

Energy Metabolism and Allocation in Selfish Immune System and Brain: A Beneficial Role of Insulin Resistance in Aging

Ali Almajwal¹, Iftikhar Alam^{1,2*}, Falak Zeb³, Sadia Fatima⁴

¹Clinical Nutrition, Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

²Department of Human Nutrition and Dietetics, Bacha Khan University Charsadda, Charsadda, Pakistan

³Department of Nutrition and Food Hygiene, School of Public Health, Nanjing Medical University, Nanjing, China

⁴Department of Biochemistry, Institute of Basic Medical Sciences, Khyber Medical University, Peshawar, Pakistan

Email: *aalmajwal123@yahoo.com, falak106@gmail.com

How to cite this paper: Almajwal, A., Alam, I., Zeb, F. and Fatima, S. (2019) Energy Metabolism and Allocation in Selfish Immune System and Brain: A Beneficial Role of Insulin Resistance in Aging. *Food and Nutrition Sciences*, 10, 64-80.

<https://doi.org/10.4236/fns.2019.101006>

Received: November 29, 2018

Accepted: January 12, 2019

Published: January 15, 2019

Copyright © 2019 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

There is relatively limited knowledge concerning our understanding of how our immune system and brain take most of the available energy in a selfish manner to compensate for their own needs on priority in high energy demanding situations. The main objective of this review is to understand the energy allocation to immune system and brain in infections and/or fight or flight situations. The immune system and brain behave in a selfish manner as they allocate themselves majority of the total available energy. Insulin resistance (IR) is used as a tool for energy allocation by these systems. The immune system is activated as a response to stress and infection. Similarly, the brain gets activated as a response to any external environmental impulse, anxiety, and/or mental factor. These situations need to be dealt in a way to minimize their adverse health effects. The immune system and the brain in such situations need enormous energy for activation which is derived from the energy quota otherwise allocated to other organs. This maximum flux of energy towards these systems is achieved by making rest of the organs less responsive to insulin, a condition known as IR. As immune system and brain do not depend upon insulin for uptake of glucose, these systems are benefited from IR. IR is indicated as a beneficial role ensuring maximum energy allocation to these systems for improving health and well-being.

Keywords

Selfish Immune System, Selfish Brain, Energy Balance, Insulin Resistance

1. Introduction

Energy metabolism (EM) is the main driver of life [1] [2] [3]. One of the primary aims of human energy metabolism research is to explore the ways and mechanisms whereby the “energy balance (EB)” is ensured. EB is the relationship between “energy in” (food calories taken into the body through food and drink) and “energy out” (calories being used in the body for our daily energy requirements), which is closely related to a number of disorders, for example, obesity [4] [5] diabetes (Type II) [6] [7], hypertension [8], cardiovascular diseases (CVD) [9] [10], renal failure [11], and a wide array of immunological disorders [12]. Over the past more than hundred years, this area has been particularly investigated using both animal models as well as human subjects [13] [14]. Some other important research areas that have a close link with energy metabolism that have been extensively investigated are to (a) explore specific metabolic rates of major organs and tissues across the human life-span [15] (b) investigate energy allocation to various organs and tissues of the body [16] [17], and finally (c) investigate the factors that affect this complex network of energy metabolism [18]. In this connection, aging [19] and IR [20] have been under particular focus of research as these two traits interlinked to each other affecting various metabolic pathways of EM.

2. Aging and Insulin Resistance Relationship in Immune System and Brain

Aging is the climax of natural phenomena as far as the extent of extraordinary physical and physiological changes are concerned. Age associated IR has been investigated and studied extensively. Some of the findings suggest that IR is found in many physiological and disease states. A few examples are diabetes mellitus [21] [22], obesity [23], sepsis [24], different types of arthritis (including rheumatoid arthritis) [25], systemic lupus erythematosus [26], ankylosing spondylitis [27], trauma [28], painful states such as postoperative pain [29], migraine [30], schizophrenia [31], major depression, and mental stress [32] [33]. Thus, IR seems to be not restricted to diabetes but is a common feature in great variety of disorders. When considering these diseases, one observes two major clusters of clinical entities that are linked to insulin resistance: 1) inflammation with an activated immune/repair system, and 2) increased mental activation.

At this point, it is important to understand the question how the overall background and pathophysiology of IR is related to disease clusters. Some theories have been presented in an effort to explain the phenomenon. These include the glucose-fatty acid cycle theory [34], thrifty genotype hypothesis [35], starvation-related insulin resistance, thrifty phenotype hypothesis [36], fight infections theory of insulin resistance, central nervous resistance model, breakdown of robustness theory [6], cellular pathogen- and nutrient-sensing pathway theory (metaflammation) [37] [38], and good calories-bad calories theory [6]. However, none of these fully explain the two clusters [6].

While IR is most often regarded as a pathological state to be treated, these numbers and fact that IR is linked to so many disease states are indicative of a beneficial role of IR. It is utmost important to find an explanation why IR is an “all-time” phenomenon and a common attribute to many disease conditions that are non-diabetic in nature. Other questions of interest might be: whether IR is always a sign of abnormality? In what ways some organs (particularly those that do not depend upon insulin for glucose intake) benefit from IR? What happens if IR is acute or chronic? And finally, how does the human organism control its energy supply, particularly in the context of “aging”? The answers to these questions are the key to treating many diseases: obesity and the so-called metabolic syndrome with diabetes mellitus, hyperlipoproteinemia, hypertension and cardiovascular diseases belonging to these disorders. To answer some of these questions, relatively, a recent concept; the model of energy regulation has emerged [6], which suggests that central nervous system and the immune system are the two main areas which actually benefit from IR-related hyperglycemia because they do not become insulin-resistant. In addition, the immune system receives an added benefit from insulin because it is an important growth factor for leukocytes. IR-related hyperglycemia offers approximately 900 kJ (215 kcal) per 24 hours to the two systems. In this review we will discuss these new concepts with a focus of their possible implications in the context of aging.

3. Old Concepts New Meanings—Old Wine in New Bottles

There are always some old concepts with numerous new perspectives. The notion of physiological division of labor, for example, introduced in the 1820s by the French physiologist Henri Milne-Edwards, allowed to “*compare and study living things as if they were machines created by the industry of man.*” Inspired in the work of Adam Smith, Milne-Edwards wrote that the “*body of all living beings, whether animal or plant, resembles a factory—where the organs, comparable to workers, work incessantly to produce the phenomena that constitute the life of the individual.*” In more differentiated organisms, the functional labor could be apportioned between different instruments or systems (called by him as *appareils*) [39].

In a way, the organs and systems of the body are usually considered to behave within definite boundaries of their assigned physiological functions. In a conventional way, it has been a usual practice to designate certain physiological functions to certain body systems in a strict manner and lesser is attributed to other systems towards their possible contribution for the accomplishment of that particular function. The energy metabolism and its allocation and distribution have been a topic of great interest for researchers and biologists. There were certain beliefs about the organ systems that restricted their role(s) to a particular domain, and there were little or no consideration of the possible potential role of these systems to some other non-conventional domains of human physiology. As an example, the immune system has been conceived to perform many func-

tions for the human organism; most are of a defense nature and mainly concerning the protection of the body against foreign organisms, and maintenance of homeostasis by eliminating damaged cells. Not much, if any, have been thought of about the immune system in a non-conventional way of its functioning. A previously lesser investigated aspect of immune system was the regulation of energy metabolism; an area which seems too much diverse from the body defense. The “selfish immune system” and the “selfish brain” theories, however, came up with some new perspectives and possibilities of the potential roles of immune system and the central nervous system in the overall energy regulations.

