Reproductive Toxicology 68 (2017) 3–33

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Metabolism disrupting chemicals and metabolic disorders

Jerrold J. Heindel (PhD)[a,*], Bruce Blumberg[b], Mathew Cave[c], Ronit Machtinger[d], Alberto Mantovani[e], Michelle A. Mendez[f], Angel Nadal[g], Paola Palanza[h], Giancarlo Panzica[i], Robert Sargis[j], Laura N. Vandenberg[k], Frederick vom Saal[l]

[a] National Institute of Environmental Health Sciences, Division of Extramural Research and Training Research Triangle Park, NC, USA
[b] University of California, Department of Developmental and Cell Biology, Irvine CA, USA
[c] University of Louisville, Division of Gastroenterology, Hepatology and Nutrition, Louisville KY, USA
[d] Sheba Medical Center and Tel Aviv University, Tel Aviv, Israel
[e] Instituto Superiore di Sanita, Rome, Italy
[f] University of North Carolina at Chapel Hill, School of Public Health, Chapel Hill NC, USA
[g] Institute of Bioengineering and CIBERDEM, Miguel Hernandez University of Elche, Elche, Alicante, Spain
[h] University of Parma, Department of Neurosciences, Parma, Italy
[i] University of Turin, Department of Neuroscience and Neuroscience Institute Cavalieri Ottolenghi (NICO), Turin, Italy
[j] University of Chicago, Section of Endocrinology, Diabetes and Metabolism, Department of Medicine Chicago, IL, USA
[k] University of Massachusetts, Department of Environmental Health Sciences, School of Public Health & Health Sciences, Amherst, MA, USA
[l] University of Missouri, Department of Biological Sciences, Columbia, MO, USA

ARTICLE INFO

Article history:
Received 9 June 2016
Received in revised form 4 September 2016
Accepted 13 October 2016
Available online 17 October 2016

Keywords:
Endocrine disruptors
Obesogens
Metabolism disruptors
Developmental origins of health and disease
Obesity
Diabetes
Lipid disorders

ABSTRACT

The recent epidemics of metabolic diseases, obesity, type 2 diabetes(T2D), liver lipid disorders and metabolic syndrome have largely been attributed to genetic background and changes in diet, exercise and aging. However, there is now considerable evidence that other environmental factors may contribute to the rapid increase in the incidence of these metabolic diseases. This review will examine changes to the incidence of obesity, T2D and non-alcoholic fatty liver disease (NAFLD), the contribution of genetics to these disorders and describe the role of the endocrine system in these metabolic disorders. It will then specifically focus on the role of endocrine disrupting chemicals (EDCs) in the etiology of obesity, T2D and NAFLD while finally integrating the information on EDCs on multiple metabolic disorders that could lead to metabolic syndrome. We will specifically examine evidence linking EDC exposures during critical periods of development with metabolic diseases that manifest later in life and across generations.

1. Introduction

Metabolic syndrome (MetS) is a complex condition characterized by insulin resistance, abdominal obesity, dyslipidemia, hypertension, and hyperglycemia; it is a risk factor for cardiovascular disease, T2D, stroke, chronic kidney disease and cancers [1,2]. Its prevalence is increasing along with the increase in obesity, and it is reaching epidemic proportions affecting between 24% and 34% of the adult US population [3].

In the medical community, epidemics of metabolic diseases have largely been attributed to genetic background and changes in diet, exercise and aging. However, there is now considerable evidence that other environmental factors may contribute to the rapid increase in the incidence of obesity, T2D and other aspects of MetS observed over the past three decades [4]. One environmental factor that has begun to receive attention is a class of chemicals that can interfere with the action of hormones including metabolic hormones. These compounds, termed EDCs, are found in a wide variety of consumer products, and exposures are often widespread [5] Of particular concern is evidence that exposure to EDCs during critical periods when adipocytes are differentiating and the pancreas, liver, brain, etc. are developing can induce effects that manifest later in life, often as overt disease.

* Corresponding author at: Division of Extramural Research and Training, National Institute of Environmental Health Sciences, 12233 TW Alexander Drive, RTP, NC 27709, USA.
E-mail address: heindelj@niehs.nih.gov (J.J. Heindel).

http://dx.doi.org/10.1016/j.reprotox.2016.10.001

This review will examine changes to the incidence of obesity, T2D and NAFLD and its associated hyperlipidemia, the contribution of genetics and describe the role of the endocrine system in these metabolic disorders. It will then specifically focus on the role of EDCs in metabolic diseases, focusing on their role in the etiology of obesity, T2D and NAFLD while finally integrating the information on EDCs on multiple metabolic disorders that could lead to MetS. We will specifically examine evidence linking EDC exposures during critical periods of development with metabolic diseases that manifest later in life and across generations.

2. Metabolic diseases

2.1. Obesity

Obesity is a global epidemic that affects infants, children and adults [6]. The global prevalence of obesity has nearly doubled over the past three decades and in the US it is the highest recorded in human history [7]. For the first time worldwide, the number of obese and overweight people is greater than the number of those who are underweight [8]. This dramatic increase in the rate of abdominal obesity has been observed in both developed and developing countries [9,10].

