Energy regulation and neuroendocrine–immune control in chronic inflammatory diseases

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Abstract. Straub RH, Cutolo M, Buttgereit F, Pongratz G (University Hospital Regensburg, Regensburg, Germany; University of Genova, Genova, Italy; and Charité University Medicine Berlin, Berlin, Germany). Energy regulation and neuroendocrine–immune control in chronic inflammatory diseases (Review). *J Intern Med* 2010; doi: 10.1111/j.1365-2796.2010.02218.x

Energy regulation (EnR) is most important for homoeostatic regulation of physiological processes. Neuroendocrine pathways are involved in EnR. We can separate factors that provide energy-rich fuels to stores [parasympathetic nervous system (PSNS), insulin, insulin-like growth factor-1, oestrogens, androgens and osteocalcin] and those that provide energy-rich substrates to consumers [sympathetic nervous system (SNS), hypothalamic–pituitary–adrenal axis, thyroid hormones, glucagon and growth hormone]. In chronic inflammatory diseases (CIDs), balanced energy-rich fuel allocation to stores and consumers, normally aligned with circadian rhythms, is largely disturbed due to the vast fuel consumption of an activated immune system (up to 2000 kJ day^{-1}). Proinflammatory cytokines such as tumour necrosis factor or interleukins 1β and 6, circulating activated immune cells and sensory nerve fibres signal immune activation to the rest of the body. This signal is an appeal for energy-rich fuels as regulators are switched on to supply energy-rich fuels ('energy appeal reaction'). During evolution, adequate EnR evolved to cope with nonlife-threatening diseases, not with CIDs (huge negative selection pressure and reduced reproduction). Thus, EnR is inadequate in CIDs leading to many abnormalities, including sickness behaviour, anorexia, hypovitaminosis D, cachexia, cachectic obesity, insulin resistance, hyperinsulinaemia, dyslipidaemia, fat deposits near inflamed tissue, hypoandrogenaemia, mild hypercortisolaemia, activation of the SNS (hypertension), CID-related anaemia and osteopenia. Many of these conditions can contribute to the metabolic syndrome. These signs and symptoms become comprehensible in the context of an exaggerated call for energy-rich fuels by the immune system. We propose that the presented pathophysiological framework may lead to new therapeutical approaches and to a better understanding of CID sequence.

Keywords: bioenergetics, chronic inflammatory diseases, disease sequelae.

Introduction

The interplay between the nervous, endocrine and immune systems is recognized to be involved in the pathophysiology of chronic inflammatory diseases (CIDs) [1–6]. In addition, a recent review has highlighted the importance of adipose tissue as a store of energy-rich fuels [7]. Although, we recognize the roles of the neuroendocrine immune system and of adipose tissue in CIDs, to our knowledge these two areas have not been evaluated together with respect to energy regulation (EnR) in CIDs.

During evolution, all forms of life have become directly or indirectly dependent on energy-rich fuel availability and utilization. Organisms evolved under conditions that favoured the development of complex mechanisms for obtaining food and for regulating energy-rich fuel storage and allocation. From this point of view, it is clear that EnR takes the highest position in the hierarchy of homoeostatic control. We have recently positioned the neuroendocrine system as the most important for homoeostatic regulation in CIDs [8], but without considering the more important role of EnR. Without considering EnR, the negative and positive feedback loops between the hypothalamus and the immune system are incomplete. Similarly, the understanding of other connections between organs involved in EnR,

including the brain, gut, liver, pancreas, adrenal glands, muscle and bone, is incomplete. Considering together EnR and neuroendocrine immune interplay in the context of CIDs leads to a new understanding of many clinical symptoms and laboratory abnormalities presently described as independent phenomena.

The behaviour of the stimulated immune system with its large fuel consumption is crucial for EnR in CIDs. Because activation of the immune system is energetically very costly (25% of the basal metabolic rate, Fig. 1), EnR is very important for a stimulated immune system. When considering the multiple pathways of EnR initiated at the level of the central nervous system (CNS), the close connection between the brain, the immune system and organs related to energy metabolism becomes interpretable.

Evolutionary considerations

As we have recently discussed, homoeostatic regulatory mechanisms of the neuroendocrine and immune systems evolved to cope with nonlife-threatening inflammatory episodes but not with serve symptomatic CIDs [8, 9]. Mechanisms recruited during the symptomatic phase of CIDs are borrowed from normal healthy or nonlife-threatening inflammatory episodes [8, 9]. These include immune response to infection, control of inner and outer body surfaces, reactions to foreign bodies, wound healing, immunosurveillance in tissue, implantation of stem cells into
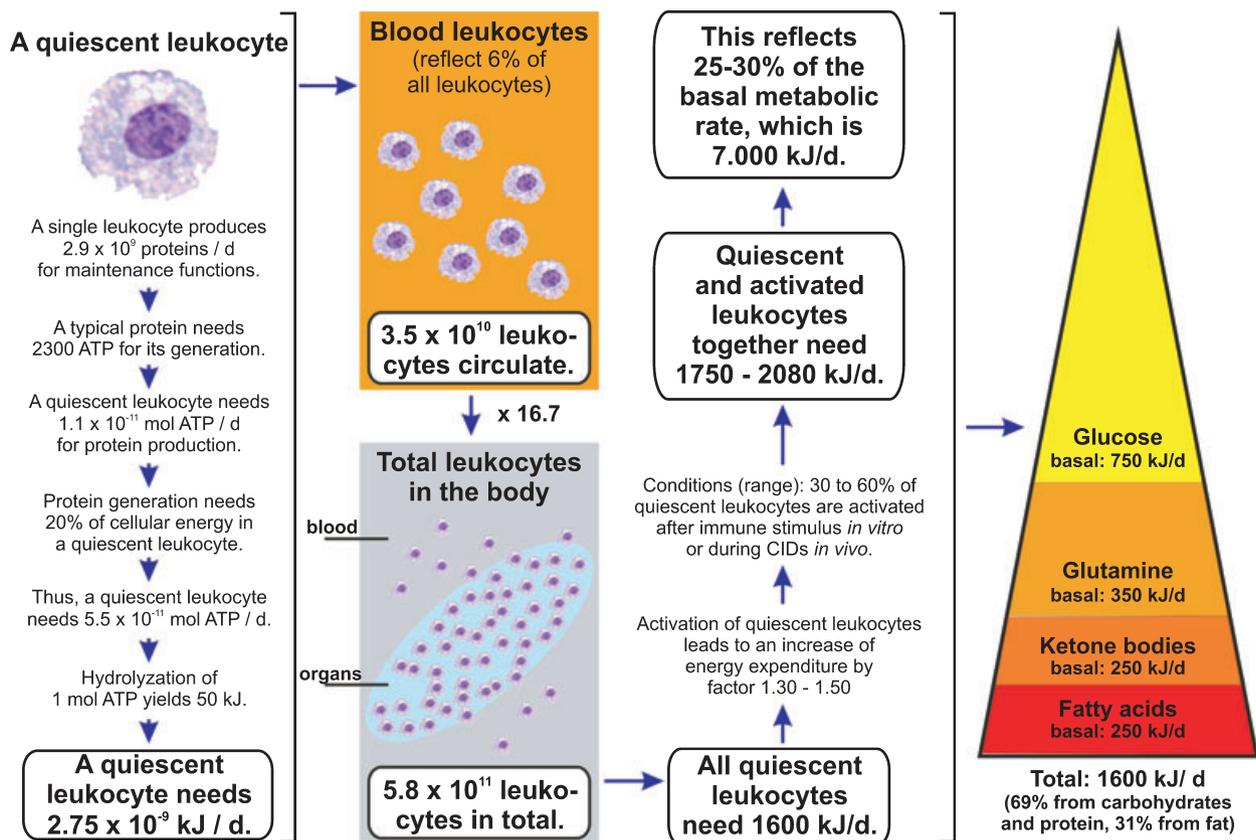

