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Energy balance and neuroendocrine-immune regulation in chronic inflammatory and neoplastic diseases - an evolutionary perspective

Jan Pieter Konsman[1] and Rainer H. Straub[2]

1. IMMUNOlogy from CONcepts and ExPeriments to Translation, CNRS UMR 5164, University of Bordeaux, 33076 Bordeaux, France
2. Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Department of Internal Medicine I, University Hospital Regensburg, Biopark I, Am Biopark 9, 93053, Regensburg, Germany.

Abstract

The central nervous and immune systems are often in competition for energy substrates. After infection or injury, energy expenditure typically increases while exploratory behavior and food intake decrease (sickness behavior). However, in the absence of food intake, animal bodies can only sustain increased expenditure for 3-7 weeks before energy substrates run out. Nevertheless, symptoms reminiscent of wasting and sickness behavior can be observed in autoimmunity, and in chronic inflammatory or brain-related disorders. The hypothesis defended here is that chronic diseases can exist because they mostly occur after reproductive age and involve responses that were selected during evolution in response to acute infection and injury. Indeed, fever and reduced food intake can increase survival in response to acute bacterial infection and are brought about by actions of pro-inflammatory cytokines on the brain resulting in autonomic, behavioral and neuroendocrine responses in a context of energy trade-offs. While these responses may be adaptive and actively brought about when an organism responds to acute infection, they seem maladaptive when lasting too long such as in chronic diseases as they contribute to a negative energy balance.

Keywords: chronic disease energy balance, evolution, inflammation

Glossary

Antagonistic pleiotropy: Principle formulated by George C. Williams in 1957 according to which the same genes can “have opposite effects on fitness” at different ages of organisms.

Energy balance: State in which energy intake and energy expenditure are compared and that can describe modifications of body weight and composition after changes in energy intake and expenditure.

Evolutionary medicine: A discipline that uses the principles of evolutionary biology. It applies this knowledge to questions of acute and chronic diseases in humans.

Selfish organs or systems: Bodily organs or systems, like the brain or the immune system, that in certain circumstances have the capacity to drain important energy flows at the potential expense of other body parts.

X.1 Introduction:

The often cited title: “Nothing makes sense in biology except in the light of evolution” was intended to emphasize the importance of “biological integration [at] levels above the molecular one” (Dobzhansky, 1964), p. 445). The light of evolution hit medicine much later, presumably because medicine was considered to be dealing only with the maladaptive pathological processes. However, when in the 1970s and 1980s evidence indicating that non-specific disease symptoms were, in certain conditions, positively linked to survival of infected animals, these symptoms started to become more considered as potentially evolutionarily selected inflammatory responses. While these responses may be adaptive and actively brought about when an organism responds to acute infection, they seem maladaptive when long-lasting as they can contribute to a negative energy balance. One of the main challenges of evolutionary medicine is therefore to explain why symptoms and pathophysiological processes that occur during chronic inflammatory and neoplastic diseases can be so prevalent. Here, the argument will be developed that these symptoms and pathophysiological processes are adaptive in response to acute infection and injury in young reproducing individuals and have been retained during evolution, even though they can be detrimental later in life during chronic conditions. Although there are many ways in which elements of neuroendocrine and immune systems interact during disease, the focus here will be on inflammation and neuroendocrine signaling involved in corticosteroid secretion and energy balance. Indeed, these interactions have been the most widely studied and can thus be compared to some extent between acute responses to infection or injury and chronic disease conditions.

X.2 Evolutionary medicine and energy regulation

X. 2.1 Evolutionary medicine fundamentals

So-called Darwinian medicine was proposed in the early 1990s with the promise to “provide[] new insights into the causes of medical disorders” by considering the signs and symptoms of infection or responses to injuries and toxins as adaptive (Williams and Nesse, 1991), p. 1). For example,

susceptibility to breast and ovarian cancer has been suggested to be related to “genotypes selected for high fertility” (Greaves, 2007), p. 219) and predisposition to chronic inflammatory disease to “immunodysregulation resulting from lack of exposure to microorganisms” in childhood (Rook, 2010), p. 70). Although the terms Darwinian medicine and evolutionary medicine have been used in parallel for some time, the latter has been adopted progressively because it “is more general and acknowledges other important aspects of the theory of evolution [other than natural selection and adaptation] such as symbiosis [and] the role of epigenetic processes” (Methot, 2011), p. 76).

