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POTENTIAL ROLE OF ORGANOTIN COMPOUNDS (EDCs) IN AETIOPATHOGENESIS OF OBESITY

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Abstract- Obesity in human has been a major concern of attention of scientists, medical professionals and health care providers since last two decades. Gradual rise in prevalence and incidence of obesity in the recent decades around the world has been a leading health problem. In the recent years, there is growing recognition that there are some chemical pollutants in the environment, which alter metabolic set points of homeostatic system in human, thus may result in development of obesity during intrauterine or adult life attributed to disruption of the feeding behavior control mechanism leading to activation of adipogenic pathways. Chemically active derivatives of Organotin compounds, identified in many household utilities such as food and cosmetics etc. has been proposed as one of the important endocrine disruptor chemical responsible for genesis of obesity. This paper reviews the existing evidences of possible role of oaganotin compounds in development of obesity in animal & human studies. Based on the evidences, we strongly supports the hypothesis that endocrines disrupting chemicals (EDC) play a potential role in development of obesity, triggering the adipocytes dysfunction or altered metabolic programming in utero and propose the areas for future research.

Keywords- Obesity, Adipogenesis, Organotin compounds, Tributyltin (TBT), Triphenyltin (TPT), Endocrine disruptors, Dysregulation

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Introduction

Numerous studies over the last two decades have been conducted in various part of the world to elucidate genesis of obesity in human and conceptualized that obesity is a complex phenomenon resulting from interaction between genetic, nutritional, behavioral and environmental factors [1-5]. Inspite of much research focusing these factors were undertaken, its exact aetiopathogenesis is still remains to be unexplained. Recent evidences indicated that dysregulation of endocrine function of adipose tissue could be a major contributor in development of various complications of obesity, however experimental data from human studies suggesting the relevance of functional significance of bioactive substances called as adipocytokines, released from adipose tissues with obese features & complications are very scanty. During the last decade, it is hypothesized that incidence of obesity may be related to increase in industrial chemical substances, contributing to increased environmental pollution [6]. It was observed that exposure of Bisphenol A (BPA) results in increased 3T3-L1 cell differentiation in to adipocytes [7]. There are evidences suggesting the links between exposure of EDCs like BPA, dioxins, and Organotin compounds with growing incidence of obesity, diabetes, infertility and other metabolic disorders [8-10] but the precise metabolic mechanism causing these disorders by the EDCs are unknown. These reports led to think that industrial chemical factors grouped as endocrine disrupting chemicals, present in environment may be the candidates responsible for altered endocrine signaling and may lead to cancer, diabetes, obesity, the metabolic syndrome, and infertility. This paper reviewed the available resources and observations of studies undertaken in the recent past about the potentials of TBT and TPT in the development of obesity. The authors have extensively searched the resources material from pub med, Google, biomed central to present this review on potential role of Organotin compound mainly TBT and TPT in genesis of obesity in human and focuses on the rationalization of experimental observation with suggested hypothesis, underlying mechanism of action of endocrine disruptor's exposure.

Tributyltin (TBT) and Triphenyltin (TPT)-Endocrine Disrupting Chemicals (EDCs)

EDCs referred to the environmental chemical pollutants, known to be present in the diet in undetectable quantity. Organotin compounds are organic derivatives of tin with hydrophobic in characteristics and potentially biocummulative in nature. Amongst the most of the EDCs studied, tributyltin (TBT) and triphenyltin (TPT) have been reported as most proactive EDCs with pronounced role in altered neuroendocrine function [11]. Other EDCs such as phthalates, polybrominated diphenyl ethers and perfluoro-compounds have also been studied and reported to have obesogenic effects on adipocyte cell biology [12]. It is proposed that exposures of biological

system especially neuroendocrine to EDCs may result in modulation of hormone synthesis, release and elimination leading to altered neuroendocrine signaling thus causing abnormal effects on adipose tissue biology. In the recent past, some of the important chemical substances identified as EDCs synthetic chemicals used in industries as solvent, lubricants, plastics, pharmaceutical agents, pesticides, alkylphenols and phthalates, household products including some cleaning products, air fresheners, hair dyes, perfumes & cosmetics, and sunscreens compounds.

