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The Selfish Immune System when the Immune System Overrides the 'Selfish' Brain

Leo Pruimboom [1,2,*], Charles L Raison[3], Frits A.J. Muskiet[1]

1 Laboratory Medicine, University Medical Center Groningen (UMCG), University of Groningen, Groningen, the the Netherlands. 2 Natura Foundation, Edisonstraat, Numansdorp, the Netherlands. 3 School of Human Ecology and School of Medicine and Public Health, University of Wisconsin Madison, Madison, WI, USA.

Abstract

The brain and the immune system are the only two systems of the human body that can dominate all others by extracting resources, including glucose. The brain dominates during daytime hours and stressful situations, whereas the immune system protects us principally at night, during periods of infection and when wounds are healing. Both systems are similarly capable of drawing on energy and other essential resources using strategies beneficial to their own function and anatomy. Human evolution has made the brain the most important of the body's systems, resulting in a shift from strong to smart. However, the immune system is very old and robust; when necessary it is activated by a variety of non-specific immune challenges such as psychoemotional stress and most often when immune activating risk factors (including endotoxemia) are not solved in an appropriate timeframe. When chronically activated, the immune system demonstrates even more selfish behaviour than the selfish brain, inducing chronic low-grade inflammation and multiple related diseases. But before castigating the immune system for this behaviour, it is crucial to recognise that it is only doing what it is made for: trying to protect us.

Key words: *immune system, selfish brain, inflammation, evolution, stress, chronic disease, Alzheimer, fibromyalgia syndrome, insulin resistance*

***Corresponding Author:** Leo Pruimboom, Laboratory Medicine, University Medical Center Groningen (UMCG), University of Groningen, P.O. Box 30.001 Groningen, the Netherlands. **Phone:** +90 372 2911100, **E-mail:** f.a.j.muskiet@umcg.nl **Received:** Jan, 2020. **Accepted:** Jan, 2020.

Introduction

1.1. The selfish brain and immune system in evolution

Low-grade inflammation; the cause of causes Chronic inflammatory diseases (CID) are increasing in frequency, while treatments for these conditions are still in their infancy (1). Many of these diseases hardly existed 200 years ago (2) and proximate interventions addressing their genuine aetiologies have not been very successful (3). Chronic inflammation involves the innate and adaptive immune system (Ghigliotti 2014), which can be considered very costly at the level of the use of resources, including energy (Bajgar, PLoS Biol. 2015;13(4):e1002135.), proteins and certain minerals, such as calcium (4) and magnesium (5-7). Long-term activation of the innate and adaptive immune system causes further maturation of antigen presenting cells (Montserrat 2016). It is therefore plausible that low-grade inflammation is a direct cause of multiple diseases related with increased activity of the innate and adapted immune system including multiple autoimmune disorders and cancer. A recent meta analysis showed a linear association between C reactive protein (CRP), a marker for low grade inflammation and risk for breast cancer (Chan 2015).

Physiological processes in all living organisms are direct consequences of evolutionary pressure promoting overall evolutionary fitness, defined as survival taking precedence over reproduction and direct survival/reproduction taking precedence over long-term survival/growth (8). Because of this precedence being set, injuries or atrophy of tissues such as skin, bone and tendons occur when resources needed for survival are scarce, including situations of starvation (9), and in times of energy depletion due to acute and even chronic inflammation (1). Many CIDs manifest at older age and therefore exert little selection pressure. Our ancestors had much lower life expectancies and rarely suffered from CIDs or the resulting adverse health consequences, and when they did this would hardly have affected survival and reproduction (Finch 2006). Nevertheless, although inflammation can affect important organs such as the liver and liver inflammatory mechanisms are essential for the maintenance of liver health (Robinson 2016), it is important to note that, even in these situations, hepatic gluconeogenesis is maintained during immune activation, providing the energy required for survival and reproduction (10, 11). During the preparation of this review, which started in 2008, other authors published the term “selfish immune system” and therefore it is obvious that this topic is highly actual at this moment (Straub. Arthritis Res Ther. 2014;16 Suppl 2:S4. Straub. Ann N Y Acad Sci. 2014;1318:7-17)

1.2. Protective role of the immune system during human evolution

Robust adaption to new environmental challenges involves epigenetic changes that influence rapid (epigenetic; individuals, some generations) and long-term (genetic; generations) adjustment of the phenotype, for instance by epimutation, single nucleotide polymorphisms and gene copy number variation (12, 13). Numerous environmental factors have shaped the human genome, including climate, food and microbial load (12). Although the first two challenges certainly show selective pressure in humans, the main selective pressure seems to derive from pathogens because of their high degree of potential lethality (14). When hominins began exploring new environments looking for food and scavenging, they were exposed to new pathogens. For example, dead meat, when spoiled, is a perfect source of pathogens such as Escherichia coli, Salmonella and other possible lethal microbes (15). The struggle to survive in new situations led to the development of an incredibly effective and robust immune system. The survival

mechanisms evolved at least four times and entailed: upregulation of anti- inflammatory and anti-pathogenic strategies (16), spontaneous physical activity (17,18), the development of a highly sophisticated behavioural immune system (19), and higher immunological reactivity, when compared with our evolutionary closest counterpart, the chimpanzee (20, 21).

The higher reactivity of the immune system enabled the exploration of new environments and, when necessary, the ability to mount a massive innate immune response to prevent lethal infection (22). This response is extremely costly and would have hardly permitted the further brain growth observed in later hominins if the pro-inflammatory reaction to pathogens had prevailed over the needs of the brain on a chronic basis. The use of the first three strategies might have been necessary because of a much lower energetic cost, thus protecting against pathogenic load, without suffering from the possible secondary damaging effects of a pro-inflammatory strategy (23). It is therefore conceivable that the combination of these three strategies 'liberated' energy for larger brains and an expansion of brain functions.

Failure of these three strategies (i.e. upregulation of anti-inflammatory and anti- pathogenic strategies, spontaneous physical activity and the development of a highly sophisticated behavioural immune system) necessitates a protective high- cost pro-inflammatory response and the entire body is then at the disposal of the immune system; "prima vivere e dopo filosofare" (first live and then philosophise). This selfish behaviour of the immune system is observed not only in acute inflammation but also in chronic inflammation, the major difference between these two states being a shift from a hypermetabolic state to a hypometabolic state. Figures 1 and 2 show how the immune system puts the body at its disposal in acute inflammatory (Figure 1) and chronic inflammatory (Figure 2) states. Observing the actual pandemic increase of non-communicable diseases, we consider that it is this selfish behaviour of the immune system that causes the majority, if not all, of these diseases. Although the selfish immune system gave humans the ability to explore the entire world, it now seems to be responsible for most modern diseases, including cardiovascular disorders, autoimmune and neurodegenerative diseases.

