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Methyl Mercury, Adipokines, 3T3-L1 Cells and Diabetes

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Abstract

Diabetes is a contributor to morbidity across the globe and is often associated with obesity and metabolic syndrome. In addition to genetic and lifestyle factors, environmental factors such as metals and persistent organic pollutants may increase the severity or lower the threshold of these conditions. Studies are showing an association between these contaminants and both insulin sensitivity and glucose transport. In cell culture, mercury and methyl mercury are toxic to adipocytes and impact the secretion of cytokines and adipokines. We propose a research model using contaminants like methyl mercury on adipocytes to enhance the existing knowledge on the mechanistic influence of adipokines and reactive oxygen species on 3T3-L1 cell functioning. With this enhanced signaling model, anti-inflammatory agents could be tested at the biochemical level and lead to studies in animal models. Prospective model studies on mixtures of contaminants can contribute to better understanding about the development or severity of diabetes.

Keywords: Adiponectin; Resistin; Methyl Mercury; 3T3-L1 cells; Diabetes

Abbreviations: MeHg: Methyl Mercury; MetS: Metabolic Syndrome; VEGF: Vascular Endothelial Growth Factor; ROS: Reactive Oxygen Species; WAT: White Adipose Tissue.

Introduction

Methyl mercury (MeHg) is historically known to pose a threat to the ecosystem. MeHg, a potent neurotoxin, bioaccumulates and biomagnifies through the ecosystem and eventually to human beings [1]. 80%-90% of organic mercury in humans is from fish and shellfish intake [2]. Arctic communities residing in rural Alaska rely highly on fish as a staple food [3]. Also, MeHg crosses the human placenta and can impair the developing fetus [4]. Recent epidemiological studies suggest a correlation between MeHg exposure and eventual development of type 2 diabetes and hypertension [5,6].

Many studies in the neurotoxicity of MeHg have been conducted to investigate the underlying mechanism [7-10]. The potential effect of MeHg on other organ or cell types has not been extensively studied. In 2003, Barnes et al. looked at the effect of inorganic mercuric chloride on the process of adipogenesis which suggested mercury exposure can inhibit the differentiation process of pre-adipocytes [11]. Later, in 2005, Barnes, et al. also concluded that the addition of mercuric chloride to the differentiated 3T3-L1 cells increased glucose transport [12].

To the best of our knowledge, only one study exists which has examined the effect of organic mercury, MeHg,

on the adipocytes, the specialized cells of the adipose tissue. In studying the cytokine Vascular Endothelium Growth Factor (VEGF) expression by 3T3-L1 cells, Vertigan, et al. observed that an exposure of 100ng/ml (0.4uM) of MeHg is cytotoxic to adipocytes [13]. Additionally, they found that 0.4uM MeHg exposure elevates the VEGF secretion during later stages of differentiation.

However, the effect of MeHg on the mature adipocytes and on adipokines associated with the development of metabolic syndrome (Met S), such as adiponectin and resistin, have not been well studied. Moreover, no study exists on mitigating the negative effects of MeHg exposure associated with the diet. Cell culture studies on 3T3-L1 cell line provide an experimental model for studying the effects of MeHg exposure and other contaminants on adipose tissue. MeHg has a high affinity for sulfhydral protein groups leading to S-mercuration. S-mercuration of cellular proteins is assumed to be involved in the mechanism underlying MeHg toxicity [8]. In the process of metabolism, MeHg undergoes reactions that increase the release of free radicals such as Reactive Oxygen Species (ROS) [2]. ROS causes oxidative stress and lipid peroxidation which has been suggested as a cause for the insulin resistance associated with type 2 diabetes [14]. Insulin resistance and dysfunctional insulin signaling lead to the onset of type 2 diabetes. Since low levels of MeHg are present in many foods, and is fat soluble, it is reasonable to investigate its relationship to adipokines. A cell culture model that can investigate MeHg mixtures with low levels of other contaminants would be useful [15].

The significance of a model focusing on the cell culture hierarchical level is threefold. First, there is a greater precision in measurement of the interaction of the adipokines in controlled experiments. Secondly, there is an increasing literature linking oxidative stress to diabetes and Met S. Thirdly, the cell culture system is easily adaptable to using multiple stressors such as mixtures of metals and endocrine disruptors. Such a design and the measure of the changes in various adipokines levels would give a more realistic picture of the impact of environmental exposure. The response of the adipokines in this model would provide the basis for new strategies in disease management.

