Advancement in Obesity Management: Leptin and Adiponectin Patents

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Received: April 30, 2008; Accepted: May12, 2008; Revised: May 16, 2008

Abstract: As the epidemic of obesity continues to infest the world population at alarming proportions, researchers have started to focus on the endocrine aspect of its basic unit: the adipocyte. The last two decades have proved beneficial in understanding the impact of adipocytes, specifically the metabolic influences of its hormones, the adipocytokines. This review focuses on our current understanding of leptin and adiponectin, two of the most studied and established adipocytokines. Patents regarding leptin and adiponectin are highlighted.

Keywords: Leptin, adiponectin, patents.

INTRODUCTION

Currently, more than 1 billion adults globally are overweight; 300 million of them are clinically obese [1]. What makes it alarming anyway? First, obesity is closely linked to a roster of chronic metabolic abnormalities including insulin resistance, type 2 diabetes mellitus, hypertension, hyperlipidemia, atherosclerosis, and even cancer. Second, obese people are far from isolated cases, they are everywhere. Obesity has reached an epidemic proportion that has easily traversed all walks of life regardless of race, age, gender or economic status, making it the single biggest public health threat ever to face mankind. And finally, although diet and exercise remain the gold standards of treatment, novel interventions have to be discovered that would give promising results in at least controlling if not preventing both the exponential growth of the obese population and the morbid complications of being chronically obese.

Leading the list of novel strategies will arguably come from the adipose tissue itself, the storage depot where accumulation of fat takes place. The recent years of medical and scientific advancement have led to the discovery that fat cells have metabolic and endocrine functions, which links obesity to a multitude of metabolic disorders. Adipose tissue is known to produce a vast array of adipocyte-derived factors, known as adipoctyokines. Although under normal conditions adipocytokines may play an influential role in energy homeostasis, triglyceride storage and the mobilization of fat, these processes can be substantially deregulated when adiposity is enhanced, in particular central adiposity. These adipocytokines include leptin, adiponectin, complement components, plasminogen activator inhibitor-1, tumor necrosis factor (TNF), interleukin-6 (IL-6), proteins of the rennin-angiotensin system and resistin [2]. The vast influence of various adipocytokines to key metabolisms of the human body has been theoretically proposed to link obesity and most of the chronic non-communicable diseases that engulfs the developed world. This review highlights the recent developments and inventions that have made adipocytokines, leptin and adiponectin in particular, more than just biomarkers but future targets for therapeutic interventions.

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LEPTIN

One of the well documented hormones of the adipose tissue in terms of physiology and pathology is leptin. It was first identified as the product of the ob gene in leptin-deficient obese (ob/ob) mice and was originally described as a circulating hormone involved in feeding behavior and energy homeostasis [3]. It is translated as a 167-amino acid protein with the first 21 amino acid residues cleaved as a peptide [4]. Human Leptin has 146 amino acid residues that consist of 4 anti-parallel α-helices that are 5-6 turns long and connected by cross-over links. Both crystal structure and nuclear magnetic resonance studies have revealed that leptin adopts a cytokine fold similar to that exhibited by the short-helix subfamily of cytokine folds [5, 6] see Fig. (**1**).

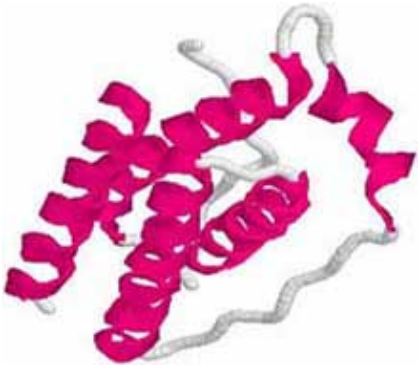

Fig. (1). Crystal Structure of Leptin [6].