“Evolutionary medicine thus consists of all areas in which evolutionary thought productively informs medical and epidemiological issues,” including physiology and metabolism (Stearns, 2012), p. 4305). In this context, the principle of antagonistic pleiotropy, according to which “genes [can] have opposite effects on fitness in the young compared to later ages” (Williams, 1957), p. 400), has been put forward to render explicit the idea that “genes being adaptive at an early age, [can be] maladaptive at older age” and lead, for example, to chronic inflammatory disorders (Straub and Schradin, 2016), p. 42). Most recently, proponents of evolutionary medicine have reached a consensus, according to which, 1) in addition to natural selection, constraints and trade-offs are among the core evolutionary processes, 2) “disease risks can be altered for organisms living in environments that differ from those in which their ancestors evolved,” and 3) disease symptoms and signs “are useful defenses, which can be pathological if dysregulated” and long-lasting (Grunspan et al., 2018), Table 2).

X.2.2 Energy balance in health and acute disease

Animal life comes with challenges such as being a potential prey and the necessity of obtaining food, which, in turn, imply risks of injury, infection, and other stressful events. It has been argued that animals weigh their “energy landscape” that includes food sources against their “fear landscape” regarding predators when they explore and move about in their environment (Gallagher et al., 2017). It is therefore not surprising that animals seem to be equipped with food and threat detection systems

(Illius et al., 2002, Douglas et al., 2005, Forbey et al., 2018, Fendt et al., 2020). In addition, animals generate and respond to their own bodily signals like hormones and cytokines after having consumed food or being injured or infected (Medzhitov, 2001, Kono and Rock, 2008, Keestra-Gounder et al., 2015, Baral et al., 2019, Donnelly et al., 2020, Olson et al., 2020).

Infections, either foodborne or injury-related, can evolve to life-threatening situations, including for humans (Lederberg, 1997, High, 2004, Smith and Lewin, 2009, Francisco et al., 2018, McNamara et al., 2018). Responses to injury or infection are energetically costly because inflammation and tissue repair increase energy expenditure and, in parallel, energy intake is often reduced due to event-associated anorexia (Hart, 1988, Goldstein and Elwyn, 1989, Archie, 2013). Indeed, "[m]ultiple bone fractures increase heat production by 15-30% … [,] sepsis [systemic inflammatory response to infection]… by 50% … [and] [e]xtensive burns … well in excess of 100%" (Blaxter, 1989), p. 218). Even though energy balance-related considerations have been part of a long tradition in endocrinology and have recently been incorporated into eco-immunology (Martin et al., 2006), this seems to have been less the case for medicine.

The fact that several of the responses to injury and infection, such as reduced activity and fever, are present in many different animals considered to represent various stages of evolution, such as lizards, mice and humans (Hart, 1988, Kluger, 1991, Walters, 1994, Sylvia and Demas, 2017, Hite et al., 2020, Lopes et al., 2021), suggests that these are evolutionarily conserved responses. In this context, it is important to keep in mind that such responses can only be transferred to offspring if they did not put at risk the survival prior to or during reproduction. Given the negative effects of the responses to injury or infection on energy balance, fever, reduced food intake and low activity can therefore be hypothesized to increase survival of young animals. Since the administration of antipyretics, force-feeding or sleep deprivation increases mortality in experimental models of bacterial infection in young adult rodents (Murray and Murray, 1979, Vaughn et al., 1980, Friese et al., 2009, Wang et al., 2016),

fever, reduced food intake and increased sleep seem indeed to enhance survival when animals capable of reproduction are subject to bacterial infection.