Since there is an increasing variety of the type of metals which the general population is exposed too, a significant public health issue understanding the impact of various metals, as well as mixtures, on the etiology of hypertension and diabetes. Studies in model systems are needed to clarify the underlying mechanisms such as the role of the balance of antioxidants [15,16].

Adipokines and Anti-Inflammatory Agents

Adipokines such as adiponectin and resistin are proteins which are secreted from the adipocytes and are potential markers for metabolic syndrome [17]. Anti-inflammatory agents may mitigate the effect of MeHg by reducing the amount of ROS formed. A natural compound derived from black tea, possess anti- inflammatory properties and it might be a potential therapeutic candidate for reducing inflammation [18]. Theaflavin-3,3'-digigallate possess several active properties, one of which is the ability to fight ovarian cancer [19,20]. Natural products like organic tea compounds might protect individuals exposed to the normal concentration of MeHg found in Alaskan subsistence foods [21].

Obesity has also been linked with type 2 diabetes [22-24]. Preliminary investigations regarding the effects of MeHg exposure on adipocytes will enhance the existing knowledge in this area of research. A central question would be "If MeHg increases basal ROS levels, would it interfere with adiponectin and resistin secretion patterns, thereby alternating insulin sensitivity and regulation of glucose transport?" Natural compounds such as theaflavin-3,3'-digigallate should be tested to observe their effect on MeHg interference on adipokines secretion.

Alaskans eat, on average, more fish than the average American, since many living in rural Alaska have to rely on fish for subsistence [25-29]. Obesity rates are rising among Alaska Native populations and the amount of mercury found in the environment in Arctic regions has also been rising [30]. Little research is performed on the effect of MeHg exposure on organs other than brain. Thus far, Barnes et al and Vertigan, et al. have studied the effects on the 3T3 –L1 cells. Vertigan, et al. found that MeHg exposure of 100ng/ml is cytotoxic to the 3T3 L1 cells and also increase VEGF secretion during later stages of differentiation [11-13]. Studies to observe the effect of MeHg on ROS levels and the effect of theaflavin-3,3'-digigallate, or other anti-oxidants would contribute to the knowledge characterizing the system.

Epidemiological studies suggest a correlation between the mercury exposure and eventual development of obesity and/or diabetes [5,6]. About 2 out of every 3 Alaskan adults are now overweight or obese [31]. The likelihood of American Indian and Alaska Native adults to have diagnosed diabetes compared with non-Hispanic whites was 2.3 times higher in 2009 (16.1% vs. 7.1%)

[32]. However this correlation remains controversial as some studies suggests no such correlation between mercury and the development of any metabolic syndrome [33]. Regardless, more investigations are needed to more fully understand the effects of MeHg on adipose tissue.

Adipose tissue is a major endocrine systems present in the human body. Initially, it was considered only for storing excess fat tissue, but now that myth has been put to rest and adipose tissue is shown to be actively involved in regulation processes. Recent studies have shown that adipose tissue produces large amounts of biologically active and specific proteins also known as adipokines which play key roles in glucose and energy metabolism [17,34].

Adipose tissue is made up of highly specialized cells known as adipocytes, used for the storage and release of lipids. Other cell types in adipose tissue include blood cells, endothelial cells, pericytes and adipose precursor cells [35]. In recent studies, adipose tissue and adipokines were found to be involved in the pathogenesis of type 2 diabetes [36-38]. The common cell type used for in vitro studies for the phenomenon of adipogenesis and adipokines are the 3T3-L1 cell line, a well-characterized adipocyte line from mice which can acquire an adipocyte-like phenotype. During the differentiation process, 3T3-L1 cells can be induced to differentiate under controlled laboratory conditions using a standard differentiation protocol and are widely accepted as a physiologically faithful in vitro representation of adipogenesis [11-13,39].