4. Selfish Immune System

4.1. Background

Selfish immune system is a theoretical concept recently articulated by Rainer Straub [6] with inspiration of “selfish brain theory”. The “selfish immune system” and the “selfish brain” concepts put immune system and brain hierarchically above the rest of the organism in allocating energy/nutrition. Different organs have different energy needs (Table 1). For example, brain is of high energy consumption [40] [41], but of low energy capacity [42] [43]. In addition, the brain also exhibits substrate specificity with the preference of lactate, ketones and glucose [44] [45]. During the “fight-or-flight” response or trauma/infection, the organism vitally depends on either the immune system and thus these organs are privileged in energy allocation.

4.2. Immune System Energy Regulation and Allocation

Immune response is energetically a highly demanding process as activated immune/repair system required huge amounts of energy (25% - 30% of the basal metabolic rate). For example, as previously reported [46] [47] [48] [49], the energy consumption in case of extensive burn wounds (up to 20,000 kJ/day or 4777 kcal/day) is approximately the same as during military jungle training (also 20,000 kJ/day) and more than during military arctic training (~18,000 kJ/day or 4302 Kcal/day). Although burn wounds represent the extreme end of the spectrum, it demonstrates the high energy consumption of the immune system (another number on energy expenditure of the immune system is 15,000 kJ/day or 3585 Kcal/day in sepsis).

Energy is a limited resource for all vertebrates; a key determinant of survival and reproduction. Since time to total consumption of stored energy is ~19 - 43 days, an acute energy-consuming change of homeostasis must be started and terminated within this time frame, as otherwise permanent damage and finally death may occur. One of the best known example of such a situation is fever, which is caused by proteins (cytokines) that are produced by activated immune cells. Fever comes at a metabolic cost: A 175-pound man would require more than 250 calories daily to maintain a fever of approximately 2° Fahrenheit. To

put that expenditure in context, the same man requires 373 calories daily for his brain and 168 calories daily for his heart [50]. Other immune activities that require energy include producing proteins and generating new immune cells in order to fight against infection [51].

5. Selfish Brain

5.1. Background

Brain also behaves in a selfish manner and allocates most of the energy for itself. Brain is also a high energy consuming organ despite its relatively small mass. According to the “Selfish Brain” theory, cerebral energy homeostasis has highest priority in human energy metabolism. The pathologist Marie Krieger was the first to provide evidence that the brain behaves in a “selfish” manner. She showed that the human brain mass is preserved during inanition, while all the organs of the body such as heart, liver, spleen, kidneys, and pancreas lose about 40% of their mass [52]. Her seminal findings have been confirmed both in humans and animals in adult and fetal life by using modern state-of-the-art techniques [53]-[58]. These observations provide clear evidence that the brain must actively demand energy from the body in order to maintain cerebral energy homeostasis.

5.2. Mechanisms for Energy Allocation and Regulation to Brain

In case of environmental stresses, the typical energy pathway resembles the sequence of events as shown in **Figure 1**. As elaborated by Peters *et al.*, [58], brain regulates energy homeostasis via “brain-pull mechanisms”, that function by demanding energy from the body. Two brain-pull mechanisms have been detected so far: first, allocative brain-pull mechanisms, which activate the stress system to favor glucose allocation to the brain, and, second, direct astrocytic brain-pull mechanisms, which enhance glucose transport through the blood-brain barrier. The “body-pull functions” demand energy from the near environment by initiating ingestive behavior to replenish body stores and blood glucose concentrations. In this connection, mechanisms driven by extracellular cerebral glucose, which is closely related to blood glucose, fulfill the function of exerting ingestive body-pull. Cerebral supply chain; The supply chain of the brain with the central nervous system as the final consumer; describes the energy fluxes from the remote environment to the near environment, through the body and finally toward the brain. The brain regulates energy homeostasis via brain-pull mechanisms of cerebral insulin suppression (CIS). With cerebral activation of the stress systems, energy particularly glucose is allocated to the brain. With activation of the sympathetic nervous system, insulin secretion from the beta cells is suppressed and the insulin-dependent glucose uptake into body periphery becomes limited. As a consequence of CIS, glucose is available via insulin-independent transport across the blood brain barrier. In this way, CIS can be interpreted as a brain-pull mechanism.

Table 1. Fuel reserves in organs of a typical 70-kg man.

Organ	Available energy in kcal (kJ)		
	Glucose or glycogen	Triacylglycerol's	Mobilizable proteins
Blood	60 (250)	45 (200)	0 (0)
Liver	400 (1700)	450 (2000)	400 (1700)
Brain	8 (30)	0 (0)	0 (0)
Muscle	1200 (5000)	450 (2000)	24,000 (100,000)
Adipose tissue	80 (330)	135,000 (560,000)	40 (170)

Source: After G. F. Cahill, Jr. Clin. Endocrinol. Metab. 5 (1976):398.

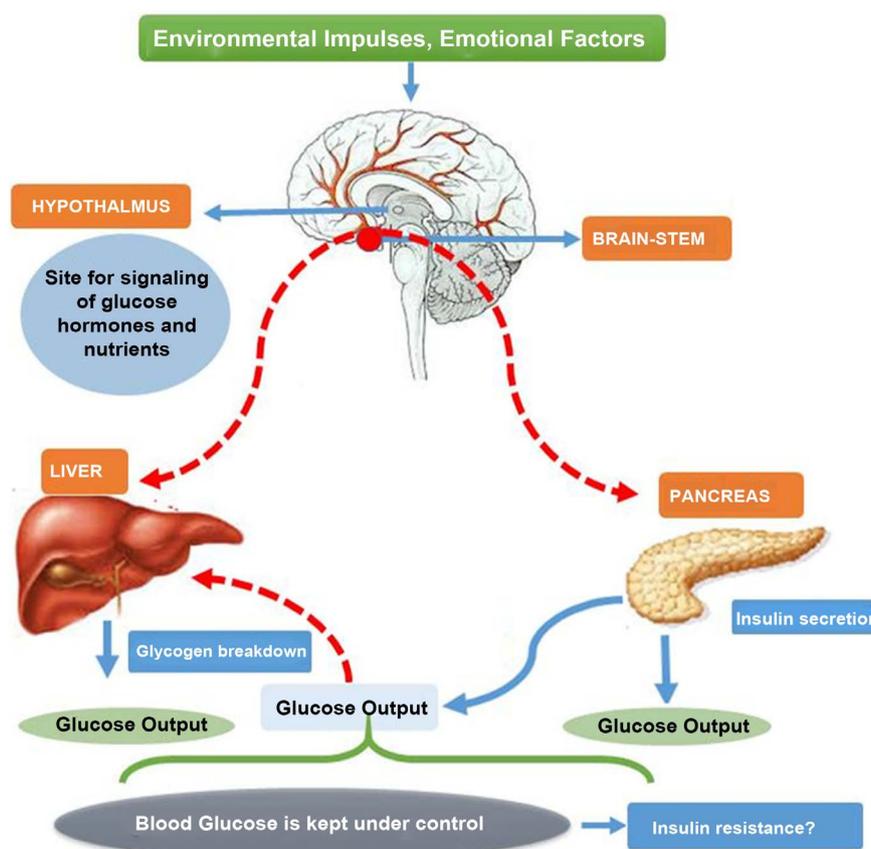


Figure 1. Pathway of glucose metabolism. Generally glucose metabolism involves these main organs. They work in a close coordination to ensure steady supply of glucose to all organs of the body. The glucose metabolism takes place in these basic steps: (A). The hypothalamus senses the signals, (B) and then it influences the brain stem, (C) where the autonomous nervous system has its origination, (D) this in turn, controls liver glucose output, glucagon and insulin release.

