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REVIEWS: CURRENT TOPICS

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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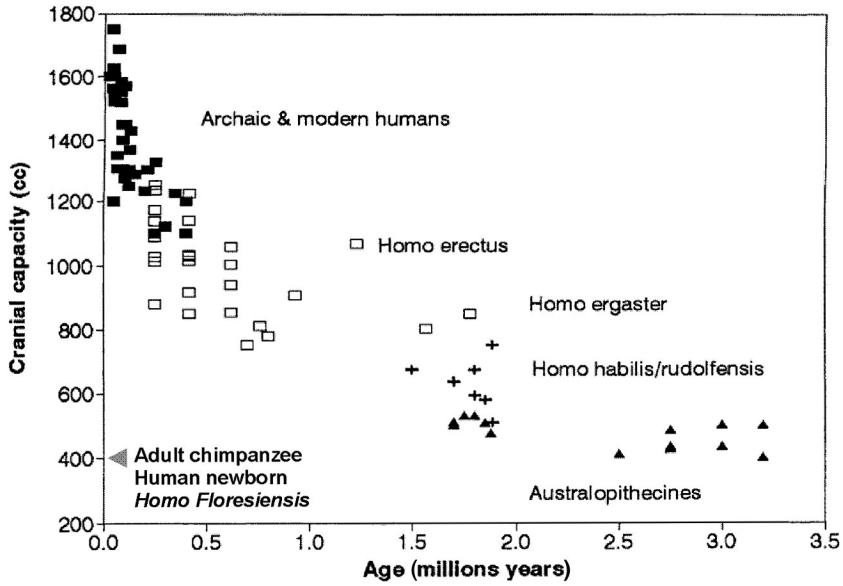

Fig. 1. Evolution of our brain size within the past 3.5 million years. Our brain has grown fast since the *Homo erectus* (1.7-2.0 million years ago). The newborn *Homo sapiens*, the adult chimpanzee and the *Homo floresiensis* [18] have brain volumes of around 400 ml.
Adapted from Aiello and Wheeler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

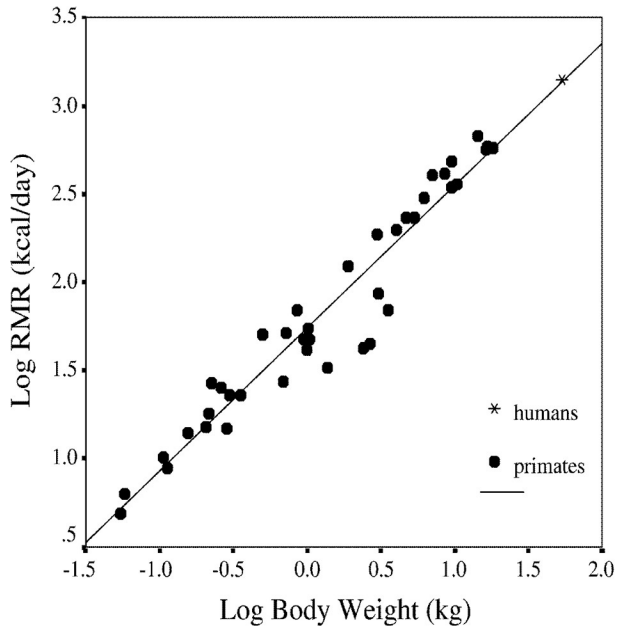

Fig. 2. Relationship between body weight and basal metabolism in 51 land mammals (20 non-primates, 30 primates, and humans). RMR, resting metabolic rate. Adapted from Leonard et al. [11] with permission from Elsevier.

a "proof of principle" demonstrated by the differences in the beak lengths of Darwins" legendary Galapagos finches [24–26]. Compared with our close (vegetarian) relatives in the primate world, we possess a relatively long small intestine and a relatively short large intestine, which corresponds with the digestion of high quality food (such as meat and fish) in the small intestine, and the lesser need of a long colon for the digestion of complex carbohydrates (e.g., fiber) from a typically vegetarian diet [19]. Unlike our near primates, such as the gorilla, our teeth and the attachments of our jaw muscles are not specialized for the processing of tough vegetarian food. Also our muscle mass became adapted, since its current size is relatively small compared to our body weight. For instance, when compared with the chimpanzee, we are definitely weak. On the other hand, we have a relatively sizeable fat mass, which probably serves as a guarantee for the high energy requirement of our brain.

Our brain's energy consumption is quite stable. Unlike other organs, the energy consumption of the brain can not be down-regulated at times of a negative energy balance or fasting [11,20]. Our brain also gets spared during prolonged fasting, while other organs such as the liver, spleen, kidneys and even the heart, are sacrificed for energy generation [27]. This hierarchy also applies to the prenatal brain, whose development is conserved during intrauterine growth restriction [28]. An example is the Indian "thin fat baby," with a birth weight of 2700 g. Compared with its 3,500 g counterpart from the UK, this infant has a similar brain size and a relatively large fat compartment, at the expense of the somatic growth of the skeletal muscle, kidneys, liver and the pancreas [28]. Our brain ranks high in the functional hierarchy and should be provided with the necessary energy at all times.

Apart from its large size, there is nothing special about our brain within the primate world. Compared with other species, primates have a very economical space-saving brain, but among the primates, brain weight correlates with the number of neurons [29–32] and intelligence [33]. Actually, our brain is no more than an oversized primate brain [29]. What does distinguish us from other species is the high ratio between our brain size and our body weight, which is also named encephalization quotient (EQ) (Fig. 3). Toothed whales (brain weight 9000 g) and African elephants (4200 g) have much larger brains than humans, but they have lower EQs [34]. Among the primates, EQ does not correlate with intelligence [33]. Our high EQ has major implications for our energy management, particularly at times of "glucose shortage". Under normal circumstances, our brain functions almost entirely on glucose, consuming up to 130 g/day [27]. Compared with the apparently unlimited storage capacity for fat, we only dispose of a small reserve of glucose that is stored as glycogen in the liver (up to 100–120 g; mobilizable) and muscles (360 g; for local usage), while some glycogen can even be found in brain's astrocytes [35]. With the exception of the glycerol moiety, we can not convert fat into glucose. The reduced carbohydrate intake that came along during evolution with the transition from vegetarians to omnivores rendered us strongly dependent on gluconeogenesis from (glucogenic) amino acids. This was possible because we simultaneously consumed more protein from meat and fish, which is also referred to as the "carnivore connection" [36]. After the depletion of our glycogen reserves, for instance after an overnight fast, we obtain the necessary glucose for our brain via gluconeogenesis from glycerol and amino acids. Under normal conditions, these amino acids derive from our dietary proteins after a meal, but during starvation, they become extracted from our tissues by catabolism of functional proteins, at the expense of our lean body mass. Under such circumstances of severe glucose deficit, the energetic need of our brain becomes increasingly covered by ketone bodies from fat [37,38].

A glucose deficit leads to competition between organs for the available glucose. As previously mentioned, this occurs during fasting, but also during pregnancy and infection/inflammation. Fasting is characterized by a generalized shortage of glucose (and other macronutrients), but in case of pregnancy and inflammation we deal with active compartments competing with the brain for the available glucose, i.e., the growing child and the activated immune system, respectively. During competition between organs for glucose, we fulfill the high glucose needs of the brain by a reallocation of the energy-rich nutrients, and to that end, we need to become insulin resistant.

3. Reallocation of energy-rich nutrients by insulin resistance

The developing child grows fast in the third trimester of pregnancy. In this period, the supply of the necessary building blocks like glucose and fatty acids should be independent of the maternal metabolic status, which is known as the state of "accelerated starvation" and "facilitated anabolism" [38]. Glucose crosses the placenta without restriction. Fetal needs are directive, since the developing fetus is high in the evolutionary hierarchy. If necessary, the fetal needs become covered at the expense of the mother, which is known as the "depletion syndrome".

During infection/inflammation we deal with the metabolic needs of an activated immune system for acute survival. The inactive immune system consumes about 23%[2] of our basal metabolism, of which as much as 69% derives from glucose (47%) and the glycogenic amino acid glutamine (22%). Upon activation, the energy requirement of our immune system may increase with about 9–30% of our basal metabolic rate. In multiple fractures, sepsis and extensive burns, we deal with increases up to 15–30, 50, and 100% of our basal metabolism, respectively [3,4,39].

