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Role of Inflammatory mediators in Obesity

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ABSTRACT :
Obesity is classified via an overabundance of fat in the body. It is indeed a long-term medical condition which really raises the chance of developing many disorders and health complications, including such heart disease, diabetes, high blood pressure, and some cancers.Obesity is a disease in which inflammation plays a major part.There are a number of inflammatory mediators that play an important role in the development of obesity.These inflammatory factors interrupt regular cell-to-cell communication across adipose & its components, resulting in a change in physiological and immune status as well as a disrupted physiology and secretion that is abnormal can exacerbate the inflammatory process in obesity.We look at how inflammation affects adipose tissue &how it contributes to the development of obesity. In this review article, we understand the mechanism of inflammatory mediators that induce obesity.
Keywords : Obesity , cytokines , adipocytes , macrophages,Inflammation, Interleukins.

I. INTRODUCTION :

Obesity is now a global problem, with about a third of the worldwide and now identified as severely obese [1]. Obesity is more common in females than males, and it gets worse as become older. Obesity in kids and teenagers is on the rise at an accelerated rate [2]. As a result, obesity, or the development of extra weight, has a detrimental effect over almost most biological functions of the human body and it has become a major global crisis [3].Due to the process of inflammation, obesity is persuade and is characterised by an increment in the amount and stimulation of immune system, such as macrophages, neutrophils, and T helper cells, result in the formation of proapoptotic cytokine factors (TNF-), interleukins, and thereby disrupting anti-inflammatory cells and lowering adiponectin production, predisposing to vasculitis [4]. Inflammation caused by obesity has been linked to the development of insulin resistance, (T2DM), heart disease, and metabolic disease. It's also implicated in the pathogenesis of other conditions including eczema, renal failure, polycystic ovary syndrome (PCOS), and leukemia [5]. The adaptation about the modern Western behavior is correlated with a rise in the prevalence of metabolic disease in all over the world [6 -7]. The secretion of proinflamma-tory factors by adipocytes, such as tumour necrosis factor (TNF)-a, interleukin (IL)-6, leptin, and plasminogenactivator inhibitor-1, causes systemic inflammation in obesity [8-9]. Therefore , the aim of this article is to evaluate the effect of inflammation and its mediators induced obesity.

Inflammation:

At some of the most general level, a disease or injury induces an inflammatory state which involves the synchronized transmission of blood products to the inflammation site [10].The whole reaction has also been better explained as a result of bacterial infection , where it is activated by Toll-like receptors and (nucleotide-binding oligomerization-domain protein)-like receptors of the body's immune response [11] .The development of a number of inflammatory mediators, including proinflammatory cytokines, leukotrienes, and components of proteases , is stimulated by tissue activated macrophages and immediate perception of inflammation [12].Certain mediators have a significant and immediate result of inducing an involved inflammatory reaction: serum protein and leukocytes, which are normally restricted to red blood cells vessels, now gain access to the extravascular tissues at the infection site via venules [13].Inflammation is the internal body rapid reaction to pathogens, hazardous substances like chemicals, or bodily injury significant harm to its cells and tissues[14].Acute inflammation is a fast reaction that normally leads to healing: leukocytes invade the injured section, replacing the stimulus and restoring the area[15].Chronic inflammation, on the other hand, is a long-term, excitotoxic, and malignant response that includes effective inflammation, cell destruction, and wound healing efforts[16].Many common health problems and disorders, like allergic, coronary artery disease,

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leukemia, joint problems, and immune disorders, are associated with chronic inflammatory response[17].The ancients categorised inflammation into five groups based on specific analysis: redness (rubor), swelling (tumour), fire (calor), pain (dolor), and loss of function (functio laesa).The First four signs were named by Celsusand the last one were named by Galen[18]. Generally inflammation is caused by (a) Infective agents like bacteria,viruses and their toxins , fungi and parasites (b) Immunological agents like cell mediated and antigen antibody reaction (c) Physical agents like heat, cold , radiations and trauma (d) Chemical agents like organic or inorganic poisons (e) Inert materials such as foreign bodies[19].

Inflammatory mediators :

Any carrier that induces an inflammatory reaction by interfering with blood vessels, inflammatory cytokines, or other cells shown in Figure-1.

Figure-1 :Inflammatory mediators : These mediators that triggers and controls inflammatory responses and are divided into two types cell derived and plasma derived mediators. These mediators stimulates many cells that trigger the activation of many cells and induces inflammation.