Among biological systems and organs, the 'threat-detecting' nervous and immune systems are capable of shunting energy flows to assure its own functions at the potential detriment of other bodily organs and systems and have therefore been coined 'selfish' (Straub, 2017). If one considers the brain as an 'information-processing' system it is not surprising that, in particular in primates and human beings, it requires a lot of energy relative to its weight and that techniques sensitive to glucose and oxygen consumption have been proposed to image brain 'information-processing' activities (Shulman et al., 2004, Herculano-Houzel, 2012, Magistretti and Allaman, 2015, Bordone et al., 2019). For example, during acute visual activity or a card sorting task, brain glucose uptake increases between 10-50%, and often more than oxygen consumption (Fox et al., 1988, Madsen et al., 1995). Interestingly, restricting caloric intake lowers plasma concentrations of glucose and creatine, a nitrogenous organic acid high-energy substrate, but increases cerebral concentrations of creatine, while reducing brain glucose uptake (Wijeyesekera et al., 2012, Guo et al., 2015). Moreover, caloric restriction has repeatedly been shown to induce only minor changes in brain mass as opposed to important reductions in body mass (Sprengell et al., 2021). These findings can be interpreted to suggest that the brain can use different energy substrates and obtain these from peripheral tissues, for example, from muscle in the case of creatine.

Although the immune system is less easy to circumscribe than the nervous system, it can be estimated to be composed of 5.8×10^{11} leukocytes, which, when activated, require a 25-30% increase of basal metabolic rate (Straub et al., 2010). While the initial inflammatory response is typically fueled by glucose and glycolysis, later phases are often characterized by the mobilization and utilization of a variety of energy-providing substrates and pathways, including proteolysis and fatty acid oxidation (Straub et al., 2010, Liu et al., 2012). Chronic caloric restriction attenuates fever and reduces circulating

interleukin-6 concentrations after systemic administration of bacterial lipopolysaccharide (MacDonald et al., 2011, MacDonald et al., 2012, MacDonald et al., 2014). However, and although a 20 h fast or chronic intermittent fasting in mice reduces the number of circulating monocytes and induces a more "quiescent" metabolism, monocyte mobilization after inoculation with *Listeria monocytogenes* or a skin injury is not altered (Jordan et al., 2019). Thus, the immune system, like the central nervous system, seems to assure different energy substrate flows and, both, are capable of maintaining functional reactivity in conditions of limited energy intake.

X.2.3 Why chronic disease?

The central nervous and immune systems can be considered to be often in competition for energy provided by the rest of the body. This competition, in the case of a response to acute infection or injury, may express as sickness behavior, characterized by decreased energy expenditure in the form of locomotor activity. However, even though reduced locomotor behavior can mitigate the negative energy balance of responding to infection or injury with fever and tissue repair, animal bodies, in the absence of food intake, can typically only sustain such responses for 3-7 weeks before energy substrates run out (Straub, 2012). Nevertheless it is well known that many disease symptoms and processes occur beyond this time frame. Indeed, chronic symptoms reminiscent of sickness behavior or chronic inflammation and tissue growth can be observed in chronic brain-related disorders, autoimmunity, and cancer. Before addressing the question of how (proximate causation in medicine) this can be brought about, it is interesting to consider why this may be the case (ultimate causation). Indeed, given the suffering, handicaps and costs associated with autoimmune and chronic inflammatory diseases, cancer and depression, one may well wonder why these conditions seem to be so frequent and have not been selected against more during evolution.

One way to start addressing the "why question" involves 1) postulating that these chronic disease symptoms and processes are related to positively selected responses to acute tissue infection, acute

injury or acute stressful events, 2) appealing to the antagonistic pleiotropy principle (Williams, 1957) to propose that "genes being adaptive at an early age, [can be] maladaptive at older age" (Straub and Schradin, 2016), p. 42), and 3) keeping in mind that many of the chronic disease symptoms and processes emerge after reproductive age and may therefore have little influence on transmission of genes to offspring. So the same kind of responses may occur both in acute and chronic conditions and be adaptive in the former and maladaptive in the latter. But often the triggering events seem to be different between acute and chronic disease. In the case of an acute infection or injury, the host may detect so-called pathogen- or danger-associated molecular patterns (PAMPs or DAMPs), while in the case of chronic infections, microorganisms often seem to have developed strategies to escape such detection. In chronic autoimmune disease, the host seems to be mounting immune responses against self-components, whereas in cancer the immune system does not seem to detect transformed-self. Indeed, in cancer, reactivity of the immune system often fails because of cancer-driven immunosuppression.