The way we save glucose for our brain during starvation, for the brain and the fetus during pregnancy, and for the brain and immune system during infection/inflammation, is by causing insulin resistance in selected insulin-dependent tissues. These tissues are thereby forced to switch to the burning of fat. Due to insulin resistance, the adipose tissue compartment will be encouraged to distribute free fatty acids, while the liver will be encouraged to produce glucose via gluconeogenesis and to distribute triglycerides via very low-density lipoprotein (VLDL). The aforementioned (asymmetric) "thin fat baby"

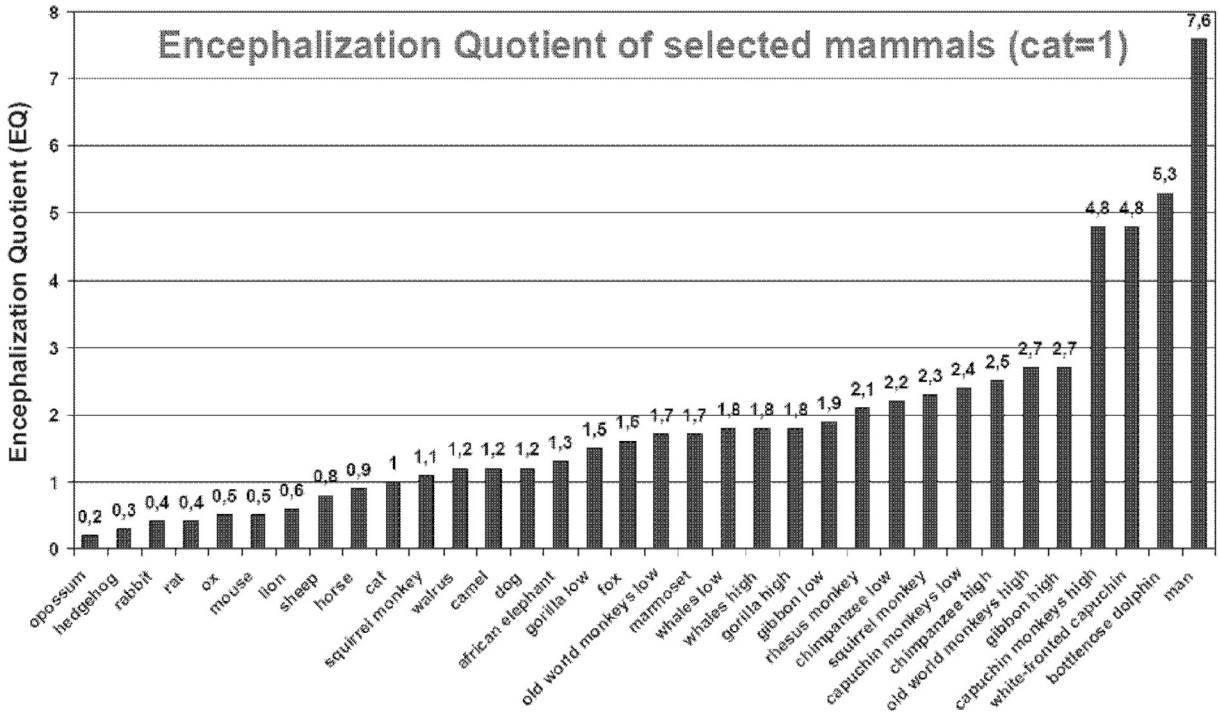

Fig. 3. Encephalization quotient of selected mammals. The EQ has been normalized with the cat as a reference.
Data adapted from Roth and Dicke [34].

with its spared brain, relatively high adipose tissue compartment, and the growth restricted body (islets of Langerhans included), has relatively high cord plasma insulin and glucose concentrations at birth [28]. These characteristics of insulin resistance and diabetes mellitus are probably necessary for the postpartum, saving of as much as possible of the available glucose for the brain, whereas the other organs are provided with fatty acids from the sizeable adipose tissue stores. This intrauterine 'programming', that follows the prediction of a thrifty postnatal life comes along with health risks, notably when the prediction proves false [40,41]. According to the "Barker hypothesis," at adult age, these children have a higher chance of diseases related to the metabolic syndrome, especially when they are raised in our current obesogenic society. The unfavorable interaction of their high EQ with a high body weight is already demonstrable at the age of 8 years [42]. Essentially, their postnatal risk is attributable to a (probably epigenetic) "intrauterine programming," that traces back to the high hierarchical ranking of our brain in both growth and energy needs, also referred to as "the selfish brain" [43].

Glucose intolerance [26] and insulin resistance have been reported in calorie restriction, extreme fasting and anorexia nervosa, and may even cause, under these circumstances, diabetes mellitus type 2, notably in those subjects sensitive to its development [44]. According to textbooks, insulin resistance during the third trimester of pregnancy is caused by the hormonal environment, among which HPL, progesterone, estrogens, prolactin and cortisol are mentioned. However, placental tumor necrosis factor alpha (TNFα) correlates best with measures of maternal insulin resistance [45,46]. Pregnancy is therefore sometimes referred to as a physiological state of systemic low grade inflammation [47]. As a consequence of reduced insulin sensitivity, maternal circulating concentrations of energy-rich nutrients, such as glucose and fat, tend to increase, promoting their transport across the placenta. Under non-pregnant conditions, this situation would resemble pathology, but is tolerable during the 9 months of a pregnancy, while the largest changes occur during the third trimester.

During infection and inflammation, the signals for metabolic adaptation become transmitted by pro-inflammatory cytokines. The resulting insulin resistance causes reallocation of energy (i.e. the aim of the process; see above), which illustrates that inflammation and metabolism are highly integrated [49–51]. At the molecular level, the interaction takes place through the influences of the nuclear factor kappa B (NFκB) and the AP-1 Fos/June inflammatory pathways on the PI3K/Akt signal transduction pathway for nutrient metabolism and the Ras/MAPK pathway for gene expression, which are both part of the insulin signal transduction [48,52]. To put it simply: the activated inflammatory signal transduction pathway causes inhibition of the postreceptor insulin signaling pathway, which becomes noticeable by what we know as insulin resistance (Fig. 4). Insulin resistance especially refers to a grossly diminished reduction of the circulating glucose concentration by insulin. However, insulin has many functions, and thereby exerts different effects in the various organs carrying the insulin receptor. Consequently, the "resistance" affects the many insulin signal transduction pathways at various degrees, and thereby works out differently with respect to the various insulin functions [1,53]. Some processes are impaired (i.e., are genuinely "resistant"), while others remain intact and become excessively stimulated by the compensatory hyperinsulinemia. This compensatory increase of the circulating insulin levels aims at the prevention of a disturbed glucose homeostasis and thereby the onset of type 2 diabetes mellitus. The persistence of compensatory hyperinsulinism is responsible for most, if not all, of the abnormalities that belong to the metabolic syndrome [1].

In muscle and fat cells, insulin resistance induces a diminished glucose uptake and therefore a reduced storage of glucose as glycogen and triglycerides. In fat cells, it causes decreased uptake of circulating lipids, increased hydrolysis of stored triglycerides and their mobilization as free fatty acids and glycerol. In liver cells, insulin resistance induces the inability to suppress glucose production and secretion, in addition to decreased glycogen synthesis and storage. The hereby promoted reallocation of energy-rich substrates (glucose to the brain,

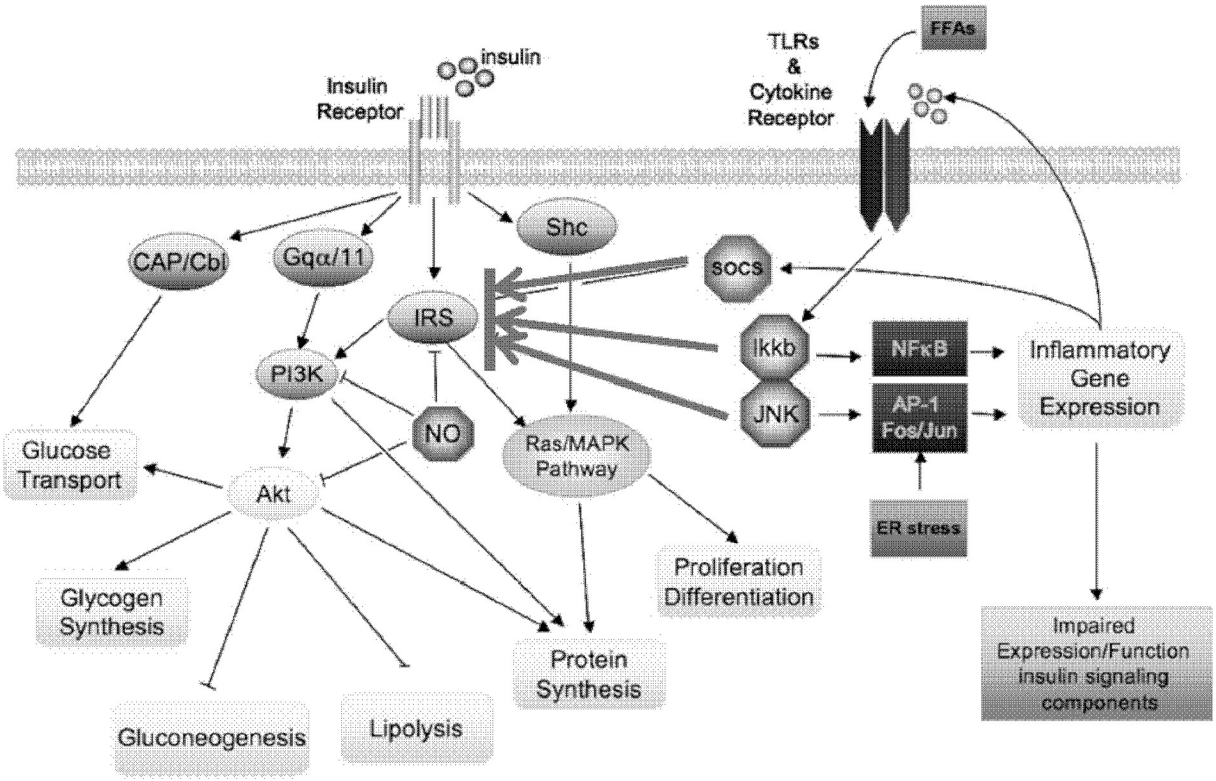

Fig. 4. Mechanistic connection between inflammation and insulin resistance. The NFκB and AP-1 Fos/June inflammatory pathways inhibit the PI3K/AKT signal transduction pathway for nutrient metabolism and the Ras/MAPK pathway for gene expression, both part of the insulin signaling. CAP, Cbl associated protein; Cbl, Proto-oncogene product; ER, endoplasmic reticulum; FFAs, free fatty acids; Gqα/11, heterotrimeric G protein; Ikkb, I kappa B kinase Beta; IRS, insulin receptor substrate; JNK, C-jun N-terminal kinase; NFkB, nuclear factor kappa B; NO, nitric oxide; Ras/MAPK; PI3K, phosphatidylinositol 3-kinase; Ras-mitogen activated protein kinase; Shc, Src homology 2 containing protein; SOCS, supressor of cytokine signaling; TLRs, Toll-like receptors.
Adapted from de Luca and Olefsky [48] with permission from Elsevier.

fetus and immune system; fat to the fetus and the organs that became insulin resistant) and the compensatory hyperinsulinemia, are meant for short-term survival, and their persistence as a chronic state are at the basis of the ultimate changes that we recognize as the symptoms of the metabolic syndrome, including the changes in glucose and lipid homeostasis [3,4] and the increasing blood pressure. For example, the concomitant hypertension has been explained by a disbalance between the effects of insulin on renal sodium reabsorption and NO-mediated vasodilatation, in which the latter effect, but not the first, becomes compromised by insulin resistance, causing salt sensitivity and hypertension [54].

