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Zymosan A, an Old Tool in Experimental Pharmacology with Newer Applications

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Abstract

Insulin resistance (IR) is an important link between obesity and post obesity complications varying from diabetes mellitus to neurological insults such as cognitive dysfunction and Alzheimer's disease. Currently available high calorific diet induced preclinical models mimic clinical pathologies of various metabolic disorders but they are highly time consuming. Zymosan A, a well-known inflammagen has recently been used to induce reversible IR conditions in rodent models. Though, the insulin resistance lasts as long as zymosan is injected to animals, but the pathogenesis that resembles to that of obesity, IR and metabolic syndrome. However, high fat or high carbohydrate diet could be used in combination with zymosan to develop a novel animal model of IR where both inducers act synergistically to exert their primary actions. The combination of these two approaches may help in development of a robust experimental model of IR and post IR complications within a very short duration. Such preclinical models will help the researchers to better understand the pathological evolution of long term metabolic disruptions like metabolic syndrome and others.

Keywords: Zymosan; Insulin resistance; High fat diet; High carbohydrate diet; Diabetes; Obesity; animal model; Metabolic syndrome; Metabolic complications

Abbreviations: AKT: Protein Kinase B; CD 14: Cluster of Differentiation 14; GSK 3: GSK 3: Glycogen Synthase Kinase 3; HFCS: High Fructose Corn Syrup; HFD: High Fat Diet; IL: Interleukin; IR: Insulin Resistance; IRS 1: Insulin Receptor Substrate 1; JAK: Janus Kinase; LTB4: Leukotriene B4; MIP: Macrophage Inflammatory Protein; NFκB: Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells; PI3K: Phosphor Inositide 3-Kinase; PMNs: Polymorphonuclear Cells; ROS: Reactive Oxygen Species; STAT: Signal Transducer and Activator of Transcription; T2DM: Type 2 Diabetes Mellitus; TLR: Toll Like Receptor

Introduction

Insulin is the major pancreatic hormone that regulates the glucose homeostasis in our body. The pathological state in which the production of insulin is decreased, mostly due to beta cell destruction is known as insulin deficiency whereas the situation in which insulin secretion is normal and muscle cells are unable to respond to the systemically available insulin is referred to as insulin insensitivity or insulin resistance (IR) [1]. In such resistant states, the body cells fail to take up the glucose from blood stream and this leads to elevated blood sugar levels, referred to as hyperglycemia. IR is a primary pathological result of obesity and hypertriglyceridemia [2] that leads to a wide range of secondary complications such as type 2 diabetes (T2DM) [3], metabolic syndrome (Syndrome X) [4,5], cardiovascular events [6,7], stroke [8] including recently discovered link between hypertriglyceridemia, insulin resistance, altered brain glucose homeostasis, Alzheimer's disease [9,10] and cognitive dysfunctions [11-13]. The pathophysiology of insulin resistance is very complex with number of known etiologies, most of which are diet or nutrition related. Over-nutrition or obesity triggered inflammation in adipose tissue [7,14], altered lipid metabolism resulting in hypertriglyceridemia [15] and distorted gastrointestinal microbiota (dysbiosis) [16-18] and all of the contributing factors are interrelated at variable degrees to rise to the final state of IR. The complexity and multi factorial etiologies of IR sum up to make it very hard to replicate and develop a heterogeneous animal model for the purpose of understanding the pathogenesis of IR and its secondary complications and pharmacological screening of chemical entities. Hence the new chemical entities need to be screened in more than one animal models of IR to determine their safety and efficacy. Currently, a number of preclinical testing systems including transgenic models are available for the purpose of IR research. Among various available models of IR, diet-induced animal models are affordable, extensively studied and utilized for the research purposes [19]. Diet-induced animal models involve the use of high calorie

containing food sources such as fats (vegetable oil and animal fat consisting high amounts of saturated fats) [20,21], fructose corn syrup [22,23] and sucrose [24] alone or in combination [25,26] to induce IR. Though, these dietary animal models induce the disease with similar pathophysiological mechanisms to that of clinical cases, the development of pathological hallmarks of IR takes 12-24 weeks of time which makes these models tedious and cumbersome to use [25,27].