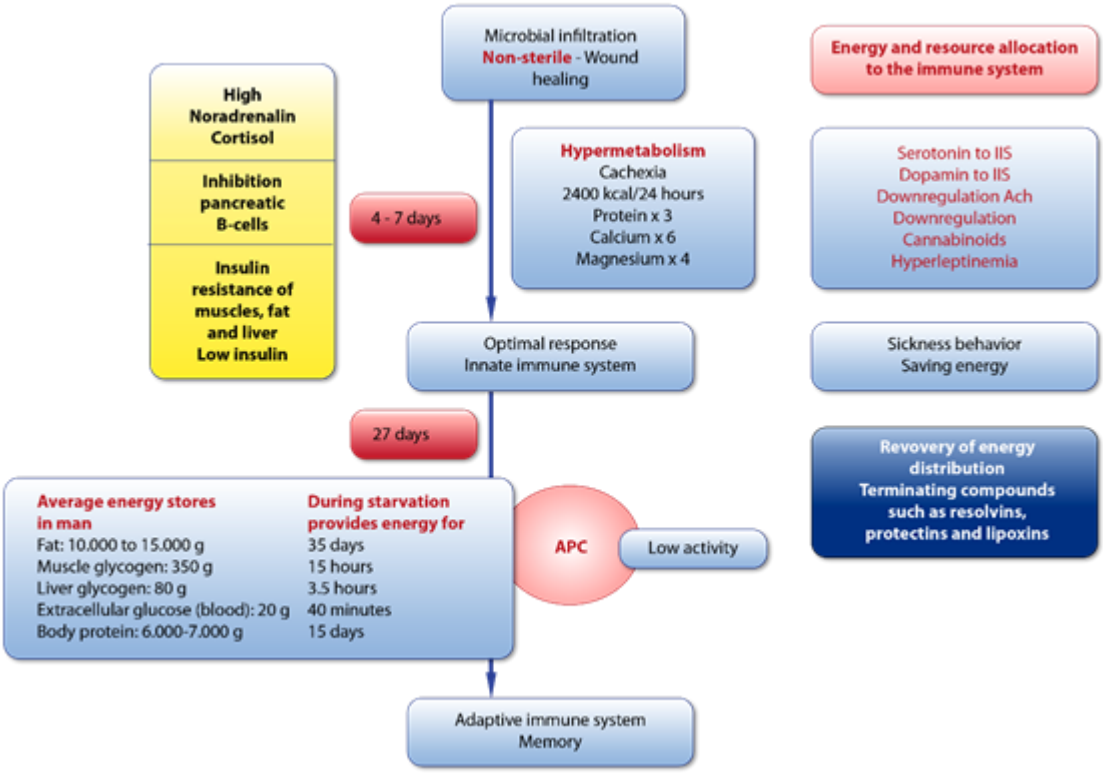

Figure 1. The immune/metabolic response during acute inflammation. The increased need for energy during acute inflammation causes a hypermetabolic state and allocation of resources, including proteins and minerals, to the immune system. Insulin levels are down-regulated by inhibition of pancreatic B-cells and glucose can be used by the immune system through development of adaptive insulin resistance of competing organs such as muscles, fat and liver. Short-term use of neurotransmitters by the immune system increases the activity level of the innate immune inflammatory response, 'helping' the need to mount an intense but optimal reaction that will resolve in a maximum of 4 to 7 days. Sickness behaviour induced by hyperleptinaemia and pro-inflammatory cytokines further saves energy, induces sleep and adaptive cachexia. The optimal IIS response is short-term and will moderately activate antigen-presenting cells. The adaptive immune system will produce anti-inflammatory memory cells that can be recruited when the host encounters a different immune challenge of the same type. This adaptive immune response generally ends after a maximum of 27 days, leaving sufficient energy to maintain health of the organs disposed of during the start of the immune response. Resolving substances such as protectins and resolvins finish immune activation and homeostasis of the whole body is recovered through normalised energy distribution. Ach, acetylcholine; APC, antigen presenting cell; IIS, innate immune system.

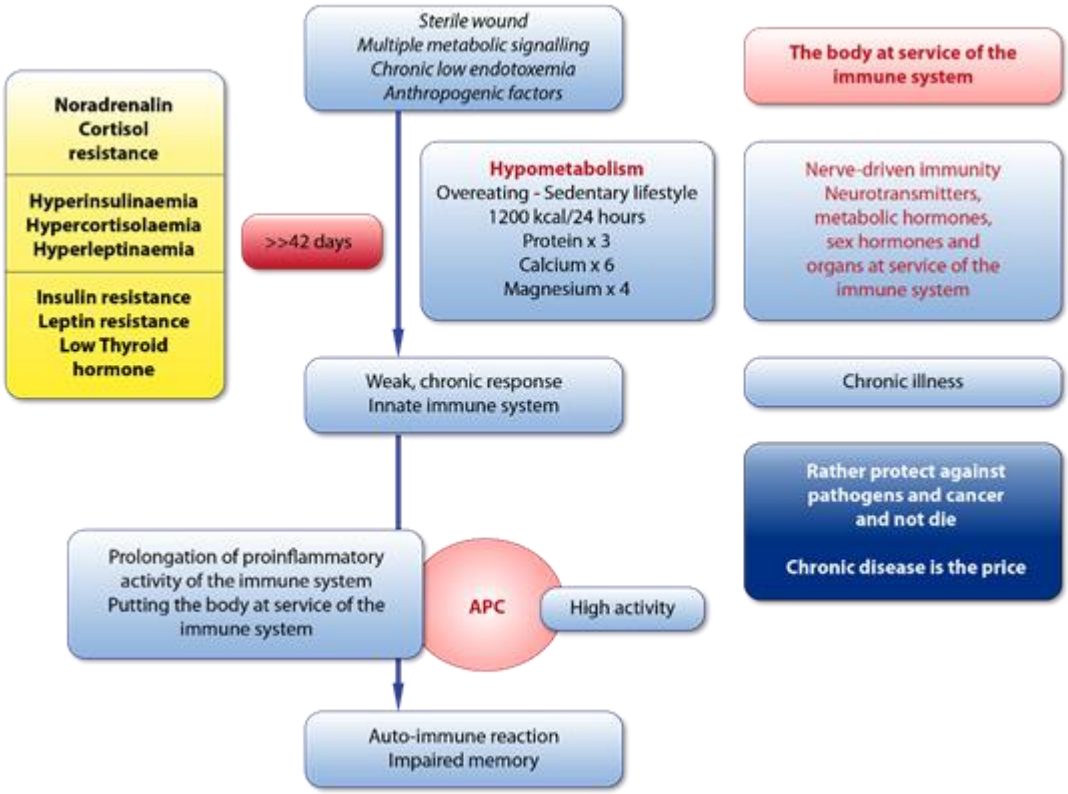

Figure 2. Chronic low-grade inflammation and hypometabolism. In the modern world, long-term pro-inflammatory activity of the immune system is frequently caused by anthropogenic factors and other conditions that challenge the immune system only weakly, but chronically. In normal situations any inflammation would produce a compensatory immune suppression, which is why low-grade inflammation needs a logical explanation. To maintain pro-inflammatory activity, the immune system itself puts the entire body at its disposal, but at the same time protects the body against multiple organ failure by inducing a hypometabolic state. Cortisol and noradrenaline induce gluconeogenesis and this extra glucose is allocated to the immune system by increasing insulin resistance of competing organs. At the same time, leptin reactivates the immune system, whereas brain regions associated with satiety develop leptin resistance, inducing increased food craving. Low thyroid hormone (rT3>T3) decreases total energy expenditure (protective hypometabolism) and rT3 is needed to fight pathogens. Nerve-driven immunity provides the immune system software (serotonin and dopamine) to maintain pro-inflammatory activity, whereas immune-suppressive mediators are down-regulated (cannabinoids and acetylcholine). Retraction of sympathetic fibres of inflamed/immune tissue and increase of sensory fibres are hardware strategies of nerve-driven immunity. Chronic pro-inflammatory activity is further maintained by a shift from an anti-inflammatory androgenic to a pro- inflammatory oestrogenic state in both males and females. The total picture of this 'selfish immune system behaviour' might be considered protective when it does not last too long; it is however highly deleterious when the human body starts developing all kinds of modern disorders such as autoimmune diseases, neurodegeneration and other maladies. Nevertheless, even today it is usually better to develop a CNCD than to die of cancer or infection.

1.3. Acute inflammation resolves itself; controlled resolution

The immune system is self-regulating through negative biofeedback mechanisms, just like any other system in the human body. Acute inflammation induces the production of several substances responsible for finishing the immune reaction, including arachidonic acid derived lipoxins, EPA-derived protectins and DHA-derived resolvins (1), but only if the aforementioned fatty acids, notably the fish-derived fatty acids EPA and DHA, are available in sufficient amounts (24-26). These substances decrease the activity of pro-inflammatory cells of the innate immune system and, at the same time, stimulate migration of phagocytizing macrophages to the danger zone/battlefield (27-29).

Another more intrinsic negative biofeedback signal is lactic acid. The activated immune system uses (cytoplasmic) glycolysis as energy metabolism, in which 90% of glucose molecules are converted into lactic acid, a metabolic shift from mitochondrial oxidative phosphorylation (MOP) to cytoplasmic substrate level phosphorylation (SLP) (30). This metabolic shift seems counterintuitive when considering that only 2 molecules of ATP are generated from 1 molecule of glucose during SLP, whereas MOP yields 36 molecules of ATP. This is, however, conceivable in the light of the velocity of SLP which is a hundred times faster than MOP (30, 31). A second benefit of SLP is that the glucose molecule is only partially used for ATP generation. Lactic acid and other macromolecules are metabolites of SLP that confer several favourable positive conditions during acute inflammation that guarantee cell division and cytokine production and render the immune system to a state independent of food and oxygen. The immune system's capacity to engage in SLP is also known as the 'Warburg effect', which not only provides the immune system with fast energy, but also the precursor (glucose) needed for the synthesis of structural elements for the production of all DNA, RNA, organelles and the majority of cell membranes (for an excellent review, see 32). The oxygen-independent fermentation of glucose in the cytoplasm thus leads to the production of amino acids as precursors of proteins, (deoxy)ribose for DNA and RNA, glycerol for lipids and NADPH through the pentose phosphate pathway, needed for the production of phospholipids and glutathione (32). The activated immune system is now capable of growth and proliferation, largely without the need to uptake oxygen and building blocks. Considering the sickness behaviour associated with acute infectious disorders, characterised by cachexia {food absence} and even diaphragmatic breakdown {low oxygen} (33, 34), this makes sense.