Notwithstanding the (in)capacity of the immune system to efficiently detect tumor cells, many cancers have been related to chronic infection, inflammation and tissue repair (Furman et al., 2019, Fishbein et al., 2021, Iriana et al., 2021, Okada et al., 2021). Interestingly, tumors can shunt energy streams towards cancer tissue in ways similar to those of the immune system in chronic inflammatory conditions and autoimmune diseases (Cheng et al., 2014, Goretzki et al., 2021, Schuster et al., 2021, Suchard and Savulescu, 2021, Vaupel and Multhoff, 2021). Moreover, all these conditions can lead to states of cachexia or lean tissue wasting, even though this is sometimes hidden by obesity (Tisdale, 2002, Delano and Moldawer, 2006, Straub et al., 2010, Baracos et al., 2018, Santo et al., 2018, Biswas and Acharyya, 2020, Olson et al., 2020, Berardi et al., 2021). Importantly, caloric restriction can improve anti-tumor immunity (Farazi et al., 2014, Kishton et al., 2017). Overall, this suggests that evolution may have selected the 'selfish' bodily systems of the brain and the immune system, provided that their activation does not last beyond 3-7 weeks. However longer activation of such systems may

occur due to erroneous continuous stimulation and result in systems that seem to be on an 'ego-trip' for example in chronic inflammatory disease (immunity against an autoantigen) and cancer (erroneous growth pathways and missing cell death).

In case of chronic activation of these systems, so when they are on an 'ego-trip', reducing behavioral activity is not the only way to save energy and mitigate tissue wasting. Indeed, different forms of storage and memory may allow for saving of energy and, thus, for more flexible responses of the organism and may therefore have been selected for during evolution. In particular, in a terrestrial environment where food sources may be more scattered than in a marine environment, the possibility for an organism to be able to store nutrients in some form would be an obvious advantage for survival. Interestingly, while many organisms from yeast to *C. Elegans* can synthesize triacylglycerol and form lipid droplets, and insects contain a fat body, only vertebrates have adipose tissue (Ottaviani et al., 2011). Although storage in fat tissues has been most widely studied, it is important to keep in mind that nutrient storage also occurs in the liver and skeletal muscle of mammals (Efeyan et al., 2015). These forms of storage correspond to what Walter Cannon called "storage by segregation" and that he proposed "to be subject to nervous or neuro-endocrine government" (Cannon, 1929), p. 407).

In addition, to nutrient storage, it has also been argued that "[e]volutionary pressure to optimize decision-making has led to the inevitable exploitation of past history" or memory, which "can be defined as experience-dependent modification of internal structure, in a stimulus-specific manner that alters the way the system will respond to stimuli in the future as a function of its past" (Baluska and Levin, 2016), pp. 1-2). Neural memory enables an organism to rapidly get to already encountered food sources while "immune memory … leads to shorter, more effective and, finally, less energy-consuming reactions towards microbes" (Straub and Schradin, 2016), p. 44). In this context, it is also interesting to note that dietary restriction results in an accumulation of memory T-cells in the bone marrow and enhanced protection against infections and tumors (Collins et al., 2019). Similarly, "immunological

tolerance versus harmless foreign antigens (e.g. of microbes on the skin) or harmless autoantigens" can be considered "a memory function that spares energy reserves" (Straub and Schradin, 2016), p. 44). Besides these neural and immune memories, other "environmental and/or physiological events" may "leave[] traces in a labile intracellular or extracellular medium which can be read as memories in the future by cells making decisions" (Baluska and Levin, 2016), p. 4), for example in the form of epigenetic modifications of chromatin (Ginsburg and Jablonka, 2009). The possibility that fatty acids, in addition to constituting a nutrient storage system in adipose tissues, could represent some memory system has recently been put forward as a stimulating perspective (Straub, 2020).

Taken together, the evidence discussed above suggests that chronic diseases ultimately exist because they mostly occur after reproductive age, when natural selection no longer has an effect on the genes that are transmitted to offspring, and involve responses that were selected during evolution in response to acute infection and injury. These responses are typically driven by the immune system and/or the brain that take control of the organism's physiology and behavior. While the immune system and the brain can thus be considered to act 'selfishly' when the responses are adaptive to overcome acutely dangerous events, such as infection, it seems that they are on an 'ego-trip' during chronic inflammatory diseases and/or chronic brain activation and to put the organism's energy balance and tissue integrity at stake. Even though forms of memory and reduced behavioral activity can mitigate the consequences of chronic immune or central nervous activation or cancer somewhat, survival is nevertheless often threatened in these chronic conditions.

