Bringing equine adipose tissue into focus

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REVIEW ARTICLE

Bringing equine adipose tissue into focus

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Summary

Adipose tissue is not only required for energy storage but is an essential endocrine organ with a central role in the pathology of obesity. The understanding of its role, both in human and equine medicine, is continually evolving. With obesity being an ever-growing problem in equine populations, gaining owner compliance is critical when implementing management plans. The aim of this review is to encourage the inclusion of the concept of adiposity in discussions with horse owners on obesity and metabolic syndrome. In doing this, we hope to improve clients' understanding and, therefore, maximise the impact of diagnostic tests, monitoring tools and management.

KEYWORDS
adipose tissue, horse, obesity

INTRODUCTION

Adipose tissue (AT) is a multifaceted organ, essential for health. Whilst its role in lipid storage is well established, understanding the importance of AT as an endocrine organ, with a central role in the pathology of obesity, is evolving. Helping clients to understand the systemic impacts of excess AT can maximise the impact of diagnostic tests, monitoring tools, management and owner compliance.

ADIPOSE TISSUE AS A STORAGE ORGAN

The amount of AT varies hugely between individual horses and is affected by factors such as age, sex and breed (Wallis & Raffan, 2020). Estimation of body fat content by deuterium oxide dilution found AT to account for 2.7%–35.6% of total body weight in horses (Dugdale et al., 2012). There are two distinct types of AT: white AT and brown AT. The white AT predominates and is specialised for energy storage. The brown AT, named due to its colouration from the high concentration of mitochondria, has a role in thermoregulation and, as a consequence, is abundant in neonates and animals in hibernation (Kiranmayi & Bhargav, 2019). Most adult mammals have very low quantities of brown AT and indeed, this form has not been described at all in the adult horse. There is great interest in brown AT pharmacological activation as a novel therapeutic target in human obesity (Liu et al., 2022); further research into brown AT in horse may, therefore, be of interest.

White AT is primarily an energy storage organ and is composed of adipocytes, in which lipid accumulates, as well as connective tissue, immune cells and blood vessels. AT can store almost 100 times more megajoules of energy than muscle, and this resource allows mammals to cope with changes in energy availability over time. Humans with congenital lipoatrophy (Berardinelli-Seip syndrome), who have a functional failure of their AT, rapidly develop severe insulin resistance and hepatic lipidosis, leading to liver failure and cardiovascular disease (Garg, 2004). This demonstrates that AT is an essential component of energy homeostasis and should not be viewed as always detrimental to health.

Adipocytes are developed from mesenchymal stem cells in a process called adipogenesis; a complex multistep process which includes the formation of pre-adipocytes from undifferentiated stem cells and the formation of mature adipocytes from these pre-adipocytes by accumulation of lipid. Equine adipose mesenchymal stem cells (MSCs) are well understood due to their regular use in the developments of biological therapeutics for the treatment of musculoskeletal disorders (stem cell therapy), which has evolved due to their relative ease of acquisition and robust response to in vitro manipulation (Marycz et al., 2016). The in vitro characteristics of equine AT MSCs are very similar to those of humans, including the

pre-adipocyte response to insulin and glucocorticoid stimulation, which induces lipid accumulation and drives differentiation to mature adipocytes (Bukowska et al., 2021).

Adipocytes within WAT store fat as triglyceride (triacylglycerol) in one large lipid droplet per cell. Triglycerides from dietary fat are absorbed from the gut and transported to the AT in the form of chylomicrons. AT, as well as liver, can also synthesise triglycerides from excess carbohydrates, a process known as de novo lipogenesis (DNL) (Ameer et al., 2014). The starting substrate for DNL varies greatly between species, with horses using acetate, unlike humans who primarily use glucose or pigs who can use either (Suagee et al., 2010). AT, as opposed to the liver, is the primary site of DNL in horses in contrast to humans (Adolph et al., 2019; Suagee et al., 2010), which may explain why fatty liver is less common in horses than other species. Aberrant DNL is associated with insulin resistance and cardiovascular risk in humans and is a potential link between excess carbohydrate intake and these conditions (Ameer et al., 2014); however, very little is known about changes in DNL in equine disease.

In the face of increased caloric intake, AT can expand through hyperplasia (increased adipocyte numbers derived from pre-adipocytes) or by hypertrophy (increase in individual cell size via lipid accumulation). The capacity for hyperplasia varies between AT depots, as discussed later. When required, the stored triglycerides are broken down into glycerol and free fatty acids by lipolysis. Lipolysis is predominantly controlled by insulin in the fed state through actions on adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). These fatty acids are then available to mitochondria for respiration. The ability and speed with which AT mobilises stored triglycerides is one of the main distinguishing features between AT depots.