Mechanism of Action of Organotin Compounds

The TBT and TPT are PPARγ and RXR agonists and reported to stimulate the differentiation of pre-adipocyte cells of adipose tissue and influence the expression of PPARγ and RXR gene in adipose tissue & liver [13]. It is highlighted that high affinity of these obesogens to nuclear hormone receptors is likely mechanism for mediating obesogenic effects on adipose tissue biology to promote obesity in human. However there are reports suggesting that TBT and TPT may act many ways like nonsteroid hormone as in case of serotonin receptor, dopamine or norepinephrine receptor, hydrocarbon receptor, enzymatic pathways responsible for steroid biosynthesis and hormonal signaling but structural variation of physiological system has been the peculiar limitation to predict the hypothetical mechanism of action of TBT and TPT in human. The action of TBT and TPT varies significantly with numerous factors such as (i) what is the age at which body has exposed to TBT and TPT (ii) latent period required for producing visible effects (iii) multiplicity of contamination whether single or multiple contaminants to ruled out synergistic effects, (iv) quantum of exposure dose (v) route of exposure and (vi) complexity of mechanism of action [14-17]. However it is reported that molecular effects of the organotin compounds mediates their effects by blocking steroid induced transcription on their receptor membrane and thus may alter molecular mechanism such as inhibition of histone deacylase activity, changes the DNA methylation, activation of phosphorylation of cofactors like p60, and finally leading to increase action of TBT and TPT by decreasing breakdown of the disruptor-receptor complex [18].

Route of Exposure

Presence of organotin compounds in blood suggests that human body is exposed widely to these types of EDCs. It is reported that there are two major ways, through which the human body exposed to organotin compounds (i) indirect route through use of house hold items contaminated with TBT such as dipers, nepkins, bakery pouches, siliconised parchment, sponges, gloves, cellphone wraps etc which have organic derivatives of organotin compounds like polyurethane, monobutyltin, dibutyltin and tributyltin. The second route of exposure is direct ingestion of food stuff such as fruit juices and other eatables stored in packs, sea foods mainly fishes, oysters, and crabs, preservatives used for storage of food products, tap waters running through the PVC pipes, which has been reported to be contaminated with derivatives of these compounds [19,20]. Although level of bioavailability of these contaminants may vary in different food stuff, but their effects on human body cannot be ruled out. Exposure to use of disinfectants in house hold, such as polish, wax, deodorants, sprays and laundry wash have also been reported to increase the blood level of organotin compounds [21]. However these observation need to be interpreted with caution because method of measurements of organotin compound is a complex and multi-step process with numerous technological limitations.

Obesogenic Effects of Organotin Compounds on Human

Obesogenic function of concentration of organotin compounds in human blood is largely unknown. The potential effects of organotin compound on humans has been reported based on the observation reported by studies carried out on different mammals like rats, rabbits or pigs and approximated qualitative intake by human exposed to these compound directly or indirectly [22-24]. Recent studies reported measurement of circulatory level of TBT and TPT in blood and observed that these compound have direct action on hematological properties such as suppression of immune system mediated by action on viability of thrombocytes. It is reported that decreased viability of thrombocytes and concentration of natural kill cell (lymphocytes) were lower in subjects having higher level of TBT [25]. Mokdad, et al. [26] for the first time demonstrated that oral administration of TBT in “in vivo model” specifically activate key region of central nervous system controlling food intake areas [26], suggesting potential role in development of obesity. In a similar experimental study, it is reported that increase in TBT ingestion exhibit direct relationship with increase in body weight in mammal [27], possibly mediated by modulating secretion of key hormones responsible for energy homeostasis. It is demonstrated that TBT and TPT are PPARγ and RXR agonists and known to promote differentiation of preadipocyte 3T3-L1 cells into adipocyte cells leading to modulation of expression of PPARγ/RXR target genes in liver and adipose tissue, thus acting as potential obesogens [28]. These evidences appears to be quite convincing to believe the direct potential role of TBT in genesis of obesity. However, more clinic-molecular studies are warranted to elucidate relevance of clinical presentation with molecular modulation in development of obesity.

Summary

The observations from the experimental and human studies presented in this paper serve to provide perspective overview of potential role of organotin compounds exposure to human health. The hypothetical postulation about leading role of TPT and TBT in aetiopathogenesis of obesity seems to be appealing concept and deserve a focused approach for further investigation involving evaluation of altered homeostatic metabolic set point, disrupting food control process and measurement of adipogenesis and their correlation with circulating level of TBT and TPT in blood. The authors presume that determination of organotin compounds in blood in subjects using of contaminated food stuff or exposed indirectly with organotin compounds and controls might be helpful to establish the role of these compounds in genesis of obesity. The review on one of the identified obesogen organotin tributyltin demonstrate convincing link between development of obesity and direct and indirect exposure of organotin compound for further research.

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