Reaven coined the term "metabolic syndrome" and subsequently renamed it the "insulin resistance syndrome" [1]. However, it becomes increasingly clear that we could better refer to it as the "chronic systemic low-grade inflammation induced energy reallocation syndrome". The reason for this broader name derives from the recognition that insulin resistance is only part of the many simultaneously occurring adaptations. To their currently known extent, these adaptations and consequences are composed of: (i) reduced insulin sensitivity (glucose and lipid redistribution, hypertension), (ii) increased sympathetic nervous system activity (stimulation of lipolysis, gluconeogenesis and glycogenolysis), (iii) increased activity of the HPA-axis [hypothalamus-pituitary-adrenal gland (stress) axis, mild cortisol increase, gluconeogenesis, with cortisol resistance in the immune system], (iv) decreased activity of the HPG-axis (hypothalamus-pituitary-gonadal gland axis; decreased androgens for gluconeogenesis from muscle proteins, sarcopenia, androgen/estrogen disbalance, inhibition of sexual activity and reproduction), (v) IGF-1 resistance (insulin-like growth factor-1; no investment in growth) and vi) the occurrence of "sickness behavior" (energy-saving, sleep, anorexia, minimal activity of muscles, brain, and gut) [3].

The HPT-axis (hypothalamic-pituitary-thyroid axis) has a central role in our energy management. The adaptation of thyroid function in subjects with the metabolic syndrome is yet unclear, possibly due to the many concerted changes, such as an altered thyroid hormone binding capacity, tissue uptake, conversion of T_4 into T_3, and tissue-specific receptor expression and function. For example, T_4 may become converted into the highly active T_3 within the target cell and thereby, without visible changes of circulating hormone concentrations, bind to the intracellular thyroid hormone receptor [55]. Whether intracellular T_4 is converted into T_3 or the inactive reverse T_3 (rT_3), or is used as a source of iodine to kill bacteria, depends on several factors, including cytokines, that determine the expression pattern of the three involved deiodinases [55–57]. In euthyroid subjects, free T_4 (FT_4) is associated with insulin resistance, inversely related to total- and LDL-cholesterol, while also a positive relationship between thyroid-stimulating hormone (TSH) and triglycerides has been documented [58]. The reported changes during metabolic syndrome [59], low-grade inflammation and insulin resistance [60] are inconsistent, but do bear great resemblance with subclinical hypothyroidism, with high-normal or slightly elevated TSH, and normal FT_4 concentrations [61,62]. Insulin resistance has recently been associated with an increased T_3/rT_3 ratio, which is a measure of peripheral thyroid hormone metabolism and suggests increased thyroid hormone activity [63]. In contrast, during fasting, energy expenditure becomes down-regulated, resulting in a normal or decreased TSH and decreased serum thyroid hormone concentrations

[64]. Down-regulation of the HPT-axis with reductions of T_3, T_4 and TSH, and an increase of rT_3 (and thus a decrease of the T_3/rT_3 ratio) occurs progressively with the severity of the "non-thyroidal illness syndrome" (also called the "Low T_3 syndrome" and "euthyroid sick syndrome") [55] which is explained as an adaptation of the body to prevent excessive (protein) catabolism as part of the acute phase response [56].

All of the above mentioned adaptations of our metabolism are associated with changes in the serum lipoprotein profile, which are part of the metabolic syndrome. The purpose of these changes will be explored in more detail below.

4. Changes in serum lipoproteins

The quantitative and qualitative changes in the composition of serum lipoproteins resulting from an inflammatory trigger have, in addition to the reallocation of energy-rich nutrients (fatty acids to the insulin resistant organs), at least two other goals [5–10,65]. These are: (i) the modulation of the immune response by which we protect ourselves from the harmful effects of invading bacteria, viruses and parasites, and (ii) the restoration of the hereby inflicted damage. However, if the subsequent changes in structure and function of lipoproteins persist, they contribute to the development of atherosclerosis [66]. These long-term complications have not exerted selection pressure during evolution and, consequently, no solution has come into existence via the habitual process of spontaneous mutation and natural selection.

The inflammatory trigger during an infection with Gram-negative bacteria is initiated by lipopolysaccharides (LPS). Circulating lipoproteins aid in the clearance of this LPS. Hence, lipoproteins do not only have functions in transporting lipids to and from tissues, but also play important roles in limiting the inflammatory response [67]. The ability of lipoproteins to bind LPS is proportional to the cholesterol content of the lipoprotein [68], but the phospholipids/cholesterol ratio of the lipoprotein is the principal determinant of the LPS-binding capacity [69]. The available phospholipid surface is thus of special importance and is, under normal circumstances, the largest for the circulating HDL. However, critically ill patients exhibit decreases of both esterified cholesterol and HDL (see below) and in those patients, LPS is mainly taken up in the phospholipid layers of LDL and VLDL. Binding of LPS to lipoproteins prevents activation of LPS-responsive cells and encourages LPS clearance via the liver to the bile. In line with this mechanism, it has been observed that a decrease in plasma lipoproteins in experimental models increases LPS-induced lethality [69].

The protective role of LDL is already known for some time, and this process has probably been exploited during evolution. Currently, there are over a thousand LDL-receptor mutations, many of which lead to a reduced or absent hepatic uptake of LDL particles, and consequently, to an elevated serum LDL-cholesterol [70]. The carriers of these mutations have "familial hypercholesterolemia" (FH; incidence about 1/400 in The Netherlands) or "defective apo-B100," if the mutation is located in the LDL-receptor ligand. They constitute autosomal dominant disorders with a high risk of premature atherosclerosis and mortality from CVD [71]. The arising question is why evolution has preserved so many apparently detrimental mutations in the LDL-receptor. Research with data from the population registry office in The Netherlands showed that subjects with FH lived longer until 1800, which turned into a shorter lifespan than the general population after 1800 [72]. Important support for an explanation came from studies with LDL-receptor knockout mice, and also with transgenic mice overexpressing apo-A1, the structural protein of HDL. These mutants have a high LDL- and HDL-cholesterol, respectively, are resistant to LPS-induced mortality, and have better survival of severe Gram-negative infection compared with the wild type [66,73]. In other words, FH might have become widespread during evolution due to the modulating effect of a high LDL (i.e., "a high cholesterol") during Gram-negative infections, that were much more common in the past. This benefit might have become a risk following the introduction of a typically Western lifestyle (see below), to which subjects with FH seem particularly sensitive [72].

As mentioned above, among the lipoproteins, notably HDL has the capacity to bind LPS and thereby to prevent an LPS-induced activation of monocytes and the subsequent secretion of proinflammatory cytokines [5]. However, during the "lipidemia of sepsis," the HDL concentration decreases while also the HDL particles decrease in size [6]. Their function changes as part of the acute phase response: the immunomodulatory properties vanish to a high extent and HDL even becomes proinflammatory. The apo-A1 and cholesterol esters are lost from the HDL particle, the activities of HDL-associated enzymes and exchange proteins decrease, and these proteins are, among others, replaced by serum amyloid A (SAA) [5,6]. Like C-reactive protein, SAA is produced in the liver as part of the acute phase response. SAA is 90% located in HDL, prevents the uptake of cholesterol by the liver and directs it to other cells such as macrophages [8,66]. Both the decreasing HDL-cholesterol and the concomitantly reduced "cholesterol reverse transport," promote the accumulation of cholesterol in the tissues, where it is needed for the synthesis of steroid hormones (e.g., cortisol) in the adrenal glands, the immune system and for the synthesis of cellular membranes that became damaged by the infection [66]. Also, the formation of small dense LDL [74] might be functional because these particles are poorly cleared by the LDL-receptor, easily penetrate the subendothelial space and by their binding to the subendothelial matrix, take their cholesterol cargo to the sites of damage in a highly efficient manner. It appears that there are numerous mechanisms that jointly cause the active inhibition of the reverse cholesterol transport in response to an acute phase response (Fig. 5) [66,75].

