WOULD-BE-WORLDS OF ADIPOBIOLOGY IN THE EXPOSOME OF GLOBESITY

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Abstract
The obesity epidemic has become global meriting the term of "globesity". At the heart of it lies our increasing sedentary lifestyle together with detrimental dietary habits. The genetic background, in particular, our "thrifty genes" also take part of the responsibility for this pandemic. Interestingly, mounting epidemiological evidence links obesity with increases in intrauterine influences, epigenetics, viruses, microbiota, climate changes, sleep debt, and xenobiotics including endocrine disruptors, among others. In this respect, it may be worthwhile to consider that all these factors, that conform our lifelong exposure profile or "exposome", may be partly contributing to the global obesity epidemic. Consequently, an exposomic approach underlines the need for biomonitoring of xenobiotics accumulation in human body, particularly in adipose tissue. It may be time to try to better identify these potential drivers and stimulate analysis on the impact of the "exposome" in light of the increasing overweight and obesity trends.

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I am a citizen of the world.
Homo obesus, a paraphrase from Diogenes (412-323 BC)

The Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group reported that in adults obesity is increasing worldwide despite the fact that many countries have successfully reduced blood pressure and have shown that interventions on metabolic mediators might partially mitigate the health effects of rising the body mass index (1,2). The Homo obesus has been described as a recent phenotypic expression of the Homo sapiens (3,4). In particular, the Homo obesus or obese man has been classified as a species deficient in metabotrophic factors (metabotrophins), including endogenous neurotrophic proteins, which play essential roles in the maintenance of glucose, lipid, energy and vascular homeostasis, as well as in improving metabolism-related processes such as inflammation and wound healing (3).

New insights for better understanding population changes and their interaction with the environment are
therefore welcome. Our “thrifty genes” together with profound lifestyle changes, characterized by an energy-dense diet, especially due to high-fat foods, as well as a stubborn sedentariness have been advocated as the main reasons for the escalating overweight and obesity trends of the past decades. Nonetheless, findings in different scenarios are partially questioning this view. On the one hand, the results of the genome-wide association scans for obesity-related traits performed by huge consortia are probing that the impact of the most relevant genes are in reality small (5). Moreover, the adverse genetic make-up can be effectively counteracted by physical activity (6,7). Interestingly, it has been shown that obesity spreads more through social ties than via familial heritage (8), a fact that reinforces the relative relevance of genetics. On the other hand, epigenetics has gained protagonism in explaining how specific environmental exposures are able to confer an increased risk for the development of obesity and other diseases via direct influence on the human genome regulation (9). Noteworthy, during the past decades sociocultural circumstances have prompted important reproductive performance changes that have translated into an increased maternal age together with higher fecundity among people with elevated adiposity (10). In this respect, it has to be stressed that older mothers are at risk of delivering either small or large for gestational age babies, and both of them are well-known to be more prone to become obese adults. Thus, the detrimental effect on the baby’s birthweight in either direction conditions the likelihood of developing obesity at a later stage, as demonstrated by recent studies in developmental programming (11 and references therein). Further, the field of energy homeostasis in humans has experimented a substantial turn with the identification of brown adipose tissue in adults (12). The additional possibility of stimulation of these brown adipose tissue depots via sympathetic activation as is the case in response to cold exposure (13) provides a further plausible link between the obesity pandemic, climate change and global warming (14). Another unsuspected key player in energy control and metabolism that has gained a lot of special attention in the last years is the gut microbiome (15). Interestingly, alterations of the gut microbiome are associated with obesity at the same time as being responsive to weight loss since gut microbes can impact host metabolism with effects on deposition of energy in fat stores, insulin resistance, and inflammation. Conversely, the restoration of the gut microbiota to a physiological balance of the different phyla ameliorates the derangements accompanying obesity, aiding in the maintenance of a normal weight (16).

Infeco-obesity, i.e. the relation between infectious agents and the development of excess weight, has been a topic that has gathered renewed attention as a potential external driver of the obesity pandemic. In this regard, associations between the presence of antibodies against in particular adenovirus-36 and Chlamydia pneumoniae and the development of obesity have been established (17,18). These infectious agents are able to infect fat cells and interfere the control of transcription factors and enzymes towards triglyceride accumulation as well as differentiation of preadipocytes into mature adipocytes.