Leptin is an essential feature of human obesity with total body fat mass > % body fat > BMI as the best predictors of circulating leptin levels [7]. In human beings, there is a highly organized pattern of leptin secretion over a 24-h period. The circadian pattern is characterized by basal levels between 08:00 and 12:00 hours, rising progressively to peak between 24:00 and 04:00 hours and receding steadily to lowest point by 12:00 hours [5].

Although, the rate of leptin production is related to adiposity, a large portion of the inter-individual variability in plasma leptin concentration is independent of body fatness. It

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is leptin resistance and not leptin deficiency per se which is regarded as a pathogenic mechanism in human obesity [8]. Among its vital functions, leptin acts via hypothalamic receptors to inhibit feeding and increase thermogenesis, resulting in a decreased body weight [9]. Evidence also suggests that leptin has inhibitory role on insulin secretion, and levels above 20ng/ml help predict development of gestational diabetes mellitus [10]. Somasundar and colleagues demonstrated that leptin elicits proliferative effects in some cancer cell types, but not all. These findings suggest that circulating leptin could act *in vivo* as a growth factor in esophageal, breast, and prostate cancers, thus supporting the link between obesity and the risk of developing certain cancers [11]. The above mentioned findings are just a fraction of how leptin influences over-all body metabolism, making it a very promising target for therapeutic interventions for a multitude of metabolic diseases.

RECENT PATENTS ON LEPTIN

High-dose leptin is now being researched as a potential therapy for obesity, and high levels of leptin are found in extreme obesity due to leptin resistance and also in renal failure. Injection of leptin elicits a mild localized inflammation, but the physiological basis for this reaction has not been established [12]. Administration of recombinant leptin is performed intravenously, intra-muscularly, intraperitoneal, and through other parenteral routes to treat obesity, diabetes, and reproductive abnormalities [13]. Leptin injections evoke weight loss by causing a reduction in food consumption and an increase in energy expenditure. Furthermore, leptin of mammals as a drug has an action to improve brain function which is effective to prevent and to treat dementia such as Alzheimer's disease, cerebral apoplexy and to cure sequelae of apoplexy, in addition to the known actions to regulate food intake and to increase energy consumption [14]. Oosman and colleagues recently introduced the concept of transplanting gut-derived cells that are engineered to produce leptin, under the regulation of an inducing agent, mifepristone among obese, diabetic ob/ob mice and to mice fed on a high-fat diet [15]. They found out that transplantation of these cells offers a therapeutic effect in leptin-deficient mice alone. Kirwin and Funanage's recent invention on the other hand included suspending isolated native leptin-containing milk fat globules in a suitable medium for administration to a subject. It may be administered orally as well as by intravenous, intramuscular, intraperitoneal, other enteral routes of administration, and other parenteral routes of administration. This invention included a method for treating growth or maturational-related disorders in newborns as well as subjects having conditions that can be treated by the administration of leptin [16].

The patents mentioned are just a few of the good reasons why leptin can be utilized as a drug at least for a selected group of the general population. Nevertheless, the therapeutic claims of leptin are still far from being established. Leptin has been proven to be remarkably effective in reducing body weight in both mice and humans, but these are subjects who bear mutations in the ob gene, which are rather a rarity for most obese humans. Researchers have also expressed some concern that leptin may exacerbate insulin resistance or contribute to type 2 diabetes [17], not to mention its proliferative effects in many human cancer types [11]. Further developments such as other modes of administration that might yield better results as well as clinical trials for long term side effects and consequences should be done in order to strengthen or refute the current claims of leptin.