Fig. 1 *An estimate of daily energy expenditure by leucocytes. In the original studies [13–17], leucocytes were activated with concanavalin A, or leucocytes were taken from patients with rheumatic or infectious diseases. The information for all calculations is derived from [13–17]. For comparison, metabolic rate is typically 10 000 kJ day^{-1} in a normal subject, and 30 000 kJ day^{-1} during heavy work (e.g., a cyclist of the Tour de France). The store of energy-rich fuels is mainly provided by adipose tissue and amounts to approximately 500 000 kJ. The right side of the figure shows energy utilization by immune cells. Immune cells use glucose, glutamine, ketone bodies and fatty acids in different amounts. Glucose and glutamine are the main energy-rich sources.*

injured tissue, implantation of blastocysts into the uterine epithelium and immune phenomena facilitating semi-allogenic pregnancy.

Similarly, pathways of EnR, to which the neuroendocrine immune system is closely linked, have evolved to cope optimally with normal life and brief inflammatory episodes, rather than with CIDs. Usually, these inflammatory episodes last for a short period of time, as prolonged episodes would have resulted in a negative selection pressure. After a prolonged period of time, most inflammatory problems are resolved because the situation becomes energetically too costly and therefore incompatible with life (Fig. 1) [8, 9]. When activation of the immune system becomes long-lived due to the immune attack of auto-antigens or harmless foreign antigens (e.g., bacteria on the body surface – see Crohn's patients), the typical EnR is no longer appropriate [8, 9]. Therefore, incorrect programmes of EnR will lead to abnormalities in CIDs, as demonstrated in this review.

Estimation of energy demands in healthy individuals

Usually we need 7000 kJ day^{-1} to cover basal metabolic activities [10]. With a moderate work load, about 10 000 kJ day^{-1} are needed (approximately the standard metabolic rate), but a cyclist during the *Tour de France* would require 30 000 kJ day^{-1} (which can be maintained only for a short period of time) [10]. The majority of an individual's caloric intake is lost as heat and only 10–15% is used for muscular work [11, 12]. After consumption and absorption of food, energy-rich fuels are stored in the liver or skeletal muscle (as glycogen or protein) and in adipose tissue (as triglycerides) [10]. Under modern healthy conditions, fuel stores in adipose tissue contain approximately 13 kg fat (equivalent to 500 000 kJ, which would theoretically last for 2.4 months without eating). The small glycogen store in the liver (about 150 g) provides 2500 kJ for the entire body for only half a day [10]. The glycogen store in skeletal muscle of 300 g (equivalent to 5000 kJ) is not available for the entire body because muscle glycogen is only used locally [10]. The main supporters of energy-rich fuel storage in liver, muscle and adipose tissue are insulin and the parasympathetic nervous system (PSNS).

During short-term activity, systemically available energy-rich fuels are supplied by the liver (breakdown of glycogen and gluconeogenesis), but when activity lasts for several hours, fat stores start to break down (triglyceride lipolysis). Provision of energy-rich fuels to the entire body in the form of glucose and fatty acids is mainly mediated by the sympathetic nervous system (SNS: adrenaline and noradrenaline via β2-adrenoceptors), the hypothalamic–pituitary–hormonal axes (cortisol and growth hormone) and the pancreas (glucagon). During starvation, energy-rich fuels are primarily supplied by protein breakdown (during the first 3 days, the exploitable protein store of 6–7 kg is equivalent to approximately 50 000 kJ) and adipose tissue (from day 3 onwards, triglyceride breakdown and fatty acid conversion to ketone bodies in the liver) [10]. Fat cannot be used for gluconeogenesis [10]. The sequential utilization of muscle protein (first few days) and then lipids is important in cachexia-related obesity in CIDs (see below).

As demonstrated in Fig. 1, an estimate of energy expenditure of leucocytes (including lymphocytes, granulocytes and macrophages) demonstrates that approximately 1600 kJ day^{-1} is needed when these cells are not activated (in the basal metabolic state, excluding cellular movement), and this can rise to 1.750–2.080 kJ day^{-1} in the activated state (information for all calculations are derived from references [13–17]). It appears from these calculations that an increase in metabolic rate of approximately 9–30% is usual. It is known that activation of leucocytes occurs with minor surgery, which increases heat production by <10% of the metabolic rate [12]. The metabolic rate is increased with multiple bone fractures by 15–30%, sepsis leads to an increase of 50% and extensive burns cause a large increase of 100% or more [12].

Leucocytes use all types of fuels, but approximately 70% is from glucose and glutamine (Fig. 1) [18, 19]. In comparison, the CNS needs about 2000 kJ day^{-1} in the form of glucose (or from ketone bodies during starvation) [10]. A recent positron emission tomography study in human subjects [20] and detailed human studies (reviewed in ref. [11]) have shown that other parts of the body need similar amounts of energy-rich fuels (muscle: 2500 kJ day^{-1} at rest and 6.400 kJ day^{-1} when activated; thoracic organs, 1600–2400 kJ day^{-1}; abdominal organs, 3000–3700 kJ day^{-1}). Because of these requirements, it is unclear how energy-rich fuels can be provided to the immune system when energy is limited.