The environmental obesogen hypothesis postulates that chemical pollutants, such as persistent organic pollutants (POP) including pesticides and polychlorinated biphenyls, are able to promote obesity by altering homeostatic metabolic set-points, disrupting appetite regulation, altering lipid homeostasis to promote adipocyte hypertrophy, and/or stimulating adipogenic pathways that enhance adipocyte hyperplasia during development or adulthood (19). In the same view, endocrine disrupting chemicals reportedly are able to trigger endogenous hormonal dysregulation that predisposes to weight gain. A number of different endocrine disrupting chemicals are known to interfere with adipogenesis like the organotin tributyltin, which exerts high-affinity nuclear hormone receptor-mediated effects on fat cells to favour long-term obesogenic changes that translate into epidemiological impact (10,19,20). Phthalates, bisphenol A, polybrominated diphenyl ethers, and perfluro-compounds embody potential obesogens exhibiting a direct link between exposure, transcriptional network modulation and adipogenic phenotypes. Of note, the levels in humans of these compounds are on the rise during the last decades (10).

Noteworthy, the adipose tissue is the major reservoir of POP, also various cancerogenic polycyclic aromatic hydrocarbons, which are implicated in the development of obesity-related diseases and cancer. Accordingly, xenobiotic-metabolizing cytochromes p450 (CYP) are expressed in adipose tissue. And are inducible through mechanisms similar to those in the liver, namely, CYP1A1 and CYP1B1 can bioactivate xenoestrogens (dioxin and pesticides) and carcinogenic benzo(a)pyrenes. Consequently, an adipocentric approach underlines the need for human biomonitoring of xenobiotics accumulation in adipose tissue. Such studies open a new field of adipobiology that was conceptualized as adipotoxicology (21, also see Yanev in this volume of Adipobiology).

Circadian regulation of energy homeostasis is controlled by an endogenous biological clock that is located in the hypothalamic suprachiasmatic nucleus (SCN). The synchronization of photic information that travels directly from light-sensitive ganglion cells in the retina to the SCN, accommodates the individuals’ physiology and behaviour to the external day-night cycle. Noteworthy, the increase in the prevalence of globesity is paralleled by the elevated exposure to light at night and shift
work (22). Light cues are the most potent signals for the circadian clock, while other factors such as food consumption also influence clock signalling. By favouring optimal adaptive functioning, the circadian clock conditions subjects to predictable circumstances such as sleep and food availability. Consequently, clock function disruption produces circadian and metabolic disturbances with alterations in the timing of food intake and other metabolic signals, leading to excess weight gain (23). Alterations in the chronobiology (also in adipose tissue, see 24) as well as sleep curtailment are followed by increases in body mass index and undermine dietary effects to decrease adiposity. Thus, sleep debt is accompanied by increased hunger, higher plasma levels of the orexigenic hormone, ghrelin, and reduced concentrations of the anorexigenic hormone, leptin, in volunteers following a caloric restriction, but not when they were on a surplus of energy (25,26). Not surprisingly, lack of sleep is known to exert relevant effects on multiple neuroendocrine signals clearly involved in substrate utilization control such as the circulating levels of cortisol, catecholamines, thyroid, and growth hormone.

Last but not least, through a very elegant cross-species analysis the group of Professor Allison has pragmatically shown a plurality of obesity epidemics in mammalians living with or around humans (27). Most interestingly, part of these animals were obese even when living in animal houses and thus separately of humans as well as in the absence of those factors characteristically perceived as the primary determinants of the human obesity epidemic due to their adverse influence on diet and physical activity. Taken together, all this accumulating evidence can lead us to consider that the development of obesity over the past decades is probably influenced by other factors that we have not been able to appreciate in their full extension.

The measure of all the exposures of an individual in a lifetime and how those exposures relate to disease is what was designated the “exposome”; its analysis has been a logical step forward after the human genome mapping success (28). Of great importance is the fact that the exposure of a given subject begins before birth and finishes with the person’s death. The exposome, therefore, includes exposures (internal and external, positive and negative ones) during our whole life from our environment, diet, lifestyle, and so on, that will interplay with our specific genetic, epigenetic and physiologic background to finally conform our health status (29). In this respect, environmental exposures have been shown to play an outstanding role in common chronic diseases like cardiometabolic diseases (atherosclerosis, hypertension, obesity, type 2 diabetes, metabolic syndrome) and cancer, which constitute a major health burden in economically developed countries (30). However, due to the complexity of unravelling genetic susceptibility with the plentiful potential exposure-dis-

ease associations it is difficult to establish the individual’s exposome and its true contribution to the person’s well-being and disease. Therefore, it will be important to try to develop the adequate tools and study designs to better identify the contribution of the “exposome” to the globesity and its related diseases. This is particularly important in the case of childhood and adolescent obesity, because due to the longer exposure, the detrimental effects produced on weight gain and comorbidities are expected to translate in more dramatic clinical outcomes (30).

Altogether, the present Dance Round reminds us that in the life of each individual, “I” (human being) can not be detached from “my circumstance” (world), which led the great José Ortega y Gasset to write in 1914 his famous maxim Yo soy yo y mi circunstancia (I am I and my circumstance), in his Meditaciones del Quijote.

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