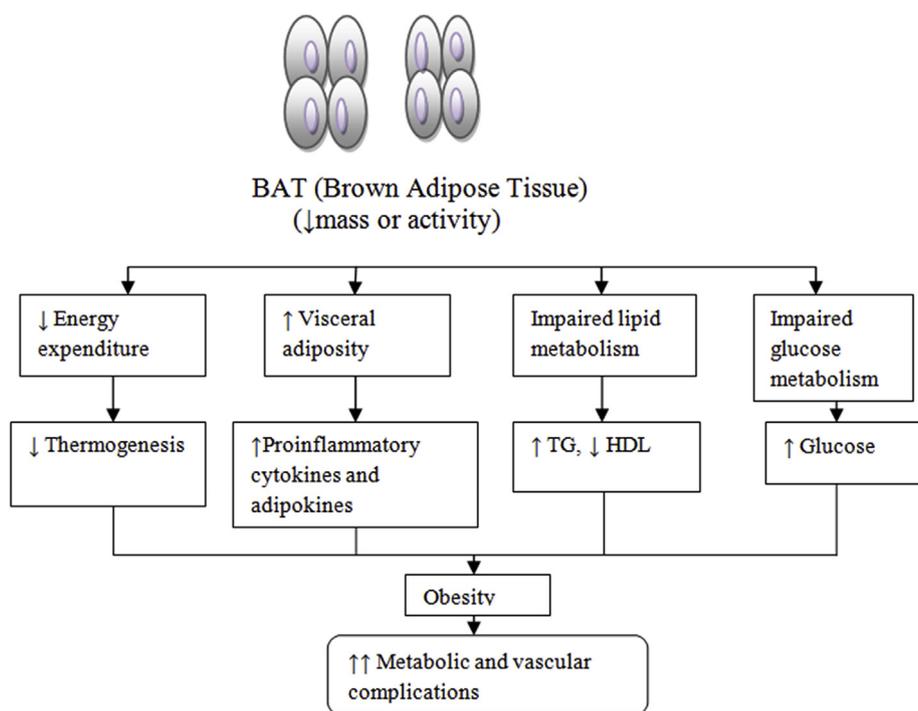
**7. Role of interleukins**

Interleukins are the pleiotropic cytokines. The level of Interleukins (IL) has been shown high in overweight patients. Among IL family some interleukins like IL-1 $\alpha$ , IL-1 receptor antagonist (IL-1ra), IL-1 $\beta$ , IL-6 and IL-18 are proved as promising target to treat obesity (Osborn et al., 2008). These pro inflammatory cytokines are produced by adipose

tissue, elevated in adult obesity and share a similar signal transduction pathway (Juge-Aubry et al., 2003). IL-6 plays an important role in regulation of various inflammatory mediators in host defense mechanism (Wang et al., 2003). The nature of IL-6 is lipolytic and found as a marker in visceral adiposity to stimulate the lipolysis in human and affect's oxidation of fats (Nagasawa et al., 2006; Akira et al., 1993). Inactivation of IL-6 receptor gene in cells displays increased inflammation, which leads to obesity (Hall et al., 2003).

**8. Role of TNF- $\alpha$**

TNF- $\alpha$  was first identified in adipose tissue of rodents in 1993,



**Fig. 2.** The figure showing the role of BATs in obesity. It indicates the change (↓) in amount of BATs in the body leads to alteration in lipid metabolism and as disease progress, the expression of cytokines and adipokines also results in vascular complications (Rodbell et al., 1965; Himms-Hagen, 1990).