X.3 Neuroendocrine-immune system interactions: focus on the hypothalamo-pituitary-adrenal axis and energy balance signals

X.3.1 Possible origins of neuroendocrine-immune system interactions

After considering why (ultimate causation) chronic symptoms reminiscent of sickness behavior or chronic inflammation and tissue repair can be observed in cancer, autoimmune and chronic

inflammatory diseases, it is now time to address the question of how (proximate causation) this can be brought about by interactions between the neuroendocrine and immune systems. In this context it is worth considering that neuroendocrine and immune systems may have a common cellular ancestor (see also chapter 1). This hypothesis was first put forward based on the observation that a common set of molecules involved in inflammation, phagocytosis and stress response, such as proopiomelanocortin-derived peptides and cytokines, exist in invertebrates and vertebrates and has subsequently been corroborated by protein-folding recognition algorithms (Ottaviani and Franceschi, 1997, Ottaviani et al., 2007). Another interesting and related hypothesis indicating evolutionary ancient interactions between the neuroendocrine and immune system emerged after the finding that neurons of the primitive nervous system of the freshwater polyp *Hydra* can not only alter the production of antimicrobial peptides in other cell types (Kasahara and Bosch, 2003), but can in some cases also secrete antimicrobial peptides themselves (Augustin et al., 2017, Klimovich et al., 2020).

Although evolutionarily ancient, less complex organism are useful to indicate a possible common origin or the first kind of interactions between neuroendocrine and immune cells, it is important to keep in mind that these labels may not neatly correspond to the functions of cells and tissues of these organisms. Indeed, the labels neuroendocrine and immune have emerged mainly in the context of the study of mammals, for which it makes sense to talk about neuroendocrine and immune systems. However, in mammals the wealth of potential interactions between neuroendocrine and immune system elements may be perceived as close to overwhelming making it challenging to determine where to start. Here, some of such interactions will first be considered for healthy organisms, next for animals (including humans) in response to an acute infection or injury and finally for chronic disease conditions.

Under physiological conditions, animals show rhythms of neuroendocrine and immune responses that may be linked. Indeed, ectotherm vertebrates show seasonal variations in immune system components that seem to be mediated by corticosteroid and sex hormones as a result of

neuroendocrine modulation (Zapata et al., 1992). In endotherm mammals, like rodents, circadian patterns of peripheral immune cells, mediators and responses, such as the number of peripheral leukocytes, cytokine concentrations and natural killer cell function, are regulated by the superchiasmatic nucleus of the hypothalamus indicating communication through the autonomic nervous system or neuroendocrine systems (Arjona and Sarkar, 2008);Mavroudis, 2013 #7196;Prendergast, 2013 #7197;Jacquelot, 2021 #7198}. In healthy human beings, correlations have been found between circadian variations in neuroendocrine hormones and immune cell populations indicating causal relationships or a common cause (Mazzoccoli et al., 2010a, Straub et al., 2010, Mazzoccoli et al., 2011).

X.3.2 Interactions between the hypothalamo-pituitary-adrenal axis and pro-inflammatory cytokines in acute disease models

Work in animal models of acute infection and injury has allowed to establish some causal interactions between the neuroendocrine and immune system. Several decades ago it was shown that exposure of rats to new antigens increases firing rate of hypothalamic neurons and that administration of the pro-inflammatory cytokine interleukin-1 results in activation of corticotropin-releasing hormone (CRH)-containing hypothalamic neurons, which, in turn, stimulated adrenocorticotropic hormone (ACTH) release from the pituitary (Besedovsky et al., 1977, Berkenbosch et al., 1987). These findings gave rise to a set of studies showing that prostaglandin synthesis at the interface between the nervous system and peripheral tissues and brainstem to hypothalamus catecholaminergic projection are involved in activation of hypothalamic CRH neurons after administration of interleukin-1 (Ericsson et al., 1994, Ericsson et al., 1997, Lacroix and Rivest, 1997, Ek et al., 1998, Matsuwaki et al., 2014). The resulting release of glucocorticoids from the adrenal glands (activation of the Hypothalamo-Pituitary Adrenal (HPA-)axis), in turn, mobilizes energy from liver, adipose tissue and muscle to sustain the inflammatory response, and, at higher concentrations, inhibits the synthesis and action of pro-inflammatory mediators (Straub, 2014). Although other neuroendocrine axes are also altered in