Lactic acid supports the role of lipoxins, resolvins and protectins in finishing the inflammatory response in a maximum of 4 to 7 days. Finishing the inflammatory response in time protects the body against possible deleterious secondary effects caused by the immune system itself. Not only have intrinsic mechanisms emerged to end an acute inflammatory response, but brain-coordinated strategies, including the production of substances such as cortisol (35), certain cannabinoids (36), acetylcholine (37) and catecholamines (38, 39), are able to switch off the immune system. These inhibiting mechanisms are activated through coordinated processes during acute inflammation and the same holds true for the serotonin and dopamine pathways (see chapter 'behaviour at the disposal of the immune system'). Observing the multiple mechanisms responsible for inhibiting the pro-inflammatory activity of the immune system, it can only be concluded

that the inflammatory response should be finalised in time, leading to controlled resolution even after infection (40).

Therefore, why is immune-inhibition absent when people suffer from weak inflammation caused by anthropogenic factors (AF)? AF activate the immune system through indirect pathways and causes a weak, 'cold' inflammation, without any of the typical signs of 'hot' inflammation (41). Usually adipocytes are activated by AF, such as high caloric food intake and psycho-emotional stress. Although this type of inflammation is not as strong, it still produces a metabolic shift of the immune system, giving rise to the production of substantial amounts of lactic acid, which serves as a potent immune suppressor through the creation of significant acidosis (42, 43). The question therefore remains how the immune system 'manages' its activity for years and years, in spite of intrinsic and extrinsic mechanisms that inhibit the immune system and generally protect the body, but especially the selfish brain, against secondary damaging effects.

We suggest that the immune system manages long-term activity by pursuing at least two strategies, firstly to achieve energy (glucose) and secondly to reactivate itself. The first strategy has to induce constant gluconeogenesis and energy allocation to the immune system and the second strategy has to reactivate the immune system. Pro-inflammatory immune system activity depends on several conditions. 1. Pro-inflammatory cytokines have to be produced through activation of the key regulator of the immune system being nuclear factor-κB (NFkB), 2. Immune cell growth and cell proliferation depends on activation of the mammalian target of rhapamacin (mTOR), 3. cytoplasmic glycolysis is needed for the production of macromolecules and energy during immune activation and this requires the activation of hypoxia-induced factor-1 (HIF-1) and 4. The activated immune system demands large amounts of glucose and therefore a higher number of glucose transporters type 1, achieved by upregulation of c-myc (44-46).

Strategies used by the immune system to reactivate itself include:

- Insulin resistance and high insulin levels
- Leptin resistance and hyperleptinaemia
- Low thyroid hormone syndrome
- Catecholamine resistance of the immune system
- Cortisol resistance of the immune system
- Systemic androgens to oestrogens shift
- Peripheral serotonin recruitment
- Peripheral dopamine recruitment

The majority of these different strategies are associated with sickness behaviour exhibited during acute infection (47). This behaviour is characterised by symptoms such as cachexia, fatigue, increased sleep and fever. It suggests that the activated immune system itself is responsible for fasting during infection and 'senses' that food will not be available under these conditions. The outcome is the mentioned shift from MOP to SLP, resulting in immune cell proliferation and activity becoming independent from food intake, all to enable the infection to be cured (48). Chronic activity of the immune system, during which the same metabolic shift occurs, would require a large amount of glucose, which is the basic energy fuel of the activated immune system and, of which, the limited availability

constitutes the basic problem in chronic non-communicable diseases (CNCD) (48). This 'nutrition-independent' state may be responsible for the recently evidenced decrease in basal metabolic rate in chronic inflammatory disorders, rendering the subject vulnerable to the development of multiple metabolic disorders, including metabolic syndrome and diabetes mellitus type 2 (49).

In summary, the metabolic shift observed in conditions of an activated immune system renders the system glucose-dependent and will therefore activate all strategies to maintain glucose homeostasis through systemic gluconeogenesis (35). The immune system can apply multiple strategies to maintain activity, although at a low level and puts the whole body at its disposal, including the brain, if necessary. This selfish behaviour has a protective effect during acute infection, but may have a dramatically deleterious effect in the long run, evidenced by the number of people suffering from CNCD in our society (50, 51). Low-grade inflammation should therefore be regarded as the cause for the majority, if not all, cases of CNCD. Treatment should therefore target the strategies used by the immune system to maintain its activity over a prolonged period of time. The only way to provide the correct treatment is to understand the ways the immune system puts the whole body at its disposal, which is the aim of this review.

1.4. The selfish immune system; brain damage leads to more brain damage caused by the immune system and overriding the brain as most dominant organ.

The immune system is one of the systems with a high level of biological robustness (52). Some diseases and their effects produced by the robust character of the immune system will not necessarily benefit the host, but that is the price to pay. We provide evidence that the mechanisms leading to pathologies affecting the whole body, including the brain, should be considered robust and part of the survival strategies developed during hominin evolution (53).

The interactive neuro-endocrine-immune system evolved to cope with acute immunological challenges such as infection and wound healing, but is also activated by non-immunological danger for which it was not designed (2, 54). Theories explaining biological priorities consistently put the human brain in first place (55, 56). However, brain functions, blood circulation and anatomy are disrupted in those suffering from Alzheimer's disease, Parkinson's disease, fibromyalgia syndrome (FMS), chronic fatigue syndrome (CFS) and depression (57-60), which suggests that certain pathophysiological processes override the protective behaviour of the selfish brain.

FMS depression and Alzheimer's disease (AD) are obviously not diseases of choice, but may rather reflect the involuntary alternative of suffering from a low energetic state leading to a non-permissive brain disorder (e.g. AD, depression and FMS), rather than dying from multiple organ failure (61-63) caused by a chronic activated pro-inflammatory immune system.

Rogers (64) stated that "Inflammation seems 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" and the same holds true for people who suffer a stroke (65, 66). The inflammatory response of the immune system causing severe secondary damage to the brain after traumatic brain injury or ischaemic stroke seems maladaptive in the face of the 'selfish'

brain hypothesis. It would, however, correspond with the 'selfish' immune system hypothesis, which states that danger gives precedence to the immune system, and thereby overriding the selfish brain.

It may even be the case that dramatic inflammatory response following brain injury is not caused by the injury itself, but by the presence of infectious pathogens. Pre-existing infection is present in one third of clinical ischaemic stroke patients (67). Clinical data suggest that stroke risk peaks at three days after infection onset and that this risk remains high for three months (68). Almost three out of every four

people in the world who suffer a fatal stroke live in developing countries and malaria, Chagas disease and Gnathostomiasis seem to be the major causes for this surprising fact (69). Children and young adults are less susceptible to all-cause strokes with the

exception of infectious stroke and diseases such as sickle cell disease. A recent case-control study revealed that pre-existing infection is an independent risk factor for stroke in 33% of affected children also in developed countries, such as the USA where 2,400 children suffer from strokes every year (70). These data suggest that a possible pathogenic presence 'programmed' a severe pro-inflammatory immune response when the brain or the heart muscle are damaged. The selfish behaviour of the immune in these cases should be considered as adaptive but also possibly deleterious. Nevertheless the fact that people suffering from immune suppression after stroke are highly susceptible for sepsis and dead (71) suggests that the selfish behaviour of the immune system should be considered as needed when damage to the heart or the brain has been done.

2. It's all about energy – The selfish immune system

2.1. Robustness and energy reallocation between visceral organs, muscles, the immune system and the brain

The immune system is one of the energetically most costly systems in humans when 'activated'. Consequently, immune metabolism has a profound effect on the functioning of the body. Metabolic conflicts between organs seem to explain the emergence of several disorders and, more specifically, modern non-communicable diseases such as autoimmune disorders (72).

Anthropogenic danger signals, such as psychoemotional stress and sleep deprivation, are capable of activating the immune system and a chronically activated immune system demands high energy, protein and immune-specific minerals such as calcium (2). Such high costs would never have permitted the development of the phylogenetic newer metabolic expensive brain in general and, more specifically, the neocortex during evolution. A recent review describes how exercise (searching for food, water and shelter) in primates and early hominids produced a shift from a pro-inflammatory immune reaction with a high metabolic demand to an anti-inflammatory response with a low metabolic demand (23). This shift made it possible to allocate energy to other organs e.g. the brain without large amounts of energy, proteins and minerals having to be invested in the immune system, whilst at the same time maintaining protection against microbes.