Summarizing thus far, we humans are extremely sensitive to glucose deficits, because our large brain functions mainly on glucose. During starvation, pregnancy and infection/inflammation, we become insulin resistant, along with many other adaptations. The goal is the reallocation of energy-rich substrates to spare glucose for the brain,

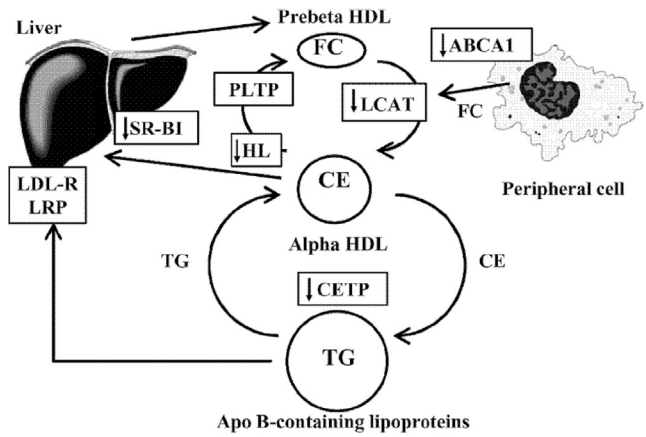

Fig. 5. Changes in reverse cholesterol transport during the acute phase response. Lipopolysaccharides (LPS) and cytokines reduce the ABCA1 (ATP-binding cassette transporter A1) and the cholesterol efflux from peripheral cells to HDL. LPS reduces the activities of various proteins involved in HDL metabolism, such as lecithin-cholesterol acyltransferase (LCAT), cholesterol ester transfer protein (CETP) and hepatic lipase (HL). LPS and cytokines also down-regulate hepatic scavenger receptor class B type 1 (SRB1), resulting in a decreased cholesterol ester (CE) uptake in the liver. FC, free cholesterol; LDL-R, LDL receptor; LRP, LDL receptor-related protein; PLTP, phospholipid transfer protein.
Adapted from Khovidhunkit et al.[66] with permission from The American Society for Biochemistry and Molecular Biology.

the rapidly growing infant during the third trimester of pregnancy, and our activated immune system that also functions mainly on glucose. Under these conditions, the insulin resistant tissues are supplied with fatty acids. Other goals of the changes in the serum lipoprotein composition are their role in the modulation of the immune response by the clearance of LPS during infection/inflammation and the redirection of cholesterol to tissues for local damage repair. The metabolic adaptations caused by inflammation illustrate the intimate relationship between our immune system and metabolism. This relation is designed for the short term. In a chronic state it eventually causes the metabolic syndrome and its sequelae. We are ourselves the cause of the chronicity. Our current Western lifestyle contains many false inflammatory triggers and is also characterized by a lack of inflammation suppressing factors. These will be described in more detail below.

5. Lifestyle-induced chronic systemic low grade inflammation

An inflammatory reaction is the reflection of an activated immune system that aims to protect us from invading pathogens or reacts to a sterile infection. If an activated immune system is uncontrolled, the resulting secondary reactions have the ability to kill us. Rogers [76] expresses it as follows: "…inflammation may be useful when controlled, but deadly when it is not. For example, head trauma may kill hundreds of thousands of neurons, but the secondary inflammatory response to head trauma may kill millions of neurons or the patient". It is clear that an inflammatory reaction that has started should subsequently be ended.

There are many factors in our current Western lifestyle that jointly cause a state of chronic systemic low grade inflammation, which in turn leads to chronically compromised insulin sensitivity, compensatory hyperinsulinemia and, eventually, the diseases related to the metabolic syndrome. Lifestyle factors that cause inflammation can be subdivided into an unbalanced composition of the diet (usually referred to as "malnutrition") [78–80] and non-food related factors [77], which partly exert their influence via obesity [81] (Table 1). Among the pro-inflammatory factors in our current diet, we find: the consumption of saturated fatty acids [82] and industrially produced trans fatty acids [83,84], a high ω6/ω3 fatty acid ratio [85–87], a low intake of long-chain polyunsaturated fatty acids (LCP) of the ω3 series (LCPω3) from fish [88,89], a low status of vitamin D [90–92], vitamin K [93] and magnesium [94–96], the "endotoxemia" of a high-fat low-fiber diet [97,98], the consumption of carbohydrates with a high glycemic index and a diet with a high glycemic load [99,100], a disbalance between the many micronutrients that make up our antioxidant/pro-oxidant network [101–103], and a low intake of fruit and vegetables [103,104]. The "dietary inflammation index" of the University of North Carolina is composed of 42 anti- and proinflammatory food products and nutrients. In this index, a magnesium deficit scores high in the list of pro-inflammatory stimuli [105]. Magnesium has many functions, some of them, not surprisingly, related to our energy metabolism and immune system, e.g., it is the cation most intimately connected to ATP [95]. Indirect diet-related factors are an abnormal composition of the bacterial flora in the mouth [106], gut [106,107], and gingivae [108–110]. Chronic stress [111,112], (passive) smoking and environmental pollution [77], insufficient physical activity [113–118] and insufficient sleep [119–123] are also involved.

All of the above listed lifestyle factors exhibit interaction and are therefore difficult to study in isolation. As an example, the bacterial flora may change secondary to the composition of our diet. An inflammatory reaction might be at the basis of the observed relation between the abnormal bacterial species in both our oral cavity and intestine and our serum HDL- and LDL-cholesterol [106]. Saturated fats may cause an inflammatory reaction especially when they are combined with a carbohydrate-rich diet, notably carbohydrates with a high glycemic index, and especially in subjects with the insulin resistance syndrome [124–128].

6. Mechanisms of lifestyle-induced inflammation

Diets high in refined starches, sugar, saturated and trans fats, and low in LCPω3, natural antioxidants, and fiber from fruits and vegetables, have been shown to promote inflammation [82–84,129–131] (Table 1). As most chronic (inflammatory) diseases have been linked to diet, modifying it could prevent, delay or even heal these diseases. Obviously, inflammation is an essential process for survival, but our immune system should be carefully controlled to limit the unavoidably associated collateral damage [132]. For instance, wound healing and other immune challenges become controlled in our body by a process coined by Serhan et al. [133–135] as *resoleomics*, using metabolites produced from the LCP arachidonic acid (AA), EPA and DHA [85,133–136]. However, our inflammatory and resolution genes operate nowadays in a completely different environment than the one to which they became adapted through mutation and natural selection. In most (if not all) chronic diseases typical of Western societies, the inflammatory response is not concluded because of suboptimal or supramaximal responses [137,138].

It has been estimated that 10% of all deaths in the Netherlands are attributable to unfavorable dietary composition and 5% to overweight. In this scenario, the major contributors to diet-associated death were insufficient intakes of fish, vegetables and fruits, with less important roles for too high intakes of saturated and *trans* fatty acids [139]. The consumption of fish, fruit and vegetables is considered too low in most Western countries [139–143]. In the USA, low dietary ω3 fatty acids and high dietary *trans* fatty acids may have accounted for up to 84,000 and 82,000 deaths, respectively, in 2005, while a low intake of fruit and vegetables might have been responsible for 58,000 deaths [144]. The Dutch [145] and the American Heart Association (AHA) [146] dietary guidelines recommend to consume at least two servings of fish per week (particularly fatty fish), but in 1998, the average fish consumption in The Netherlands amounted to hardly 3 times per month [139]. Only about 7% of the 9–13 year-old Dutch children eat fish twice or more per week and 10% never eat fish [147]. In the USA, the estimated intake of fish in 2007 was about 0.7 kg per month, per person. More preoccupying is the fact that the USA is considered the third largest consumer of seafood in the world [148,149]. Despite improvements of the fatty acid contents of food products, only 5% of the Dutch population follows a diet with the recommended fatty acid pattern [139]. Eating fish once weekly was associated with a 15% lower risk of CVD death compared with a consumption of less than once per month [150], while each 20 g/day increase in fish consumption was related to a 7% lower risk of CVD mortality [151].

The current Dutch recommendation for adults is 200 g fruits and 200 g vegetables per day [139], while in the USA, 4–5 servings of fruits and 4–5 servings of vegetables are recommended in a 2,000 kcal diet [152]. Between 1988 and 1998, the consumption of fruit and vegetables in The Netherlands declined by 15–20%, and currently, less than 25% of the Dutch population follows the recommendations regarding the consumption of fruit, vegetables and dietary fiber [139]. As an example, currently 99% and 95% of the 9–13-year-old Dutch do not adhere to the advice of consuming 150 g/day vegetables and 200 g/day fruits, respectively [147]. Meta analyses of prospective studies indicated that <3 vs. >5 servings of fruits and vegetable per day correspond with a 17% reduction in coronary heart disease [153] and 26% reduction in stroke [154], while the relation of low intakes with mouth, pharynx, esophagus, lung, stomach, colon and rectum cancer is considered substantially convincing [155].

In view of the numerous nutrients present in our food and their many mechanisms of action in the inflammatory response, we

Table 1
Environmental factors that may cause chronic systemic low grade inflammation

Pro-inflammatory				Anti-inflammatory			
Lifestyle	Exercise	Too little (inactivity)		Lifestyle	Exercise/physical activity/fitness		
		Too much					
	Nutrition	Alcohol (excessive)			Nutrition	Alcohol	
		Excessive energy intake				Energy intake (restricted)	
		Starvation					
		'Fast food'/Western style diet				Mediterranean diet	
		Fat	High-fat diet			Fat	Fish/fish oil
			Saturated fats				Mono-unsaturated fats
			Trans fatty acids				Olive oil
			High ω6/ω3 ratio				Low ω6/ω3 ratio
		Fiber (low intake)				Fiber (high intake)	
		Fructose				Nuts	
		Glucose	High glucose/GI foods			Low GI foods	
			Glycemic load			Grapes/raisins	
			Glycemic status			Dairy calcium	
			Sugar-sweetened drinks			Eggs	
		Meat (domesticated)				Lean meats (wild)	
		Salt				Soy protein	
						Fruits/vegetables	
						Cocoa/chocolate (dark)	
						Herbs and spices	
						Tea/green tea	
						Capsaicin (pepper)	
						Garlic	
						Pepper	
	Obesity				'Healthy obesity'		
	Weight gain				Weight loss		
	Smoking				Smoking cessation		
	'Unhealthy lifestyle'				Intensive lifestyle change		
	Stress/anxiety/depression/burn out						
	Sleep deprivation						
Age							
Environment	Socioeconomic status (low)						
	Perceived organizational injustice						
	Air pollution (indoor/outdoor)						
	Second-hand smoking						
	'Sick building syndrome'						
	Atmospheric CO2						

Adapted from Egger and Dixon [77].

selected two nutrient classes, i.e. the LCP from fish (LCPω3; notably EPA and DHA), and the antioxidants in fruit and vegetables, to illustrate the many dietary components involved in our pro-inflammatory/anti-inflammatory balance. However, before embarking into these nutrient classes, it should be emphasized that our food is in reality composed of biological systems, such as meat, fish, vegetables and fruits, in which nutrients obey to the balance that comes along with living material. Therefore, focusing on specific, presently known mechanisms without sufficient knowledge of the many possible interactions between the numerous nutrients in our food should be regarded as a serious limitation. This is a reductionist approach, whereas system dynamics and holistic approximations would be more appropriate.