Cell derived mediators :

- Vasoactive amines :

Histamine: Histamine modulates the roles of monocytes, T cells, macrophages, neutrophils, eosinophils, B cells, and dendritic cells, among other immune regulatory mechanisms[20]. Inflammatory mediators such as histamine, eicosanoids, chemokines, cytokines, and reactive oxygen are formed by some of these cells[21]. Mast cell histamine, for example, is a main factor in the production of inflammation by controlling leucocytes ageing process & stimulation and leading their relocation to the site where they trigger inflammatory response [22]. Histamine is mainly produced by mast cells. Histamine is involved in a variety of pathological processes, including gastric secretion, inflammatory mrdiators secretion , as well as the management of vasodilatory and vascular bronchio constriction[23].It also has the ability to act as a neurotransmitter. The pharmacological functions of histamine are determined through its interaction only with 4 categories of histamine receptors: Histamine 1Receptor, Histamine 2 Receptor, Histamine 3 Receptor , or Histamine 4 Receptor, which are G - protein coupled receptors[24].

Multiple histamine receptors are found on different cells :

Histamine Receptor – Histamine 1 Receptor

G – Proteins – Gq / 11

Response in different types of cells – Nerve cells , T- cells, Endothelial cells, Epithelial cells, B cells, Dendritic cells, Natural killer cells.

⇩

Histamine Receptor - Histamine 2 Receptor

G- Proteins – G alpha S

Response in different types of cells – Human mast cells , T- cells, Monocytes, Basophils , Neutrophils, Hepatocytes, Nerve cells .

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Histamine Receptor – Histamine 3 Receptor

G – Proteins – Gi/o

Response in different types of cells - Mast cells (LAD2),Dendritic cells, Neuroblastoma cell line , Histaminergic neurons.

Histamine Receptor – Histamine 4 Receptor

G – Proteins – Gi/os

Response in different types of cells – Human mast cells (Skin , intestinal mast cells, LAD2),Nerve cell ,Natural killer cells , Myeloid cells, Macrophage, T-cells.

5 - Hydroxy tryptamine / Serotonin :

Enteramine was the name given to the smooth muscle contracting substance found in enterochromaffin cells of the gut mucosa, and Serotonin was the name given to the vasoconstrictor substance that appeared in the serum when blood clotted. Both were discovered to be 5-hydroxytryptamine in the early 1950s (5-HT)[25]. The intestines contain about 90% of the body's 5-HT, with platelets and the brain accounting for the remainder. It's also present in the stings of wasps and scorpions, and it's found in a variety of invertebrates and plants [26].

Synthesis and degradation of 5-HT :

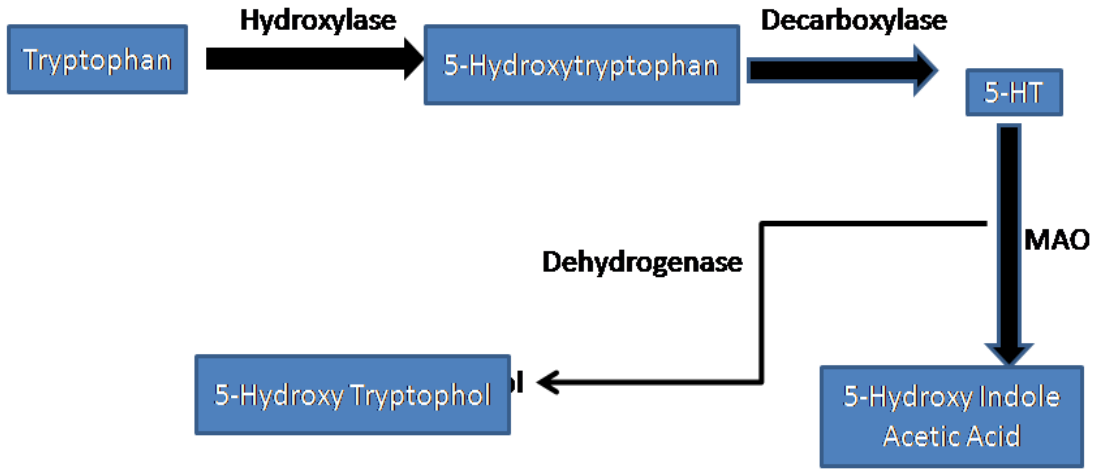

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Figure-2 : **Synthesis and degradation of 5-HT**: 5-HT is a monoamine neurotransmitter.It is synthesized from the amino acid tryptophan and degraded primarily by MAO and to a small extent by a dehydrogenase. The decarboxylase is non-specific, acts onDOPA as well as 5-hydroxytryptophan (5-HTP) to produce DA and 5-HT respectively.