response to acute infection or injury, the most detailed knowledge of interactions between the immune and neuroendocrine systems has been obtained regarding activation of the HPA-axis in animal models of infection.

X.3.3 Interactions between neuroendocrine signaling underlying energy balance and pro-inflammatory cytokines in acute disease models

Another set of neuroendocrine pathways that are modified during host immune activation in response to detection of microbial fragments are those involved in the regulation of food intake. As outlined above, reduced food intake in response to bacterial infection can be considered an adaptive response. The pathways underlying different aspects of food intake can therefore be expected to be altered by immune mediators. Gastrointestinal tract-derived ghrelin and adipose tissue-produced leptin are respectively orexigenic and anorexigenic hormones through their actions on the nervous system, but also have anabolic and catabolic effects on metabolism, respectively (Shan and Yeo, 2011, Frago and Chowen, 2015, Klockars et al., 2019). Interestingly, bacterial lipopolysaccharide and interleukin-1 increase the synthesis of leptin and decrease that of ghrelin (Grunfeld and Feingold, 1996, Sarraf et al., 1997, Faggioni et al., 1998, Asakawa et al., 2001, Basa et al., 2003, Wang et al., 2006)). In addition, it has recently been shown that interleukin-1 can also directly act on orexigenic and anabolic hypothalamic neurons that constitute targets for ghrelin and leptin (Chaskiel et al., 2019). Thus, pro-inflammatory immune mediators interact with neuroendocrine systems regulating energy intake and expenditure, but the inverse equally occurs as part of the reactions to limit inflammatory responses (see above). Finally, and in regard of the previous section, it is important to point out that neuroendocrine and immune responses and interactions during acute infection-induced inflammation and injury-related wound healing seem to occur in a context of energy trade-offs in a wide variety of animals (French et al., 2011, Ashley and Demas, 2017, Sylvia and Demas, 2017).

X.3.4 Interactions between neuroendocrine and immune systems in chronic disease

In chronic diseases, such as arthritis and cancer, the circadian rhythms of neuroendocrine hormones, cytokines and leukocyte populations as well as their phasic or antiphasic relationship are often altered (Lissoni et al., 2007, Cutolo and Straub, 2008, Meyer-Hermann et al., 2009, Mazzoccoli et al., 2010b, Sierakowski and Cutolo, 2011). These observations, along with the energy costs of long-term activation of immune responses, raise the question of how this is brought about. However, and in contrast to acute diseases, much less is known about the etiology of chronic diseases and about the possible transitions from acute to chronic conditions.

While evidence in favor of a link between a gastrointestinal infectious episode and chronic gut-related symptoms certainly exists, it is not yet clear if and how it can cause a first flare of chronic inflammatory bowel disease (Chervy et al., 2020, Axelrad et al., 2021). Similarly, epidemiology has linked *Helicobacter Pylori* infection and autoimmune diseases such as rheumatoid arthritis, but biomedical research has yet to elucidate the mechanisms that could explain such a connection (Youssefi et al., 2021). As outlined above, many cancers have been related to chronic infection, inflammation and tissue repair/growth with some of the mediating mechanisms being progressively unraveled (Furman et al., 2019, Fishbein et al., 2021, Iriana et al., 2021, Okada et al., 2021). So beyond some similarity in terms of symptoms and pathophysiological processes, like inflammation, between the acute response to tissue infection or injury and chronic conditions, such as arthritis, cancer and inflammatory bowel disease, discussed above, there are also epidemiological associations between infection and these chronic conditions.