2.2. Energy and energetic conflict as the driving force behind evolution

Changes in energy allocation between organs are a consequence of energy conflicts that affect all animals, but non-human primates and humans in particular (73, 74). Several scenarios have been proposed, with the brain being the organ to benefit from loss of colon

length and high caloric dense food [the expensive tissue hypothesis] (73, 74)], a decrease in muscle mass, an increase in fat mass (57), cooking (75), human locomotion costing less energy (76) and, very recently, a change in the expression of glucose transporters beneficial to the brain (77). To our knowledge, as yet it has not been suggested that immune function may also have benefitted from a smaller gut, a lower energy demand for locomotion, an increase in fat mass and tissue-specific differences in the expression of glucose transporters. The latter entails a higher expression of GLUT1 in activated immune cells, when energy is needed to protect against pathogens and other immune challenges (78), at the expense of GLUT4 expression in muscles and adipocytes (79-82).

The work of Fedrigo et al. (77) shows that glucose transport capacity has been essential for brain growth and function during human evolution. They demonstrated that human brain cells express more activity of the SLC2A1 gene, which is the genetic code for the production of GLUT-1 glucose transporters compared with the chimpanzee and macaque (human > chimpanzee > macaque). At the same time, SLC2A4 expression in muscle is significantly higher in chimpanzee > human > macaque.

Logical reasoning makes it plausible that a concomitant per gram tissue reduction of SLC2A4 in skeletal muscle and an increase of SLC2A1 in the brain will lead to higher glucose uptake by the brain at a given plasma glucose concentration. This would result in a shift of glucose allocation away from the body (strong) and towards the brain (smart).

2.3. Glucose to the immune system – prioritising energy guidance

Along a similar vein, the same holds true for glucose allocation to the immune system. The energy demand of lymphocytes and leukocytes increases dramatically upon activation (2, 4) and all activated immune cells express GLUT1 glucose transporters (78, 83). Higher expression of GLUT1 will promote energy allocation to the immune system, which could be considered to be an 'energy demand reaction' (84). Glucose allocation to the immune system maintains its function even under strong energy restriction (72).

The foregoing demonstrates that activation of the immune system through danger signs will attract and redistribute energy, favouring the brain and the immune system. Prolonged activation of the immune system (as has been observed in people with CIDs) would allocate glucose chronically to the immune system through immune-controlled down-regulation of GLUT1 transporters at the level of the blood-brain barrier and would decrease GLUT4 transporters at the level of muscle and adipose tissue (85-88).

3. Evolution shaped the selfish immune system

3.1. Evolution and the human selfish immune system - over-reactivity of the human immune system when compared with chimpanzees

It has been shown that the human immune system is relatively over-reactive when compared with our closest evolutionary relative, the chimpanzee (89). The increased activity of the human immune system holds true for both the innate and the adaptive immune systems (90). It seems that all major cell groups of the human immune system show lower levels of mediators capable of down-regulation of the immune response against pathogens and phytohaemagglutinin (20). These mediators, called inhibitory sialic acid-recognising Ig-superfamily lectins (SIGLEC), are expressed on most immune cells including B lymphocytes (91). The difference between chimpanzees and humans is three-fold. Firstly, humans express different SIGLECs; secondly, humans exhibit lower SIGLEC

numbers and little or none are present on T lymphocytes, and thirdly, they show a lower production rate of inhibitory SIGLECs when challenged with pathogens or other immune stimuli (91, 92).
The observed development of a more reactive immune response in humans is probably a consequence of being faced by unique immune challenges to numerous pathogens through scavenging, increased population density, hunting and migration (93, 94).

3.2. The selfish brain is less selfish than the much more ancient immune system.

The brain is selfish in almost every situation, including mild and severe stress (95) and multiple studies support the 'selfish brain' hypothesis. Acute mild mental stress requires 12% additional energy from the human brain (96) and the same holds when humans are challenged by intense exercise (97). The group of Peters showed that social stress also augments the brain's energy need (98) and that the brain switches to the use of ketone bodies (99) and lactic acid (99) when glucose is unavailable. Therefore, several lines of research give evidence for the 'selfish brain' hypothesis in which it is stated that brain energy is maintained through multiple pathways, including activation of central stress axes and the use of multiple energy sources (glucose, ketone bodies, lactic acid). Immune activation also produces activity of central stress axes and a state of high arousal of the central nervous system, the purpose being to sense and avoid further danger (100). An acute inflammatory response produces energy allocation to the immune system until this is resolved, and only when the system is challenged by mono-metabolic danger signals (100). However, multi-metabolic risk factors produce an energetic conflict between the immune system and the brain. The combined need for resources (energy-producing macronutrients, blood, oxygen) of the stressed brain, of the activated immune system and of other organs responsible for maintaining organ functions during multiple metabolic signalling challenges, caused by psychogenic, psychosocial and physical factors at the same time, would probably override the maximum capacity of energy uptake by the gut and, although speculative, would demand a maintained heart rate of around 180/minute and a chronically increased blood pressure at around 160/120 mm Hg. This would lead to severe damage to the heart and probably the brain, which is contrary to the evolutionary drive of maintaining brain function and anatomy against at any cost (98). The only feasible response to maintain life throughout chronic situations of high energy demands of 'conflicting' organs, is the 'creation' of an organ-specific low thyroid hormone syndrome and other adaptations with the purpose of lowering the activity of all organs and puts the body at the disposal of the immune system. This is evidenced by the development of immunological sickness behaviour, immunologically induced secondary damage of vital organs, protective depression, gluconeogenesis by the liver and kidneys, and the use of metabolic hormones and neurotransmitters by the immune system to benefit its pro-inflammatory activity and thereby protect against possible lethal pathogens (101, 102, 103, 104).
It is definitely true that the brain 'behaves' selfishly in almost every situation, including an energy deficient intra-uterine environment. Nevertheless, although it seems that one of the most fundamental biological drivers in humans is supplying the brain with nutrients and energy, how is it possible for people to suffer from diseases related with lack of brain energy?' Something has to be so wrong that it may even cause a reaction that overrides this interest and 'accept' the collateral damage to the selfish brain. Acute sepsis, severe burn wounds, multiple traumata and major surgery are known to allocate up to 100% of resting

energy expenditure to the immune system, but these are acute situations which often lead to instant death, even in children (3, 4, 105-108). Neurodegenerative disease, fibromyalgia, and chronic fatigue disorders develop slowly and should therefore be caused by factors that demand long-term energy allocation to systems other than the brain, e.g. the immune system, ultimately affecting the transport of resources to the selfish brain. Sedentary lifestyle, overeating, childhood abuse, oral sepsis, chronic life stress, leaky barriers, perceived social stress, environmental toxins, social jetlag, meal frequency and even father-daughter conflict all activate the immune system and an energy demand response based on activation of the SAM and HPA axes (109-113). This latter response should provide energy for, primarily, the brain and secondarily, the immune system. When brain allocation fails, brain functions and possibly anatomy will be disturbed. The latter occurs in people suffering from acute infection, but also in those suffering from Alzheimer's disease, FMS, CFS, depression and other diseases affecting the central nervous system. It seems that multiple metabolic danger signals produce a state mimicking acute life threatening danger, allocating energy to the immune system and disposing of energy from the rest of the body, including the brain.

4. Genetic and environmental evidence supporting the hypothesis

4.1. Genetic evidence for the selfish immune system hypothesis

Depression and other maladies, including FMS and neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases, are related to increased immune activity (122, 123, 124). All of these disorders seem to have a genetic predisposition and the majority of the genes related with neuro-degenerative disorders and depression influence the immune system. Raison hypothesised that if depression is related to certain polymorphisms, then these genes are primarily protective in the face of infection (for review see 125). The same holds for genes related to Alzheimer's disease and FMS.

The gene most widely accepted to be associated with Alzheimer's disease susceptibility is ApoE 4 (apolipoprotein E4), although many others have been proposed as Alzgenes (126). Classical functions of apolipoprotein E relate to metabolism (transporter of lipids in the periphery and in the central nervous system (127)). More recently, it was found that ApoE influences the innate and adaptive immune systems (128). The overall influence of ApoE on the innate immune system is complex and depends on ApoE polymorphism. ApoE4 induces an inflammatory response, whereas ApoE3 inhibits inflammation and enhances repair (see references in 128). The pro-inflammatory activity of ApoE4 is classically seen as deleterious, but can also be considered protective in the light of the pathogen-host defence (PATHOS-D) hypothesis proposed by Raison and Miller (125). In our recent evolution, the share of the ApoE3 allele appears to have increased at the expense of the ancestral ApoE4 (129). ApoE3 has spread significantly in first world populations, whereas the prevalence of ApoE4 is still very high in cultures historically exposed to disease-causing pathogens (127, 130-132). The observation seems consistent with the protective role of ApoE4 against infection. The Yoruban population in Nigeria has a 70% lower incidence of dementia when compared to African Americans. This difference is probably caused by the lifelong low-fat diet of the Yorubans (133).