6. Sickness Behaviour as a Main Tool for Energy Allocation to Immune System and Brain

During infection, calories must be made available for the increased energetic demands of the immune system. How our immune system and brain make

sure the supply of required energy to them in infections/stress has been partly explained by the phenomena known as sickness behaviour [59] thus accompanying fever [60], lethargy, depression, anxiety, malaise, loss of appetite, sleepiness [61] [62] [63], hyperalgesia [64], reduction in grooming [65], and failure to concentrate [66]. Sickness behavior is a motivational state that reorganizes the organism's priorities to cope with infectious pathogens [67]. It has been suggested as relevant to understanding depression [66] and some aspects of the suffering that occurs in cancer [67]. Sick animals and humans provide such calories with a dramatic decrease in activity caused by increased fatigue and decreased interest in pleasurable pursuits such as food, socializing, and sex [68]. The responses of sleep and withdrawal that dominate sickness behavior conserve energy that is then available for use by the immune system. Sickness behavior is initiated by the host and not by the infectious agent; these changes can also be induced by experimental injection with a noninfectious substance that activates the immune system. Furthermore, this response has been conserved during evolution. Even caterpillars and crickets show decreased interest in food and courtship during infection [69].

An acute infectious disease can be self-limiting and involve an innate immune response of 2 to 3 days; the subsequent phase of the adaptive immune response can last approximately 3 to 4 weeks. Similarly, many transient inflammatory episodes include a healing phase that involves adaptive immune responses. The typical germinal center reaction of affinity maturation of B cells occurs for 3 to 4 weeks from the beginning to end [70] [71]. The accompanying proliferative T cell response undergoes a similar time course. The response of the adaptive immune system with a maximum of proliferation until days 12 to 14 and subsequent contraction until days 21 to 28 is surprisingly constant in various acute infectious diseases [72].

Acute self-limiting infectious diseases can be very energy consuming although, in the presence of disease-induced sickness behavior and related anorexia [73] [74]. Intake of energy-rich substrates can be significantly inhibited. To explain these seemingly disparate observations, it can be proposed that sickness behavior represents an element of an adaptive program that has been positively selected for transient immune and inflammatory reactions to limit energy utilization for such activities as foraging and courtship behavior [65] [75]. In such situation, the immune response can not last forever because energy stores run empty. Furthermore, sickness behavior can restrain activity and, for example, confine the affected individual to a safe place to keep away predators [65] [75]. In considering energy stores available during these responses, it is important to note that storage occurs primarily in fat tissue (12 kg of triglycerides in the body of a contemporary person, 500,000 kJ), as well as in the liver (150 g glycogen, 2,500 kJ) or muscles (300 g glycogen, 5000 kJ; 6 - 7 kg muscle protein, 50,000 kJ) [3] [76]. Under conditions of sickness behavior and anorexia without uptake of energy-rich substrates but an increased sickness-related metabolic rate, the total amount of stored energy would only last for 19 to 43 days in females and 28 to

41 days in males.

6.1. IR and Its Beneficiaries—The Immune System and Brain

The non-insulin-dependent tissues play a vital role in IR, which, as a result, increases circulating glucose (hyperglycemia) and free fatty acids (**Figure 2**). Energetic substances are not taken up in adipose tissue, liver, and muscle, and thus are now freely available to all non-insulin-dependent tissues. The two main profiteers of hyperglycemia are the central nervous system and the immune system. Both of these organs do not become insulin resistant. In contrast, the immune system profits from insulin because it is an important growth factor for leukocytes and, with the help of insulin, major glucose transporters like glucose transporter-3 and glucose transporter-4 are up regulated on all leukocyte subpopulations [77]. Insulin resistance-related hyperglycemia offers approximately 900 kJ (215 kcal) per 24 hours to the two systems. While insulin resistance is most often regarded as a pathological state to be treated, these numbers and the fact that insulin resistance is linked to so many diseases and disease states are indicative of a beneficial role of insulin resistance.

6.2. Glucose Uptake and Insulin Resistance during Aging

Immune cells, upon activation, switch their metabolism to increased aerobic glycolysis to support rapid synthesis of macromolecules; this switch is associated with increased glucose consumption by immune cells. Increased aerobic glycolysis was originally described by Otto Warburg in cancer cells and it is now recognized as being common for proliferating cells [78] for example during development [79]. According to Straub, IR, leading to lower consumption of glucose and hyperglycemia, is a physiological way for the brain or immune system to use energy/nutrition during acute stress from the rest of the organism because brain and immune cells themselves do not become insulin resistant. This is “wise-selfishness”, because this selfish behaviour of the immune system or brain is for short time and subsides gradually. Chronic insulin resistance, caused by chronic inflammation or by chronic mental activation, on the other hand, is “foolish-selfishness” as it leads to various pathologies such as diabetes, obesity, metabolic syndrome or chronic inflammatory diseases.

As another example, inflammation is lifesaving when controlled and lasting for a short duration, but deadly when not. Danger appears to put the immune system on top in hierarchy, which overrides the “selfish brain”. The longer inflammation lasts the more organs and substances are co-opted by the immune system. Chronic stress and low-grade inflammation can become immune suppressive [80], which in itself can be protective to prevent further damage. It's been found that Alzheimer's disease AD patients show a higher body temperature [81], but low brain metabolism and temperature, as you would expect when the body is inflamed, but the brain “disposed” of. On the contrary, healthy older people demonstrate lower body temperature and energy saving strategies like