X.3.5 Interactions between the HPA-axis and pro-inflammatory cytokines in chronic disease and their animal models

Although bacterial sepsis has long been considered a subacute condition characterized by systemic inflammatory responses and high mortality, successful reduction of short-term mortality (< 30 days) has recently revealed long-term mortality and morbidity as emerging clinical challenges (Delano and

Ward, 2016). Interestingly, plasma cortisol concentrations during the first 24h after diagnosis correlate with both short- and long-term mortality in sepsis (De Castro et al., 2019) and septic shock-related long-term mortality is associated with less frequent administration of corticosteroids (Nesseler et al., 2013). But, circulating corticosteroid concentrations should not be taken to reflect activity of the HPA-axis in sepsis as lower than expected ACTH concentrations and loss of diurnal cortisol and ACTH rhythms are often observed (Kanczkowski et al., 2015, Peeters et al., 2017). Instead, increased cortisol concentrations may be due to direct adrenal or peripheral immune cell action of bacterial fragments and pro-inflammatory cytokines (Engstrom et al., 2008, Kanczkowski et al., 2013) and lower breakdown of corticosteroids (Peeters et al., 2017).

Contrary to sepsis, the clinical benefits of corticosteroid administration on symptoms and disease processes in arthritis has been well-established (Da Silva and Bijlsma, 2000, Spies et al., 2014). In chronic rheumatoid arthritis "cortisol secretion appears to be inadequate in relation to inflammation" with cortisol/ATCTH and cortisol/pro-inflammatory cytokine ratios being lower than expected (Spies et al., 2014), p. 2). Interestingly, the diurnal rhythm of cortisol secretion in rheumatoid arthritis patients with low to moderate disease activity does not differ from that of healthy individuals with pro-inflammatory cytokine levels peaking when cortisol is low (Straub and Cutolo, 2007). These observations thus provide a good rationale for attempts to 'time' the therapeutic effects of corticosteroids during the day-night cycle (Spies et al., 2014). But regardless of the issue of the therapeutic use of corticosteroids, it is clear both in sepsis and arthritis that the lower cortisol/ACTH ratios indicate endocrine dysfunction. However, it does not yet seem clear that the whole neuroendocrine axis would be involved. Although patient-specific psychological stress-induced activation of the HPA-axis can be hypothesized to influence rheumatoid arthritis disease and symptoms, daily stressor- and worrying-associated exacerbated disease activity and symptoms have been found to be independent of plasma cortisol concentrations (Evers et al., 2014). Similarly,

psychological stress has been proposed to predispose to tumor growth in part via HPA-axis activation (Shin et al., 2016, Colon-Echevarria et al., 2019).

While research on patients suffering from chronic conditions is certainly most relevant, animal models of such conditions are not only useful to determine potential pathophysiological mechanisms, but can also provide insight into early events that typically occur before a patient consults a physician. Thus, it has been shown in animal models that neurons of the paraventricular nucleus of the hypothalamus, many of which control HPA-axis activity, express Fos immediate-early gene cellular activation markers at onset of sepsis, arthritis-related hyperalgesia and cancer-associated anorexia but also during chronic disease phases (Harbuz and Jessop, 1999, Konsman and Blomqvist, 2005, Carlson et al., 2007, Nishimura et al., 2020). So transcriptional activation at the hypothalamic stage of the HPA-axis may occur both during the initial and chronic phases of animal models of arthritis, cancer and sepsis.

X.3.6 Interactions between neuroendocrine signaling underlying energy balance and cytokines in chronic disease

In terms of energy balance, cancer, chronic inflammatory bowel disease and rheumatoid arthritis are all conditions in which food intake does often not match energy expenditure and that can lead to wasting of lean tissue or cachexia (often in the form of cachectic obesity). In fact, reduced food intake is not adaptive when energy expenditure is chronically increased. Interestingly, rodents fully recover their food intake after a couple of days in standardized experimental models of infection (Valles et al., 2000, Crowell et al., 2017), but display a progressive loss of recovery of food consumption in cancer models (Konsman and Blomqvist, 2005, Pourtau et al., 2011). Indeed, the lack of compensatory food intake in response to weight loss seems to characterize the cancer-associated anorexia cachexia syndrome (Olson et al., 2020) and the same seems to be the case in autoimmune diseases, such as arthritis. In terms of interactions between neuroendocrine and immune systems, it is important to point out that many tumors seem to be capable of ‘high-jacking’ cytokine and leptin signaling to