6.1. Fatty acids and inflammation

The media are consistently reporting on advises to reduce fat consumption to avoid risks associated with obesity, CVD, diabetes and other chronic diseases and conditions. Among the macronutrients, fat does indeed contain the highest amount of energy per gram. However, from a thermodynamic point of view, a "calorie is a calorie" [156], implying that any macronutrient consumed in disbalance with energy expenditure and thermogenesis might cause obesity. A recent in-depth study revealed that "a calorie is not a calorie" in a metabolic sense, showing that isocaloric diets with different macronutrient compositions have different effects on resting and total energy expenditure with decreasing energy expenditures in the sequence low-fat diet<low-glycemic diet<very low-carbohydrate diet [157], and thereby suggesting that the diet with the highest protein and fat content gives rise to the lowest weight gain. However, whether the intake of fat *per se* and, as a matter of fact, any isolated nutrient [158], can be held responsible for the epidemics of obesity, remains controversial and counter intuitive [159–161]. Moreover, it is becoming increasingly clear that about 10–25% of obese subjects have little CVD and type 2 diabetes mellitus risk (a condition coined "healthy obesity") [162,163], that lean physically unfit subjects have higher risk of CVD mortality than obese, but fit, subjects [164], and that it is the quality and not the quantity of fat that conveys a major health hazard [165]. The type of dietary fat affects vital functions of the cell and its ability to resist dysfunction, e.g., by influencing the interaction with receptors, by determining basic membrane characteristics and by producing highly active lipid mediators [166,167].

Saturated fat intake has been associated with inflammation [168,169]. However, the widely promoted reduction of saturated fatty acids is increasingly criticized [170] and also the AHA advisory to replace saturated fatty acids in favor of linoleic acid (LA) to 5–10 en% [171]. Insufficient intake of particular fatty acids is, on the other hand, likely to contribute to health hazards, including increased risk of infection [172], dysregulated chronobiological activity and impaired cognitive and sensory functions (especially in infants) [173]. Among these important fatty acids are the LCPω3 derived from fish, of which EPA and DHA are the most important members. In 2003, the intake of EPA+DHA by adults in The Netherlands amounted to approximately 90 mg/day (women 84 mg/day and men 103 mg/day) [174], while the

recommendation is 450 mg/day [175]. This recommendation is based on an optimal effect in preventing CVD (anti-arrhythmic effect), but there is good evidence that higher intakes may convey additional favorable effects because of their anti-thrombotic properties and their ability to reduce blood pressure, heart rate and triglyceride levels [131]. It was calculated that our Paleolithic ancestors living in the water-land ecosystem had daily intakes of 6–14 g EPA+DHA [176], which correspond with the intakes by traditionally living Greenland Eskimos [177], who, because of their low incidence of CVD, were at the basis of the research on the beneficial effects of fish oil that started in the 70s [178–180].

Both EPA and DHA must be in balance with AA, which is the major LCPω6 derived from meat, poultry, eggs [181–183] and also lean fish [184,185]. Each of these LCPs may be synthesized by desaturation, chain elongation and chain shortening from the parent "essential fatty acids" LA (converted to AA) and alpha-linolenic acid (ALA) (converted to EPA and DHA) [186], even though the production of EPA, and notably DHA, occurs with difficulty in humans [187]. Included among the symptoms of LA, LCPω3 and LCPω6 deficiencies are fatigue, dermatological problems, immune problems, weakness, gastrointestinal disorders, heart and circulatory problems, growth retardation, development or aggravation of breast and prostate cancer, rheumatoid arthritis, asthma, preeclampsia, depression, schizophrenia, and attention deficit hyperactivity disorder [173,188–190].

LCPω3 are implicated in many diseases and conditions, including CVD, psychiatric diseases, pregnancy complications and suboptimal (neuro) development [86,191–196]. Moreover, a growing number of studies indicate the protective effects of dietary LCPω3 on mood symptoms, cognitive decline, depression [197,198], Alzheimer's disease [199] and, more generally, impaired quality of life both in the elderly [200,201] and younger [202] populations. LCPω3 are involved in numerous processes including energy generation, growth, cell division, transfer of oxygen from the air to the bloodstream, hemoglobin synthesis, normal nerve impulse transmission and brain function. Many different mechanisms are operational: LCPω3 mediate potent anti-inflammatory and insulin sensitizing effects through their interaction with a membrane receptor named G-protein-coupled receptor 120 (GPR120) [203,204]; they act at the gene expressional level by binding to nuclear receptors, such as the peroxisome proliferator activated receptors (PPARs) [205–207]; and they modulate physical and metabolic properties of membranes through their incorporation into phospholipids and thereby impact on the formation of lipid rafts [134,208,209]. Important common denominators in each of these interactions seem to be their anti-inflammatory and metabolic effects, again illustrating the intimate connection between the immune system and metabolism [50,51].

The modernization of food manufacturing, preservation processes and food choices have dramatically altered the balance between LCPω3 and LCPω6 in the Western diet, notably by increasing the intake of LA from refined vegetable oils and a concomitant decrease in the intake of LCPω3 from fish [210,211]. It is gaining acceptance that it is not the amount of fat but the balance between the different types of fatty acids that is important [211,212]. A high ω6/ω3 fatty acid ratio has been demonstrated to have an inflammatory effect [86,212,213], while a higher intake of LCPω3 in the form of EPA and DHA regulates the production of inflammatory and resolving cytokines and decreases LA levels in both plasma phospholipids and cell membranes [183,214]. The conversions of LA and ALA to AA and to EPA+DHA, respectively, depend on the same enzymes in the desaturase and elongase cascade, with Δ6-desaturase as a rate-limiting enzyme [215] that functions twice in the biosynthesis of DHA [216]. Increased consumption of ALA gives rise to an increased ALA/LA ratio and EPA+DHA content in cell membranes that comes together with a reduction of the AA content [216,217], and thereby influences the balance between inflammation and its subsequent resolution (Fig. 6) [218–220]. Conversely, a higher LA level in plasma phospholipids and cell membranes emerges as a major factor responsible for incomplete *resoleomics* reactions and the associated immune paralysis [214,220,221] (Fig. 6), which is attributed to the competitive inhibition of LA in the conversion of ALA to EPA and DHA and also to the competition of LA in the incorporation of EPA and DHA into cellular phospholipids [183,214,216].

LCPω3 and LCPω6 have distinct functions in the inflammatory reaction and its resolution. In the first phase of the inflammatory process, the pro-inflammatory eicosanoids leukotrienes-B_4 and prostagladins-E_2 and D_2 (PGE_2 and PGD_2) [222,223] are generated by macrophages from their precursor AA with the help of the lipid-oxidizing enzyme lipoxygenase-5 (LOX-5) and cyclo-oxygenase-2 (COX-2) [224–226]. At the same time, PGE_2 and/or PGD_2, although initially pro-inflammatory, determine the switch to the next phase: the resolution of the inflammation [227] via the so-called "eicosanoid-switch". The production of the LOX-5 enzyme becomes limited, while anti-inflammatory lipoxins (LXs) are produced from AA through the activation of lipoxygenase-12 (LOX-12), lipoxygenase-15 and acetylated COX-2 [228]. At the site of inflammation, LOX-12 produced by platelets converts LTA_4 to LXA_4 and LXB_4. Along with AA, both LOX-12 and −15 are involved in the biosynthesis of specialized bioactive lipid mediators, coined resolvins, (neuro)protectins [135] and maresins [229], which derive from EPA and DHA (Fig. 7) [85,134,172]. Several studies have illustrated the involvement of these lipid mediators in vascular inflammation and atherosclerosis [85,228,230,231]. They possess potent anti-inflammatory and pro-resolving actions that stimulate the resolution of acute inflammation by reducing and/or limiting the production of a large proportion of the pro-inflammatory cytokines produced by macrophages. Furthermore, LXA_4, protectin D1 and resolvin D1 stimulate the phagocytic activity of macrophages toward apoptotic cells and inhibit inflammatory cell recruitment [232,233], thereby protecting tissues from excessive damage by the oxidative stress that comes along with immune defense mechanisms and others. By their inhibitory actions on the recruitment of inflammatory cells, they allow the resolution phase to set in [234] and finish the inflammatory process with the return to homeostasis [136,227].