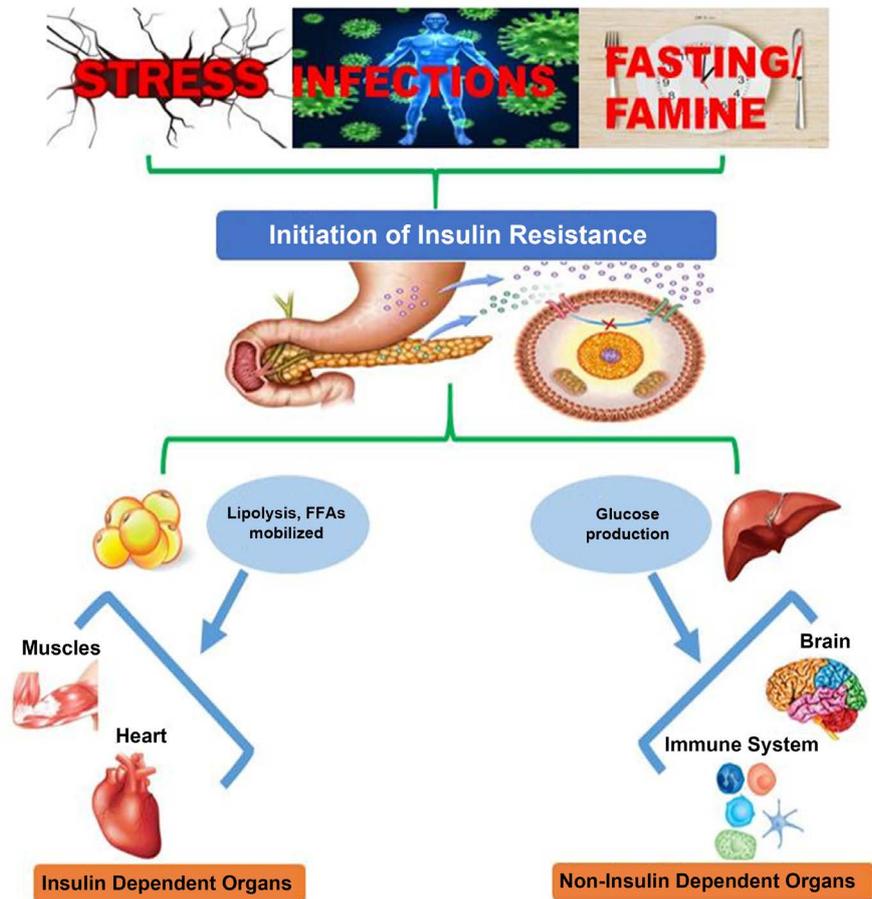


Figure 2. Insulin resistance and energy allocation. In response to the external factors (stress, infections, fasting and/or famine) insulin resistance initiated. The liver and adipose tissues react to IR. Liver starts making glucose from its glycogen stores. Adipose tissues start making free fatty acids (FFA) as a result of lipolysis. The FFAs are mobilized to skeletal muscles, cardiac muscles and all other parts that use FFA for energy generation. These organs cannot use glucose as a fuel in situations of IR. The reason is they need insulin for glucose uptake. The glucose made in the liver is mobilized to the brain and immune system. These organs can use glucose as they do not depend upon insulin for glucose uptake.

slightly lower metabolism, but normal brain function. The same strategy used in all mammals and humans during calorie restriction [82]. Whilst humans can't truly hibernate in the strict sense of the word, a number of parallels can be drawn. During the reduced physiological activity of torpor [83] animals showed Alzheimer-anatomy [84]. But unlike humans, these changes disappear 72 hours after emerging. Persistent low-grade inflammation can produce a metabolically-induced hibernation [85] through reduced activity of the thyroid gland in order to conserve energy to divert to the immune system. If it is possible, then why AD develops because of an evolutionary conserved mammalian hibernation response that causes a low brain metabolic rate in order to put the immune system at rest? In this way, the pathways leading to AD, whilst pathological, are actually protective [86].

7. Final Words and Future Outlooks

The human brain and the immune system have become so important for human physiology and evolutionary fitness that both systems have developed selfish behaviours by their capabilities to pull on energy and other resources, with the solemn purpose to maintain their own anatomies and optimal functioning [17] [40] [58] [87] [88] and for the selfish immune system [6] [85]. Upon challenge, an optimal human response therefore depends on the flexibility to (re)distribute energy, and thereby in first instance prevent energy conflicts between the brain and the immune system. The circadian rhythm, allowing the brain to dominate daytimes and the immune system to exploit night times, illustrates how evolution shaped collaboration between these two highly selfish systems, while avoiding conflict [46]. The selfish behaviour of the immune system may, from a pathophysiological point of view, explain why lower gastrointestinal system (LGI) disturbs the functioning of many other organs, including the brain. LGI puts the immune system on top of hierarchic priorities as evidenced by the observation that the system even endorses breakdown of an essential muscle like the diaphragm. Based on these arguments and scientific facts, we may conclude that “foolish selfish” would mean pursuing the narrow self-interest in ways that will work for the immune system and brain but might later bring animosity toward the whole organism, while a “wise-selfish” would mean seeing that the well-being of the immune system and the brain lie in the welfare of all the rest of organs and system of the body.

How these selfish behaviors of the immune system and brain can be exploited in old age. As we have previously reported that the aged are already having a malfunctioning in their energy metabolism and energy allocation mechanism [89], more prone to pro-inflammatory diets [90], disturbed by changes in their body composition [91] and have compromised immunity [92] [93] [94] [95]. For example, old age develops defective responses to counteract low blood sugar, leaving them more exposed to the serious consequences of disabling hypoglycaemia. Age associated changes in the brain's ability to sense glucose may cause this defect. As a clear understanding of how the brain of the elderly regulate glucose may allow us to develop new and better treatments for age-associated abnormalities in glucose metabolism resulting in diseases like diabetes. It also raises some interesting questions. Is the rise in diabetes, the consequence of a selfish immune system or a selfish brain promoting glucose levels to cover their own high energy requirements? Is this similar to a selfish immune system or a selfish brain promoting hunger to cause obesity? Indeed, the parallel epidemics of obesity and diabetes may have a common origin in hypothalamic dysfunction. In rodents, high fat diet consumption leads to defective hypothalamic glucose-sensing and hypothalamic inflammation, both of which lead to insulin resistance and glucose intolerance. So is the major form of diabetes, in fact, a disease of the immune system or the brain? The future research should also focus on the allocation of other nutritional resources. Whether the selfish immune

system and brain have any role in the same way as they have in the energy allocation?

Acknowledgements

We acknowledge Prof. Dr. Graham Pawelec, University of Tuebingen Germany, for his English editing, constructive comments and revisions of the manuscript.

Conflicts of Interest

The authors have no conflict of interest regarding this paper.

