

Supplementary Table 1 | Adaptive programmes in chronic inflammatory diseases and during ageing that protect against energy shortages

Symptom(s)	Chronic consequence(s)	Homeostasis	Chronic inflammatory diseases and ageing
Daytime fatigue and low mood	Low levels of physical activity	<ul style="list-style-type: none"> <li>Reduces energy expenditure in the brain and muscles</li> <li>Confinement to a safe place and withdrawal from harmful situations</li> </ul>	<ul style="list-style-type: none"> <li>Occurs frequently</li> <li>Pain and sleeping problems are the major drivers</li> </ul>
Sleeping alterations	Low levels of physical and mental activity	<ul style="list-style-type: none"> <li>Reduces energy expenditure in the brain and muscles</li> <li>Confinement to a safe place and withdrawal from harmful situations</li> </ul>	Occurs frequently
Loss of appetite and anorexia	Low appetite, malnutrition and muscle wasting	<ul style="list-style-type: none"> <li>Reduces energy expenditure in the brain and muscles used for foraging</li> <li>Confinement to a safe place and withdrawal from harmful situations</li> </ul>	<ul style="list-style-type: none"> <li>Occurs frequently</li> <li>Consequence of sickness behaviour and low parasympathetic activity</li> </ul>
Inflammation-induced anaemia	Low levels of physical activity	<ul style="list-style-type: none"> <li>Bacterial defence mechanism<sup>1</sup></li> <li>Reduces energy expenditure in the brain and muscles</li> <li>Confinement to a safe place and withdrawal from harmful situations</li> </ul>	Occurs frequently in chronic inflammatory diseases, in which iron is stored intracellularly as indicated by high levels of serum ferritin
Muscle wasting	Low levels of physical activity, frailty and frequent falling	<ul style="list-style-type: none"> <li>Redistribution of glucogenic amino acids used as energy-rich fuels</li> <li>Reduces energy expenditure in the muscles</li> <li>Confinement to a safe place and withdrawal from harmful situations</li> </ul>	<ul style="list-style-type: none"> <li>Occurs frequently</li> <li>Consequence of anorexia, low levels of physical activity and the loss of anabolic hormones*</li> </ul>
Bone loss	Fractures and low levels of physical activity	Calcium, phosphate and magnesium liberated from the bone to supply non-skeletal tissue during anorexia	<ul style="list-style-type: none"> <li>Occurs frequently</li> <li>Consequence of anorexia, low levels of physical activity, increased levels of cortisol and catecholamines<sup>‡</sup> and the loss of anabolic hormones*</li> </ul>
Insulin resistance	Hyperinsulinaemia drives inflammation and increases blood pressure	Redistribution of stored energy-rich fuels to the immune system or to the brain	<ul style="list-style-type: none"> <li>Occurs frequently</li> <li>Consequence of inflammation in chronic inflammatory diseases and of inflammation or high levels of activity in the stress axes<sup>‡</sup> during ageing</li> <li>Consequence of low levels of physical activity</li> </ul>
Decreased fertility and loss of sexual interest	Low levels of physical activity and sexual dysfunction and loss of sexual interest	<ul style="list-style-type: none"> <li>Decreased courtship behaviour spares energy, causing muscle and bone loss</li> <li>Release of energy-rich fuels and calcium</li> </ul>	<ul style="list-style-type: none"> <li>Occurs frequently</li> <li>Consequence of low levels of hypothalamus–pituitary–gonadal axis activity in chronic inflammatory diseases and low levels of hormones during ageing</li> </ul>
High blood pressure	Cardiovascular disease	Reduction of water loss; a typical sign of acute inflammation, wounding and haemorrhage	<ul style="list-style-type: none"> <li>Occurs frequently</li> <li>Consequence of high levels of activity in the sympathetic nervous and renin–angiotensin–aldosterone systems leading to water retention</li> </ul>
Increased blood coagulation	Thrombosis and embolism	<ul style="list-style-type: none"> <li>Necessary after wounding and haemorrhage</li> <li>Reduces energy expenditure in erythropoiesis and prevents loss of energy-rich fuels through blood loss</li> </ul>	<ul style="list-style-type: none"> <li>Occurs frequently</li> <li>Consequence of high activity of the sympathetic nervous and renin–angiotensin–aldosterone systems</li> </ul>

\*Anabolic hormones are androgens and oestrogens. In chronic inflammatory diseases, the hypothalamus–pituitary–gonadal axis is blocked, whereas during ageing, a natural decline in levels of these hormones occurs.

<sup>‡</sup>Stress axes are active in chronic inflammatory diseases and during ageing and favour the sympathetic nervous system over the hypothalamus–pituitary–adrenal axis.

References:

1. Weinberg, E. D. Iron availability and infection. *Biochim. Biophys. Acta* **1790**, 600–605 (2009).