Circadian allocation of energy-rich fuels in healthy individuals

Fuel allocation to the immune system is time dependent as demonstrated in Fig. 2. In a fasting subject, fuel provision to the body starts by activation of the hypothalamic–pituitary–adrenal (HPA) axis and the
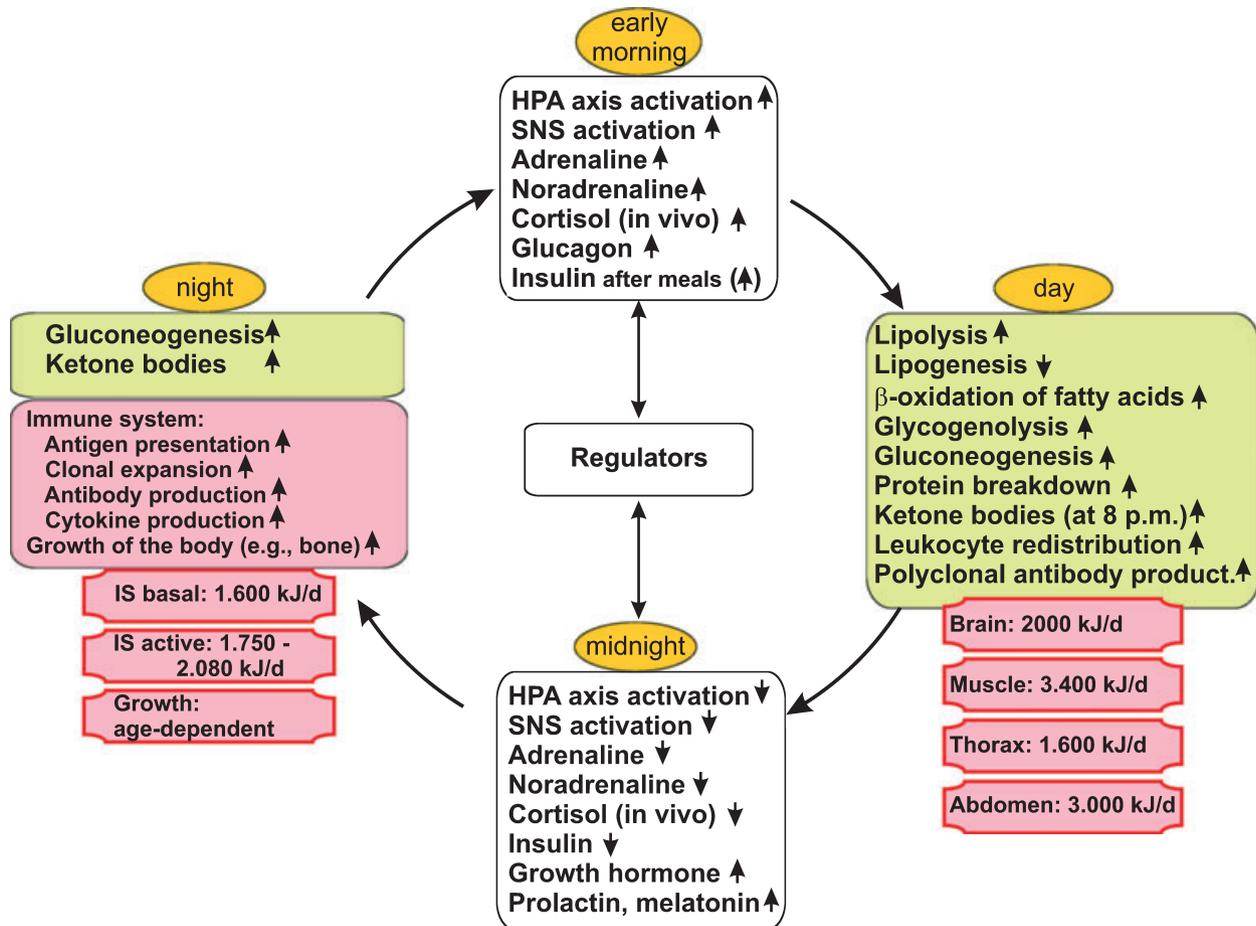
Fig. 2 *Circadian rhythm of fuel allocation in a fasting subject. In the morning, activation of the hypothalamic–pituitary–adrenal (HPA) axis, the sympathetic nervous system (SNS) and glucagon from pancreatic islets stimulate lipolysis, inhibit lipogenesis, induce β-oxidation of fatty acids, break down glycogen and induce gluconeogenesis. At the same time, leucocyte redistribution and polyclonal antibody production are supported [22, 142], but many aspects of immune function are inhibited due to the immunosuppressive effects of cortisol in combination with noradrenaline. At midnight, the activities of the HPA axis and the SNS are low, but growth hormone, prolactin and melatonin are secreted to a large extent shortly after sleep onset. This leads to activation of the immune system (IS) with clonal expansion of antigen-specific lymphocytes, antibody production and cytokine spillover into the systemic circulation. Increasing circulating cytokines are coincidental with waking up in the morning and activation of the HPA axis and the SNS. In addition, body growth occurs mainly during sleep. In the fasting state, insulin levels are usually low so that energy-rich fuels are not stored in liver, fat tissue and muscles.*

SNS in the morning (Fig. 2). Hormones of the HPA axis and the SNS including glucagon support fuel provision mainly for brain and muscle by stimulating triglyceride lipolysis, *β*-oxidation of fatty acids, glycogenolysis, gluconeogenesis and some protein breakdown. In addition, these hormones inhibit many aspects of the immune system, but not secretion of natural polyclonal antibodies (supported by the SNS) or leucocyte traffic in the blood (supported by the SNS and HPA axis; for example, intravenous injection of cortisol or noradrenaline in a clinical

emergency results in increased blood leucocyte levels) [21–24]. Leucocyte traffic in the blood is needed for immunosurveillance of the tissue, and this occurs during the daytime.

Hormone levels starting to decrease in the afternoon and reach a minimum at midnight; this prevents energy-rich fuel provision to brain and muscles. In parallel, hormonal inhibition of the immune system is largely decreased (Fig. 2). In contrast, during the night, energy-rich fuels are mainly allocated to the

immune system and – in children-growth of the body (Fig. 2). Shortly after sleep onset, growth hormone which stimulates gluconeogenesis is important hormone for glucose allocation to the immune system. As immune cells use mainly glucose, growth hormone-associated provision of glucose is important for nightly immune activation (glucose is up-regulated after sleep [25]). In addition, serum levels of ketone bodies, free fatty acids and glycerol rise from 8 p.m. until midnight by threefold to sevenfold [26], which represents another important fuel source for immune cells (Fig. 1). It is noteworthy that infections lead to 'sickness behaviour', which increases sleep time and time in bed [27, 28] and, thus, allocation of energy-rich fuels to the activated immune system [29].

In this regard, the circadian rhythms of the neuroendocrine and immune systems belong to an important programme necessary for allocation of energy-rich fuels to daytime and nighttime consumers. Because brain and muscles need much energy-rich fuel during the day, the major activities of the immune system occur during sleep. Evaluation of EnR during the period of a day is important to understand the general principles of fuel storage and supply by neuroendocrine pathways.

EnR in local inflammation and spillover inflammation

As the immune system needs much energy-rich fuel [30], local inflammation in the tissue must be supported by fuel provision from local or systemic stores. If local inflammation is confined to a small area (e.g., from a rose thorn with attached bacteria in the skin), local fuel stores and circulating glucose are preferentially used (note that the immune system does not store energy-rich fuels). We hypothesize that local stores are made available by extracellular protein breakdown by matrix metalloproteinases yielding substrates such as proline, hydroxyproline, glycine and glucuronic acids. These substrates can be used in ATP-generating pathways (Table 1). It has been shown that cells of starved animals demonstrate inhibited transcription of inflammation-related genes but strongly increased transcription of genes involved in matrix degradation [31]. In addition, local lipolysis leads to release of free fatty acids, which can be used as energy-rich substrates by immune cells (Fig. 1). An important element in local inflammation is an adequate supply of calcium and phosphorus, which can be provided by increased local bone turnover when inflammation is in the proximity of bones (see below). Proinflammatory cytokines [tumour necrosis factor (TNF), interleukin (IL)-6 and IL-1β] and parathyroid hormone (PTH)-related peptide are instrumental in increasing bone turnover [32]. Calcium is an essential element for functioning of the immune system, which can be demonstrated by considering human immunodeficiency as a consequence of calcium channel defects [33].

Strong inflammation results in a spillover of cytokines (e.g., IL-6), leading to increase in circulating activated immune cells and stimulation of sensory nerves signal inflammation to the rest of the body (Fig. 3). The point of this is not inhibition of the immune system, as is often thought (the classical view including negative feedback), but it is rather an appeal for energy-rich fuels: an 'energy appeal reaction'. This has been recently demonstrated by injection of IL-1β which resulted in rapid hypoglycaemia as a consequence of fuel allocation to the immune system [34]. Spillover inflammation activates the HPA axis (cortisol) and the SNS (adrenaline, noradrenaline), and induces sickness behaviour (cessation of muscle, brain and gut activity). It also reduces sexual activity and reproduction [down-regulation of the hypothalamic–pituitary–gonadal (HPG) axis]. All this is part of a programme to allocate energy-rich fuels to the immune system by mobilizing glucose and ketone bodies from the liver, amino acids from distant muscles, lipids from distant fat stores and calcium from distant bone (Fig. 3) [35]. We hypothesize that spillover inflammation involves the entire body to divert