ADIPOSE TISSUE AS AN ENDOCRINE ORGAN

In addition to its primary role in storage, AT is the largest endocrine organ in the body, producing and responding to hormonal signals and critical in the cross-talk between metabolic organs, which govern energy homeostasis (Figure 1). Adipocytes secrete bioactive peptides (adipokines and adipocytokines), which can act locally (autocrine/paracrine) or systemically (endocrine). AT also possesses a complex receptor profile, which allows it to respond to endocrine and nervous system input. Finally, adipocytes are able to exert fine control over endocrine signalling through their enzyme machinery, important in the metabolism of hormones, particularly steroid hormones. Our understanding of the equine adipocyte endocrine profile is more limited than that of humans or rodents, but some data have been published.

Adipokines

Leptin is a critical regulator of energy storage through appetite/satiety control: when energy stores are adequate, leptin signals to the hypothalamus to reduce appetite drive, thus reducing food intake. As in other species, leptin is secreted from equine adipocytes in proportion to body fat mass. Indeed, animals with increased body fat (without disease) have higher plasma and AT expression of leptin (Buff et al., 2002; Staub et al., 2019).

Adiponectin is produced almost exclusively by adipocytes (Fang & Judd, 2011) and it acts primarily on muscle and liver to increase insulin sensitivity and reduce inflammation. In most species, including horses, there is an inverse relationship between fat mass and plasma adiponectin (Kearns et al., 2006).

Resistin is also an AT-specific protein, whose transcription is induced during differentiation of adipocytes. In rodents, it has been shown to decrease gluconeogenesis in the liver (Banerjee et al., 2004). Numerous human studies have failed to demonstrate a reliable association between resistin levels, obesity and/or insulin dysregulation. In contrast, resistin may be a marker of inflammation (Banerjee & Lazar, 2003), consistent with recent findings in horses (Fuentes-Romero et al., 2021).

Adipocytokines

Adipocytes, stromovascular elements and inflammatory cells all contribute to adipocytokine secretion. Cytokines released include interleukin 6 (IL-6), tumour necrosis factor alpha (TNFα), monocyte chemoprotectant protein-1 (MCP1) and interleukin 1 beta (IL1β). The actions of the adipocytokines are diverse and are not limited to inflammatory effects such as chemoattraction and immune cell activation. For example, TNFα suppresses free fatty acid and glucose uptake into adipocytes in humans (Ruan et al., 2002). Little is known about the actions of these cytokines in equine AT but expression of several, including *TNFα*, *IL1β*, IL-6 and *MCP1*, has been shown (Basinska et al., 2015; Reynolds et al., 2019). The analysis of these cytokines has been proposed as a potential diagnostic target in equine metabolic syndrome but are not widely available and will require careful interpretation because of their lack of disease specificity.

Steroid hormones

Adipose tissue is crucial for the action and metabolism of steroid hormones, particularly glucocorticoids and sex steroids. Furthermore, glucocorticoids are essential in the differentiation of mature adipocytes. AT in humans and horses contains high levels of glucocorticoid receptor (GR) and also the metabolising enzyme 11β-hydroxysteroid dehydrogenase type 1 (HSD1), which metabolises inactive cortisone into active cortisol and thus potentiates activation of GR (Morgan et al., 2018). Horses predominantly metabolise endogenous cortisol through the carbonyl reductase 1 pathway, which is very active in AT and produces a metabolite (20-beta dihydrocortisol), which impairs glucose tolerance (Bell et al., 2021; Morgan et al., 2017). Less is known about sex steroid metabolism