References

- [1] Arlettaz, R., Christe, P. and Schaub, M. (2017) Food Availability as a Major Driver in the Evolution of Life-History Strategies of Sibling Species. *Ecology and Evolution*, **7**, 4163-4172. <https://doi.org/10.1002/ece3.2909>
- [2] Careau, V., Thomas, D., Humphries, M.M. and Réale, D. (2008) Energy Metabolism and Animal Personality. *Oikos*, **117**, 641-653. <https://doi.org/10.1111/j.0030-1299.2008.16513.x>
- [3] Blaxter, K. (1989) Energy Metabolism in Animals and Man. Cambridge University Press CUP Archive, Cambridge.
- [4] Romieu, I., Dossus, L., Barquera, S., Blottière, H.M., Franks, P.W., Gunter, M., Hwalla, N., Hursting, S.D., Leitzmann, M., Margetts, B. and Nishida, C. (2017) Energy Balance and Obesity: What Are the Main Drivers? *Cancer Cause Control*, **28**, 247-258. <https://doi.org/10.1007/s10552-017-0869-z>
- [5] Hill, J.O., Wyatt, H.R. and Peters, J.C. (2012) Energy Balance and Obesity. *Circulation*, **126**, 126-132. <https://doi.org/10.1161/CIRCULATIONAHA.111.087213>
- [6] Straub, R.H. (2014) Insulin Resistance, Selfish Brain, and Selfish Immune System: An Evolutionarily Positively Selected Program Used in Chronic Inflammatory Diseases. *Arthritis Research & Therapy*, **16**, S4. <https://doi.org/10.1186/ar4688>
- [7] Spiegelman, B.M. and Flier, J.S. (2001) Obesity and the Regulation of Energy Balance. *Cell*, **104**, 531-543. [https://doi.org/10.1016/S0092-8674\(01\)00240-9](https://doi.org/10.1016/S0092-8674(01)00240-9)
- [8] Chaput, J.P. (2014) Sleep Patterns, Diet Quality and Energy Balance. *Physiology & Behavior*, **134**, 86-91. <https://doi.org/10.1016/j.physbeh.2013.09.006>
- [9] Triggiani, A.I., Valenzano, A., Ciliberti, M.A., Moscatelli, F., Villani, S., Monda, M., Messina, G., Federici, A., Babiloni, C. and Cibelli G. (2017) Heart Rate Variability Is Reduced in Underweight and Overweight Healthy Adult Women. *Clinical Physiology and Functional Imaging*, **37**, 162-167. <https://doi.org/10.1111/cpf.12281>
- [10] Lichtenstein, A.H., Appel, L.J., Brands, M., Carnethon, M., Daniels, S., Franch, H.A., Franklin, B., Kris-Etherton, P., Harris, W.S., Howard, B. and Karanja, N. (2006) Summary of American Heart Association diet and Lifestyle Recommendations Revision. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **26**, 2186-2191. <https://doi.org/10.1161/01.ATV.0000238352.25222.5e>
- [11] Dvir, D., Cohen, J. and Singer, P. (2006) Computerized Energy Balance and Complications in Critically Ill Patients: An Observational Study. *Clinical Nutrition*, **25**, 37-44. <https://doi.org/10.1016/j.clnu.2005.10.010>
- [12] Yamagata, A.S., Mansur, R.B., Rizzo, L.B., Rosenstock, T., McIntyre, R.S. and Brietzke, E. (2017) Selfish Brain and Selfish Immune System Interplay: A Theoretical Framework for Metabolic Comorbidities of Mood Disorders. *Neuroscience &*

- Biobehavioral Reviews*, **72**, 43-49. <https://doi.org/10.1016/j.neubiorev.2016.11.010>
- [13] Birkett, S. and de Lange, K. (2001) Limitations of Conventional Models and a Conceptual Framework for a Nutrient Flow Representation of Energy Utilization by Animals. *British Journal of Nutrition*, **86**, 647-659. <https://doi.org/10.1079/BJN2001441>
- [14] Dauncey, M.J. (1991) Whole-Body Calorimetry in Man and Animals. *Thermo-chimica Acta*, **193**, 1-40. [https://doi.org/10.1016/0040-6031\(91\)80171-E](https://doi.org/10.1016/0040-6031(91)80171-E)
- [15] Wang, Z., Ying, Z., Bosy-Westphal, A., Zhang, J., Schautz, B., Later, W., Heymsfield, S.B. and Müller, M.J. (2010) Specific Metabolic Rates of Major Organs and Tissues across Adulthood: Evaluation by Mechanistic Model of Resting Energy Expenditure. *The American Journal of Clinical Nutrition*, **92**, 1369-1377. <https://doi.org/10.3945/ajcn.2010.29885>
- [16] Navarrete, A., van Schaik, C.P. and Isler, K. (2011) Energetics and the Evolution of Human Brain Size. *Nature*, **480**, 91-93. <https://doi.org/10.1038/nature10629>
- [17] Peters, A., Schweiger, U., Pellerin, L., Hubold, C., Oltmanns, K.M., Conrad, M., Schultes, B., Born, J. and Fehm, H.L. (2004) The Selfish Brain: Competition for Energy Resources. *Neuroscience & Biobehavioral Reviews*, **28**, 143-180. <https://doi.org/10.1016/j.neubiorev.2004.03.002>
- [18] Pan, Y., Mansfield, K.D., Bertozzi, C.C., Rudenko, V., Chan, D.A., Giaccia, A.J. and Simon, M.C. (2007) Multiple Factors Affecting Cellular Redox Status and Energy Metabolism Modulate Hypoxia-Inducible Factor Prolyl Hydroxylase Activity *in Vivo* and *in Vitro*. *Molecular and Cellular Biology*, **27**, 912-925. <https://doi.org/10.1128/MCB.01223-06>
- [19] Camandola, S. and Mattson, M.P. (2017) Brain Metabolism in Health, Aging, and Neurodegeneration. *The EMBO Journal*, **36**, 1474-1492. <https://doi.org/10.15252/emj.201695810>
- [20] Murray, A.J., Lygate, C.A., Cole, M.A., Carr, C.A., Radda, G.K., Neubauer, S. and Clarke, K. (2006) Insulin Resistance, Abnormal Energy Metabolism and Increased Ischemic Damage in the Chronically Infarcted Rat Heart. *Cardiovascular Research*, **71**, 149-157. <https://doi.org/10.1016/j.cardiores.2006.02.031>
- [21] Kingwell, K. (2017) Diabetes: Turning down Galectin 3 to Combat Insulin Resistance. *Nature Reviews Drug Discovery*, **16**, 18. <https://doi.org/10.1038/nrd.2016.276>
- [22] Saltiel, A. and Olefsky, J.M. (2017) Inflammatory Mechanisms Linking Obesity and Metabolic Disease. *Journal of Clinical Investigation*, **127**, 1-4. <https://doi.org/10.1172/JCI92035>
- [23] Furukawa, S., Fujita, T., Shimabukuro, M., Iwaki, M., Yamada, Y., Nakajima, Y., Nakayama, O., Makishima, M., Matsuda, M. and Shimomura, I. (2017) Increased Oxidative Stress in Obesity and Its Impact on Metabolic Syndrome. *Journal of Clinical Investigation*, **114**, 1752-1761. <https://doi.org/10.1172/JCI21625>
- [24] Suhaimi, F.M., Chase, J.G., Pretty, C.G., Shaw, G.M., Razak, N.N. and Jamaludin, U.K. (2017) Insulin Sensitivity and Sepsis Score: A Correlation between Model-Based Metric and Sepsis Scoring System in Critically Ill Patients. *Biomedical Signal Processing and Control*, **32**, 112-123. <https://doi.org/10.1016/j.bspc.2016.08.005>
- [25] Rosa, I.A.D.L., Rodriguez-Cuenca, S., Jimenez-Gomez, Y., Ruiz-Limon, P., Perez-Sanchez, C., Abalos, M.C., Collantes, E., Vidal-Puig, A., Escudero-Contreras, A., Lopez-Pedraza, C. and Barbarroja, N. (2017) AB0092 Effect of Methotrexate, Leflunomide and Hydroxychloroquine on the Insulin Resistance and Obesity Associated with Rheumatoid Arthritis: Obese Mouse Models of Rheumatoid Arthritis.

