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Lifestyle and nutritional imbalances associated with Western diseases: causes and consequences of chronic systemic low-grade inflammation in an evolutionary context

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Abstract

In this review, we focus on lifestyle changes, especially dietary habits, that are at the basis of chronic systemic low grade inflammation, insulin resistance and Western diseases. Our sensitivity to develop insulin resistance traces back to our rapid brain growth in the past 2.5 million years. An inflammatory reaction jeopardizes the high glucose needs of our brain, causing various adaptations, including insulin resistance, functional reallocation of energy-rich nutrients and changing serum lipoprotein composition. The latter aims at redistribution of lipids, modulation of the immune reaction, and active inhibition of reverse cholesterol transport for damage repair. With the advent of the agricultural and industrial revolutions, we have introduced numerous false inflammatory triggers in our lifestyle, driving us to a state of chronic systemic low grade inflammation that eventually leads to typically Western diseases via an evolutionary conserved interaction between our immune system and metabolism. The underlying triggers are an abnormal dietary composition and microbial flora, insufficient physical activity and sleep, chronic stress and environmental pollution. The disturbance of our inflammatory/anti-inflammatory balance is illustrated by dietary fatty acids and antioxidants. The current decrease in years without chronic disease is rather due to "nurture" than "nature," since less than 5% of the typically Western diseases are primary attributable to genetic factors. Resolution of the conflict between environment and our ancient genome might be the only effective manner for "healthy aging," and to achieve this we might have to return to the lifestyle of the Paleolithic era as translated to the 21st century culture.

Keywords: Chronic systemic low grade inflammation; Evolution; Brain; Encephalization quotient; Immune system; Diet; Fatty acids; Fish oil; Fruits; Vegetables; Antioxidant network; Metabolic syndrome; Glucose; Homeostasis; Insulin resistance; Cholesterol; Lifestyle; Antioxidants; Resoleomics; Pro-inflammatory nutrients; Anti-inflammatory nutrients

1. Introduction

In recent years, it has become clear that chronic systemic low grade inflammation is at the basis of many, if not all, typically Western diseases centered on the metabolic syndrome. The latter is the combination of an excessive body weight, impaired glucose homeostasis, hypertension and atherogenic dyslipidemia (the "deadly quartet"), that constitutes a risk for diabetes mellitus type 2, cardiovascular disease (CVD), certain cancers (breast, colorectal, pancreas), neurodegenerative diseases (e.g., Alzheimer's disease), pregnancy complications (gestational diabetes, preeclampsia), fertility problems (polycystic ovarian syndrome) and other diseases [1]. Systemic inflammation causes insulin resistance and a compensatory hyperinsulinemia that strives to keep glucose homeostasis in balance. Our glucose homeostasis ranks high in the hierarchy of energy equilibrium, but becomes ultimately compromised under continuous inflammatory conditions via glucotoxicity, lipotoxicity, or both, leading to the development of beta-cell dysfunction and eventually Type 2 diabetes mellitus [2].

Insulin resistance has a bad name. The ultimate aim of this survival strategy is, however, deeply anchored in our evolution, during which our brain has grown tremendously. The goal of reduced insulin sensitivity is, among others, the reallocation of energy-rich nutrients because of an activated immune system [3,4], limitation of the immune response, and the repair of the inflicted damage. To that end, serum lipoproteins adopt a pattern that bears resemblance with the "hyperlipidemia of sepsis," accompanied by seemingly inconsistent changes in serum cholesterol, increased triglycerides, decreased high-density lipoprotein (HDL) cholesterol, and an increase of "small dense" low-density lipoprotein (LDL) particles, of which the latter three constitute the triad of atherogenic dyslipidemia that is part of the metabolic syndrome [5–10].

From the perspective of our brain growth during evolution, we address the question of why *Homo sapiens* is so sensitive to the development of insulin resistance. The purpose and the underlying mechanisms leading to insulin resistance and the associated dyslipidemia are subsequently discussed in more detail. We argue that our current Western lifestyle is the cause of many false inflammatory

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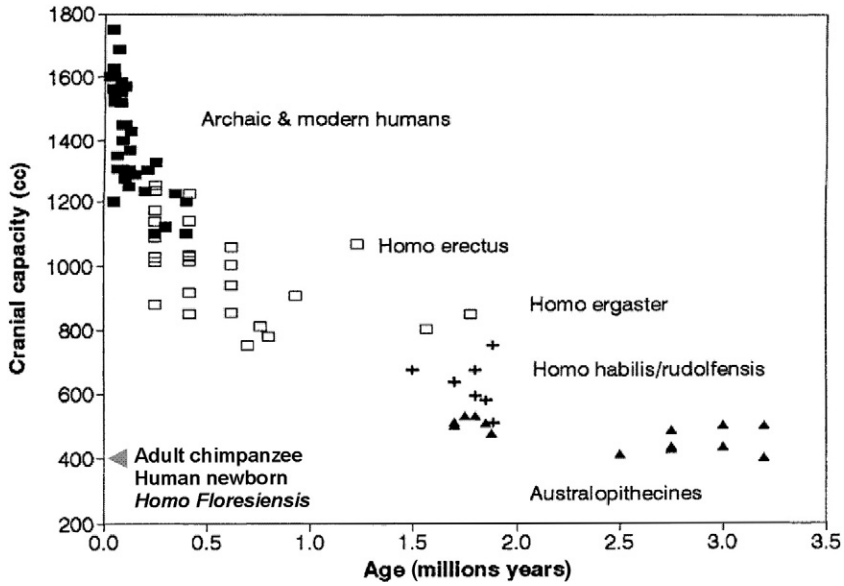