ADIPONECTIN

Adiponectin is a 30-kDa collagen-like protein, clinically noted to be anti-atherogenic and anti-diabetic at elevated levels [18]. The protein forms the basic unit of a trimer, which self associates to form hexamers then multimers of high molecular weight (HMW) see Fig. (**2**). HMW adiponectin seems to be the most active ones in relation to insulin sensitivity [19]. AdipoR1 and AdipoR2 are the receptors of adiponectin, with AdipoR1 being expressed in muscle tissues as high-affinity receptor for globular adiponectin and low affinity for full-length adiponectin, whereas AdipoR2 is abundantly found in the liver and serves as intermediate-affinity receptors for both forms of adiponectin. The function of adiponectin in various glycemic and lipid processes can be explained by activation of AMP-activated protein kinase (AMPK) and stimulation of PPAR (Peroxisome proliferator-activated receptor) alpha, which lead to increased glucose uptake and oxidation of fatty acids in skeletal muscle and decreased hepatic glucose output [20]. In skeletal muscle, adiponectin increases expression of molecules involved in fatty-acid transport such as CD36, in combustion of fatty acid such as acyl-coenzyme A oxidase, and in energy dissipation such as uncoupling protein 2, leading to decreased triglyceride contents [21, 22]. Worthy to note is the clinical significance of adiponectin in which increased serum concentrations translate to increased insulin sensitivity and glucose tolerance as well as its inverse association to leptin levels. It can therefore be speculated that adiponectin, or drugs that stimulate adiponectin secretion or action, could play a role in disease states combined with insulin resistance, mainly type II diabetes mellitus, metabolic syndrome, and obesity. Therapy with adiponectin may be advantageous in reversing insulin resistance in lipodystrophic disorders and metabolic syndrome [23].

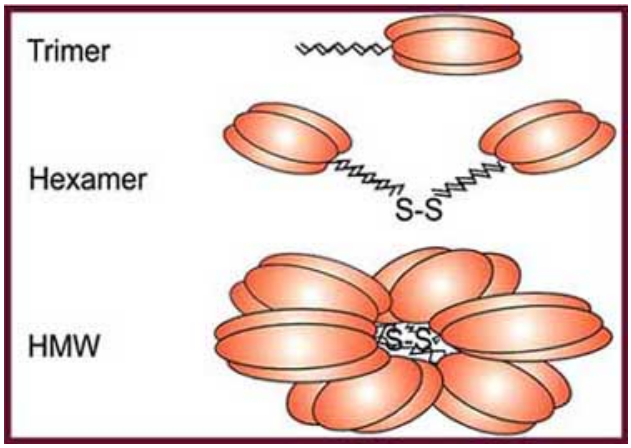

Fig. (2). Multimeric structures of adiponectin [37].

ADIPONECTIN AS A BIOMARKER

Adiponectin is a powerful marker of diabetes risk in subjects at high risk for diabetes [24]. Owing to its negative

associations to various metabolic abnormalities including obesity itself, improvement in its levels owing to the simplest lifestyle and dietary modifications can therefore translate to reduction of risk. Hypoadiponectinemia has been shown to increase breast cancer risk among women [25]. This can be explained partly by the insulin resistance brought about by obesity, which is strongly linked to breast cancer [26]. In prostate cancer, adiponectin was observed to be higher in locally advanced relative to organ-confined prostate cancer and may thus serve as an auxiliary marker providing further improvement to PSA (prostate-specific antigen) for discrimination between PT2 and PT3 stages [27]. Although much has been documented in terms of its cardiovascular significance, there are still other pathologic states that are currently being investigated for possible associations to adiponectin levels. Matsumoto and colleagues assessed the odds of cerebrovascular disease at different plasma levels of adiponectin among 5243 subjects and found that adiponectin levels are not independently associated with stroke or brain infarction [28]. Contrary to their findings, Bang and colleagues revealed that symptomatic intracranial atherosclerosis is associated with lower serum adiponectin levels compared to ischemic stroke subtypes [29].