Annals of the Rheumatic Diseases, **76**, 1078.

- [26] Sánchez-Pérez, H., Tejera-Segura, B., de Vera-González, A., González-Delgado, A., Olmos, J.M., Hernández, J.L., Corrales, A., López-Mejías, R., González-Gay, M.A. and Ferraz-Amaro, I. (2017) Insulin Resistance in Systemic Lupus Erythematosus Patients: Contributing Factors and Relationship with Subclinical Atherosclerosis. *Clinical and Experimental Rheumatology*, **35**, 885-892.
- [27] Cefle, A., Karadag, D.T., Bilen, M., Sener, S.Y., Isik, O.O. and Yazici, A. (2016) AB0668 Effects of Infliximab Treatment in Terms of Metabolic Parameters and Insulin Resistance in Ankylosing Spondylitis Patients. *Annals of the Rheumatic Diseases*, **75**, 1133. <https://doi.org/10.1136/annrheumdis-2016-eular.5493>
- [28] Blessing, E.M., Reus, V., Mellon, S.H., Wolkowitz, O.M., Flory, J.D., Bierer, L., Lindqvist, D., Dhabhar, F., Li, M., Qian, M. and Abu-Amara, D. (2017) Biological Predictors of Insulin Resistance Associated with Posttraumatic Stress Disorder in Young Military Veterans. *Psychoneuroendocrinology*, **82**, 91-97. <https://doi.org/10.1016/j.psyneuen.2017.04.016>
- [29] Greisen, J., Juhl, C.B., Grøfte, T., Vilstrup, H., Jensen, T.S. and Schmitz, O. (2001) Acute Pain Induces Insulin Resistance in Humans. *Anesthesiology*, **95**, 578-584. <https://doi.org/10.1097/0000542-200109000-00007>
- [30] Martins-Oliveira, M.R.D., Akerman, S., Holland, P.R., Hoffmann, J.R., Tavares, I. and Goadsby, P.J. (2017) Neuroendocrine Signaling Modulates Specific Neural Networks Relevant to Migraine. *Neurobiology of Disease*, **101**, 16-26. <https://doi.org/10.1016/j.nbd.2017.01.005>
- [31] Steiner, J., Berger, M., Guest, P.C., Dobrowolny, H., Westphal, S., Schiltz, K. and Sarnyai Z. (2017) Assessment of Insulin Resistance Among Drug-Naive Patients With First-Episode Schizophrenia in the Context of Hormonal Stress Axis Activation. *JAMA psychiatry*, **74**, 968-970. <https://doi.org/10.1001/jamapsychiatry.2017.1983>
- [32] Greenhalgh, A.M., Gonzalez-Blanco, L., Garcia-Rizo, C., Fernandez-Egea, E., Miller, B., Arroyo, M.B. and Kirkpatrick, B. (2017) Meta-Analysis of Glucose Tolerance, Insulin, and Insulin Resistance in Antipsychotic-Naive Patients with Non Affective Psychosis. *Schizophrenia Research*, **179**, 57-63. <https://doi.org/10.1016/j.schres.2016.09.026>
- [33] Suzanne, M. (2017) Insulin Resistance and Neurodegeneration: Progress towards the Development of New Therapeutics for Alzheimer's Disease. *Drugs*, **1**, 1-9.
- [34] Brøns, C. and Grønnet, L.G. (2017) Mechanisms in Endocrinology: Skeletal Muscle Lipotoxicity in Insulin Resistance and Type 2 Diabetes: A Causal Mechanism or an Innocent Bystander? *European Journal of Endocrinology*, **176**, 67-78. <https://doi.org/10.1530/EJE-16-0488>
- [35] Forouhi, N.G. and Wareham, N.J. (2014) Epidemiology of Diabetes. *Medicine*, **42**, 698-702. <https://doi.org/10.1016/j.mpmed.2014.09.007>
- [36] Genné-Bacon, E.A. (2014) Thinking Evolutionarily about Obesity. *The Yale Journal of Biology and Medicine*, **87**, 99.
- [37] Hotamisligil, G.S. (2017) Inflammation, Metaflammation and Immunometabolic Disorders. *Nature*, **542**, 177-185. <https://doi.org/10.1038/nature21363>
- [38] Aiello, A., Accardi, G., Candore, G., Gambino, C.M., Mirisola, M., Taormina, G., Varrasso, C. and Caruso, C. (2017) Nutrient Sensing Pathways as Therapeutic Targets for Healthy Ageing. *Expert Opinion on Therapeutic Targets*, **21**, 371-380.
- [39] Brain, M. (2015) *The Pulse of Modernism: Physiological Aesthetics in Fin-de-Siècle Europe*. University of Washington Press, Seattle, 384.

- [40] Peters, A., Pellerin, L., Dallman, M.F., Oltmanns, K.M., Schweiger, U., Born, J. and Fehm, H.L. (2007) Causes of Obesity: Looking beyond the Hypothalamus. *Progress in Neurobiology*, **81**, 61-88. <https://doi.org/10.1016/j.pneurobio.2006.12.004>
- [41] Shulman, R.G., Rothman, D.L., Behar, K.L. and Hyder, F. (2004) Energetic Basis of Brain Activity: Implications for Neuroimaging. *Trends in Neurosciences*, **27**, 489-495. <https://doi.org/10.1016/j.tins.2004.06.005>
- [42] Brown, A.M. and Ransom, B.R. (2007) Astrocyte Glycogen and Brain Energy Metabolism. *Glia*, **55**, 1263-1271. <https://doi.org/10.1002/glia.20557>
- [43] Bélanger, M., Allaman, I. and Magistretti, P.J. (2011) Brain Energy Metabolism: Focus on Astrocyte-Neuron Metabolic Cooperation. *Cell Metabolism*, **14**, 724-738. <https://doi.org/10.1016/j.cmet.2011.08.016>
- [44] Erecinska, M., Cherian, S. and Silver, I.A. (2004) Energy Metabolism in Ammalian Brain during Development. *Progress in Neurobiology*, **73**, 397-445. <https://doi.org/10.1016/j.pneurobio.2004.06.003>
- [45] Ebert, D., Haller, R.G. and Walton, M.E. (2003) Energy Contribution of Octanoate to Intact Rat Brain Metabolism Measured by ¹³C Nuclear Magnetic Resonance Spectroscopy. *Journal of Neuroscience*, **23**, 5928-5935. <https://doi.org/10.1523/JNEUROSCI.23-13-05928.2003>
- [46] Straub, R.H. (2012) Evolutionary Medicine and Chronic Inflammatory State-Known and New Concepts in Pathophysiology. *Journal of Molecular Medicine*, **90**, 523-534. <https://doi.org/10.1007/s00109-012-0861-8>
- [47] Forbes-Ewan, C.H., Morrissey, B.L. and Gregg, G.C. (1989) Use of Doubly Labeled Water Technique in Soldiers Training for Jungle Warfare. *Journal of Applied Physiology*, **67**, 14-18. <https://doi.org/10.1152/jappl.1989.67.1.14>
- [48] Jones, P.J., Jacobs, I. and Morris, A. (1993) Adequacy of Food Rations in Soldiers during an Arctic Exercise Measured by Doubly Labeled Water. *Journal of Applied Physiology*, **75**, 1790-1797. <https://doi.org/10.1152/jappl.1993.75.4.1790>
- [49] Straub, R.H. and Schradin, C. (2016) Chronic Inflammatory Systemic Diseases: An Evolutionary Trade-Off between Acutely Beneficial but Chronically Harmful Programs. *Evolution, Medicine, and Public Health*, **201**, 37-51. <https://doi.org/10.1093/emph/eow001>
- [50] Elia, M. (1992) Organ and Tissue Contribution to Metabolic Rate. In: Kinney, J.M. and Tucker, H.N., Eds., *Energy Metabolism: Tissue Determinants and Cellular Corollaries*, Raven Press, New York, 61-79.
- [51] Buttgereit, F., Burmester, G.R. and Brand, M.D. (2000) Bioenergetics of Immune Functions: Fundamental and Therapeutic Aspects. *Immunology Today*, **21**, 192-199. [https://doi.org/10.1016/S0167-5699\(00\)01593-0](https://doi.org/10.1016/S0167-5699(00)01593-0)
- [52] Hitze, B., Hubold, C., Van Dyken, R., Schlichting, K., Lehnert, H., Entringer, S. and Peters, A. (2010) How the Selfish Brain Organizes Its Supply and Demand. *Frontiers in Neuroenergetics*, **2**, 7. <https://doi.org/10.3389/fnene.2010.00007>
- [53] Goodman, M.N., Lowell, B., Belur, E. and Ruderman, N.B. (1984) Sites of Protein Conservation and Loss during Starvation: Influence of Adiposity. *American Journal of Physiology*, **246**, E383-E390. <https://doi.org/10.1152/ajpendo.1984.246.5.E383>
- [54] Gong, Q.Y., Roberts, N., Garden, A.S. and Whitehouse, G.H. (1998) Fetal and Fetal Brain Volume Estimation in the Third Trimester of Human Pregnancy Using Gradient Echo MR Imaging. *Magnetic Resonance Imaging*, **16**, 235-240. [https://doi.org/10.1016/S0730-725X\(97\)00281-6](https://doi.org/10.1016/S0730-725X(97)00281-6)
- [55] Miller, S.L., Green, L.R., Peebles, D.M., Hanson, M.A. and Blanco, C.E. (2002) Effects of Chronic Hypoxia and Protein Malnutrition on Growth in the Developing

