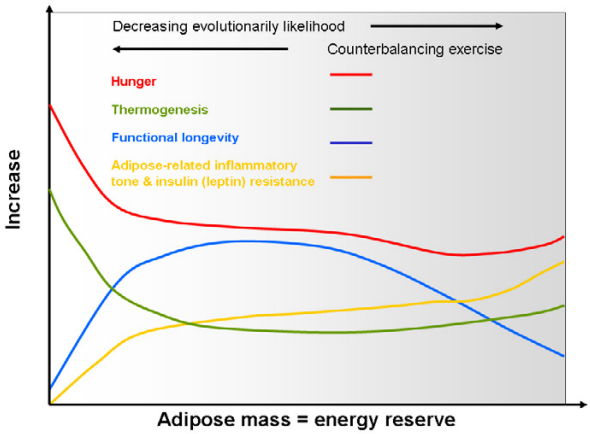

Figure 2
Relationship between energy storage, inflammation, thermogenesis, hunger and survival. As fat mass increases, it sends out a proportionally bigger inflammatory signal that also induces insulin resistance: this might compensate for the normal inflammatory suppression of orexia. Thus, it is a normal survival response selected for by evolution, as both storage of energy, and the ability to mount a strong immune response, were strong survival traits. It is likely that during ancient times there was never such a thing as a 'free lunch'; before the advent of civilisation it was unlikely that there were extended periods (e.g. beyond a year) when food was plentiful and there was little need to move to get it.

lipotoxicity. We suggest that the ability to utilize lipids as fuel has to have co-evolved with the ability to suppress oxidative stress: PPARs may well be a very important part of the solution. In contrast, carbohydrate metabolism has become associated with inflammation.

Fat versus glucose: PPARs and energy source switching

Carbohydrate is an essential fuel source for the CNS and immune system, but excess carbohydrate is stored as energy-dense fat, a process that requires mitochondria and the participation of PPARs. The ability to store and metabolize fat is an important survival mechanism as it provides energy when food is scarce; it is far more energy dense than glycogen. During fasting, glycerol can be released from adipose stores, which can then be used by the liver for gluconeogenesis – thus providing carbohydrate to for the CNS. Studies indicate that the evolution of a longer lifespan has been associated with the development of a higher body mass and an increased percentage of body fat [13,42]. Thus, fat storage is a positive survival trait and the adipogenic function of PPAR γ makes it tightly linked into long-term survival.

Fats, in addition to being stored, must also be readily made available for oxidation. PPAR α and PPAR δ are active in muscle and ensure entry of fats into the β-oxidation pathway, as illustrated by their upregulation during endurance exercise [43,44] or thermogenesis [18]. However, although an increased lifespan is dependent on the ability of an organism to store and utilize energy-dense fat, there is an inherent problem in using fats as an energy substrate; they are highly susceptible to ROS damage, which is especially true for unsaturated fatty acids (because of readily oxidisable double-bonds) [45].

Under normal conditions, oxygen utilization is closely coupled to energy production and expenditure. However, in hypoxic circumstances, for example during localised biological stress induced by injury/infection (where blood flow is compromised), the production of mitochondrial ROS is significantly increased due to a reduction of oxygen as an electron acceptor. This may have become part of an ancient mitochondrial-based oxygen sensing/signalling mechanism, which involves the hypoxia-induced factor-1 (HIF-1) transcription factor [46]. It is also likely that ROS signalling plays a key role in the activation of NFkB [47] and thus, in inflammation [48]. During hypoxia, carbohydrate becomes the more important fuel source as it is more oxygen-efficient and if necessary, can undergo anaerobic respiration (fats cannot be burnt without oxygen and mitochondria). HIF-1 can inhibit both PPAR α and PPAR γ expression [49,50], but may require NFκB for full activity [51,52]. Certainly, activation of NFkB in cardiac muscle can suppress the transcriptional activity of both PPAR α & δ, suggesting a switch to carbohydrate metabolism [33].

As indicated above, HIF-1 downregulates PPAR activity in a hypoxic environment causing a switch to carbohydrate burning. However, the increased ROS production may well be negatively regulated PPARs, as oxidised lipids are potent ligands for the PPARs. Thus, although hypoxia can trigger ROS production and the ability to switch off beta-oxidation, the process is self-regulated by the anti-inflammation actions of the PPARs – thus ensuring minimal duration of oxidative stress. Certainly, PPAR α is known to suppress the dehydrogenase pyruvate complex (PDC), by upregulation of pyruvate dehyrogenase kinase 4 (PDK4) during starvation [53], which would reinforce its role in energy switching and carbohydrate sparing.

PPARs and uncoupling proteins: managing ROS and lipids

PPAR activation can increase the expression of mitochondrial UCPs [54-57] – a family of homologues that can 'uncouple' the proton gradient in the mitochondria and so reduce ROS [58]. The activity of UCPs is increased during starvation and by a ketogenic diet [59,60]. They can be directly activated by fatty acids [61], with unsaturated fatty acids being particularly effective [62-64].