expressed both in mature adipocytes and the stromal-vascular cells (Hotamisligil et al., 1993). The secretion of TNF-α from stromal-vascular leads to body weight loss (in vivo) and suppressed lipogenesis (in vitro) (Cerami et al., 1985), by suppression of lipoprotein lipase and induction of proteolysis through the ubiquitin-proteasome proteolytic pathway (Tracey et al., 1990). Its production by adipose tissue is correlated with existence of insulin resistance, obesity and hyperinsulinemia (Wang and Trayhurn, 2006). It modulates glucose transport

in insulin sensitive tissue and insulin resistance in tissue by IR signalling (Hotamisligil et al., 1993). Its activated two of its subtype receptors in human adipose tissue and acts as an inhibitor of adipocyte differentiation, by suppressing release of peroxisome proliferator-activated receptor-γ2, lipoprotein lipase, glycerol-3-phosphate dehydrogenase and glucose transporter type 4 (Peraldi et al., 1997). TNF-α also affects the expression of several adipocyte-secreted factors, including interleukin (IL)-6, monocyte chemoattractant protein (MCP)-1 and nerve

**Table 3**  
Different peptides and their target used for obesity treatment.

S. No.	Target/Peptides	Drugs	Manufacturing Company/Assignee
	Y5-receptor antagonist	Velneperit MK-0557	Schering Corporation Shionogi USA, Inc
	Leptin analogue	Metreleptin	Takeda Pharmaceutical Company Limited, Japan
	Amylin analogue	Pramlintide	Amylin Pharmaceuticals, Inc.
	Leptin sensitizer	PTP1B blocker Calbiochem CAS765317-72-4	Merk millipore
	Leptin sensitizer	4- phenyl butyrate (PBA)	Sigma-Aldrich, USA
	Leptin sensitizer	Tauroursodeoxycholic Acid (TUDCA)	Children's Medical Center Corporation, USA
	AgRP inhibitor	TTT-435	TransTech Pharma vTv Therapeutics Inc. 4170 Mendenhall Oaks Pkwy., High Point, NC
	Y2/Y4-receptor agonist	Obinepitide	7TM Pharma, Denmark
	Y4-receptor agonist	TM30339	7TM Pharma, Denmark
	CCK1R agonist	GI181771X	GSK, UK
	GLP1R agonist	Lixisenatide	Zealand Pharma, Denmark
	GLP1R agonist	CJC-1134-PC	Conju Chem Biotechnologies Inc., U.S.
	GLP1R agonist	Albiglutide	GSK, UK
	GLP1R agonist	Taspoglutide	Roche, Switzerland
	GLP1R agonist	LY2189265	Eli Lilly, US
	GLP1R agonist	Liraglutide (Saxenda)*	Novo Nordisk, Denmark
	Y2R agonist	PYY3-36	Merck
	GLP1R agonist	OXM, albiglutide	GSK, UK
	OXM analogue	TKS1225	Thiakis/Wyeth/Pfizer
	NOX-B11	Ghrelin vaccine	PROLOR Biotech
	GOAT inhibitors	Ghrelin inhibitors	Pfizer
	AOD-9604	GH lipolytic domain analogue	Alizyme
	T-BVT	White adipose tissue selective 11β-HSD1 inhibitor	Phosphagenics
	SRT1720	SIRT1 activators	Takeda Pharmaceutical Company Limited
	NOX-B11	Ghrelin vaccine	Amylin Pharmaceuticals, Inc.
	GOAT inhibitors	Ghrelin inhibitors	Syracuse University
	ATL-962 (Cetlistat)	Lipase inhibitor	Alizyme; Takeda