Accordingly, LCPω3 given at doses of hundreds of milligrams to grams per day, exhibits beneficial actions in many inflammatory diseases [88,190,194,235,236]. For example, DHA has been shown to suppress NFκB activation and COX-2 expression in a macrophage cell line [168,237]. Different studies demonstrated the nutrigenetic modulation of the 12/15-LOX by providing endogenous anti-inflammatory signals and protection during the progression of atherogenesis [231,238,239], which seem to be totally annulled in the presence of Western diet induced hyperlipidemia. As some eicosanoids regulate the production of inflammatory cytokines [85,134,135] an LCPω3-induced decrease in pro-inflammatory eicosanoid production might affect the production of pro-inflammatory cytokines. Equally important is the observation that LCPω3 also modulate the activation of transcription factors involved in the expression of inflammatory genes (e.g., NFκB, phosphatidylinositol 3-kinase (PI3K)) [240]. Hence, a high fish consumption, and especially fatty fish, rich in EPA and DHA, seems of crucial importance in the primary and secondary prevention of (Western) chronic diseases [241,242], although it should be emphasized that fish is not a synonym of fish oil and also that insufficient fish consumption is certainly not the only factor involved in the pro-inflammatory Western lifestyle (Table 1).

6.2. Role of the antioxidant network

The largest contributor to mortality and morbidity worldwide is age-related, non communicable disease, including cancer, CVD,

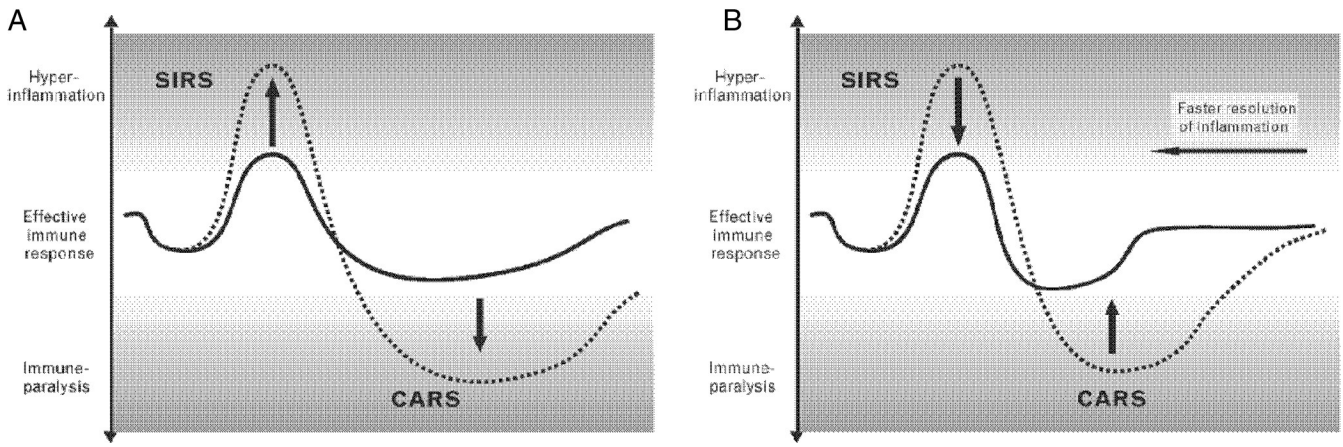

Fig. 6. Postulated LCPω6 and LCPω3 involvement in the inflammatory reaction in sepsis and its subsequent resolution. Sepsis causes a systemic inflammatory response giving rise to the "systemic inflammatory response syndrome" (SIRS). The inflammatory response is followed by a compensatory anti-inflammatory response (CARS), characterized by a weakened host defense and augmented susceptibility to secondary infections. An inflammatory response should not only be initiated, but also stopped to limit collateral damage produced by the immune system and to prevent immune paralysis. LCPω6 (AA) are involved in the initiation of the inflammatory reaction, while LCPω3 (EPA and DHA) are involved in its resolution (see also Figure 7). Panel A) A high LCPω6/LCPω3 ratio, e.g., low fish intake, intensifies the SIRS reaching a state of hyper-inflammation, while the CARS leads to a state of immune paralysis. Panel B) A low LCPω6/LCPω3 ratio dampens both the SIRS and CARS, resulting in a more balanced immune response and preventing hyper-inflammation and immune-paralysis. SIRS, systemic inflammatory response syndrome; CARS, compensatory anti-inflammatory response syndrome.
Adapted from Mayer et al. [220] with permission from Wolters Kluwer Health.

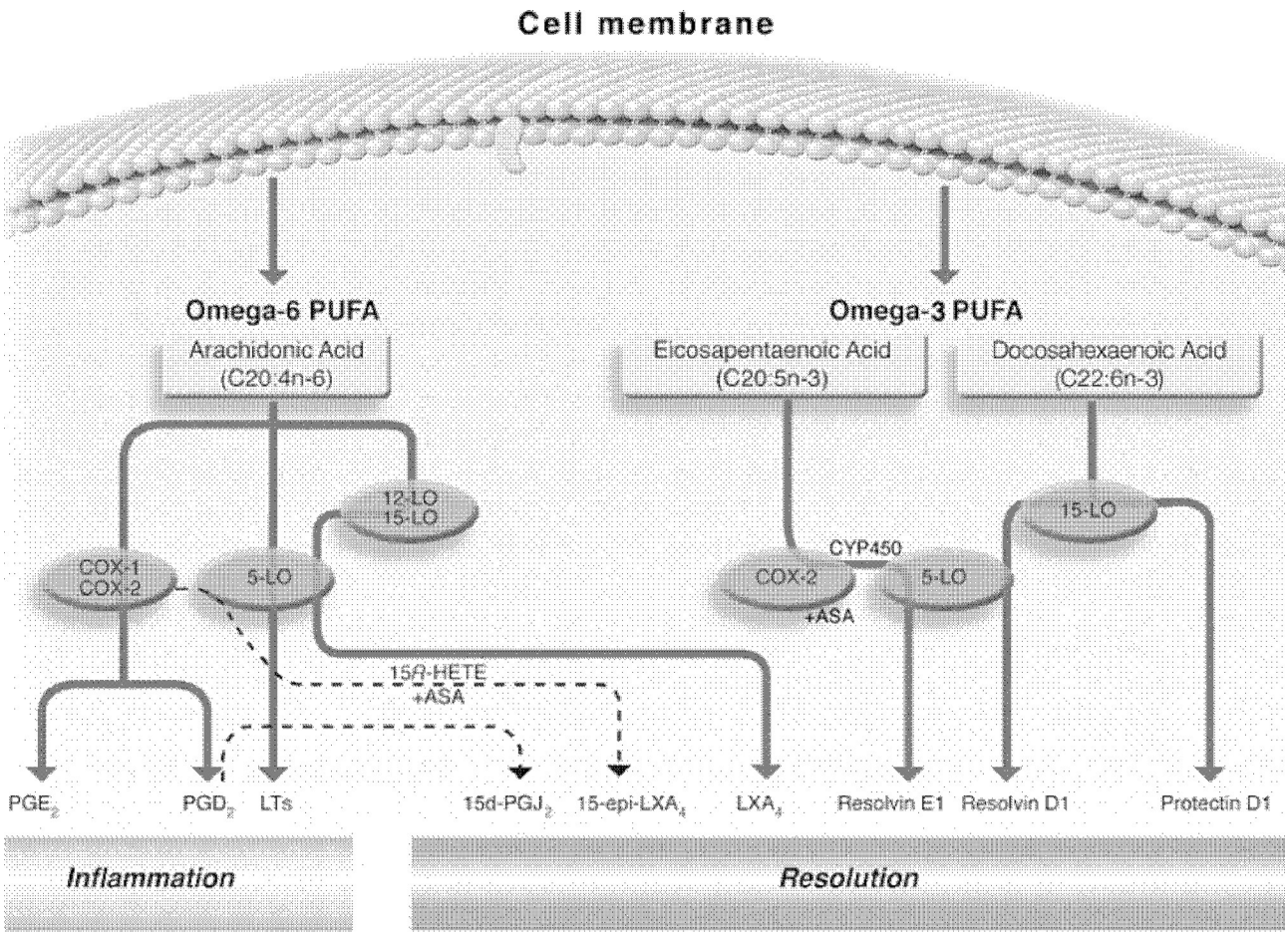

Fig. 7. Biosynthesis of inflammatory and resolving lipid mediators. AA is released from membrane phospholipids by phospholipase A_2 (PLA_2) and metabolized by COXs or 5-LO to form inflammatory mediators, such as prostaglandins and leukotrienes. During the process of resolution, there is a "switch" from the biosynthesis of inflammatory mediators to the formation of lipid derivatives with anti-inflammatory and pro-resolving properties, including lipoxins and 15-d-PGJ_2. EPA and DHA are converted to potent anti-inflammatory and pro-resolving lipid mediators like resolvins (E1 and D1) and protectins. ASA, acetylsalicylic acid, CYP450, cytochrome P450, COX-1, cyclo-oxygenasa-1, COX-2, cyclo-oxygenasa-2; 5-LO, 5-lipo-oxygenase; 12-LO, 12-lipo-oxygenase; 15-LO, 15-lipo-oxygenase; PGE_2, prostagladin-E_2; PGD_2, prostaglandin-D_2; LTs, leukotrienes; 15d-PGJ_2,15-deoxy-delta-12,14-prostaglandin J_2; 15-epi-LXA_4, 15-epi-lipoxin A_4; LXA_4, lipoxin A_4.
Adapted from González-Périz and Clària [243] with permission.

neurodegenerative diseases and diabetes [244]. Even though these are multi-factorial diseases with many pathophysiological mechanisms, a common finding is oxidation-induced damage through oxidative stress [245,246]. Appropriate antioxidant intake has been proposed as a solution to counteract the deleterious effects of reactive oxygen species (ROS; e.g., hydrogen peroxide, hypochlorite anion, superoxide anion and hydroxyl radical), with substantial evidence upholding the contention that: a diet rich in natural antioxidants supports health [104,246], is associated with lower oxidative stress and inflammation [77,103,140], and is therefore associated with lower risk of cancer, CVD, Alzheimer's disease, cataracts, and some of the functional declines associated with aging [247–251].