- Chick. *American Journal of Obstetrics and Gynecology*, **186**, 261-267.
<https://doi.org/10.1067/mob.2002.119629>
- [56] Kind, K.L., Roberts, C.T., Sohlstrom, A.I., Katsman, A., Clifton, P.M., Robinson, J.S. and Owens, J.A. (2005) Chronic Maternal Feed Restriction Impairs Growth But Increases Adiposity of the Fetal Guinea Pig. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **288**, R119-R126.
<https://doi.org/10.1152/ajpregu.00360.2004>
- [57] Muhlau, M., Gaser, C., Ilg, R., Conrad, B., Leibl, C., Cebulla, M.H., Backmund, H., Gerlinghoff, M., Lommer, P., Schnebel, A., Wohlschlagler, A.M., Zimmer, C. and Nunnemann, S. (2007) Gray Matter Decrease of the Anterior Cingulate Cortex in Anorexia Nervosa. *American Journal of Psychiatry*, **164**, 1850-1857.
<https://doi.org/10.1176/appi.ajp.2007.06111861>
- [58] Peters, A., Kubera, B., Hubold, C. and Langemann, D. (2011) The Selfish Brain: Stress and Eating Behavior. *Frontiers in Neuroscience*, **5**, 74.
<https://doi.org/10.3389/fnins.2011.00074>
- [59] Hart, B.L. (1988) Biological Basis of the Behavior of Sick Animals. *Neuroscience & Biobehavioral Reviews*, **12**, 123-137. [https://doi.org/10.1016/S0149-7634\(88\)80004-6](https://doi.org/10.1016/S0149-7634(88)80004-6)
- [60] Exton, M.S. (1997) Infection-Induced Anorexia: Active Host Defence Strategy. *Appetite*, **29**, 369-383. <https://doi.org/10.1006/appe.1997.0116>
- [61] Kent, S., Bluthé, R.M., Dantzer, R., Hardwick, A.J., Kelley, K.W., Rothwell, N.J. and Vannice, J.L. (1992) Different Receptor Mechanisms Mediate the Pyrogenic and Behavioral Effects of Interleukin 1. *Proceedings of the National Academy of Sciences*, **89**, 9117-9120. <https://doi.org/10.1073/pnas.89.19.9117>
- [62] Medzhitov, R., Schneider, D.S. and Soares, M.P. (2012) Disease Tolerance as a Defense Strategy. *Science*, **335**, 936-941. <https://doi.org/10.1126/science.1214935>
- [63] Mullington, J., Korth, C., Hermann, D.M., Orth, A., Galanos, C., Holsboer, F. and Pollmächer, T. (2000) Dose-Dependent Effects of Endotoxin on Human Sleep. *American Journal of Physiology-Regulatory Integrative and Comparative Physiology*, **278**, R947-R955. <https://doi.org/10.1152/ajpregu.2000.278.4.R947>
- [64] Maier, S.F., Wiertelak, E.P., Martin, D. and Watkins, L.R. (1993) Interleukin-1 Mediates the Behavioral Hyperalgesia Produced by Lithium Chloride and Endotoxin. *Brain Research*, **623**, 321-324. [https://doi.org/10.1016/0006-8993\(93\)91446-Y](https://doi.org/10.1016/0006-8993(93)91446-Y)
- [65] Dantzer, R. and Kelley, K.W. (2007) Twenty Years of Research on Cytokine-Induced Sickness Behavior. *Brain, Behavior, and Immunity*, **21**, 153-160.
<https://doi.org/10.1016/j.bbi.2006.09.006>
- [66] Dantzer, R. (2001) Cytokine-Induced Sickness Behavior: Where Do We Stand? *Brain, Behavior, and Immunity*, **15**, 7-24. <https://doi.org/10.1006/brbi.2000.0613>
- [67] Johnson, R.W. (2002) The Concept of Sickness Behavior: A Brief Chronological Account of Four Key Discoveries. *Veterinary Immunology and Immunopathology*, **87**, 443-450. [https://doi.org/10.1016/S0165-2427\(02\)00069-7](https://doi.org/10.1016/S0165-2427(02)00069-7)
- [68] Larson, S.J. and Dunn, A.J. (2001) Behavioral Effects of Cytokines. *Brain, Behavior, and Immunity*, **15**, 371-387. <https://doi.org/10.1006/brbi.2001.0643>
- [69] Adamo, S.A. (2006) Comparative Psychoneuroimmunology: Evidence from the Insects. *Behavioral and Cognitive Neuroscience Reviews*, **5**, 128-140.
<https://doi.org/10.1177/1534582306289580>
- [70] Meyer-Hermann, M.E. and Maini, P.K. (2005) Cutting Edge: Back to "One-Way" Germinal Centers. *The Journal of Immunology*, **174**, 2489-2493.
<https://doi.org/10.4049/jimmunol.174.5.2489>