Obesity among children and adolescents has similarly increased [6]. Approximately one third of US children are overweight or obese, and over 60% of obese children will become obese adults [11]. There is also an obesity epidemic among infants six months of age and younger; an age group where food choices and limited physical activity cannot explain this outcome [12].

The obesity epidemic is not limited to humans but has also been observed as upward trends in body weight among primates and rodents living in research colonies, as well as among feral rodents, horses and domestic dogs and cats [13].

Staggering health care costs are associated with treating the co-morbidities that typically accompany obesity [14] including cardiovascular disease, hypertension, dyslipidemia, liver and gallbladder disease, insulin resistance, hyperglycemia and T2D [9]. Obesity is also associated with neurodegenerative diseases, cancers and obstructive sleep apnea. Thus, determining the factors that contribute to obesity has become a major public health issue.

2.2. Type 2 diabetes

The American Diabetes Association (ADA) defines Diabetes Mellitus (DM) as: "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both" [15]. DM can result from a deterioration in function and/or a loss of mass of pancreatic tissue [16]. T2D (formerly known as adult-onset or non-insulin-dependent diabetes or DM) accounts for 90–95% of diabetes cases and is characterized by increased insulin resistance and pancreatic beta cell dysfunction. More than 11% of individuals in the US older than 20 have diagnosed or undiagnosed T2D [7] and another 35% are estimated to be pre-diabetic. The World Health Organization (WHO) estimates that 347 million people globally suffer from diabetes (90% of which is T2D) [17]. Adolescents and even children have experienced significant increases in the prevalence of this disease over short periods [14,18].

Obesity is the main environmental factor driving the increased incidence of T2D; 70% of the risk associated with T2D is related to weight gain. Obesity is associated with insulin resistance that promotes beta cell proliferation, leading to hyperinsulinemia typical of early stages of T2D and MetS. However, obesity is neither necessary nor sufficient to cause T2D; these conditions can occur independently. Indeed, 20% of adults with T2D were not overweight and 57% of obese individuals do not have T2D [19].

2.3. Nonalcoholic fatty liver disease and hyperlipidemia

Liver is the central organ for lipid metabolism. Nonalcoholic fatty liver disease (NAFLD), characterized by excess triglyceride accumulation within hepatocytes, or steatosis, is considered by some to be the hepatic manifestation of obesity and MetS. NAFLD is the most common liver disease, and it affects 25% of the global population [20] and almost 8% of children [21]. NAFLD and its more severe form, nonalcoholic steatohepatitis (NASH), are associated with increased liver-related and overall mortality [20], and NAFLD is a risk factor for cardiovascular disease [22]. The metabolic condition most commonly associated with NAFLD is hyperlipidemia (69%), although NAFLD is also associated with obesity (51%), MetS (43%) and T2D (23%) [20]. NAFLD was initially thought to occur predominantly in women [23] but increasing evidence indicates that males and perhaps post-menopausal females are more susceptible to NAFLD [21,24].

Hyperlipidemia is an elevation in blood triglycerides (hypertriglyceridemia), cholesterol (hypercholesterolemia), phospholipids, or a combination thereof. While there is an association between NAFLD and hyperlipidemia, not all patients with one disorder are affected by the other. The prevalence of hypertriglyceridemia in US adults is 25%, although it declined from 33% in 2001–2004 [25]. Total and LDL cholesterol have also been declining, and these favorable changes may be attributed to increased awareness and utilization of lipid lowering medications [26]. Among adolescents and US children, the prevalence of hyperlipidemia was 20% (1999–2012) [27].

2.4. Metabolic syndrome

The International Diabetes Federation estimates that 20–25% of the world's adult population have MetS, which it defines as: "a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure" (https://www.idf.org/metabolic-syndrome). The etiology of MetS is still a matter of research but insulin resistance and central obesity are significant contributors. Although there is still substantial debate, it is likely that components of MetS arise from insulin resistance. When insulin resistance occurs, there is an increase of fasting glucose and impaired glucose tolerance, often due to the abnormal expression of gluconeogenic enzymes. This metabolic state induces further insulin release, ultimately resulting in hyperinsulinemia. Hyperinsulinemia then simulates transcription factors such as Srebp-1c in the liver, which drive hypertriglyceridemia and hepatic steatosis [28]. In addition, the overproduction and secretion of insulin by pancreatic β-cells can result in their exhaustion and death, initiating the onset of T2D. The most prevalent form of insulin resistance is associated with abdominal obesity and dysfunction of adipose tissue, indicating an important central role for obesity in MetS.

2.5. Genetic contributions to metabolic diseases

2.5.1. Genetic factors in obesity

While the hereditary origins of obesity have long been assumed, a genetic contribution to obesity became evident only in the last two decades [29]. Evidence from twins and animal studies indicates that genetic factors account for 40–70% of the variation in BMI [30–33]. Although several single genes are linked to obesity, studies have confirmed that the genetic basis of high BMI is mainly polygenic (i.e., resulting from polymorphisms in several genes that are associated with appetite and metabolism) or results from single nucleotide polymorphisms [SNPs] rather than a single gene mutation [34]. Three SNPs are significantly related to obesity: one in FTO (fat mass and the obesity-associated gene), one near