Journal of Trace Elements in Medicine and Biology 30 (2015) 195–201

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

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

Review

Iron metabolism in obesity: How interaction between homoeostatic mechanisms can interfere with their original purpose. Part I: Underlying homoeostatic mechanisms of energy storage and iron metabolisms and their interaction

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ARTICLE INFO

Article history:
Received 9 September 2014
Accepted 29 October 2014

Keywords:
Iron metabolism
Obesity
Inflammation
History
Epidemiology

ABSTRACT

Adipose tissue plasticity mediated by inflammation is an important evolutionary achievement to survive seasonal climate changes. It permits to store excessive calories and to release them if required, using inflammatory cells to remove the debris. This process is regulated by a complex interaction of cytokines (TNF-α, IL-6), adipokines (adiponectin, apelin, liptin), adhesion molecules (ICAM-1, VCAM-1, E-selectin) and transcription factors (NF-κB, HIF-1α). Iron mediates electron transfer as an essential component of e.g. myeloperoxidase, hemoglobin, cytochrome C and ribonucleotide reductase. Conversely, unbound iron can catalyze oxidation of lipids, proteins, and DNA. To balance the essential with the potentially toxic function requires an efficient iron homoeostasis. This is mediated by hepcidin's interaction with the iron-exporter ferroportin, to adapt intestinal iron absorption and body iron-sequestration to changes in demand. In addition, the interaction of iron-responsive elements (IRE) and iron-responsive proteins (IRP), the IRE/IRP-mechanism, regulates cellular iron homoeostasis. Obesity-induced inflammation interacts with both these mechanisms and disturbs iron availability by impairing its absorption, and by sequestering it in the reticuloendothelial system. Both mechanisms lead to anemia and reduce physical fitness which, in a vicious cycle, can support the development of pathological obesity. Thus, interaction between these two sets of beneficial regulatory mechanisms can become detrimental in situations of ample calorie supply.

Contents

Abbreviations: AT, adipose tissue; BMI, body mass index; BMP-6, bone morphogenetic protein 6; BMPR-II, bone morphogenetic protein receptor type II; CRP, C-reactive protein; DALY, disability-adjusted life year; DMT1, divalent metal transporter 1; ER, endoplasmic reticulum; HIF2-α, hypoxia-inducible factor 1, alpha subunit; H-ferritin, human ferritin; ICAM-1, intercellular adhesion molecule 1; IL-1, interleukin 1; IL-6, interleukin 6; IRP, iron regulatory protein; IRE, iron-responsive element; IRP/IRE system, iron regulatory protein/iron-responsive element system; Jak2/STAT3, Janus kinase 2/Signal transducer and activator of transcription 3; L-ferritin, ferritin light chain; MCP-1, monocyte chemotactic protein 1; mRNA, messenger RNA; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; RES, reticulo-endothelial system; SMAD proteins, Sma and Mad related proteins; STAT3, signal transducer and activator of transcription 3; TfR1, transferrin receptor protein 1; TLR-4, Toll-like receptor 4; TMPRSS6, transmembrane protease, serine 6; TNF-R1, tumor necrosis factor receptor superfamily, member 1A; TNF-α, tumor necrosis factor alpha; UTR, untranslated region; VCAM-1, vascular cell adhesion protein 1.

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http://dx.doi.org/10.1016/j.jtemb.2014.10.011
0946-672X/

André Gide coined the sentence "*L' intelligence c'est la faculté d'adaptation*" or "Intelligence is the ability to adapt". This sentence credits evolution with high intelligence, though this process obviously has no master-plan. Its strategy is to pursue an ample number of parallel alternatives in order to "let the fittest survive" [1]. By "fittest" Darwin meant those individuals within a species that are most apt to survive *to reproductive age* and, thus, be the most prolific and fertile of their group, making a relatively greater contribution to the next generation. Many alternatives are extinguished that way; so far, however, some "best picks" have always survived and thrived, even during the large extinction of species at the end of the Mesozoic Age, when environmental changes were harsh and dinosaurs became extinct. Thus, retrospectively, the strategy of continuous evolution and selection appears successful, though it is surely not in line with the Hippocratic principle of "*primum nil nocere*" (i.e. the first priority is to avoid harm); ethical considerations are obviously not in the scope of evolution.