Table 1 *Components of extracellular matrix and breakdown*

Extracellular matrix components	Direct product	Indirect product	Route of ATP provision
Collagen → proline, hydroxyproline	Glutamate	α-Ketoglutarate	Citric acid cycle
Collagen → glycine	Serine	Pyruvate	Citric acid cycle
[a]Glycosaminoglycans → glucuronic acid	UDP-P-glucose	Pyruvate	Glycolysis
[a]Glycosaminoglycans → N-acetylglucosamine	Fructose-6P	Pyruvate	Glycolysis

[a]Typical glycosaminoglycans are hyaluronic acid, chondroitin sulphates, dermatan sulphate, heparin, heparan sulphate and keratin sulphate. Proteoglycans such as aggrecan are large matrix molecules that contain glycosaminoglycans.
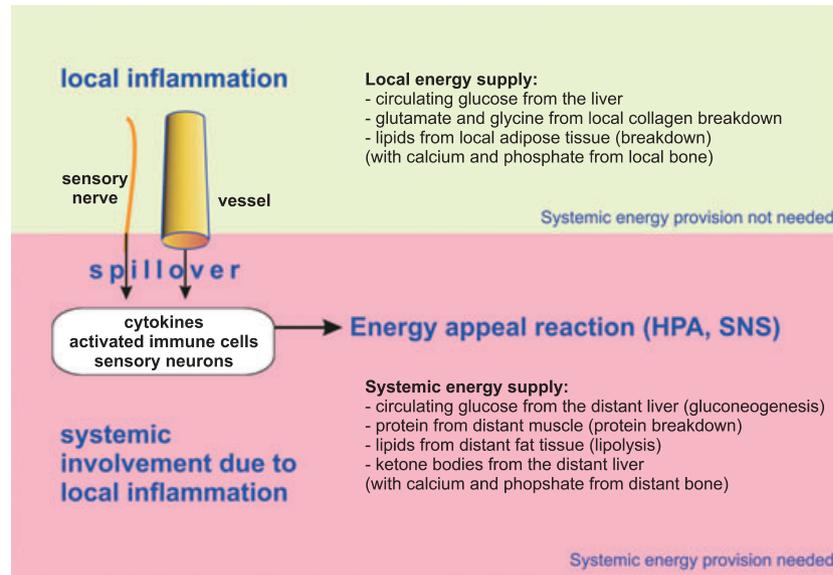
Fig. 3 *Local and spillover inflammation. Local inflammation does not switch on a programme of systemic provision of energy-rich fuels. Inflammatory cells use local supplies of energy-rich fuels. When inflammation reaches a certain threshold, spillover of cytokines/ activated immune cells and stimulation of sensory nerve fibres signal inflammation to the rest of the body leading to an 'energy appeal reaction'. Initially, the energy appeal reaction is mainly driven by the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis. These neuroendocrine systems provide fuels for the inflammatory process.*

fuels to the activated immune system. As EnR and the neuroendocrine immune interplay have not evolved to cope with long-lasting CIDs [9], the coordination of interlinked pathways will not function in CIDs as expected for short-lasting diseases. The abnormal control leads to multiple disease-related sequelae, the pathogenesis of which can be explained by alterations of EnR and, subsequently, changes in the neuroendocrine immune pathways (Fig. 4).

In the following sections, these abnormal mechanisms of EnR are explained in the context of the well-known facets of CIDs.

Anorexia

In CIDs, sickness behaviour increases the time spent at rest [27, 28] and energy-rich fuels are allocated to the immune system (and not to active abdominal organs or muscles) therefore intake of energy-rich fuels should be lower than expected. Indeed, poor nutrient status in patients with rheumatic diseases has been reported (recently reviewed in [36]). Intake of energy-rich fuels is reduced in rheumatoid arthritis (RA) [37, 38], systemic sclerosis [39], multiple sclerosis [40], juvenile chronic arthritis [41] and other CIDs. It is noteworthy that decreased fuel intake is often linked to lowered levels of vitamin D, other lipid-soluble vitamins, iron, zinc, copper, magnesium, and others. It has been reported that intake of energy-rich fuels in RA patients is inversely related to stimulated IL-1β production from peripheral blood cells [42], which demonstrates that the energy appeal reaction by spillover inflammation is the driving force of anorexia. IL-1β is an important cytokine with respect to sickness behaviour [27, 28], and chronic sickness behaviour has a deleterious effect on fuel provision leading to inflammation-related anorexia and depressive-like symptoms.

The energy appeal reaction evolved to support allocation of energy-rich fuels to the immune system during short-lasting inflammatory diseases (not longer than 3–5 weeks) because exercise in the course of food acquisition would have deviated energy-rich fuels to muscle and brain. Thus, the 3–5 week inflammation programme initiates a short period of mild starvation, which leads to degradation of body fuels. It is important to note that, initially, glycogen (first half day) and protein (from the first to third day, mainly from muscle) are used to maintain glucose homoeostasis [43]. In a full starvation programme (from day 3 onwards), liver-derived ketone bodies are usually used; these are glucose substitutes in brain, muscle and immune
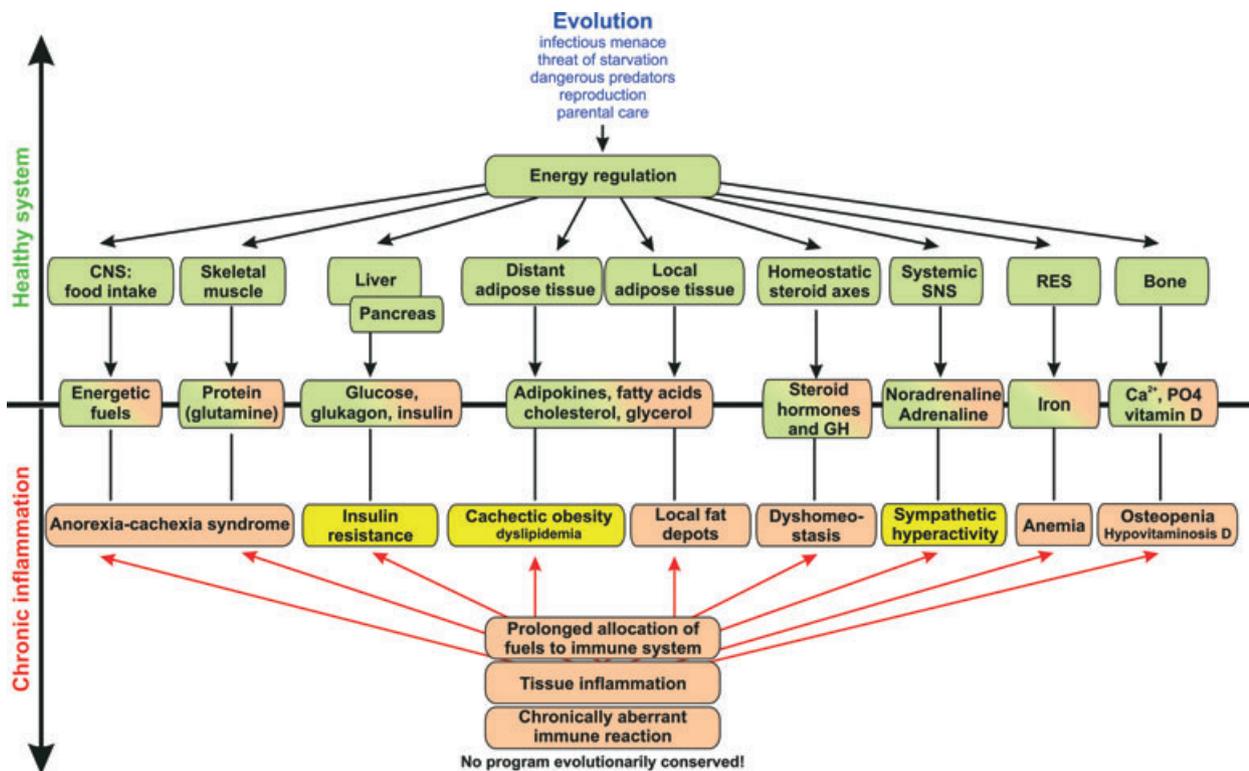
Fig. 4 *Organs involved in normal energy regulation (EnR) (green boxes) with their respective regulators (green–orange boxes) and abnormalities in chronic inflammatory diseases (orange and yellow boxes). EnR evolved to cope with nonlife-threatening, short-lasting inflammatory episodes under the influence of environmental factors (blue text). The chronically aberrant immune reaction and subsequent systemic inflammation lead to disturbed EnR (bottom orange boxes). The consequences include a multitude of abnormalities observed in chronic inflammatory diseases (orange and yellow boxes). Abnormalities in yellow boxes are part of the metabolic syndrome.*