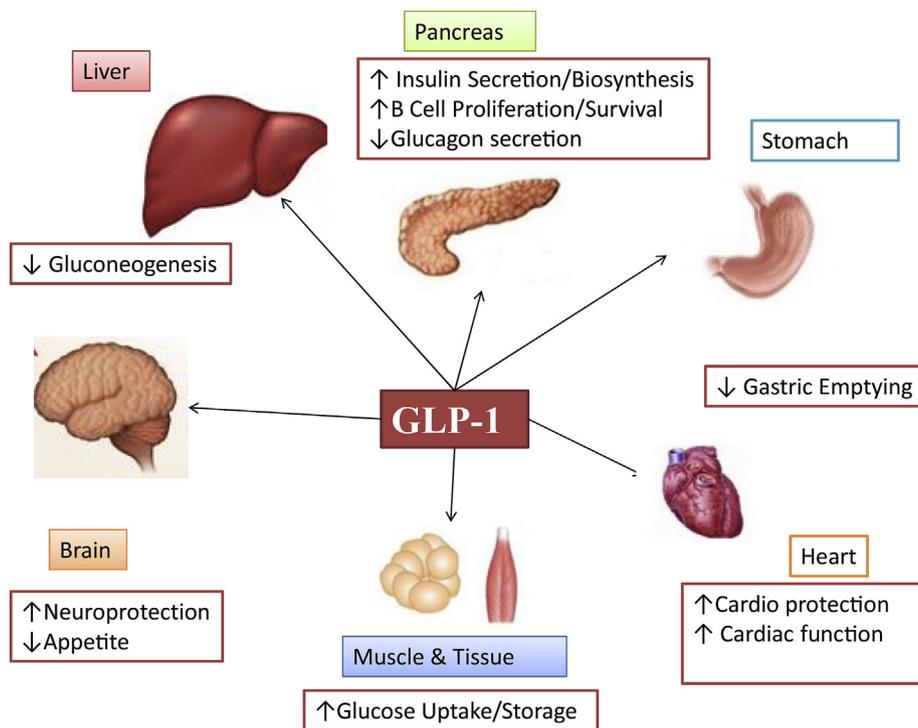


Fig. 3. GLP-1 coordinated activities in liver, brain, pancreas, heart, muscle and adipose tissue.