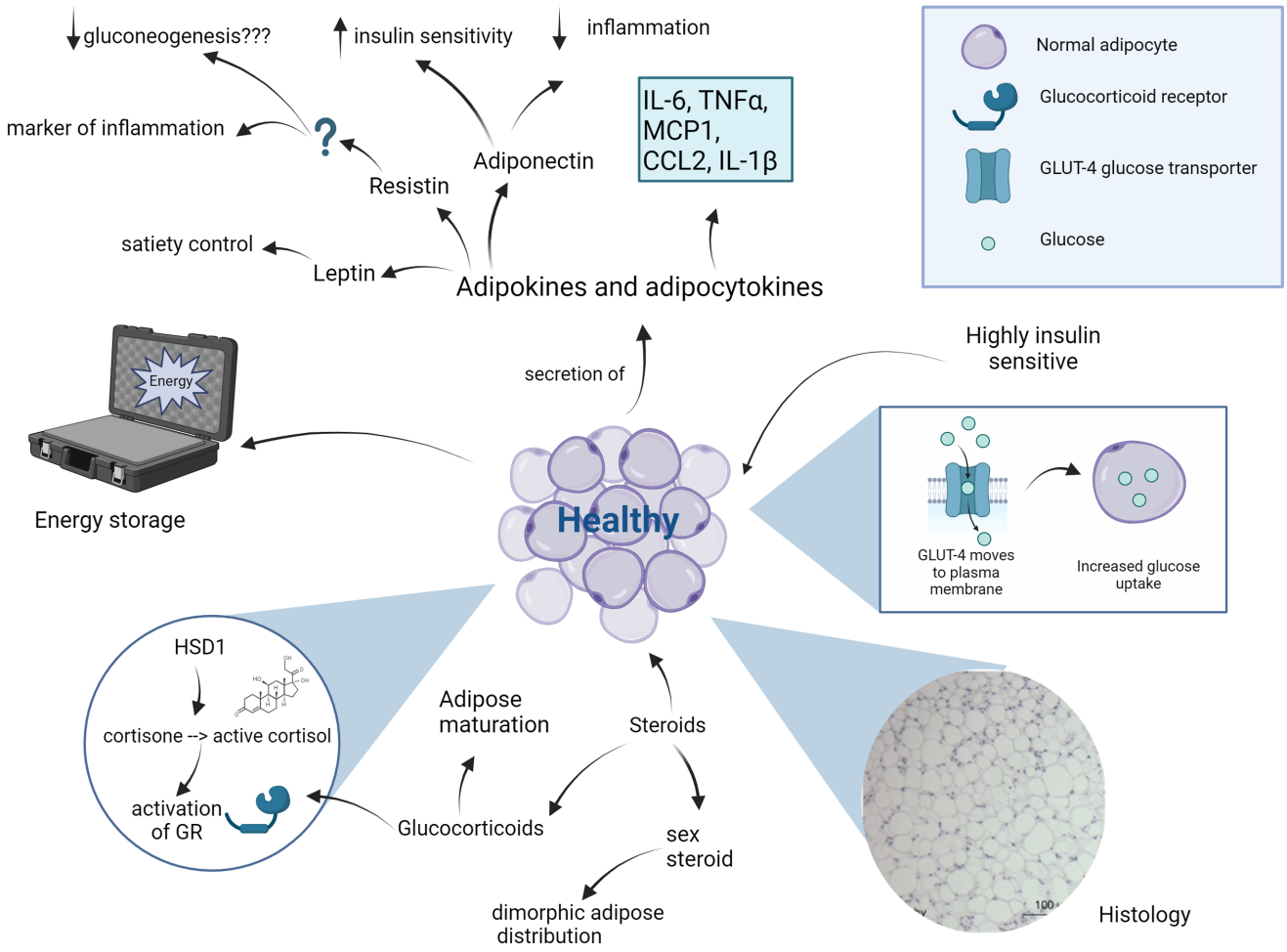

FIGURE 1 Diagram showing some of the key functions of adipose tissue. Created with BioRender.com.

and receptors in equine AT, though sexually dimorphic patterns of AT distribution are noted (such as the large nuchal crest adipose depots common in stallions) suggesting androgens may impact AT deposition.

Insulin

Adipocytes are exquisitely sensitive to the effects of insulin. Binding of insulin to its receptor initiates the movement of the insulin-sensitive glucose transporter GLUT4 from cytosolic sequestration to the plasma membrane to allow uptake of glucose into the adipocyte. Adipocyte GLUT4 trafficking not only keeps substrate available for DNL but also seems to mediate the cross-talk of AT with liver and muscle to maintain systemic glucose homeostasis (Abel et al., 2001). GLUT4 trafficking is evident in equine adipocytes, but there is a suggestion that more complex and additional insulin signalling pathways may also contribute to glucose uptake (Warnken et al., 2017). Insulin also suppresses lipolysis in equine and human adipocytes (Duncan et al., 2007; Warnken et al., 2017) and this acts to regulate the availability of free fatty acids and glycerol for hepatic gluconeogenesis.

HEALTHY ADIPOSE TISSUE

Not all adipose tissue is created equal

The anatomical location of AT appears to impart several important characteristics, most likely due to the slightly different role AT plays in each different site. The simplest distinction is that of subcutaneous AT (SAT), which lies immediately underneath the skin and visceral AT (VAT) which surrounds organs. In addition to these two major categories, AT within the bone marrow, around the heart (epicardial) and blood vessels and in/around skeletal muscle have all been found to have distinct phenotypes in humans and rodents. Very little is known about these tissue-specific depots in the horse, so this review will focus on what is known about SAT and VAT.