All 5-HT receptors (except 5-HT3) are G protein-coupled receptors that work by reducing (5-HT1) or increasing (5-HT4, 5-HT6,5-HT7) cAMP production or generating IP3/DAG (5-HT2) as second messengers. The 5-HT3 is a ligand-gated cation (Na+,K+) channel that causes rapid depolarization when activated [27].

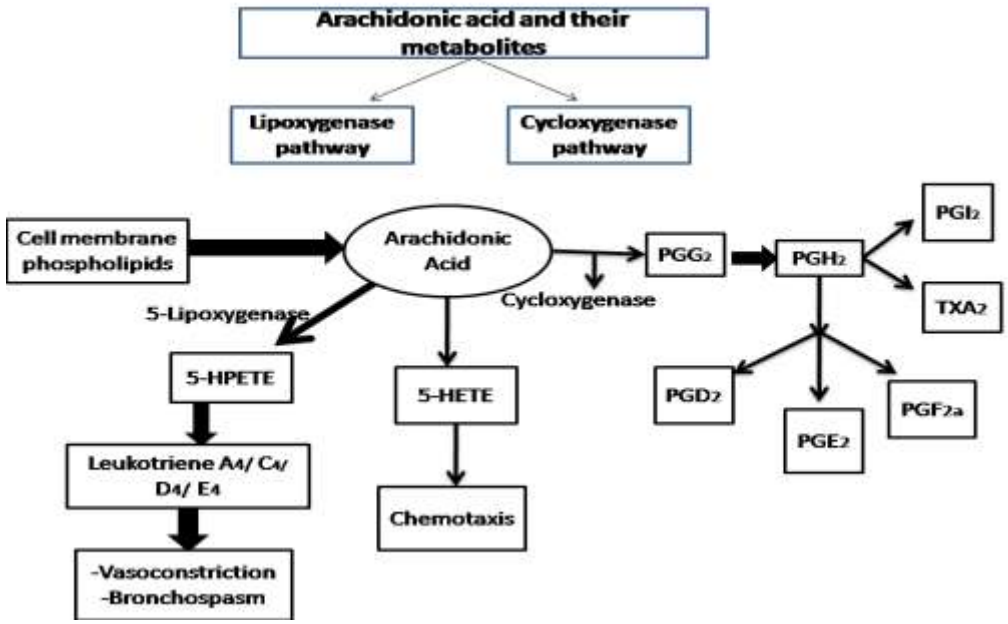
Lysosomal Components :

Lysosomal granules are found in inflammatory cells such as neutrophils and monocytes. Neutrophill granules – are the first phagocytes to arrive at the site of inflammation [28]. Enzymes and other agents are contained in their cytoplasmic granules, which are used to dissolve and degrade the engulfed particles [29]. Polymorphonuclear neutrophils (PMNs) or Segment Neutrophils (Segs) are oxygen-dependent metabolic pathways that produce toxic oxygen nitrogen products that kill pathogens [30]. Granules of Neutrophils: Primary & Azurophils : myeloperoxidase,acid hydrolases ,acid phosphatase, lusozyme, Phospholipase.Secondary or specific – alkaline phosphatase,lactoferrin , vitamin B12 binding proteins, collagenase.Tertiary – gelatinase and acid hydrolases .Granules of monocytes and tissue macrophages: acid proteases,collagenase,elastase,plaminogen activator and more active in long term inflammation [31].

Platelet activating factor :

It's a bioactive inflammatory facilitator with a lot of energy. PAF is a strong in situ chemical (mainly as a phosphate enhancer) which is produced mainly through immunoglobulin E (IgE) antibody basophiles and immature mast cells activated via pathogens[32]. Large amounts of PAF production may trigger respiratory irritability, anaphylactic shock, direct cytotoxic shock, osteoarthritis, coronary artery disease, and a number of other undesirable reactions [33]. PAF's biosynthesis that induces platelet aggregation, blood clots, and artrial fibrillation at low doses, and generates analgesic effect and inflammatory diseases with in tissue at larger doses[34].