- [71] Meyer-Hermann, M. (2002) A Mathematical Model for the Germinal Center Morphology and Affinity Maturation. *Journal of Theoretical Biology*, **216**, 273-300. <https://doi.org/10.1006/jtbi.2002.2550>
- [72] Murphy, K.M., Travers, P. and Walport, M. (2011) Janeway's Immunobiology. Taylor & Francis, Oxford.
- [73] Straub, R.H., Cutolo, M., Buttgereit, F. and Pongratz, G. (2010) Energy Regulation and Neuroendocrine-Immune Control in Chronic Inflammatory Diseases. *Journal of Internal Medicine*, **267**, 543-560. <https://doi.org/10.1111/j.1365-2796.2010.02218.x>
- [74] Konsman, J.P., Parnet, P. and Dantzer, R. (2002) Cytokine-Induced Sickness Behaviour: Mechanisms and Implications. *Trends in Neurosciences*, **25**, 154-159. [https://doi.org/10.1016/S0166-2236\(00\)02088-9](https://doi.org/10.1016/S0166-2236(00)02088-9)
- [75] Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W. and Kelley, K.W. (2008) From Inflammation to Sickness and Depression: When the Immune System Subjugates the Brain. *Nature Reviews Neuroscience*, **9**, 46-56. <https://doi.org/10.1038/nrn2297>
- [76] Rolfe, D.F. and Brown, G.C. (1997) Cellular Energy Utilization and Molecular Origin of Standard Metabolic Rate in Mammals. *Physiological Reviews*, **77**, 731-758. <https://doi.org/10.1152/physrev.1997.77.3.731>
- [77] Calder, P.C., Dimitriadis, G. and Newsholme, P. (2007) Glucose Metabolism in Lymphoid and Inflammatory Cells and Tissues. *Current Opinion in Clinical Nutrition & Metabolic Care*, **10**, 531-540. <https://doi.org/10.1097/MCO.0b013e3281e72ad4>
- [78] Vander, H.M.G., Cantley, L.C. and Thompson, C.B. (2009) Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. *Science*, **324**, 1029-1033. <https://doi.org/10.1126/science.1160809>
- [79] Tennessen, J.M., Baker, K.D., Lam, G., Evans, J. and Thummel, C.S. (2011) The Drosophila Estrogen-Related Receptor Directs a Metabolic Switch That Supports Developmental Growth. *Cell Metabolism*, **13**, 139-148. <https://doi.org/10.1016/j.cmet.2011.01.005>
- [80] Dhabhar, F.S. (2009) Enhancing versus Suppressive Effects of Stress on Immune Function: Implications for Immunoprotection and Immunopathology. *Neuroimmunomodulation*, **16**, 300-317. <https://doi.org/10.1159/000216188>
- [81] Klegeris, A., Schulzer, M., Harper, D.G. and McGeer, P.L. (2007) Increase in Core Body Temperature of Alzheimer's Disease Patients as a Possible Indicator of Chronic Neuroinflammation: A Meta-Analysis. *Gerontology*, **53**, 7-11. <https://doi.org/10.1159/000095386>
- [82] Soare, A., Cangemi, R., Omodei, D., Holloszy, J.O. and Fontana, L. (2011) Long-Term Calorie Restriction, But Not Endurance Exercise, Lowers Core Body Temperature in Humans. *Aging-US*, **3**, 374. <https://doi.org/10.18632/aging.100280>
- [83] Geiser, F. (2004) Metabolic Rate and Body Temperature Reduction during Hibernation and Daily Torpor. *Annual Review of Physiology*, **66**, 239-274. <https://doi.org/10.1146/annurev.physiol.66.032102.115105>
- [84] Stieler, J.T., Bullmann, T., Kohl, F., Tøien, Ø., Brückner, M.K., Härtig, W., Barnes, B.M. and Arendt, T. (2011) The Physiological Link between Metabolic Rate Depression and Tau Phosphorylation in Mammalian Hibernation. *PLoS ONE*, **6**, e14530. <https://doi.org/10.1371/journal.pone.0014530>
- [85] Pruijboom, L. (2011) Physical Inactivity Is a Disease Synonymous for a Non-Permissive Brain Disorder. *Medical Hypotheses*, **77**, 708-713.

- <https://doi.org/10.1016/j.mehy.2011.07.022>
- [86] Reser, J.E. (2009) Alzheimer's Disease and Natural Cognitive Aging May Represent Adaptive Metabolism Reduction Programs. *Behavioral and Brain Functions*, **5**, 13. <https://doi.org/10.1186/1744-9081-5-13>
- [87] Kubera, B., Hubold, C., Zug, S. and Wischnath, H. (2012) The Brain's Supply and Demand in Obesity. *Frontiers in Neuroengineering*, **4**, 4.
- [88] Peters, A. (2009) Build-Ups in the Supply Chain of the Brain: On the Neuroenergetic Cause of Obesity and Type 2 Diabetes. *Frontiers in Neuroengineering*, **1**, 2.
- [89] Alam, I., Alam, I., Paracha, P.I. and Pawelec, G. (2012) Higher Estimates of Daily Dietary Net Endogenous Acid Production (NEAP) in the Elderly as Compared to the Young in a Healthy, Free-Living Elderly Population of Pakistan. *Clinical Interventions in Aging*, **7**, 565-573. <https://doi.org/10.2147/CIA.S37158>
- [90] Alam, I., Shivappa, N., Hebert, J.R., Pawelec, G. and Larbi, A. (2018) Relationships between the Inflammatory Potential of the Diet, Aging and Anthropometric Measurements in a Cross-Sectional Study in Pakistan. *Nutrition and Healthy Aging*, **4**, 335-343. <https://doi.org/10.3233/NHA-180042>
- [91] Alam, I., Larbi, A., Pawelec, G. and Paracha, P.I. (2011) Relationship between Anthropometric Variables and Nutrient Intake in Apparently Healthy Male Elderly Individuals: A Study from Pakistan. *Nutrition Journal*, **10**, 111. <https://doi.org/10.1186/1475-2891-10-111>
- [92] Alam, I., Larbi, A. and Pawelec, G. (2012) Nutritional Status Influences Peripheral Immune Cell Phenotypes in Healthy Men in Rural Pakistan. *Immunity & Ageing*, **9**, 16. <https://doi.org/10.1186/1742-4933-9-16>
- [93] Alam, I., Goldeck, D., Larbi, A. and Pawelec, G. (2013) Aging Affects the Proportions of T and B Cells in a Group of Elderly Men in a Developing Country—A Pilot Study from Pakistan. *Age*, **35**, 1521-1530. <https://doi.org/10.1007/s11357-012-9455-1>
- [94] Alam, I. and Pawelec, G. (2012) Aging, Nutrition and Immunity—Their Relationship and Interaction. *Nutrition and Aging*, **1**, 151-165.
- [95] Alam, I., Ng, T.P. and Larbi, A. (2012) Does Inflammation Determine Whether Obesity Is Metabolically Healthy or Unhealthy? The Aging Perspective. *Mediators of Inflammation*, **2012**, Article ID: 456456. <https://doi.org/10.1155/2012/456456>