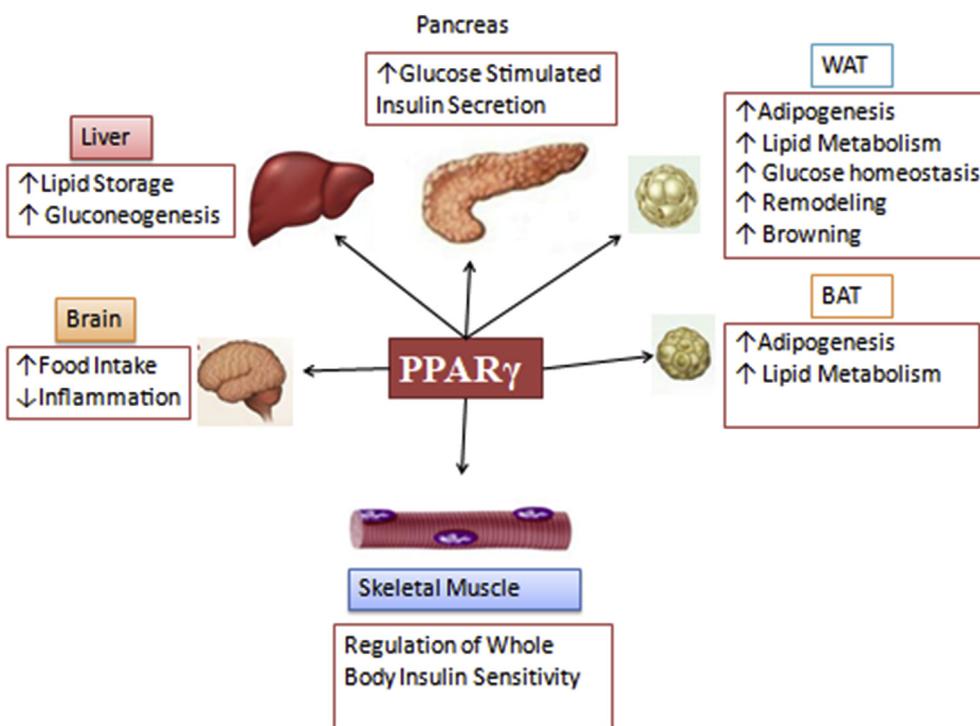


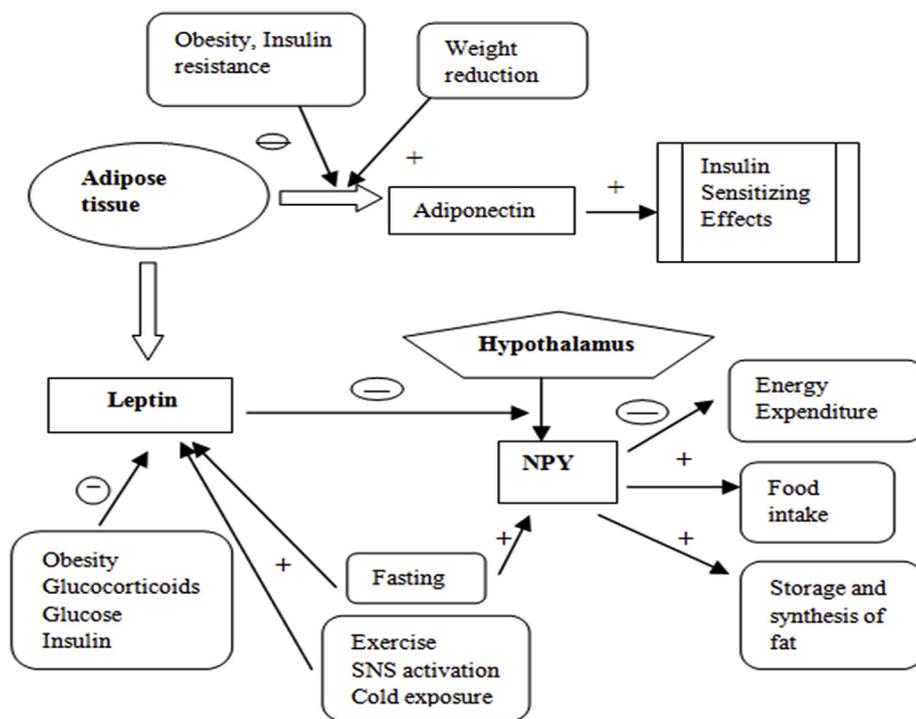
Fig. 4. PPAR-γ coordinated activities in liver, brain, pancreas, muscle and adipose tissue.

growth factor, whose levels are substantially increased with the administration of TNF-α in vitro (Wang and Trayhurn, 2006; Peraldi et al., 1997). Finally, in the obese state, TNF-α also contributes to the elevated plasminogen activator inhibitor-1 levels associated with obesity and acute inflammatory conditions (Pandey et al., 2003). TNF-α and its two receptors are expressed in human adipose tissue. In obesity induced inflammation, it mediate the insulin resistance by Intracellular pathways including JNK, IKKb/NF-κB and factors mediating ER stress. This

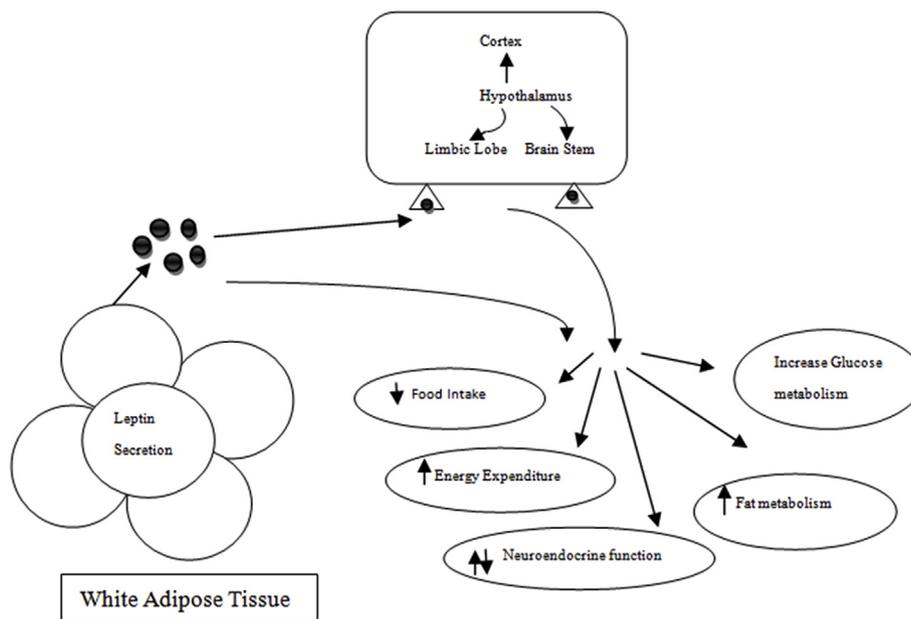
also results in accumulation of immune cells like T-lymphocyte and other mast cells to promote release of TNF-α in obesity.