cells leading to muscle sparing. Free fatty acids cannot be used for gluconeogenesis [10], and, therefore, proteolysis is the only way to provide glucose. In the chronic phase of inflammatory disease, this causes a negative effect on muscle proteins because the full starvation ketone programme is not used (see below).

All these programmes evolved to cope with transient inflammatory episodes, but prolonged use of in CIDs leads to pathology.

Cachexia and cachectic obesity

As early as 1949, generalized muscle wasting was described in patients with RA [44]. In the 1990s, Roubenoff *et al.* described a highly increased catabolic state in RA [45]. At this time, they linked rheumatic cachexia to glucocorticoid therapy [45]. Later, the same authors demonstrated that rheumatic cachexia was also driven by proinflammatory cytokines [42]. Rheu-

matic cachexia occurred at elevated resting energy expenditure (12% higher) and lower physical activity [42]. Higher energy expenditure in the presence of low physical activity is indicative of energy utilization by the immune system (not brain and muscles). In addition, accelerated whole-body protein catabolism was observed (cachexia). More recently, Walsmith and Roubenoff stated '…low physical activity predisposes to fat gain and is believed to precipitate a negative reinforcing cycle of muscle loss, reduced physical function, and fat gain in RA, which leads to cachectic obesity' [46]. Cachectic obesity denotes the relative increase of fat mass in relation to lean mass (muscle) without large changes in body mass index (BMI).

Protein degradation in the muscle is necessary to maintain glucose homoeostasis during a period when ketone bodies are not available (during the first 3 days of starvation). Thus, inflammation-induced increase in circulating catabolic cytokines such as

TNF [47, 48] and IL-1β [48], the loss of anabolic androgenic hormones, insulin-like growth factor-1 (IGF-1) resistance [49], and increased levels of myostatin are all vital parts of the glucose homoeostasis programme. It is important to note that the well-known loss of adrenal androgens in rheumatic diseases [50–52] is part of this fuel allocation programme (protein degradation and attenuation of reproductive processes).

With regard to EnR, leptin-induced inhibition of adrenal androgen generation [53] is another important part of the glucose homoeostasis programme in inflammation. Fat gain relative to lean mass during chronic inflammation [42] leads to relatively elevated leptin levels that support the negative reinforcing cycle of androgen deficiency, muscle loss and fat gain, ultimately leading to cachectic obesity.

Several studies have shown a negative correlation between BMI at study entry and radiographic disease progression or mortality rate in patients with RA [54–57]. This effect was paradoxical because a higher mortality rate might be predicted in patients with a higher BMI. However, considering fuel allocation to the activated immune system, patients with initially high BMIs had lower inflammatory activity, as demonstrated in two studies [54, 55]. Patients with initially higher BMIs have a less severe course of inflammatory disease (with less erosions) leading to less allocation of energy-rich fuels from muscle/fat to the immune system. We hypothesize that a higher BMI is a predictive factor for milder disease.

Insulin resistance

Endocrine imbalances with unresponsiveness to hyperglycaemia, insulin resistance and increased gluconeogenesis were demonstrated about 60 years ago in patients with RA and ankylosing spondylitis using an early version of the glucose tolerance test [44]. These early results were later supported by the finding that basal serum insulin levels and the maximum insulin response to glucose loading were significantly higher in patients with RA than in control subjects [58]. It was concluded that impaired glucose handling in RA is due to peripheral insulin resistance mediated by the inflammatory process [58]. Using the euglycaemic hyperinsulinaemic glucose clamp technique, it was shown that RA patients had significantly increased basal plasma insulin levels compared with control subjects and a lower glucose disappearance rate, which was positively associated with inflammation [58]. The authors concluded that patients with

RA demonstrated impaired glucose handling as a consequence of peripheral insulin resistance [59]. Others have demonstrated that serum levels of C-reactive protein and disease activity negatively correlated with insulin sensitivity in RA [60, 61]. Recently, it has become increasingly more apparent that insulin resistance is not a phenomenon of RA alone but is a general principle in CIDs [62–64]. Insulin resistance is an independent risk factor for atherosclerosis in RA [65]. However, the general principle behind this common phenomenon in terms of EnR remains unclear.

Energy-rich fuels are needed to feed the immune system (mainly glucose and glutamine, other glucogenic amino acids, ketone bodies and free fatty acids, Fig. 1). During activation of the immune system, degraded muscle proteins are used for gluconeogenesis in the liver. In the presence of an elevated SNS activity (see below) and slightly increased activity of the HPA axis (albeit relatively low increase in relation to inflammation, see below), gluconeogenesis results in somewhat higher circulating glucose levels (fructosamine and pentosidine are elevated [66, 67]), and increased levels of free fatty acids (such as the 20 : 3ω6 and 20 : 4ω6 fatty acids [68–72]). Free fatty acids induce insulin resistance [73] and, in parallel, proinflammatory cytokines such as TNF can disturb insulin receptor and IGF-1 receptor signalling [49, 74], which is clearly shown by the improvement of insulin resistance and IGF-1 resistance associated with TNF neutralizing therapy [49, 75, 76]. Furthermore, the shift from normal body composition to cachectic obesity with increased relative fat mass supports the hypothesis of insulin resistance due to many adipose tissue-related proinflammatory factors (adipokines) such as TNF, IL-6, leptin and resistin [7, 73, 77]. A detailed description of these adipokines and their actions is beyond the constraints of this review. Although all elements together contribute to insulin resistance, the increased proinflammatory load with elevated circulating cytokines is probably of most importance in CIDs. With regard to EnR, insulin resistance inhibits storage of fuels in liver, adipose tissue and muscle, which leads to allocation of fuels to activated immune cells.

It is important to note that immune cells take up glucose via GLUT1, GLUT3 and GLUT4 glucose transporters that are activated by specific immune stimuli such as lipopolysaccharide, anti-CD3 antibodies, cytokines (e.g., IL-7, IL-4), hormones (e.g., leptin) and insulin [19, 78]. In addition, glycolysis and pentose phosphate pathways are switched on in activated immune cells [78]. Immune cells do not become insulin

resistant. In contrast, insulin is important for glucose uptake, cytokine synthesis and activation of immune cells [19, 79]. In this context, it is important to note that the macrophage differentiation marker GLUT5 [79], which is a poor glucose transporter but an excellent fructose transporter, might be involved in fructose uptake after inflammation-induced degradation of the extracellular matrix, which contains large amounts of the fructose precursor N-acetylglucosamine (Table 1). In conclusion, the energy appeal reaction increases the insulin resistance of liver, adipose tissue and muscle in order to allocate energy-rich fuels to the activated immune system, which does not become insulin resistant.