Arachidonic acid and their metabolites :



Cytokines :

An inflammatory cytokine seems to be a form of cytokine that facilitates inflammatory actions and is ingested by immune system as well as certain cell lines[35]. T helper cells (Th) and neutrophils generate production of cytokines, which have been included in the activation of inflammatory responses[36]. Monoclonal

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antibodies which nullify inflammatory cells or certain receptors are being used to manage chronic inflammation[37]. Interleukin-1 (IL-1), IL-12, and IL-18, as well as tumour necrosis factor (TNF), interferon gamma (IFN), and granulocyte-macrophage group stimulating factor (GM-CSF), are inflammatory cytokines (GM-CSF) [38]. Inflammatory cytokines initiate the innate immune response by triggering the inflammatory reaction and managing the host resistance towards microbes[39]. Some inflammatory cytokines also secondary functions, like growth factors. Abnormal discomfort is sometimes triggered via pro-inflammatory cytokines like IL-1, IL-6, and TNF-alpha [40]. Although macrophages generate IL-1, it may also be detected in nociceptive DRG neurons. IL-6 is involved in the neuronal response to injury [41].

Plasma Derived Mediators

- The Kinn system :

Plasma kinins are polypeptides that are separated from plasma globulin kininogen by kallikerin enzymes. Kallidin (decapeptide) and Bradykinin are two essential plasma kinins (Non Peptide) [42]. Plasma Low molecular weight Kininogen and High molecular weight Kininogen are also believed to contain kininogens [43]. Bradykinin is made up of molecules with a high molecular weight[44]. Plasma kalliikrein activates HMW Kininogen [45]. The activity of tissue kallikrein, on the other hand, produces kallidin from both LMW and HMW kininogen [46]. Bradykinin can also be made from kallidin by using amino peptidase to remove the lysine residue [47].Kallikreins are glycoprotein enzymes that are formed as prekallikerins in the liver and found in plasma as well as several tissues such as the kidney, pancreas, and intestine [48]. Hageman factor (Factor XII) activates prekallikrein, which is activated by tissue damage and interaction with negatively charged surfaces [49]. Trypsin, a proteolytic enzyme found in snakes, also produces kinins.Inflammation is regulated by kinins, which cause redness, exudation, pain, and the activation of leukocytes [50]. Local kinin production can be triggered by tissue injury, which then triggers the above defence and healing processes [51]. When B2 receptors on macrophages are activated, they produce IL-1, TNF-alpha, and other inflammatory mediators [52].

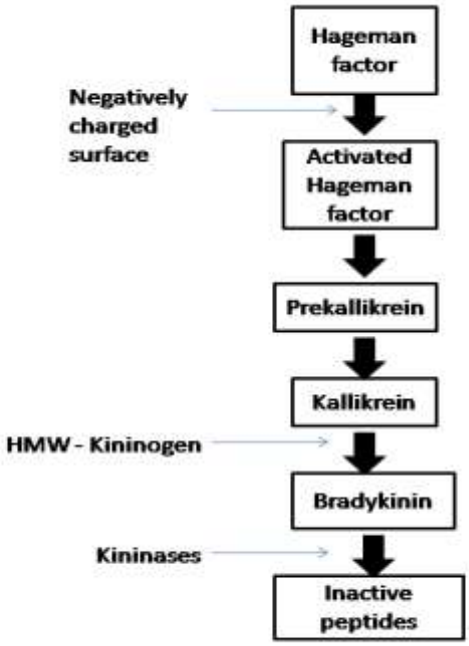

Figure-3 : The kinin system- The Kinin are the peptides of 9-11 amino acid generated from plasma proteins called kininogens by specific proteases called kallikreins.Hagmen factor activates prekallikrein activators to give kallikrein . Kallikrein acts as kininogen to give bradykinin. Bradykinin are short lived rapidly degraded by kininases present in plasma and tissue.

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Obesity – an chronic inflammatory disorder :

Obesity has been designated as the world's leading chronic health problem for adults by the World Health Organization (WHO), and it is quickly becoming a more serious issue than malnutrition [53]. In 2014, about 1.9 billion adults (18 years and older) were overweight. By 2030, 60 percent of the world's population, or 3.3 billion people, would be overweight (2.2 billion) or obese (1.1 billion) if current trends continue [54].According to an increasing body of evidence, obesity is related to cardiovascular, endocrine, neurological, and diabetes disorders [55]. When the body mass index (BMI) is greater than or equal to 30 kg/m2 of height, it is referred to as obesity. Obesity is a metabolic disorder that has spread like wildfire throughout the United States [56]. Obesity is a powerful, contributing risk factor for a variety of diseases, include type-2 diabetes , coronary artery disease, fatty liver disease, joint problems, body's immune damage, heart disease, and even certain tumors [57].Obesity is linked to many significant auto immune and metabolism problems.Because of the link between these dangerous diseases or their incidence, it is unsurprising that even more people are dying with overweight and obesity than from starvation around the world [58].The development of factors with inflammatory potential is triggered by carbohydrate accumulation, increasing metabolic requirements just at stage of adipose tissue, and hyperlipidemia [59].Obesity raises levels of many pro-inflammatory cytokines, including TNFa, IL6, CC-chemokine ligand 2 (CCL2/MCP1), IL1 and others, maybe not in adipose tissue but in many other metabolic disorders including the liver, brain, pancreas, and likely skeletal muscle [60].