PROTECTION FROM ADIPONECTIN

The protective effect of adiponectin in the progression of insulin resistance, cardiovascular events and its strong influence in the individual components of metabolic syndrome has indeed made it a very promising therapeutic target. Fujita and colleagues found that in cultured cardiac fibroblasts, adiponectin improved the reduction of AMP-activated protein kinase (AMPK) activity and elevation of extracellular signal-regulated kinase 1/2 (ERK1/2) activity induced by Angiontensin II, implicating that adiponectin protects against Ang II-induced cardiac fibrosis possibly through AMPK-dependent PPAR-alpha activation [30]. Treatment of adiponectin also protects the endothelial monolayer from Ang II or TNF-alpha-induced hyperpermeability by modulating microtubule and cytoskeleton stability via a cAMP/ PKA signaling cascade [31]. Among patients harboring cardiovascular diseases, adiponectin protects against metabolic and vascular diseases and indicates a high mortality risk due to compensatory up regulation [32].

RECENT PATENTS ON ADIPONECTIN

Patents on adiponectin will revolve around either as a prognostic indicator, or as a therapeutic agent. As a prognostic indicator, Maeda and Yamamoto recently discovered adiponectin as a stress marker for sepsis, hypercytokinemia, multiple organ failure and as an endotoxin neutralizing agent. This approach is totally different from the conventional means but nevertheless the use of an endotoxin-neutralizing agent described in the present invention enables efficient treatment of sepsis, multiple organ failure (MOF), DIC (Disseminated Intravascular Coagulation) , respiratory failure (ARDS), liver cirrhosis, fatty liver, liver failure, inflammatory bowel disease, peritonitis, organ transplantation, dialysis, burns, trauma, intravenous hyperalimentation, and serious acute pancreatitis. The human adiponectin according to the invention is used as a preparation in various forms. Specific examples include, but not particularly limited to, injections, suspensions, suppositories, ointment, creams, gels, adhesive skin patches, and inhalants. Particularly, the injections are prepared by dissolving human adiponectin in an appropriate solvent and may be supplemented with a buffer and a preservative [33].

Suguru and colleagues discovered a latex reagent as a new approach for adiponectin method and analysis. In this patent, a latex reagent for adiponectin analysis (composed of suspension of latex particles having deposited on a substance specifically bonded to adiponectin and its resultant mixture) is optically analyzed to determine the degree of coagulation of the latex particles. According to the latex reagent for adiponectin analysis and method of analysis, the biological liquid as a test sample need not be diluted or treated beforehand. The analysis is speedy and simple, and facilities for examination are not limited [34].

Moving on to therapeutic patents, much of the recent inventions on adiponectin concentrated on agents that enhance levels, owing to its ability to diminish risk. Zolotukhin and Tennant invented a method of modulating adiponectin activity in a subject using a recombinant adeno-associated virus (rAAV) vector comprising a nucleic acid sequence that encodes full-length adiponectin polypeptide operably linked to an expression control sequence [35]. On the other hand, Yoshiko and Yoko invented a composition containing an adiponectin enhancer comprising as an active ingredient sesamin and/or episesamin. This present invention provides foods, beverages, health foods, pharmaceuticals and feeds which comprise sesamin and/or an analogue thereof as an active ingredient and which can prevent or ameliorate obesity and lifestyle related diseases which are fundamentally caused by accumulation of enlarged adipocytes, as well as a process for their production [36]. Finally, Kadowaki and colleagues invented an insulin resistance improving which contains as an active component, a C-terminal globular domain of adiponectin, adiponectin or a gene for the domain of adiponectin. The invention also provides a therapeutic agent for type 2 diabetes, which contains as an active component, a C-terminal globular domain of adiponectin, adiponectin or a gene for the domain of adiponectin. The invention reverses insulin resistance induced from a high fat diet and associated with obesity, and therefore enables treatment of type 2 diabetes [37].

CURRENT & FUTURE DEVELOPMENTS

The recent patents on leptin and adiponectin remain promising yet premature. Further studies on a large scale are still needed to confirm their efficacy as therapeutic agents in the management of obesity. Worthy to mention are the adverse effects encountered when administering these adipocytokines and the long term related complications potentially in store for chronic users. Clinical trials are also required to establish their full pharmaceutical potential as the next generation of anti-obesity drugs and its related complications.

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