### 9. Role of PPARs in obesity

Scientists have reported four types PPARs in human body; α, β, γ, and δ, each of which is expressed in a tissue-specific manner. PPARs have been suggested to relate to the crossroads of obesity, diabetes,



(a): Schematic representation of physiological actions by Leptin



(b): Schematic representation of physiological actions by Leptin.

Fig. 5. (a): Schematic representation of physiological actions by Leptin. (b): Schematic representation of physiological actions by Leptin.

inflammation, and cancer (Vitale et al., 2016). PPARs are a group of ligand-activated nuclear hormone receptors. These transcription factors exist within a protein superfamily, which includes the receptors for retinoids, vitamin D, steroids, and thyroid hormones. PPAR $\alpha$  is a type of nuclear receptor, located in tissues of liver, BATs, Muscular tissues, and on heart muscles. It is well known for metabolism and energy expenditure (Mandard et al., 2004). On activation, it suppresses the growth and differentiation into adipocytes through change in genetic

expression. It is stimulated by various stimuli like unsaturated fatty acids, Prostaglandin derivatives and its agonist (Harano et al., 2006). On activation, it maintains the fat storage in liver and its agonist acts as an anorexic (decrease the appetite) and in obesity management therapy (Tsuchida et al., 2005). the role of PPAR $\alpha$ , in liver to increase energy availability for peripheral tissue to fulfill the demands of heart, muscle, kidney, and brown AT during fasting. PPAR $\alpha$  ligands are proven for their prooxidative anti lipotoxic effects and found effective in treatment

of hypertriglyceridemia (Lalloyer et al., 2011; Staels et al., 2008). Skeletal muscles have PPAR  $\beta/\gamma$  expression to sustain the energy requirements for physical exercise by fatty acid oxidation (Holst et al., 2003). This expression is also expressed in adipocytes and macrophages to reduce the expression of pro inflammatory markers like nuclear factor kappa B (NF- $\kappa$ B) (Zoete et al., 2007; Zingarelli et al., 2010). PPAR $\gamma$  is expressed in BAT and WAT type to provide anabolic effect to promote fat storage, adipogenesis, and thermogenesis (Siersbaek et al., 2010; Ferre, 2004). PPAR $\gamma$  exist in two isoforms, PPAR $\gamma$ 1 and PPAR $\gamma$ 2, both involve in uptake of glucose and lipids (Medina-Gomez et al., 2005). When interpreting the role of PPAR isoforms on the maintenance of energy homeostasis, it is important to consider the effect that the ectopic induction of PPAR $\gamma$ 2 contributes to facilitating the re-organization of the inter-organ communication of nutrients and energy fluxes, which will help to understand how, when defective, it may lead to insulin resistance (Tontonoz and Spiegelman, 2008) [Fig. 4].