André Gide, as a Nobel Laureate for literature, was not primarily focused on the evolution of species, but rather on explaining human behavior. In the context of evolution "human behavior" translates into "self-domestication", i.e. into man modifying his own environment to serve his own requirements. The prerequisite here is that *Homo sapiens* assesses his requirements correctly and understands all implications of his endeavor. Evolution, in turn, will impose upon such man-made initiatives, as if they represent interferences with implications for the environment, for other living species and for human health and well-being. Human self-domestication encompasses the use of fire. It also includes the development of tools and arms, both of which mitigate being a victim of predation (i.e. prey) and turning him into a fierce predator himself. Crop-farming, the domestication of animal species and, more recently, industrialization and global commerce and trade improved food security and abolished many physically-taxing activities, such as long-distance walking in order to forage, gather and hunt. In the current era, even physical exercises such as stair-climbing and carrying water home from the village well is replaced by elevators and water-pipe systems.

Human evolution had to address all points of importance for survival; otherwise, *Homo sapiens* would have disappeared into evolution's archive of extinct species as a petrified relict. A closer look at the homoeostatic mechanisms that have evolved for *Homo sapiens*, therefore, should render a "short list" of the most important problems that human evolution had to tackle.

A case in point – and the topic of this review – is the recently emerging mutual interaction among obesity, inflammation and the mechanisms of mammalian iron homoeostasis. Proper analysis of homoeostatic mechanisms may help to avoid their down-side consequences. This offers an additional perspective on public health problems, one that extends beyond the straight approach to assess requirement levels for nutrients and trying to meet them. So, this review identifies and explores the mechanisms of interaction among obesity, inflammation and iron homoeostasis. It assesses the epidemiology of the obesity/iron interaction and underlines the importance of field research to understand more aspects of the related health problems.

Obesity and inflammation

Worldwide prevalence of overweight and obesity, as defined e.g. by a Body-Mass-Index (BMI) in excess of 25 kg/m^2 and 30 kg/m^2, respectively, has gained pandemic dimensions. Literature suggests that the increase in prevalence relates to a sedentary life-style and improved food security in an increasing number of countries and for increasing fractions of the population. On the one hand, these changes reflect marvelous successes in the attempt to avoid undernutrition and famine. On the other hand, they increase the prevalence of the metabolic syndrome, and the precursors of atherosclerosis, high blood pressure, and heart failure, stroke and myocardial infarction [2]. The reproduction-based survival-of-the-fittest aspect of evolution fails to correct this, as all of these non-communicable diseases only show their effects after the age of reproduction. The financial and organizational burden to care for those affected by the sequelae of this shift will be increasingly heavy on the affected industrialized and developing economies.

Tasks and issues of adipose tissue

Adipose tissue (AT) is the major energy store in mammals. It is unique among non-transformed tissues in providing an almost unlimited capacity for expansion and it can recycle the stored calories when required. Moreover, subcutaneous fat-stores serve to insulate the body for thermoregulation. These contributions are indispensable for organisms subject to the vagaries of fluctuating food-security under drastically changing climatic conditions, both seasonally and as a consequence of geographic migration. However, when expanding, blood supply of AT may reach the diffusion limit for oxygen and nutrients effectively reaching all cells; at this point, the rate of angiogenesis becomes rate-limiting for AT expansion. When metabolically healthy expansion rates are exceeded, adipocytes become necrotic, triggering constant low to medium level inflammation [3]. Such inflammation is the price the organism pays for the beneficial ability to have a flexible energy storage that waxes and wanes in response to different environmental conditions.

Adipose tissue and inflammation

Adipose tissue increases its cell number (hyperplasia) throughout childhood and adolescence; in adulthood, it expands rather by increasing the size of the individual cells (hypertrophy). Accordingly, 75% of obese children become obese adults, and less than 10% of normal weight children develop adult obesity [4]. Expanding adiposity is accompanied by increased expression of adipokine hormones and chemo-attractants [5], leading to AT's infiltration by monocytes and macrophages and, to a lesser extent, by lymphocytes. These inflammatory cells preferentially infiltrate the omental fat deposited around the visceral organs in the abdominal cavity, forming "crown-like" structure around necrotic adipocytes in advanced obesity to remove the debris [6]. Recruited macrophages switch to the pro-inflammatory M1-status and express inducible NO-synthetase (iNOS) and high levels of pro-inflammatory cytokines, such as TNF-α and IL-6 [7].