Candidate genes possibly associated with increased susceptibility to fibromyalgia syndrome have been reported, but no definite conclusions can be drawn as yet (134). The serotonin transporter gene SLC6A4 is perhaps the strongest candidate in terms of its

relation to FMS (51, 135, 136). Two major SLC6A4 polymorphisms have been identified. The short allele carrier produces a protein, which is less efficient in the reuptake of serotonin and carriers show an increased risk for the development of depression when facing psychosocial challenges. Carriers of the short allele further show higher levels of circulating pro- inflammatory cytokines compared with anti-inflammatory cytokines (IL-6/IL-10 rate) when challenged with a psychosocial stressor (137).

Another diseases with an immunological genetic background is celiac disease. Celiac disease is caused by the intake of gluten and it's interaction with a great number of genes, of which most are related with an increased reactivity of the immune system (138). More specific, it are alleles related with IL18, IL23, IL2 and IL12 that increase the susceptibility for celiac disease, but at the same time people expressing these genes are probably better protected against pathogens, including virus and bacteria (139).

4.2. Pathogens shaped genetics to the benefit of the immune system and pathogen load prioritises the immune system over the brain

If the PATHOS-D hypothesis is correct, that the microbial world is co- responsible for the chronically increased activity of the immune system and disposal of expensive brain functions, then pathogenic load should not only affect brain function and anatomy of older people, but also younger individuals. Evidence for this supporting the PATHOS-D hypothesis comes from studies investigating the development of intelligence during human evolution in general and, more recently, the past two hundred years. A recent study of Eppig (140) showed that infectious disease and the consequent immune activity is the most important predictor of lower intelligence in almost every population on earth. Nutrition was also correlated with IQ, but became insignificant when corrected for infection. The connection between pathogen load, infection and intelligence seems plausible considering the high energetic cost of infectious disease. (141).

5. Long -term immune activity: the need for reactivation and fuelling strategies

5.1. Evolutionary stored energy limits the timescale of immune activity

Both the innate and adaptive immune responses are normally self-limiting (142). The self-limiting timeframe of 28 days is probably based on the energy-resource model. A (much) longer massive activity of both systems would lead to severe secondary damage and even death because of sustained energy deficit of vital organs including the liver, kidneys and heart muscle (143). Recruitment of the adaptive immune system, although very expensive at first exposure time (141), and the generation of immune memory, should be considered beneficial from an evolutionary point of view, because of the shortening of the immune response and protection against energy depletion, when the host is newly exposed to the pathogen (64). Chronic low-grade inflammation literally means long-term low activity of the innate immune system and lack of the production of self-limiting substances, such as resolvins and protectins (129). Chronic low-grade inflammation probably starts after a non-optimal acute inflammatory response (supranormal or subnormal) and when self-limiting mechanisms or strategies fail (131). Sterile wounds, low pathogenic load and non-specific immunological challenges such as psychogenic stress activate the immune system, but lack the strength of optimal immune activation which would normally lead to complete resolution (164). Nevertheless if the factors that activate the immune system in a subnormal manner are not resolved, the capacity to maintain immune activity is essential for survival,

as evidenced in people suffering from inflammation-associated immune suppression. People suffering from inflammation-associated immune suppression (IAIS) are highly susceptible for the development of different types of cancer and secondary infections, and IAIS significantly increases the mortality rate (132, 133). IAIS is induced by immunological intrinsic (e.g lactic acid)., but also multiple brain derived strategies including the activation of the parasympathetic nervous system. This is where the immune system has to put the body at its disposal, thereby overriding the selfish brain.

5.2. The consequence: the whole body at the disposal of the selfish immune system

The way in which the immune system puts the body at its disposal might follow a coordinated sequence. The initial activation of energy demanding central stress axes allocates resources to the immune system through induction of gluconeogenesis and insulin resistance of competing organs, such as, bone, muscle, adipose tissue and the liver (1, 48). Once the innate immune system (maximum 4-7 days) and, when necessary, the adaptive immune system (27–42 days) has/have triggered the immune response, problems should have been resolved. If immune activation is required for a longer period of time, this induces further insulin resistance/hyperinsulinemia, hyperleptinaemia/leptin resistance, and hypercortisolism/glucocorticoid resistance. The possible hypermetabolic state produced by the constantly activated immune system could cause multiple organ disorders, failure and even death (MODFD). The development of a low thyroid hormone state (rT3>T3) protects the body against MODFD, putting homeostatic regulation at the disposal of the immune system. The pro-inflammatory activity can also be maintained by higher aromatase activity and the production of pro- inflammatory oestrogens (see below): a further step in putting the whole body, including the reproductive system, at the disposal of the immune system.

6. Fuelling and reactivation strategies of the immune system

6.1. Thyroid hormone prevents multiple organ failure during hypermetabolism and maintains immune homeostasis; thyroid hormone at the disposal of the selfish immune system

Immune activity depends on aerobic glycolysis (134). It is only possible to maintain aerobic glycolysis when the intrinsic inhibitory pathways of the immune system can be overruled. Low T3 and high rT3 can maintain aerobic glycolysis in immune cells. Thyroid hormone T3 induces mitochondrial activity in all kinds of cells, including immune cells (135). T3 can even strongly activate mitochondrial oxidation in cancer cells and render them more sensitive for chemotherapy (135). Intracellular T3 would therefore inhibit the inflammatory activity of the immune system, which would be highly deleterious during severe infection or other immunological challenges. Extracellular T4 and T3 are necessary for immune activation (137), but intracellular T4 is converted by deiodinase 3 (D3) into rT3 and T3 is rapidly downregulated by the same enzyme, preventing mitochondrial activation and maintenance of cytoplasmic substrate level phosphorylation through upregulation of D3 by the pro-inflammatory cytokine IL-6 (138). The final state is that of a low thyroid hormone syndrome (LTHS).

LTHS does not only benefit the immune system, but is also protective against the possible secondary damage of chronic immune system activation. These rather deleterious effects of immune activation on other organs and tissues is prevented by down-regulation of the

conversion of T4 into T3 both systemically and tissue specifically, causing the reduction of overall metabolic rate, but especially the activity of organs less important for direct survival during immune activity, such as muscle tissue, liver, kidneys, the heart muscle and the digestive system (139-141). The lower activity of these organs protects them against acute organ failure and sudden death of the host. The protection and lower metabolic rate is a product of low thyroid syndrome and high reverse T3 (rT3) (138). This state is protective initially, but can be deleterious in the long run (53).

A recent discovery by the group of Klein and Schaefer has shed new light on the interaction between the immune system and metabolism. Their group proposed a new model of controlled metabolic regulation by an activated immune system (143- 145). They showed that TSH can be produced by several tissues other than the thyroid gland. Dendritic cells (DCs) and several cells from the small intestine are capable of producing TSH and this happens mostly during bacterial or viral infection (192). Certain leukocytes also produce TSH, but with a slightly different structure and this hormone has been named TSHbeta splice variant (146). The TSHbeta splice variant seems to change the thyroid phenotype inducing a shift from T3 to rT3. This shift decreases total body metabolism because of lower systemic T3(192) and initially saves the brain by continued conversion of T4 to T3 in the brain itself (147).

The possible function of D3 expression in activated innate immune cells is intriguing. Thyroid hormones (TH) play a role in differentiation and proliferation of cells, with high T3 inducing cell differentiation and low T3 inducing cell proliferation. Granulocytes are short-lived, fully differentiated cells that migrate to the site of infection and do not proliferate, which may argue against a role for D3 induction in differentiation or proliferation of activated granulocytes. Studies in the 1960s suggested a role for thyroid hormone in the bacterial killing capacity of leukocytes. Iodide in combination with hydrogen peroxide (H2O2) provides one of the most effective antibacterial substances of the immune system. Thyroid hormones are an important source of iodide, and leukocytes generate inorganic iodide by the uptake of iodide and by de-iodinating T4, (148). In combination with the recent demonstration of D3 induction in infiltrating leukocytes during infection, we suggest that D3 induction helps to generate iodide as part of the innate immune response (147). Studies in S. pneumonia-infected D3 knockout mice indeed showed a defective bacterial clearance compared with wild-type mice, which supports this hypothesis (150). Further evidence is given by the work of Kwakkel et al, showing a dramatic increase of D3 production by neutrophils when challenged with bacterial LPS (149).