Dyslipidaemia

Insulin resistance is causally linked to dyslipidaemia with high levels of plasma triglycerides, low levels of HDL cholesterol, appearance of small dense LDL and excessive postprandial lipaemia [80]. Although, the pattern of dyslipoproteinaemia may vary between different CIDs, depending on the severity of the disease, concomitant therapy and laboratory techniques, a common phenomenon in all CIDs is a low level of HDL cholesterol and/or apolipoprotein A (apoA)-I [68, 71, 81–84]. HDL is instrumental in removing cholesterol from the tissue (so-called reverse cholesterol transport). Of importance, the loss of HDL cholesterol and the appearance of a proinflammatory subfraction of HDL with decreased apoA-I and apoA-II and increased serum amyloid A and ceruloplasmin was augmented in CIDs [85]. CID-related transition of normal HDL to proinflammatory HDL becomes understandable in the context of acute inflammatory episodes.

By the early 1990s, elevated levels of circulating cytokines were shown to contribute to the decrease in HDL fraction, which was part of the acute-phase reaction of lipid metabolism (reviewed in [86]). In addition, human subjects injected with TNF demonstrated a rapid loss of plasma HDL [87]. In a recent excellent review, the group of Grunfeld and Feingold demonstrated that acute-phase HDL is characterized by low levels of apoA-I, apoA-II and lecithin-cholesterol acyltransferase, but high levels of serum amyloid A [88]. Of importance, higher levels of serum amyloid A in HDL and increased inflammation-related secretory phospholipase A2 both support uptake of cholesterol into macrophages [88]. Upregulation of secretory phospholipase A2 also supports the uptake of cholesteryl esters into the adrenal gland, presumably for increased steroid hormone synthesis

[88]. Moreover, the HDL transport protein ABCA1 responsible for reverse cholesterol transport is also down-regulated by proinflammatory cytokines [88]. Thus, the acute-phase HDL facilitates the delivery of cholesterol and other lipids to the macrophage as a result of a general down-regulation of reverse cholesterol transport.

In the context of EnR, this response is appropriate because it increases allocation of energy-rich fuels to activated immune cells. In addition, acute-phase HDL has many direct anti-microbial effects as recently demonstrated [88]. In CIDs, this continuous occurrence of the acute-phase lipid response is deleterious, leading to increased risk of atherosclerosis.

Local adipose tissue

The detailed studies of Pond *et al.* in the early 1990s demonstrated that nearly all large lymph nodes, and many smaller ones, are embedded in adipose tissue [89]. The majority of smaller adipose depots enclose one or more lymph nodes [90]. After activation of lymph nodes by lipopolysaccharide or other proinflammatory stimuli, lipolysis and glycerol release were increased from perinodal fat depots [90]. It has been suggested that lymph node-associated adipose tissue is important as a local source of energy-rich fuels as fatty acids can be used by immune cells (Fig. 1) [89, 90].

Several CIDs, including RA, osteoarthritis, Crohn's disease, mesenteric panniculitis and Graves' ophthalmopathy, are characterized by selective hypertrophy of adipose depots in the proximity of inflammatory lesions [7]. In addition to energy-rich fuels (fatty acids), adipocytes produce proinflammatory adipokines, such as leptin, high-molecular weight isoforms of adiponectin, TNF, IL-1β, monocyte chemotactic protein-1 (MCP-1) or IL-6, as well as anti-inflammatory factors, such as trimeric adiponectin [7]. Thus, the fine-tuned balance of pro- and anti-inflammatory factors supports processes in neighbouring lymph nodes such as clonal expansion of antigen-specific lymphocytes.

In addition, fat tissue in the proximity of chronic inflammatory lesions most probably supports the local inflammatory milieu. It is important to note that adipocytes differentiate from pluripotent mesenchymal stem cells, which readily enter chronically inflamed tissue [7]. Thus, adipose tissue adjacent to inflammatory lesions can develop locally, if stimuli for adipocyte differentiation are available. Regional

adipose tissue represents a local store of energy-rich fuels necessary to nourish the neighbouring inflammatory process.

Homoeostatic steroid axes

There has been much debate about whether or not cortisol regulation is altered in patients with CIDs. Confusion was partly generated by studies carried out in patients with or without prior glucocorticoid therapy [91]. At present, the consensus is that: (i) cortisol serum levels are somewhat elevated in untreated patients with CIDs (e.g., [92]), (ii) responsivity of the HPA axis is visibly disturbed when subtle stress tests are applied [93], (iii) cortisol levels are inadequately low in relation to inflammation (e.g., [92]) and (iv) there exists a state of cortisol resistance [94, 95]. Inadequacy of cortisol relative to inflammation means that cortisol levels, which can rise to 10 times the normal level, are too low to substantially contribute to immunosuppression. In addition, adrenal androgen production is nearly switched off at the expense of cortisol production [2, 3].

With regard to EnR and allocation of energy-rich fuels to the immune system, mildly elevated levels of cortisol and severely down-regulated anabolic androgens support gluconeogenesis by muscle protein breakdown. The cortisol-to-androgen preponderance is catabolic. As cortisol and adrenaline support each other's signalling pathways, the concomitant increase in both hormones potentiates gluconeogenesis. In addition, the stimulation of lipolysis by cortisol at physiological levels is enhanced by growth hormone, leading to increased allocation of energy-rich fuels to the immune system [96]. All this is supported by cortisol resistance of immune cells [94, 95].

Another alteration of homoeostatic steroid axes is normal serum levels of oestrogens in the presence of low levels of androgens [3]. This phenomenon is attributed to the increased activity of the aromatase complex in inflamed tissue and spillover of oestrogens into the circulation [97]. The aromatase complex can be activated by proinflammatory cytokines such as TNF, IL-6 and IL-1β, which leads to a marked up-regulation of oestrogens in relation to androgens [98]. Because 17β-oestradiol can stimulate the female type of subcutaneous lipid accumulation [99, 100], increased levels of oestrogens (also in men) relative to androgens can support female-type fat distribution, cachectic obesity and even generation of regional fat depots in the proximity of inflammation. In addition, the relative increase of oestrogens to androgens aggravates muscle wasting, as seen in transsexuals [100].

All these alterations of the homoeostatic steroid axes evolved to cope optimally with short-lasting inflammatory episodes. Their long-term occurrence in CIDs is deleterious because these alterations support allocation of energy-rich fuels to the activated immune system.

The sympathetic nervous system

The SNS with its two effector arms, the adrenal medulla and peripheral sympathetic nerve fibres, is the major regulator of glycogenolysis, gluconeogenesis and lipolysis. Although the adrenal medulla generally stimulates the splanchnic organs, sympathetic nerve fibres can stimulate distinct adipose tissue regions in the body. Provision of energy-rich fuels by the SNS depends on β2-adrenergic receptor signalling. For example, catecholamines via β2-adrenoceptors activate hormone-sensitive lipase to breakdown triglycerides into glycerol and fatty acids. The α2-adrenergic receptor exerts anti-lipolytic effects [99]. Thus, an elevated systemic SNS activity supports lipolysis, gluconeogenesis and glycogenolysis. In addition, a high firing rate of sympathetic nerve fibres to adipose tissue supports local lipolysis.