## 10. Role of leptin in obesity

Leptin acts, as an internal mediator, produced by white adipose tissue. It involves in controlling of appetite. It acts by sending signals to reduce the Neuropeptide Y (NPY) production. Leptin is released chemically when people feel hungry to enhance the production of NPY by sending signal to the hypothalamus (Tontonoz and Spiegelman, 2008; Sun et al., 2007). Thus NPY stimulates the food intake and also decreases the adrenaline release to lower the energy expenditure. NPY promotes the synthesis and storage of lipid through an enzyme called lipoprotein lipase in adipocytes (Sun et al., 2007). Another role of leptin is to increase the gene expression of corticotrophin releasing factor, which reduces the food intake (Liu et al., 2009). Leptin release is also affected by melanocyte stimulating hormone (MSH) (Yang et al., 2007). So overall its role is to decrease appetite and increase in energy expenditure (Fig. 5a).

### 10.1. Mechanism of leptin action

It activates the specific leptin receptor isoforms, located in various areas of hypothalamus, cortex, cerebellum, thalamus and other endothelial lining of brain capillaries (Yang et al., 2007; Fruhbeck et al., 1998; Diamond and Eichler, 2002; Harris et al., 2001; Friedman, 1997) (Fig. 5b).

## 11. Role of renin angiotensin/aldosterone in obesity

The renin-Angiotensin-Aldosterone system (RAAS) maintains the body homeostasis and activated in response to blood loss, salt and water retention (Halaas et al., 1995; Brewster et al., 2003). In obesity or hypertension, the patient is more prone to over activation of this system in both animals and humans (Weber, 2001). The literatures suggested that RAAS is disturbed in a patient of visceral adiposity and found elevated when compared with control patients (Engeli et al., 2005; Uckaya et al., 1999). In a controlled study where RAS is non-suppressed, the rats provided with high salt and high-calorie diet, which showed its importance in regulation of hypertension or other CVS complications. This hypothesis is supported by another study, where the rise in AG-I, AG-II & renin level found significant in humans. This shifted patient to on more risk of increasing sympathetic tone, especially in CVS disease or obesity (Weber, 2001; Engeli et al., 2005).

The stimulation of sympathetic nervous system with these complication results in higher AG-II level in obese people as compare with lean individuals (Uckaya et al., 1999; Troisi et al., 1991). The expressions of this peptide were found increased in adipose tissue so why the most Angiotensin-converting enzyme inhibitors lead to weight (Uckaya et al., 1999; Troisi et al., 1991; Goossens et al., 2007; Gorzelnik et al., 2002).

## 12. Role of insulin in obesity

Insulin is a hormone that regulates the blood-glucose level within the body. The actions of insulin are mediated via the insulin receptor (IR); these receptors belong to a family of tyrosine kinase receptors and subcategorized into insulin-like growth factor (IGF) I receptor insulin binding receptor (IBR) (Aneja et al., 2004). Insulin secretion is depended on concentration of blood-glucose level, which is also correlated with the body adiposity (Patti and Kahn, 1998). In a study, direct administration of insulin causes an anorexigenic effects, which leads to reduction of body weight. So the diseases with insulin resistance or inhibitors of insulin release increase the food intake and cause weight gain (Polonsky et al., 1988; McGowan et al., 1993; Obici et al., 2002). An Insulin resistance in adipocytes leads to lipolysis and formation of more glycerol and free fatty acids in blood circulation. It is one of the contributory factors in various CVS and metabolic disease. In a visceral adipose tissue, Insulin resistance causes an Insulin Resistance Syndrome (IRS) and the availability of other cytokines & FFA further leads to change in insulin sensitivity to impair body homeostasis and lipid metabolism (Bais et al., 2014).

## 13. Conclusion

This article stated the importance of various biomarkers and their significance in relation to obesity. Authors also enlisted their role in other metabolic disorders because these complications are associated with obesity. This article will help researchers to explore the potential of mentioned peptides in drug discovery to cure metabolic disorders.

## Conflicts of interest

All authors have none conflict of interest.

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