The resulting state of immune activation, low T3, high rT3, combined with the energy demand reaction of the HPA axis and the sympathetic nervous system maintains immunological homeostasis during prolonged stress. The brain will maintain anatomy and function as long as brain metabolism can be guaranteed. The same holds for the immune system, although long-term stress and inflammation suppress immune activity (38). The latter situation could expose the host to possible infection and death. Protection of the host integrity will now depend on the use of alternative mechanisms to postpone this dangerous state whilst maintaining pro- inflammatory immune activity. This would be the time at which the immune system

1. puts every possible organ at its disposal to guarantee its own metabolic homeostasis, 2. induces resistance to hormones with pleiotropic immunological functions (leptin, insulin,

cortisol) and 3. produces a state of nerve-driven immunity, putting almost all neurotransmitters, including dopamine, serotonin, acetylcholine, glutamate and GABA at its disposal (151-155).

6.2. Gluconeogenesis and glucocorticoid resistance at the disposal of the immune system

Endogenous cortisol has several effects on the immune system, including suppression through activation of the inhibiting factor kappa B (IkB) (156), apoptosis of immune cells that are no longer needed (157) and migration of immune cells to the so-called 'battlefield' (dangerous zone) or back into the 'barracks' (lymph knots, bone marrow, thymus) (158) and through activation of macrophage migration activating factor (159). Intact cortisol signalling in the immune system would lead to suppression of the immune system, which is why immune cells show an intrinsic mechanism to develop cortisol resistance, which is essential during acute infection but at the same time co-responsible for low-grade inflammation (160). Glucocorticoid resistance (GR) of the immune system leads to hypercortisolaemia and constant gluconeogenesis. The glucose produced by GR-gluconeogenesis can cover the energetic needs of the selfish immune system. GR-gluconeogenesis can be induced in muscle, the liver, kidneys and perhaps even the pancreas (161-164). So GR serves two basic strategies to maintain immune activity: immunological GR prevents inhibition of the immune system and GR-induced hypercortisolaemia increases glucose production, necessary for the constant nourishment of chronic active selfish immune cells.

Glucocorticoid resistance itself seems to protect the host against possible viral infection, including HIV, by maintaining high activity of the anti-viral Th1 component of the adapted immune system (165, 166), although GR can be highly deleterious (167). The GR observed during chronic inflammation is universal and mostly occurs along with another ancient protective mechanism: insulin resistance (168). Cells of the immune system show inherent genetically imprinted resistance mechanisms, which protect the body against the immune-suppressive effects of glucocorticoids, although side-effects can be severe, including chronic leukaemia (160).

GR is observed in rheumatoid arthritis, inflammatory bowel disease and COPD and is mostly considered deleterious (169). Treatment of these diseases normally focuses on increasing cortisol sensitivity (170) with contrasting results (1). Increasing GC-sensitivity can even lead to higher mortality when animals are challenged with pathogens such as E. Coli (171). If intrinsic or acquired GR conveys protection against pathogenic load, than asthma, rheumatoid arthritis and inflammatory bowel disease should be associated with increased pathogenic microbial load. Indeed, the group of Siala showed that reactive and undifferentiated oligoarthritis is associated with the presence of a high number of bacteria in the synovial fluid (172, 173). Patients with arthritis also show a high incidence of glucocorticoid resistance (203). Those with chronic asthma present higher bacterial colonisation of the lower airways, linked to the severity and duration of asthma (159), whilst GR is also a characteristic of asthmatic patients (174). Inflammatory bowel disease (IBD) normally evolves with pathogenic bacteria (20) and, as mentioned above, patients suffering from IBD also show a high prevalence of GR (175).

It therefore appears that GR prevents suppression of the innate immune system and the glucocorticoids-induced shift from Th1 to Th2 activity of the adapted immune system

(175), thus maintaining protection against microbial infiltration and infection (179). GR serves the selfish immune system to maintain activity, nourish itself with glucose, but with just one purpose, which is to protect the individual from lethal infection.

6.3. Leptin and insulin at the disposal of the selfish immune system

Leptin and insulin are needed to maintain long-term activity of the immune system and the immune system itself increases the production of leptin by adipocytes via TNF□□signalling (176). Leptin is highly inflammogenic (177) and hyperleptinaemia, together with central leptin resistance, maintains pro- inflammatory activity and energy allocation to the immune system (178, 180). Proinflammatory cytokines induce leptin production by adipocytes, as does food intake.

Adipose tissue is present in immune-cell-harbouring tissues, such as lymphoid organs, bone marrow and adipocytes that infiltrate wounds (26) and so adipocyte derived leptin can have direct influence on immune cell functioning.

Leptin activates all types of immune cells and increases glucose uptake during immunological activity. The principal target of leptin-induced immune cell reactivation is the key immune response regulator nuclear factor-κB, responsible for transcription of genes encoding for IL1, IL6 and TNF□□(181). In summary, leptin activates the immune system through different pathways with a focus on the innate immune system and Th1. Under physiological circumstances, this leads to increased protection against infection and pathogenic growth. During low-grade inflammation, leptin should be considered to be a re-activator, which can perpetuate immune activity.

The strategies used by the immune system to maintain its activity and guarantee glucose availability could merely have evolved for their beneficial effects; a basic rule in evolutionary biology. This also holds true for the leptin and insulin responses observed during acute and chronic inflammation. The leptin response during inflammation supports different protective traits. Hyperleptinaemia during immune activity informs the brain about the adequacy of long-term energy stores in adipose tissue, asking for/demanding permission to produce a costly fever reaction and a short-term hypermetabolic state, following immune activation (182, 83). The hyper-leptinaemic state will also produce inflammatory cachexic behaviour, which is protective at the start when facing an acute inflammatory response, but could be deleterious when chronic, as is observed in patients and animals with chronic kidney inflammation (184).

Long-term hyperleptinaemia leads to central leptin resistance (54). Several researchers noted that hyperleptinaemia is required for the development of leptin resistance (185). Central leptin resistance is responsible for an increased risk of overeating (186) and overeating rapidly produces leptin resistance (187). Central leptin resistance can be considered to be an evolutionary advantage when energy availability is low, or when the need for energy is chronically increased as observed during prolonged immune activity (188). The beneficial effect of hyperleptinaemia and LR is observed in different situations. Hyperleptinaemia and LR protect against cardiovascular disorders by preventing lipid deposition in the heart muscle itself (189, 190), although recent publications have challenged this view (191). The influence of leptin on the anti-pathogenic function of the immune system has recently been demonstrated in two new studies from the same group (192, 193). Children with low leptin levels are more susceptible to infection (194). The required pro-inflammatory effect of leptin to fight against pathogens has also been

demonstrated in a recent in vitro study (195). The overall effect of leptin on the immune system seems to be permissive, which implies that intact leptin-signalling towards the immune system maintains Th1-Th2 functioning and, if necessary, 'permits' pro-inflammatory activity (196).

Like leptin, insulin is also recognised as a pleiotropic hormone. Energy demands of the brain, or the immune system during starvation, infection or stress are covered by gluconeogenesis and the temporary development of insulin resistance of various organs, caused by proinflammatory cytokines and stress hormones (197, 198). Energy allocation to the immune system is achieved by activating the energy- demand stress systems (sympatho-adrenomedullary, axis, SAM and hypothalamic- pituitary-adrenocortical axis, HPA) and stress systems-induced gluconeogenesis. Hyperinsulinaemia precedes stress-induced and inflammation-induced insulin resistance (199). Hyperinsulinaemia is seen immediately after a stress challenge and/or direct immunological activators, such as injuries and pathogen invasion (51, 98, 200). Low insulin levels increase the susceptibility to develop infections, suggesting that insulin protects against pathogens (201). Acute inflammation produces down-regulation of insulin levels through inhibition of pancreatic □-cells

(202) and also insulin resistance in competing organs for glucose uptake (such as liver, muscles and adipose tissue (197). In this way, glucose becomes available for the energy-demanding immune system. Chronic inflammation maintains the state of insulin resistance and enhances insulin production, leading to hyperinsulinemia (203). In the latter situation, glucose remains available for the immune system and insulin can now be used as reactivator through the mTOR pathway in immune cells, protecting against possible infections which is, however, deleterious in the long run (204). Insulin can also upregulate the specific glucose transporters on immune cells, including GLUT1, GLUT3 and GLUT4, thereby increasing glucose uptake by leukocytes and lymphocytes (205). Insulin signalling through insulin receptors on immune cells stimulate the IRS-1/PI3K/AKT pathway that activates mTOR1 and mTOR2 (206). mTOR signalling recruits c-myc, NFkB and HIF1, facilitating further glucose uptake, production of pro-inflammatory cytokines and maintenance of cytoplasmic aerobic glycolysis, respectively (207-209).