Many CIDs are accompanied by increased levels of circulating proinflammatory cytokines and an elevated activity of the SNS, which can be a substantial risk factor for cardiovascular disease [101–107]. The circulating cytokines directly stimulate the SNS in the hypothalamus but also the local proinflammatory process in vascular lesions. In addition, hyperinsulinaemia is related to increased SNS activity because insulin stimulates the SNS [108]. CIDs are accompanied by hyperinsulinaemia, as discussed above. From an EnR perspective, the somewhat higher activity of the SNS is important to sustain allocation of energy-rich fuels to the immune system and to maintain systemic circulation. Indeed, denervation of the SNS largely decreased early inflammation in animal models [109–111]. The aggravating influence of late denervation of the SNS, as recently demonstrated [110], is most probably not related to sympathetic nerve fibres but to the manipulation of anti-inflammatory tyrosine hydroxylase-positive sympathetic cells in inflamed tissue [112].

It is important to note that many components of the immune system such as macrophages, dendritic cells, neutrophils, natural killer cells and T-helper

type 1 lymphocytes are inhibited via β2-adrenergic stimulation. The parallel activation of β2-adrenoceptors to stimulate lipolysis on the one hand and to inhibit immune function on the other appears contradictory because the SNS should serve the activated immune system. The two contrasting functions of adrenergic neurotransmitters can be explained by compartmentalization. If sympathetic nerve fibres are present in adipose tissue but not in inflamed tissue, the two sympathetic functions can occur in parallel. Indeed, sympathetic nerve fibres are rapidly lost in inflamed tissue and in the activated spleen in arthritic animals [113–116]. However, sympathetic nerve fibres are present in adjacent adipose tissue (R. H. Straub, unpublished data). This compartmentalization allows parallel lipolysis (β2) and immune activation (α2 or α1).

In conclusion, elevated systemic SNS activity as the consequence of an energy appeal reaction and local retraction of sympathetic nerve fibres is crucial for the activated immune system.

The parasympathetic nervous system

The PSNS with its main neurotransmitter acetylcholine supports intake and storage of energy-rich fuels. For example, the PSNS stimulates insulin secretion and improves insulin sensitivity to allow storage of fuels in liver, fat tissue and muscle [117, 118]. The PSNS stimulates hepatic glycogen storage, and hepatic vagal denervation decreases hepatic glucose uptake [119]. Of importance, adipose tissue and muscles are not innervated by nerve fibres of the PSNS [120], which implies that the vagal influence on fuel storage is mainly directed towards hepatic glucose metabolism. Thus, the PSNS would be able to withhold energy-rich fuels from an active immune system, in contrast to the SNS. In consequence, one might expect an anti-inflammatory influence of the PSNS because this part of the autonomic nervous system would not support allocation of energy-rich fuels to the immune system.

Indeed, a recent review by Tracey demonstrated the anti-inflammatory effects of the parasympathetic neurotransmitter acetylcholine via the vagal cholinergic anti-inflammatory pathway [121]. At present, it remains unclear how cholinergic inhibition is related to inflammation in tissues that are not vagally innervated. It is possible that vagal cholinergic inhibition influences splanchnic immune cells, which influence peripheral inflammation. It is important to note that the first studies with the focus on RA demonstrated

an anti-inflammatory effect of acetylcholine on inflammation [122, 123]. As the joint is not vagally innervated, it remains to be established how the cholinergic pathway influences the joint tissue.

Inflammation-related anaemia

In CIDs, a mild to moderate normocytic normochromic anaemia is characterized by decreased serum iron and transferrin, and increased iron stores in the form of ferritin [124]. The following pathophysiological causes have been described: (i) allocation of iron to monocytes/macrophages and other cells of the reticuloendothelial system (RES) stimulated by hepcidin, (ii) reduced intestinal iron resorption initiated by hepcidin, (iii) disturbed erythropoiesis due to pro-inflammatory cytokines and reduced half-life of erythrocytes (phagocytosis by macrophages) and (iv) reduced influence of erythropoietin on erythropoiesis (little production and/or resistance). All these process are stimulated by circulating and local proinflammatory cytokines such as TNF, IL-1β or IL-6, and can be studied using anti-cytokine therapy in patients with CIDs [125, 126].

Increased iron uptake and accumulation in macrophages is necessary, for example for peroxide- and nitric oxide-generating enzymes, which are extremely important bactericidal enzymes [127]. During the process of co-evolution of bacteria and vertebrates, microbes and their hosts competed for iron [128]. As part of innate immunity, the body modifies iron metabolism to allocate iron to the RES, and therefore it is less available to microorganisms [127, 128]. In addition, iron is an essential metal for the respiratory chain complex – the cytochromes – to handle the necessary protons for ATP production. A total of 2300 ATP molecules are needed for the synthesis of one typical protein; for example, a cytokine (Fig. 1). In the case of high turnover rates of immune cells and clonal expansion of lymphocytes, iron availability is very important for functioning of the immune system [129].

How are decreased levels of serum iron and increased ferritin linked to overall EnR? First, anaemia is accompanied by reduced energy expenditure for erythropoiesis, which can be significant, as seen in sickle cell anaemia [130]. Secondly, the development of mild anaemia limits the oxygen transport capacity in general, which will increase the time spent at rest (immune cells switch to anaerobic metabolism). Thirdly, increased ferritin is linked to insulin resistance, peripheral hyperinsulinaemia, liver insulin

resistance and increased gluconeogenesis, which support glucose allocation to the immune system [131]. Finally, lower oxygen tension leads to decreased physical activity and reduced iron levels are followed by decreased myoglobin levels in skeletal muscle [127]. All these effects of anaemia corroborate allocation of energy-rich fuels to the activated immune system.

Mild anaemia, as can occur in CIDs, is often accompanied by an increase in SNS activity and glucose production [132]. Thus, we hypothesize that mild CID-related anaemia is another important factor that can drive the SNS and the HPA axis to allocate energy-rich fuels to the activated immune system.

Osteopenia

Calcium is an essential element for functioning of the immune system [33], muscles and brain. Calcium is provided by regulated absorption in the intestinal tract (vitamin D3) and kidneys (vitamin D3 and PTH), and by PTH-stimulated osteoclast activity leading to bone resorption [10]. Adequate vitamin D3 is essential for optimal calcium absorption from the gut. It is important to note that in a state of reduced intestinal calcium uptake, such as during 3–5 weeks of severe disease, calcium is provided only from bony stores. As CIDs are often accompanied by anorexia-induced vitamin D and K deficiency and hypomagnesaemia (all of which contribute to osteopenia), provision of calcium from bone is of great importance. Indeed, CIDs are accompanied by osteopenia [133], which is mediated by increased local bone turnover (and sometimes erosions) in the proximity of inflamed joints due to up-regulation of proinflammatory cytokines and PTH-related peptide [32]. In addition, IL-6 and TNF (via RANKL) are the most important factors for calcium mobilization from distant bone because circulating PTH and PTH-related peptide levels are reduced or normal in active CIDs [32, 134, 135].

However, how bone osteopenia and EnR are linked remains unknown. The first indication came from the positive correlation between increased fat mass (i.e. elevated stores of energy-rich fuels) and increased bone mineral density (BMD) (i.e. increased calcium stores); the so-called bone-protective effect of adipose tissue [136]. The positive relationship between BMD and fat mass was attributed to increased levels of 17β-oestradiol produced in fat tissue, which has bone- and fuel-sparing effects [136]. In addition, the recently identified positive influence of osteocalcin, an osteoblast hormone, on insulin sensitivity indi-

cates that bone-sparing factors such as osteocalcin can support glucose uptake and fuel storage [137]. Of importance, proinflammatory TNF and IL-6 down-regulate osteocalcin form osteoblasts [138]. This supports insulin resistance and, thus, allocation of energy-rich fuels to the immune system.