Molecular oxygen is essential to aerobic life and, at the same time, an oxidizing agent, meaning that it can gain electrons from various sources that thereby become "oxidized," while oxygen itself becomes "reduced" [252,253]. In general terms, an antioxidant is "anything that can prevent or inhibit oxidation" and these are therefore needed in all biological systems exposed to oxygen [252]. The emergence of oxygenic photosynthesis and subsequent changes in atmospheric environment [254] forced organisms to develop protective mechanisms against oxygen's toxic effects [255]. Change is implicit to evolution and evolution results in adaptation to change [256]. As a result, many enzymatic reactions central to anoxic metabolism were effectively replaced in aerobic organisms and antioxidant defense mechanisms evolved [257,258]. The continuous exposure to free radicals from a variety of sources led organisms to develop a series of systems [259] acting as a balanced and coordinated network where each one relies on the action of the others [260,261].

Oxidative stress occurs when there is a change in this balance in favor of ROS [262] that may occur under several circumstances, ranging from malnutrition to disease [263,264]. Damage by oxidation of lipids [262,265,266], nucleic acids and proteins changes the structure and function of key cellular constituents resulting in the activation of the NFκB pathway, promoting inflammation, mutation, cell damage and even death [252,260,267] and is thereby believed to underlie the deleterious changes in aging and age-related diseases [102,244]. The prevention and/or inhibition of oxidation can be achieved by several types of specialized antioxidant mechanisms depicted in Table 2 [260]. Our antioxidant system is composed of two networks (Fig. 8), namely, the antioxidant network of non-enzymatic antioxidants that we obtain mostly via the diet [268], and the antioxidant enzymes that we synthesize ourselves and that carry metal ions for their appropriate functioning in ROS clearance. Members of the non-enzymatic antioxidants are, e.g., ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), carotenoids, and the polyphenols [269,270]. For instance, quercetin, one of the most common flavonoids in the human diet, and resveratrol, a well-known stilbenoid present mostly in berries and the skin of red grapes, have demonstrated favorable effects on glucose metabolism by attenuating TNFα-mediated inflammation and insulin resistance in primary human adipocytes [271]. Typical examples of the antioxidant enzymes are superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase [252].

Table 2
Types of antioxidant action

	Action	Examples
Prevention	Protein binding/inactivation of metal ions	Transferrin, ferritin, ceruloplasmin, albumin
Enzymatic neutralization	Specific channelling of ROS into harmless products	SOD, catalase, glutathione peroxidase
Scavenging	Sacrificial interaction with ROS by expendable (recyclable or replaceble) substrates	Ascorbic acid, alpha tocopherol, uric acid, glutathione
Quenching	Absorption of electrons and/or energy	α-tocopherol, β-carotene, astaxanthin

Adapted from Benzie [260].

While the prevention of oxidative stress by enhancing the antioxidant defense mechanisms may diminish the production of inflammatory mediators and thereby slow aging and lower risk of certain diseases [102,245,249], it should at the same time be appreciated that ROS also exert essential metabolic and immune functions. For example, oxidative phosphorylation is based on electron transport [272], which renders free radicals" inevitable byproducts of mitochondrial metabolism [273]. Mitochondrial oxidants may function as signaling molecules in the communication between the mitochondria and the cytosol [273], while TNFα-induced apoptosis may involve mitochondria-derived ROS [274]. The innate immune system kills microbes by means of the respiratory burst [275]. A certain level of ROS may also be essential to trigger antioxidant responses [276]. Repeated exposure to sublethal stress has been proposed to result in enhanced stress resistance and increased survival rates, which in the dose–response curve is better known as hormesis [277]. Intracellular ROS may stimulate gene expression of antioxidant and immunoreactive proteins [278], while SOD may become up-regulated in chronic exercise through the binding of NFκB to the SOD promoter [279,280].

Consequently, certain antioxidants may inhibit mitochondrial biogenesis, interfere with the hormetic effects of ROS [281,282] or have other adverse effects. Effective prevention of ROS formation and their removal may therefore upset energy metabolism, cell signaling pathways and the immune system, and thereby paradoxically increase the risk of chronic disease [283]. Moreover, any antioxidant is also a potential pro-oxidant because in its scavenging action it gains an extra electron that can initiate a new radical reaction when transferred to an acceptor, either spontaneously or upon decomposition [284,285]. Possibly through its prooxidant action or other mechanisms [286], meta-analyses of studies with β-carotene dosages above 20 mg/day have shown increased risk of lung cancer in the total population, smokers and asbestos workers; and of stomach cancer in smokers and asbestos workers [287]. Analogously, oral antioxidants to limit muscle damage following exercise training may be detrimental to health and performance [288], while β-carotene, vitamin A and vitamin E supplements have been connected with higher risk of all-cause mortality [289], although the outcome of the latter meta-analysis has been contested [290]. Moreover, not all antioxidants are created equal. Astaxanthin, a carotenoid from the land-water ecosystem, does not appear to exhibit pro-oxidant properties [291] when supplemented alone, even at high doses [292], and has been shown to decrease oxidative stress and inflammation in various circumstances [266,293].

Chronic inflammation results in the chronic generation of free radicals, which may cause collateral damage and stimulate signaling and transcription factors associated with chronic diseases [294,295]. The hypothesis that dietary antioxidants lower the risk of chronic diseases has been developed from epidemiological studies consistently showing that consumption of fruit and vegetables is strongly associated with a reduced risk of these diseases [104,248,250]. Regular consumption of green tea [296] and red wine [103,297], both rich in polyphenols, decreases DNA damage, and the same holds for the kiwifruit [298] and watercress [299], both harboring high amounts of carotenoids and vitamin C. On a calorie basis, fruits and vegetables are not only richer in many vitamins and minerals, when compared with cereals, meat or fish, but also in antioxidants [300]. These may collectively be responsible of the aforementioned protection of fruits and vegetables in chronic diseases, including CVD [248] and cancer [249]. Plants harbor similar defense mechanisms as animals for protection against ROS [301]. Some of their antioxidants are part of their arsenal of "secondary metabolites," defined as those organic compounds that are not directly involved in

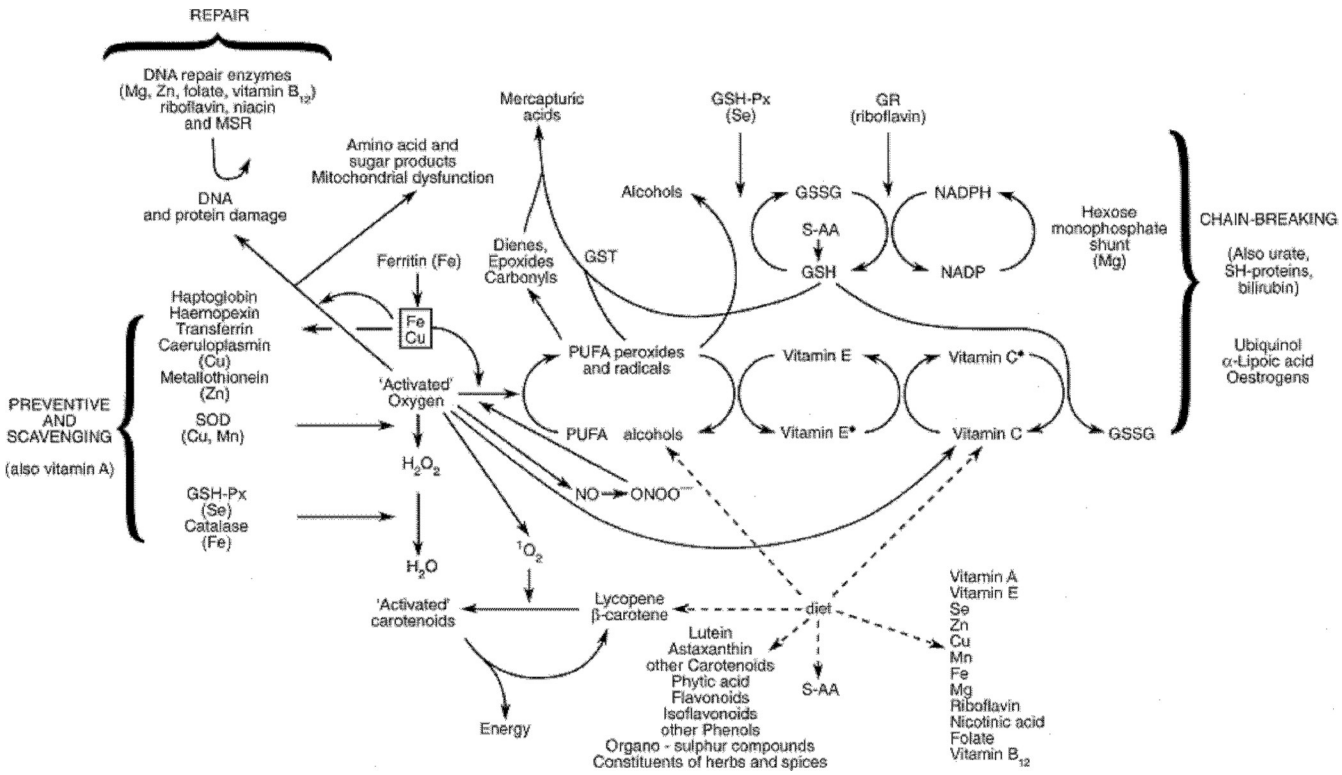

Fig. 8. Antioxidant defense mechanisms. An overview of the antioxidant system present in the human body. Various types of antioxidant systems have developed through time, reflecting different selection pressures. Different forms have developed for the same purpose, for example, SODs, peroxidases and GPx are important members of the antioxidant enzyme capacity group. Tocopherols and ascorbic acid, as representatives of the antioxidant network, are manufactured only in plants, but are needed by animals. Ascorbic acid is an essential antioxidant, but cannot be synthesized by *Homo sapiens*. In humans, therefore, antioxidant defense against toxic oxygen intermediates comprises an intricate network which is heavily influenced by nutrition. GR, glutathione reductase; GSG, reduced glutathione; GSH-Px, glutathione peroxidase; GSSG, oxidized glutathione; GST, glutathione-S-transferase; MSR, methionine sulphoxide reductase; PUFA, polyunsaturated fatty acids; S-AA, sulphur amino-acids; SH-proteins, sulphydryl proteins; SOD, superoxide dismutase; Fe Cu, transition metal-catalysed oxidant damage to biomolecules.
Adapted from Strain [304] with permission from Cambridge University Press.