It seems clear that leptin and insulin pathways are capable of fuelling and reactivating the immune system, not only during acute infection, but also to maintain long-term activation. The capacity of redistributing glucose to the immune system and away from peripheral tissues mediates the immune response and has been crucial to human survival. In other words: leptin and insulin signalling beneficial to immune system activity are vital for survival, and are meanwhile also responsible for chronic low-grade inflammation and its associated diseases.

6.4.The reproductive system at the disposal of the selfish immune system

The combined metabolic shift produced at the disposal of the pro-inflammatory activity of the immune system is directly responsible for the pro-inflammatory systemic hypoandrogenic state observed in individuals suffering from low- grade inflammatory disorders (210). This systemic hypoandrogenic state is not produced because of lower testosterone production in the sex organs. To the contrary, obese males, characterised by increased plasma leptin and low-grade inflammation, exhibit a higher testosterone-

dependent risk of prostate cancer (211), while the same holds true for the polycystic ovaria syndrome in females (212).

The testosterone boost produced by metabolic hormones precedes the increased systemic and tissue-specific conversion of testosterone into pro-inflammatory oestrogens. This shift has been observed in different diseases, including obesity and inflammation-related breast cancer (213).

The systemic shift from testosterone to oestrogens could benefit the anti- pathogenic pro-inflammatory activity of the immune system. Males with higher testosterone levels are more susceptible to parasite infection, microbial transmission
(214) and have decreased resistance against tick infection (215). Conversely, low testosterone protects against bacterial infection in general and specifically against prostate infection (216). It is therefore conceivable, but at the same time striking, that both males and females exhibit higher aromatase activities during inflammation as evidenced in patients with rheumatic diseases, characterised by high pro- inflammatory oestrogens and low testosterone levels (217). The protective effect of oestrogens against microbial infiltration and infection is supported by epidemiological data showing that postmenopausal women are disproportionately susceptible to recurrent urinary tract infections (218). Urinary tract infections (UTI) in elderly patients are more treatment resistant and oestrogen replacement diminishes UTI frequency (92, 219). Chronic inflammation and stress lead to low testosterone and high oestrogens in men (220) and high oestrogen levels protect against possible infection.

A possible negative effect of this shift from testosterone to oestrogen is the loss of fertility (32). Obese men, characterised by high aromatase activity in adipocytes
(221) and low-grade inflammation (222), have lower fertility (223). Individuals engaged in a chronic struggle against pathogens rather not reproduce, preventing damage to offspring, which is beneficial to overall reproductive success (114). The septic danger posed by non-sterile wounds is included in the selective pressure factors shaping human behaviour (phenotype) and genome (genotype). It has been shown that the shift from testosterone to oestrogen in the skin is highly protective against pathogenic infection, prolonged infection, wound healing and overall cutaneous repair (224). It is consequently conceivable that the immune system also puts the reproductive system at its disposal. Immediate survival overrules reproduction. Once again, the immune system dominates the whole body, including the timing of reproduction and, if necessary, protecting genetically-related individuals against possible pathogenic damage, or damage to the immune system itself (225). Oestrogens activate the immune system through several mechanisms including stimulation of NFkB, c-myc and mTOR, facilitating immune cell proliferation and inflammatory activity (226).

6.5. Behaviour at the disposal of the immune system: serotonin-dependent reactivation of the immune system

The observed changes in behaviour during inflammation suggest that the immune system actively affects neurophysiological function, putting behaviour at its own disposal. Pro-inflammatory cytokines such as TNF□, IL-1 beta, and IL-6 produce adaptive behavioural effects when entering the brain (47). Sickness behaviour includes social withdrawal, increased sleeping time, fatigue and exercise avoidance. This reduces energy uptake by muscles and the brain and this is reallocated to the immune response.

Several pathways explaining inflammation-induced sickness behaviour have been proposed and all of them probably contribute to this state (112). Sickness behaviour not only benefits the host's immune system in terms of energy/resource reallocation, but also helps the immune system to fight pathogens and restore homeostasis when immune activity is no longer needed (47). Pro-inflammatory cytokines (IL1□, IL6, TNF-□□and IFNy) and stress hormones, produced during inflammation, activate tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3- dioxygenase (IDO), affecting serotonin production from its precursor tryptophan and favouring the production of kynurenine and quinolinic acid (227) The resulting serotonin depletion is considered to be one of the factors causing sickness behaviour (228), which, when considered from a proximate prospective, could be considered a maladaptive response. The latter is supported by showing that quinolinic acid, produced by cells in the central nervous system, is highly neurotoxic and associated with the development of numerous neurodegenerative conditions, including Parkinson's and Alzheimer's diseases (200).

An evolutionary explanation for the underlying mechanism considers that upregulation of IDO and TDO during acute inflammation protects the host significantly by depleting tryptophan and efficiently suppressing the growth of pathogens and malignant cells (112). Serotonin further inhibits activation of the sympathetic nervous system (229), while SNS is needed for energy production and its allocation to the brain and the immune system during inflammation. Inhibition of serotonin production during inflammation will therefore favour SNS activity and energy production/allocation to the immune system.

Serotonin is present in high concentrations at the sites of inflammation and is used by activated immune cells as co-stimulator through reuptake via the serotonin transporter protein (291). This is beneficial, considering the need to mount an optimal immune response during inflammation, but could be deleterious in the long run and cause several disorders including autoimmune diseases (291). IDO will not only deplete tryptophan but also serotonin and both pathways will inhibit the immune system activity when it is no longer needed, thereby recovering tissue homeostasis and facilitating tissue repair. A feeling of sickness and even pain are common consequences of this highly effective neuroimmunological reaction but that is the price to be paid (230).

The total picture of inflammation-caused sickness behaviour should be considered beneficial to the host. Only when inflammation is supramaximal, such as in sepsis, or when inflammation lasts too long, sickness behaviour has more of a negative impact because of the possible damage caused by immune system dependent pathways. These deleterious effects to the brain show that, if necessary, the immune system will take over and override the interests of the selfish brain, supporting the 'selfish immune system' hypothesis.

6.6. Behaviour and immune system co-evolution: dopamine-dependent reactivation of the immune system

The use of dopamine as an immunological co-stimulator has been studied extensively and is of high clinical importance (232). Dopamine recruitment by the immune system has profound effects on inflammatory behaviour. Humans have engaged in exploring new environments and this demands several traits, including curiosity (17), a large brain and immune protection.

Dopamine is considered to be the main neurotransmitter responsible for curiosity (234), novelty seeking (235), motivation and aggressiveness (236). A polymorphism of the

dopamine receptor D4 (DRD4) is associated with novelty seeking, risk-taking and increased exploratory behaviour (237). Novel environments produce new immunological challenges, including climate, food availability and pathogens (238). The long allele of the DRD4 receptor is related to the migratory distance from Africa. Matthews and Butler (237) suggested that this allele been positively selected, as opposed to genetic drift.

Other behavioural traits, in addition to the association of 7R DRD4 polymorphism with environmental exploration and novelty seeking, are increased anger and a decreased feeling of disgust (239). Disgust is amongst the most intensively investigated emotions belonging to the behavioural immune system (233). Immune defence is usually a reaction following tissue damage or some pathogenic infection. It is highly costly and intense and long-term activity could result in secondary lesions and even multiple organ failure. Humans have explored new environments with constant new immunological challenges throughout evolution. The development of a pro-reactive behavioural immune system, preventing contact with possible pathogens could have been beneficial to save energy and guide them to important other physiological functions, including those of the brain and skeletal muscles (240, 19). Disgust as a proactive strategy to avoid disease, produces aversion to a wide range of factors. High levels of disgust, i.e. increased activity of the behavioural immune system, produce neophobia (241), rejection of other individuals, decrease in mating behaviour (242), food neophobia (243), prejudicial attitudes to old people (244) and even discrimination (245).

The behavioural immune system (BIS) can be very sensitive and dominate free will. However, individuals, carrying the longer allele of the DRD4 gene exhibit a higher level of novelty seeking, less disgust and more spontaneous activity (236). This implies that people with increased exploratory behaviour through DRD4 polymorphism would be at a higher risk of pathogenic infection, because of less aversion and disgust. This combination argues against the current opinion about pathogens dominating selective pressure in human evolution (246). The only feasible explanation would be that the longer allele of the DRD4 gene should have some immune function, protecting the 'seeking' carrier against pathogens.