Mechanism of inflammation and its mediators in obesity:

Obese people reported a significantly higher fibrinogen quantities in the blood [61]. The discovery of increased tumourTNF-alpha) activity in overweight animals' fatty tissue, as well as the improvement of insulin sensitivity since inactivation of all this active cytokine [62]. Adipocytes preferentially generated via obese adipocytes include (MCP-1) macrophage chemo attractant protein-1, (PAI-1) plasminogen activator inhibitor-1,(IL-6) interleukin-6 , in addition to the cytokine TNF- and these have play a very important role in the development of obesity [63]. Tumor cells also play an important role in obesity, as shown by the fact that when macrophages aggregate in the cells of adipocytes, obesity can occur [64]. Higher activation of proinflammatory cytokines causes an increase glucose production in blood [65]. It's these modulators of macrophage allocation to the target tissue: MCP-1 (monocyte chemoattractant protein-1) receptor,chemokine (c-c motif) receptor 2 (C-C motif).Genetically, deficiency of mast cells can decrease inflammation and weight [66].

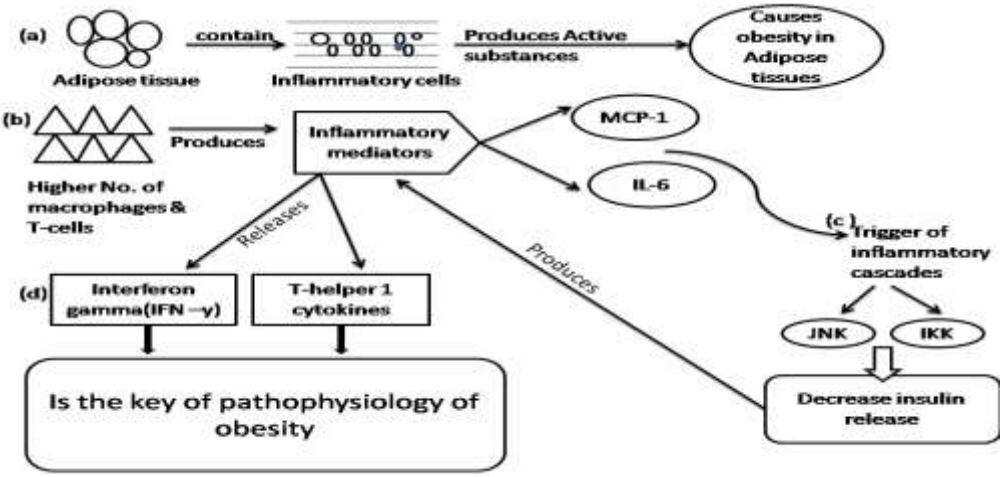

Figure 4: Mechanism of inflammatory mediators in obesity–(a) adipose tissue which is present in fat cells, contain inflammatory cells and they produces active substances & cause obesity in adipose tissues. (b) The greater no. of macrophages & T-cells produces inflammatory mediators and they secretes MCP-1 and IL-6 (c) the trigger of inflammatory cascades produces JNK and IKK and they causes decrease release of insulin & they

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also produces inflammatory mediators and releases two mediators i.e (d) interferon gamma and T-helper 1 cytokines –it is the key of pathophysiology of obesity.

Mannose receptor type 1 is a protein which is present in humans and is embedded by MRC 1 gene & therefore these greater expression of mediators such as TNF-alpha ,NO synthase can lead to inflammation at the site of adipose tissues & can cause obesity [67].

II. CONCLUSION :

Obesity is generally caused by consuming High fats diet and it exposes the body to many diseases.Researchers have identified 93 genes in fat cells that could have a significant role in the development of obesity .Deposition of fat cells in adipose tissues leads to obesity and these fat cells are Harmful to the body.Metabolic rate and immune system are inextricably linked, since both depends on homeostasis to function effectively. Obesity, type 2 diabetes, and certain serious heart disorders may all be caused by certain disorder. Obesity is a form of low-grade inflammatory disease is known as parainflammation. A great percentage of pro-inflammatory cytokines chronic inflammation and obesity have also been reported.

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