On the other hand, the SNS and the HPA axis have been shown to have important roles in breaking down fuel resources from liver, muscle and fat tissue (see above). It is not a coincidence that the major hormone of the HPA axis, cortisol, and the SNS are both able to induce osteopenia. The osteopenic effect of cortisol was described shortly after the discovery of this hormone (reviewed in [139]). The bone-resorptive effect of the SNS has recently been shown (reviewed in [140]). Thus, the major fuel-providing systems have important osteopenic effects, which are instrumental in regulation of bone turnover and, thus, calcium and phosphate availability for energy consumers (when food intake is minimal). In CIDs, elevated serum levels of cortisol and plasma catecholamines, in the presence of low levels of anabolic androgens and vitamin D (and K), support osteopenia. We hypothesize that EnR at times of an elevated need for fuels supports the energy-consuming process by provision of calcium (and phosphate) even without calcium intake.

Conclusions

A distribution programme for energy-rich fuels has evolved to regulate storage and breakdown of fuels as well as the activities of the different consumers and providers (Fig. 5). Regulation of consumers (brain, muscle and immune system) and storage sites (liver, adipose tissue and muscle) follows the circadian rhythm to distribute fuels to brain/muscle during the daytime and to the immune system at nighttime. In a healthy individual, this division of utilization of energy-rich fuels is perfectly regulated by the circadian neuroendocrine immune interplay.

In CIDs, continuous attack of auto-antigens by immune cells did not evolve as a normal programme [8, 9]. This leads to unwanted side effects apparent in CIDs, including tissue inflammation and clonal expansion of aggressive lymphocytes, anorexia, cachexia, insulin resistance, shutdown of the HPG axis, elevated tonus of the HPA axis and the SNS, anaemia, hypovitaminosis D and osteopenia. All these are part of adjusted EnR to continuously allocate energy-rich fuels to the activated immune system. The combination of inflammation-induced cachectic obesity,
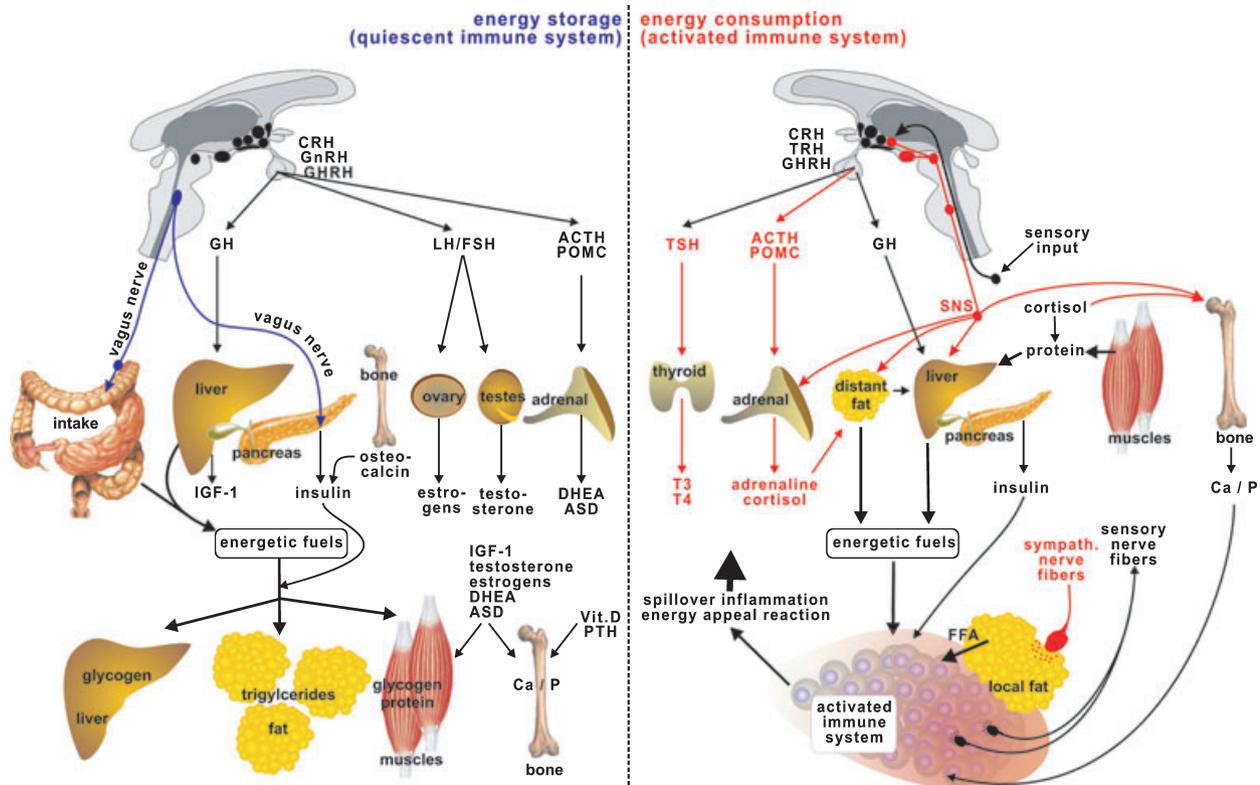
Fig. 5 *Storage and consumption of energy-rich fuels. Left panel: this demonstrates the regulators of normal fuel storage. The main elements are the parasympathetic nervous system (vagus nerve), insulin from the pancreas and gonadal and adrenal androgens. Under conditions without inflammation and with normal food intake, fuels are stored in the liver (glycogen, short-term depot), fat tissue (triglycerides, long-term store), muscles (muscle glycogen, short-term store). The important role of bone in energy regulation (EnR) has recently become known. Right panel: consumption of energy-rich fuels under the influence of an activated immune system. Inflammation induces an 'energy appeal reaction' with an increased activity of the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis, which are supported by thyroid hormones. The energy appeal reaction allocates energy-rich fuels from local/ distant fat tissue, liver and muscles to the activated immune system. Inflammation-induced insulin resistance prevents storage of fuels in liver, fat tissue and muscles but activates the immune system. Repulsion of sympathetic nerve fibres in the presence of an activated SNS supports local lipolysis (β2) but does not inhibit the immune system. The provision of calcium and phosphorus are maintained by increased local and distant bone turnover.*

hypertension, sympathetic hyperactivity, insulin resistance, hyperinsulinaemia and dyslipidaemia is known as the metabolic syndrome (Fig. 4, yellow boxes). The metabolic syndrome in CIDs is a consequence of chronic inflammation induced by spillover inflammatory activity and activation of the neuroendocrine EnR system.

In 1937, Selye and Fortier termed the activation of stress systems, the 'alarm reaction', which is the reaction of an organism 'when first confronted with a stimulus to which it is quantitatively or qualitatively not adapted' [141]. At that time, they did not include a discussion of EnR although they recognized that catabolism accompanies the stress response. We

have included EnR into the neuroendocrine immune interplay, to produce the energy appeal reaction, which includes the alarm reaction on a higher integrative level. It now appears that many independent CID-related disease phenomena can be explained by considering the neuroendocrine immune control of EnR.

Finally, it remains to be elucidated whether more availability of energy-rich fuels leads to a higher incidence and prevalence of CIDs, similar to the situation in type 2 diabetes mellitus. On the basis of the new framework, we hypothesize that new therapeutic options focusing on utilization and provision of energy-rich fuels will be found.

Contribution of authors

Rainer H. Straub: development of the new concept, draughting the paper, generating figures and final approval.

Maurizio Cutolo: discussing the contents and figures, revising the draught and final approval.

Frank Buttgereit: discussing the contents, revising the draught and final approval.

Georg Pongratz: critically discussing the new concept and the contents, revising the draught and final approval.

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