The evidence for an immune function of the long allele of the DRD4 comes from different investigations studying the influence of the expression of dopamine receptors on innate immune cells and lymphocytes of the adaptive immune system. The various immune cells express different dopamine receptors (DRD1-DRD5) (151). The net function of dopamine receptor activation is an increase in the pro- inflammatory activity of the immune system, with the exception of the wild type DRD4 (the short allele') (247). Activation of the wild type DRD4 receptor leads to the production of the immune-suppressing cytokine IL10 (232, 239). The long 7R allele, on the contrary, is associated with diminished cAMP production and reduced intracellular response (248). Reduced response will lead to lower immune quiescence (the normal function of wild type DRD4 (232, 249) and increase the pro- inflammatory effects of dopamine by activating other dopamine receptors (151). It is therefore conceivable that migration out of Africa selected the longer allele of the D4 dopamine receptor by inducing novelty seeking, while increasing protective inflammatory activity. Dopamine can stimulate the production of NFkB and pro- inflammatory cytokines such as TNF□ □and IL1, although the opposite, production of anti-inflammatory IL10, is also possible (151). This probably depends on the individual's genotype, implying that not every individual will be capable of using the dopamine mechanism as reactivation strategy.

It seems clear that dopamine (DA) plays an important role in the immune system. Dopamine is not only produced in neurons, but also in several immune cells, including T lymphocytes (232). Dopamine seems to be recruited by the immune system to protect the host against acute infiltration by pathogens. The protective effect of dopamine signalling in the immune system against new infections is evidenced by the fact that dopamine activates resting T cells, but inhibits activated T cells (151) even in the absence of other danger signals (247). This is in line with the effects of other neurotransmitters on the immune system, increasing protection against new invaders (evolutionary beneficial) but having a negative effect on the immunological memory (250). The immunological 'use' of the whole body to fight infection makes sense in an evolutionary framework, considering that humans have had to fight infections as the main cause of death for thousands of generations and, as stated before, almost all humans died because of infection before the start of the 20th century.

7. Summary and conclusion

It can be concluded that the activated immune system puts the whole body at its disposal, by reversing the functions of metabolic hormones, organs, and even the nervous system to the energetic and pro-inflammatory benefit of the immune system (Figure 3). This response is highly protective during acute inflammation/infection and even at the start of a chronic process. The longer the inflammatory response lasts, the more it contributes to (severe) loss of lean body mass (251, 252), organ dysfunction (4), brain damage and neurodegenerative diseases (69). The protective pro-inflammatory activity of the selfish immune system is no longer beneficial once severe secondary damage to organs has been caused by the immune system.

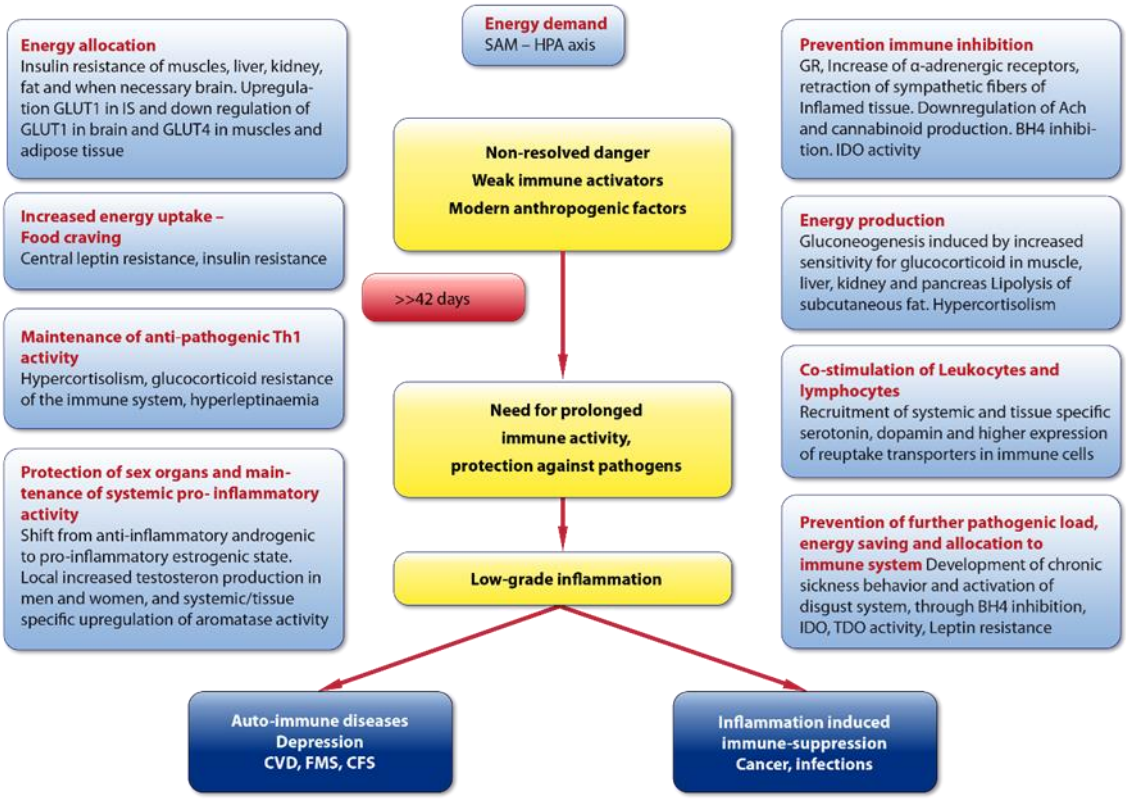

Figure 3. The total picture of the body at the disposal of the selfish immune system. If the immune system succeeds in doing so, the host is protected against inflammation-induced immune suppression, which would lead to cancer and possibly lethal infections (bottom right), but at the expense of the development of modern low-grade inflammatory diseases (bottom left). GLUT 1, glucose transporter 1: GLUT 4, glucose transporter 4; IS, immune system; SAM, sympathetic adrenal medular system; HPA, hypothalamus-pituitary-adrenal axis; GR, glucocorticoid receptor; BH4, tetrahydrobiopterin; IDO, indoleamine 2,3-deoxigenase: TDO, tryptophan 2,3-deoxigenase; CVD, cardiovascular diseases; FMS, fibromyalgia syndrome; CFS, chronic fatigue syndrome.

Life would not have been possible without an immune system, and the development of complex organisms needed an even more complex immune system. The human immune system belongs to the most complex among all living organisms and serves as the blueprint for the development of antivirus software in computer programming (254). Newer systems and organs normally dominate older systems as the most basic phylogenetical law in evolution. However, this sequence may change in the face of severe or long-term danger, known as evo-devo1 mechanisms (253, 255). Evo-devo1 can reach so far back in time that inflamed lung and kidney tissue literally resembles a swim bladder (255). Chronic disease is characterised by chronic inflammation (and vice versa) and gradual loss of functions and even anatomy. It affects the whole body, including the brain. The evidence brought together in this review shows that the immune system captures a major part of energy and resources during acute inflammation, putting the whole body at its disposal. This state relates to disposal of muscles (muscle wasting), the cardiovascular system (high blood pressure, atherosclerosis), the gut (digestive problems and food intolerance) and even the brain (loss of memory and concentration in, for instance, individuals suffering from FMS). Long-term pro- inflammatory activation of the immune system would not be possible without putting the whole body at the disposal of the immune system. Because of the immune system's capability of recruiting metabolic hormones and neurotransmitters and using them for its own benefit, it is the most selfish organ in human beings. The body at the disposal of the immune system protects the host during acute inflammation by mounting an optimal response and during chronic stress to maintain pro-inflammatory activity and to protect against possible infectious pathogens. This situation is initially protective, but becomes severely deleterious when the secondary damage to organs and tissues overrides the benefit of infectious protection. The environment in which current human beings live constantly challenges the body with multiple new metabolic signalling factors. The only organ capable of communicating with all organs involved in the energetic conflict because of these multiple metabolic signalling is the immune system. To prevent further conflict, the immune system takes over, using its robust power to put the whole body at its disposal and showing its selfish behaviour. This selfish behaviour of the immune system has saved hominins for millions of years. A slow- changing environment to which the immune system could gradually adapt, characterised these years. This selfish behaviour of the immune system has to be considered to be the main cause of the majority, if not all, modern diseases. The reason lies in the interaction between the evolutionary background of immune function, genetic development and notably, the current environment as the primary cause. Genes and functions are old; the environment is brand new and this conflict underlies

modern disease. It should, however, be noted that the immune system is only doing what it is made for: trying to protect us.

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