Fig. 1. Evolution of our brain size within the past 3.5 million years. Our brain has grown fast since the *Homo erectus* (1.7-2.0 million years ago). The newborn *Homo sapiens*, the adult chimpanzee and the *Homo floresiensis* [18] have brain volumes of around 400 ml.
Adapted from Aiello and Wheeler [19] with permission from The University of Chicago Press.

triggers which successively lead to a state of chronic systemic low grade inflammation, insulin resistance, the metabolic syndrome, and eventually to the development of the above mentioned typically Western diseases of affluence. To find a solution for the underlying conflict between our environment and our ancient genome, we also go back in time. With the reconstruction of our Paleolithic diet, we might be able to obtain information on the nutritional balance that was at the basis of our genome. We argue that insight into this balance bears greater potential for healthy aging than the information from the currently reigning paradigm of "evidence-based medicine" (EBM) and "randomized controlled trials" (RCTs) with single nutrients.

2. Our brain growth rendered us sensitive to glucose deficits

Homo sapiens and the current chimpanzees and bonobos share a common ancestor, who lived in Africa around 6 million years ago. Since about 2.5 million years ago, our brain has strongly grown from an estimated volume of 400 ml to the current volume of approximately 1400 ml (Fig. 1). This growth was enabled by the finding of a high-quality dietary source,[1] that was easy to digest and contained an ample amount of nutrients, necessary for the building and maintenance of a larger brain. The nutritional quality of primate food correlates positively with *relative* brain size and inversely with body weight, suggesting that a larger brain requires a higher dietary quality [11]. The necessary so-called "brain selective nutrients" include, among others, iodine, selenium, iron, vitamins A and D, and the fish oil fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), that jointly are abundantly available in the land-water ecosystem. There are compelling arguments that a sizeable part of our evolution occurred at places where the land meets the water [12–15], but also that we have changed our lifestyle in a too short period of time. These changes started from the agricultural revolution (around 10,000 years ago) and became accelerated since the industrial revolution (about 100–200 years ago). They created a conflict between our current lifestyle, including our diet, and our ancient genome, that, with an average effective mutation rate of 0.5% per million years, still resides for the greater part in the Paleolithic era [16,17]. It is not by chance that the above mentioned brain selective nutrients are among those of which we currently exhibit the largest deficits worldwide. These deficits are masked by enrichment and fortification of our current diet with iodine (in salt), vitamins A and D (e.g., in margarines and milk) and iron (flour, cereals).

Our brain consumes 20–25%[2] of our basal metabolism [11–17,20] and is thereby together with the liver (19%[2]), our gastrointestinal tract (15%[2]), and skeletal musculature (15%[2]) among the quantitatively most important organs in energy consumption [19]. The infant brain consumes as much as 74% of the basal metabolism [11,21]. In contrast to most other organs, the brain uses mostly glucose as an energy source. There is no other primate equipped with such a large, glucose-consuming, luxury organ as our brain. For example, our closest relative, the chimpanzee, has a brain volume of 400 ml, which consumes about 8–9% of the basal metabolism. Because of the high energy expenditure of a large brain, it was necessary to make various adjustments in the sizes of some other organs. There is a linear relationship between body weight and basal metabolism among terrestrial mammals (Fig. 2). This apparently dogmatic relationship predicts that, due to the growth of our brain, other organs with high energy consumption had to be reduced in size, what in evolution is known as a "trade-off".[3] As a consequence of this "expensive tissue hypothesis" of Aiello and Wheeler [19], our intestines, amongst others, had to become reduced in size. However, this exchange of expensive tissue probably occurred prior to, or simultaneous with, our brain growth, in which the trigger was the consumption of the easily digestible high-quality food [20] that contains the above-mentioned "brain selective nutrients" from the land-water ecosystem. Under these "conditions of existence" (Darwin), a single mutation in a growth regulatory gene is likely to have been sufficient for the brain to grow. This notion derives from the existence of genetically-determined micro- [22] and macrocephaly [23] and it is as

[1] Food quality refers to the energy content and/or the nutrient content of a diet. An increase in food quality may derive from the consumption of a diet with another composition or the modification of the diet by, e.g., cooking or genetic manipulation [11].

[2] These estimates derive from various publications and therefore do not add to 100%. They should be regarded as indications.

[3] The beneficial exchange of a certain property into another one.