Our knowledge about the functions of adipose tissue is widening over time. Adipose tissue secretes proteins generally known as adipokines to signal different functions across the body [40-41]. Adipokines such as adiponectin and resistin are potential additional biomarkers for metabolic syndrome [17]. Adiponectin is an adipokine secreted exclusively from the adipocyes with one of its major roles in energy metabolism [42,43]. It stimulates fatty acids oxidation, decreases plasma triglycerides and increases glucose sensitivity [44]. It also acts as an anti-inflammatory, anti-atherogenic, and anti-oxidative factor [45]. Lower levels of adiponectin may lead to metabolic syndromes like insulin resistance, obesity, type 2 diabetes [46,47]. Higher levels may lead to anorexia nervosa [48].

On the other hand, resistin is a relatively new and poorly studied adipokine with biological properties opposite to adiponectin [17,44]. It is produced in the stromovascular fraction of adipose tissue and blood monocytes. Human resistin is 12.5-kDa protein, which contains 108 amino acids. It circulates in human blood as a dimeric protein linked by a disulfide bond. Resistin circulates in high levels in diabetic mice models, and it is suggested that resistin is the adipokine that links obesity to type 2 diabetes [50,51]. Also, resistin is an inflammatory marker of atherosclerosis in humans [52]. The adiponectin- resistin ratio has widely been suggested by various researchers to be an indicator of metabolic risk for obesity [17,44,53]. The secretion levels adipokines, like adiponectin and resistin, may be associated with risk of development of hypertension, type 2 diabetes and the metabolic syndrome [6,16].

In this paper, we suggest potential association of MeHg with adipokine profiles in 3T3-L1 cells. The exposure to MeHg might be influenced by other stressors which would be investigated in combination to observe any synergistic interactions of MeHg and other stressors. Pancreatic beta-cells are sensitive to ROS and MeHg induces beta cell apoptosis, but 3T3-L1 cells are less characterized [16,54]. Management of antioxidant levels could be a useful treatment for human health programs. Using anti-oxidants to counteract high exposure to MeHg would be a appropriated approach to population wide studies and treatment of diabetes [6,18]. A fuller understanding will facilitate the introduction of targeted diet-based interventions as treatments.

Conclusion

Research on the effect of contaminant exposure such as MeHg should supply baseline data and address the value of antioxidant dietary supplements as a therapeutic approach of dietary MeHg exposure on the function of adipose tissue. The roles of adipokines are numerous but we are focusing on the role of contaminants in energy and fat metabolism as they are directly related to obesity and metabolic syndrome. Exposure to a contaminant or mixture may lead to change in secretion patterns of adiponectin and resistin. Imbalanced ROS levels have been detected in WAT of type 2 diabetics or Met S.

An association between mitochondrial dysfunction, oxidative stress and carbonylated proteins may play critical roles in insulin resistance. High ROS levels could lead to adipocyte hypertrophy, altered metabolism, and dysregulated adipokine secretion. Basal levels of ROS are required for the differentiation of preadipocytes into adipocyte and their normal functioning. However, diminished or excessive levels of ROS levels may contribute to WAT dysfunction following insulin resistance [55,56].

Research is needed to develop models to determine the effect of a normal level of MeHg exposure on adipocytes. This understanding will add data to the debate about mercury or other contaminants and their role at the biochemical level in metabolic syndrome. Specifically, this type of research will further develop a model system to link specific environmental contaminants to metabolic syndrome and associated diseases [6,15].

Barnes and his colleagues investigated the effect of inorganic mercury chloride on adipogenesis and glucose transport [11,12]. Vertigan, et al. showed increased VEGF secretion from differentiated cells due to MeHg exposure [13]. Their findings provide a platform for further studying MeHg species as a potential modulator of metabolic processes in adipocytes. The idea of using natural food in a model anti-oxidant system to study the mitigating effects on adipokine secretion will increase the possibility of a potential neutraceutical treatment options for insulin resistance [57]. Using a defined anti-inflammatory compound would advance the current common approach of testing complex extracts and mixtures [15].

Also, since pollutants are increasing in the environment, the regulatory implications of this research would allow for fine tuning the criteria levels for water and food regulations. The few studies on complex mixtures have suggested that both additive and synergistic effects occur with multi-toxicant exposure. From a regulatory perspective, these impacts would require a review and possible lowering of the acceptable exposed dose in a food source. Studies in a standardized cell culture system allows for better comparison between toxicants.

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