normal growth, development and reproduction, but in long term survival and fecundity [302]. The plant secondary metabolites are largely involved in the chemical defense against herbivores, microbes, viruses and competing plants, in signaling and in nitrogen storage [303]; and some (e.g., polyphenols, carotenoids) also serve functions in the protection against ROS. The underlying metabolic pathways towards secondary metabolites lead to a series of related compounds that are usually composed of few major metabolites and several minor components differing in the position of their functional groups [303]. Animals consuming fruits and vegetables may employ these plant secondary metabolite networks for their own purposes, including maintenance of inflammatory/anti-inflammatory balance, cancer chemoprevention and protection against ROS [303].

In view of the yet poorly understood complex antioxidant networks composed of many compounds, it seems improbable to find a single "magic bullet" to prevent and treat chronic diseases associated with ROS. Protective effects of fruits and vegetables may originate from their numerous phytochemicals working in concert [305] and from many different mechanisms of action that are not solely related to ROS. A purified phytochemical may not have the same health benefit as that phytochemical present in whole foods or a mixture of foods [250,306]. In biological systems, toxins may become nutrients, while nutrients may become toxic in other situations [268], for example when disbalanced with other nutrients. Rather than translating our food into an assembly of nutrients where each has to prove its health benefits by scientific means, the objective should be to embrace a eucaloric diet that provides the adequate amount of nutrients from whole foods to maintain our body homeostasis. "Adequacy" may in this sense be translated into causing an optimal interaction between our diet (and our lifestyle in general) with our genome, that is: nurture in balance with nature.

7. Evolutionary nutrition vs. randomized controlled trials

Coherence between lifestyle factors, including the composition of our diet, is quite obvious from an evolutionary point of view. After all, there was first an environment, and from this environment originated a genome that was adapted to that environment: it is the substrate (environment) that selects the organism, not *vice versa*. This is exactly what Darwin meant with "conditions of existence," as the most important driving force in evolution. In other words, our only slowly changing genome is indissolubly linked to a certain environment and lifestyle. However, we have changed this environment since the agricultural revolution and continue to do so with still increasing paste. The resulting conflict does not generate acute toxicity, but acts as an assassin in the long term. Probably, the conflict does not exert much selection pressure either, because its associated mortality occurs mainly after reproductive age.

To solve the conflict, it is virtually impossible to study all of the introduced errors in our lifestyle (Table 1) in isolation, according to the reigning paradigm of EBM [307]. EBM is widely confused with the results of RCTs and preferably the meta-analysis thereof [308,309]. This paradigm, originally designed for objective evaluation of medical treatments and drugs in particular, and named in nutrition research "Evidence Based Nutrition"; is at present misused by food scientists and Health and Nutrition advisory boards. In contrast to drugs, this

(expensive) RCT paradigm usually lends itself poorly for the study of single nutrients with meaningful outcomes [308]. For each nutrient, we are dealing with poorly researched dose–response relationships, multiple mechanisms of action, small effects causing pathology in the long-term, numerous interactions, ethical limitations regarding the choice of intervention and control groups, and the inability to patent its outcomes [309]. The RCT criteria are moreover inconsistently applied in the current development of nutritional recommendations. For example, there is no RCT-supported evidence for the saturated fat hypothesis [170], and also not for the *trans* fatty acids, while such an approach is considered mandatory for the adjustment of the vitamin D nutritional standards [310–312]. Incidentally, there was also no RCT prior to the introduction of *trans* fatty acids showing that they could be consumed without adverse effects on the long term. However, there is an RCT on the effects of smoking cessation, which showed an *equal* mortality among the quitters [313,314]. The meta-analyses of RCTs studying the influence of LCP on brain development are negative [315–318]. However, recommendations for their addition to infant formulas have been issued [196], probably because nobody wants to take chances with the brains of our offspring. By applying EBM in a rigorous manner and by merely taking a view from the "precautionary principle" (i.e., zero risk [4]) this well meant concept has become a burden in the nutritional science, that calls for replacement by appropriate risk-cost-benefit analyses such as, e.g., performed for vitamin D [319].

Our diet is composed of millions of substances that are part of a biological network. In fact, we eat "biological systems" like a banana, a fish or a piece of meat. There is a connection between the various nutrients in these systems. In other words, there is a balance and an interaction that is part of a living organism. This balance can be found in the reconstruction of our Paleolithic diet, and various attempts for this reconstruction have already been made [28,131,320–322]. Preliminary results of interventions with a Paleolithic diet are utterly positive (for a review see [323]). For example, in an indeed uncontrolled study with non-obese sedentary healthy subjects, an eucaloric Paleolithic diet resulted within 10 days in beneficial effects on three out of the four symptoms of the metabolic syndrome, i.e. blood pressure, dyslipidemia and glucose homeostasis. The fourth symptom, overweight/obesity, was deliberately not changed to prevent the attribution of any beneficial changes to weight loss [324].

8. Nurture, not nature

Less than 5% of our diseases can primarily be ascribed to heritable genetic factors [325,326]. "Genome wide association studies" (GWAS) will not make this figure change; not even if the number of patients and controls are further increased. As it could have been predicted from evolution, these GWAS identify only a few genes that are associated with typically Western diseases. Moreover, the so far identified genes merely convey low risks. In one of these disappointing GWAS, where 14,000 patients with seven major typically Western diseases and 3.000 controls were studied, it was concluded that: "… for any given trait, there will be few (if any) large effects, a handful of modest effects and a substantial number of genes generating small or very small increases in disease risk" [327]. The differences in genetic susceptibility to environmental factors is widely confused with a primary genetic origin of Western disease. Environmental factors may mimic genetic heritability, especially when the exposure has become widespread. As clearly explained by Rose [328]: "If everyone smoked 20 cigarettes a day, then clinical, case–control and cohort studies alike would lead us to conclude that lung cancer was a genetic disease; and in one sense that would be true, since if everyone is exposed to the necessary agent, then the distribution of cases is wholly determined by individual susceptibility". In other words: "disease susceptibility genes" is a misnomer from an evolutionary point of view.

Most of the currently demonstrated polymorphisms associated with typically Western diseases already existed when *Homo sapiens* emerged about 160,000 years ago in East-Africa. After all, the largest inter-individual genetic variation can be found between individuals belonging to a single population (93–95% of the total genetic variation), and only little genetic variation is on the account of differences between populations belonging to a single race (2%) and between the 5 races (3–5%) [329]. The allele that, according to current knowledge, is linked with the highest penetrance of type 2 diabetes mellitus in the general population conveys 46% higher relative risk (RR=1.46) [330]. In contrast, a woman with a body mass index of 35^{+} kg/m^2 has a one hundred-fold higher risk (RR=100) of diabetes mellitus type 2 [331], which translates into a 9,900% higher relative risk. "Genetic" diseases with relative risks below 1.5 have no practical value in Public Health. They are only important to our understanding of the etiology of the concerning disease and for drug development [326], which is part of Health Care.

Between 70 and 90% of the cases of type 2 diabetes mellitus, CVD and colon cancer can be prevented by paying more attention to nutrition, smoking, overweight and lack of physical activity [325]. Hemminki et al. [326] stated that "if the Western population was to live in the same conditions as the populations of developing countries, the risk of cancer would decrease by 90%, provided that viral infections and mycotoxin exposures could be avoided". The popular counter argument that people in developing countries have shorter life spans is not valid. The reason that we live longer in Western societies, is mainly due to the strong reduction of infectious diseases (particularly in childhood), famine and violence [332,333], and is also partly on the account of Health Care. However, together with our increasing life expectancy, there is a decrease in the number of years without chronic disease [334].

9. Conclusions

It has become clear that most, if not all, typically Western chronic illnesses find their primary cause in an unhealthy lifestyle and that systemic low grade inflammation is a common denominator. From an evolutionary point of view, the current conflict between environment and our Paleolithic genome traces back to our brain growth and the ensuing intimate relationship between inflammation and metabolism. The present disbalance between inflammatory and anti-inflammatory stimuli does not originate from a single cause and can consequently also not be solved by a single "magic bullet". Resolution of the conflict between environment and our ancient genome might be the only effective manner to arrive at "healthy aging" and to achieve this objective we might have to return to the lifestyle of the Paleolithic era according to the culture of the 21st century [16,322].

[4] The precautionary principle is a moral and political principle stating that, if an intervention or policymay cause serious or irreversible damage to society or the environment, the burden of proof lies with theproponents of the intervention or the measure if there is no scientific consensus on the future damage. The precautionary principle is particularly applicable in health care and environment; in both cases we deal with complex systems in which interventions result in unpredictable effects (source: Wikipedia).

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