promote angiogenesis and growth (Le Bitoux and Stamenkovic, 2008, Ray and Cleary, 2017, Shalapour and Karin, 2019, Angelucci et al., 2020). In this respect, the hypothalamic action of higher than expected for body weight leptin concentration and of relatively lower plasma ghrelin along with brainstem action of the macrophage inhibitory cytokine-1/growth differentiation factor 15 (MIC-1/GDF15) may explain the lack of compensatory food intake in response to weight loss in slowly-growing tumors (Pourtau et al., 2011, Borner et al., 2017). However, muscle protein degradation does not seem to be fully related to overall nutrient intake in cancer cachexia (Kawamura et al., 1982, Del Fabbro, 2019, Yang et al., 2020) indicating that food intake is not the sole factor determining the outcome of chronically-activated bodily systems that seem to be on an 'ego-trip'.

Similarly, both clinical and experimental arthritis are characterized by body weight and cell mass changes that cannot be solely explained by reduced or lack of compensatory food intake (Roubenoff et al., 1994, Roubenoff et al., 1997, Skurlova et al., 2010, Olson et al., 2020). However, loss of body weight in humans may often not be apparent in arthritis in spite of increased protein catabolism, because reduced activity may lead to fat gain (Roubenoff et al., 1994, Straub et al., 2010). Elevated pro-inflammatory cytokine production along with normal to slightly raised leptin circulating levels and less than expected increased plasma ghrelin concentration (Roubenoff et al., 1997, Skurlova et al., 2010) constitute neuroendocrine signals that will most likely not increase food intake as to mitigate protein catabolism. Moreover, the inflammation-driven activation of the neuroendocrine HPA axis and sympathetic nervous system will not only result in gluconeogenesis in the liver and lipolysis in adipose tissue, but also in muscle protein breakdown, and provide further energy substrates for sustained inflammation (Straub et al., 2010). The activation of these neuroendocrine systems can thus be considered to underlie an energy appeal reaction providing "fuels for the inflammatory processes" (Straub et al., 2010), p. 6) that serves the immune system, which seems to be on an 'ego-trip', but at the expense of a progressive loss of function, for example when it comes to energy balance and muscle function. Therefore, it seems reasonable to postulate that sustained or repeated activation of the

immune system in interaction with the neuroendocrine system plays an important role in the symptoms and disease processes of chronic inflammatory diseases (Straub, 2014, Straub, 2017).

X.4 Conclusion

In this chapter, energy balance was considered for acute and chronic diseases in the context of evolutionary medicine and neuroendocrine-immune regulations. Fever and reduced food intake seem to increase survival of bacterially- infected animals and are brought about by direct and indirect actions of pro-inflammatory cytokines on the brain. This in turn, also gives rise to activation of the HPA-axis allowing for the mobilization of energy reserves and ultimately for mitigating inflammatory responses. While these responses may be adaptive and actively brought about when an organism responds to acute infection, they seem maladaptive when lasting too long as they contribute to a negative energy balance and cachexia. One of the main challenges is therefore to explain why symptoms and pathophysiological processes, which occur during chronic inflammatory and neoplastic diseases and put the organism's energy balance at stake, can be so prevalent. The argument was developed that these symptoms and pathophysiological processes are adaptive in response to acute infection and injury in young reproducing individuals, and may therefore have been retained during evolution, but can be detrimental later in life during chronic conditions. In terms of potential immune-neuroendocrine interactions it seems that components of the HPA-axis and energy balance-related signals are less or differently activated in arthritis and cancer as compared to acute infectious disease models. For example, the HPA-axis may be readily activated by acute inflammatory signals, but much less so when these same signals occur chronically.

X.5 Key references

Grunspan et al., *Evol Med Public Health,* 2018. This review provides an insightful overview of the core principles of evolutionary medicine.
Olson et al., *J Cachexia Sarcopenia Muscle,* 2020. This review discusses metabolic and behavioral responses during starvation, protein malnutrition, and cachexia.
Straub, *Nat Rev Rheumatol,* 2017. This review lays out how the central nervous and immune systems can induce energy shortage during chronic inflammation and ageing.

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