Zymosan A, a glucan with repeating glucose units connected by β-1, 3-glycosidic link ages is an insoluble powder prepared from cell wall from *Saccharomyces cerevisiae,* consisting of protein-carbohydrate complexes [28]. Zymosan is an inflammagen majorly used as a pharmacological tool to develop animal models of rheumatoid arthritis [29], acute peritonitis, multiple organ failure [30] and IR [31]. Zymosan exerts its inflammatory actions by stimulating macrophages via TLR-2 Receptors and Neutrophil infiltration through various activated cytokines and chemokiness. Zymosan stimulated TLR-2 associates with TLR-6 and CD-14 cells, initiating the activation of macrophages [28]. Furthermore, zymosan acts directly by binding to Dectin-2 a phagocytic receptor which is expressed on the surface of macrophages and dendritic cells. Recognition of zymosan by Dectin-2 besides the activation of TLR-2 and TLR-6 augments the immune response that leads to inflammation [32]. Zymosan causes neutrophil infiltration to the site of action by stimulating the production of Leukotriene B4 (LTB4), a chemotactic agent responsible for the recruitment of various chemokines and cytokines like IL-1α, IL-15, IL-18, TNF-α, IL-8, MIP-1 α and MIP-2 [33,34]. Zymosan also exerts its action by other minor mechanisms that play a key role in inducing inflammation, which includes-systemic hypotension, increasing plasma nitric oxide levels, increasing cycloxygenase activity, increasing exudates formation and excessive reactive oxygen species (ROS) production by formation of activated polymorphonuclear(PMN)cells [30].

Being an inflammagen, Zymosan has become one of the potential tools for disease animal modeling where inflammation has major role to play to mimic the similar pathophysiology as that of humans. With varying dose, zymosan has been used to develop various preclinical disease models. The disease models include rheumatoid arthritis induced in wistar rats by injecting in rear knee joint at a dose of 1mg suspended in 50µL of sterile normal saline [29], multiple organ failure by administering intraperitoneally (i.p.) to rats at a dose of 500mg/kg [30] and acute peritonitis by i.p. injection to Balb/C Mice at a dose of 0.5mL from a zymosan stock solution of 2mg/mL [35].

Till date, there has been only one study published over the use of zymosan to induce reversible IR in preclinical setting. Mice were injected with zymosan via i.p. Route at a dose of 100mg/kg once a week for four consecutive weeks. Inflammation driven ROS production is the mechanism involved in zymosan induced IR. Zymosan causes inflammation through activation of macrophages via stimulation of TLR-2 and TLR-6, Activation of PMN cells to escalate the intracellular ROS production. In this model of IR, zymosan injection has also been held responsible for the reduced expression of various protein markers involved in insulin signaling like IRS-1, PI3-Kinase, phosphorylated GSK-3 and Akt [31].The main aim of this review is to highlight the importance of need of accelerated new animal model to study insulin resistance and associated secondary complications of IR.

Discussion

Feeding laboratory animals*adlibitum* with high calorific diets take a minimum time of 12 weeks to reach the IR state whereas a study carried out by Wang et al. [31] suggest that zymosan could successfully induce IR within just 1/3 of the time that is taken by high calorific diet to create the same situation. The only limitation of this model is that the IR is reversible and animals have returned to their normal state within 4 weeks after withdrawal of zymosan administration. Meanwhile, we hypothesize that the combinatorial use of high calorific diet and zymosan can cut short the time duration to induce IR. The use of zymosan with high calorific diet will be rational, as both of these disease inducing agents act through the analogous inflammatory pathways. Zymosan and high calorific diet acts on toll like receptors (TLRs) present on cell membrane to initiate the release of inflammatory cytokines which in turn leads to the activation of NF-κB and JAK-STAT pathways that desensitize insulin receptors towards insulin and leads to surge in unutilized levels of insulin in systemic circulation, can also be termed as insulin resistance [28,36-38].

Conclusions & Prospective

A. Insulin resistance is considered as a major mediating and facilitating factor for the development of secondary metabolic complications associated with consumption of high calorific or cafeteria or junk food. With an aim of developing a new, less time consuming and clinically relevant animal model to study and understand the pathology of various metabolic complications in which IR plays a vital role.

B. Inflammation is the common mechanism through which the high calorific diets and zymosan induce IR and their combined use shall exert a synergistic effect towards rapid onset of insulin resistant state than traditional models. This hypothesis can be adapted and utilized by the researchers working in the fields of IR, obesity, T2DM, metabolic syndrome and cognitive dysfunction associated with metabolic complications.

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