Subcutaneous versus visceral adipose tissue

The distinction between SAT and VAT is important because of the independent association of VAT with increased metabolic risk. People who carry their weight around their femorogluteal region (SAT),

which is the predominant pattern seen in women, are relatively protected from metabolic risk in obesity (Booth et al., 2014). In contrast, those who predominantly lay down VAT are at increased risk (Kwon et al., 2017). The reason for this different impact on metabolic health is not clear, but several features of SAT and VAT have been implicated in the sparse data available:

- SAT has a greater capacity for expansion by hyperplasia, which results in more abundant but smaller and 'healthier' adipocytes. VAT, however, favours hypertrophy for expansion, which results in large and less healthy adipocytes, which can more readily induce lipolysis and release fatty acids into the circulation or directly to the liver via the portal circulation (Bergman et al., 2006). A similar pattern of adipocyte size is found in horses, with peri-renal and retroperitoneal adipocytes having a significantly larger cross-sectional area than nuchal adipocytes (Bruynsteen et al., 2013).
- In humans, VAT has a more inflammatory phenotype when compared with SAT. This is the case both in 'normal' individuals and those in the face of persistent caloric excess (Ibrahim, 2010). In horses, there was increased mRNA levels of inflammatory cytokines in visceral depots compared with the nuchal depot (Bruynsteen et al., 2013).
- Leptin secretion is greater from SAT relative to VAT in humans and horses (Bruynsteen et al., 2013). In humans, adiponectin expression is higher in SAT than VAT (Fain et al., 2004) but the opposite is found in horses (Bruynsteen et al., 2013). There is also some evidence in humans and horses (Warnken et al., 2017) that SAT is more insulin sensitive than VAT, potentially contributing to 'safer' storage of lipids.

This distinction between SAT and VAT is relevant in horses because clinical measures of AT depots (body condition scoring, weigh tapes) almost exclusively measure SAT. It is important to recognise this as a limitation and remember that VAT may be more important in predicting disease risk. Body condition score is only strongly correlated with total body fat as determined by deuterium oxide dilution (eTBF%) (Dugdale et al., 2011) in lean or nonobese horses. As BCS increases, the predictive ability of BCS for adiposity reduces significantly (Dugdale et al., 2012). In addition, reliance on BCS may lead one to miss horses with body fat carried almost exclusively around the viscera, a state referred to as Thin on the Outside Fat on the Inside (TOFI) in human medicine (Thomas et al., 2012). This accumulation of VAT, which remains undetected by standard assessment techniques, could explain why outwardly nonobese horses and ponies may demonstrate an insulin-dysregulated phenotype. This explanation may enable owners to begin to understand why their horse is at risk of diseases associated with increased adiposity without appearing grossly overweight. Equally, some horses and ponies that are outwardly obese, do not demonstrate an insulin-dysregulated phenotype. Whilst we cannot yet use cross-sectional imaging techniques that are employed in human medicine, such as MRI, to identify and characterise visceral adiposity, it is worth considering abdominal ultrasound in horses if a TOFI phenotype is suspected.

Adipose tissue in obesity

Obesity is defined by the World Health Organisation (WHO) as 'abnormal or excessive fat accumulation that may impair health.' In horses, we have yet to define this parameter in a similar manner, so our definition of obesity is based solely on measures of subcutaneous fat. We do know that in obese horses, as defined by BCS, AT can account for up to 35% of body mass (Dugdale et al., 2012).

Obesity-associated AT, particularly VAT, is markedly dysfunctional in humans and directly related to the development of obesity-associated morbidities, including insulin resistance and cardiovascular risk (Santillana et al., 2023). In horses, dysfunction of obese AT is also clear (Figure 2). Reynolds et al. (2019) found marked hypertrophy of VAT adipocytes, a hallmark of dysfunctional AT in humans. Fibrosis, a key feature of human dysregulated AT, was not found in the AT of these horses but has been reported by others (Basinska et al., 2015); this discrepancy perhaps due to the chronicity of disease in the animals studied. Dysfunctional AT has also been shown to display increased expression of leptin (Reynolds et al., 2019). There is conflicting data regarding adipocytokine expression in obese AT of horses, as there is in the human literature. Whilst Burns et al. (2010) showed no change in TNFα and IL1β in obese AT, several groups have since shown increases associated with obesity and insulin dysregulation in VAT (Jayathilake et al., 2022; Reynolds et al., 2019) and SAT (Basinska et al., 2015). Basinska et al. (2015) also reported macrophage infiltration. It should be noted that the populations studied are invariably diverse in terms of disease state. In humans, obese AT expansion by hypertrophy fails to stimulate angiogenesis which is typically driven by increased cell number (hyperplasia); therefore, the blood supply eventually becomes limited and hypoxia occurs, contributing to inflammation (Hammarstedt et al., 2018). Although this has not yet been investigated, the same process may occur in the horse. The authors have found the use of the term 'unhealthy' AT useful in discussions with owners on equine obesity.

A key question in understanding how obesity results in systemic insulin resistance is whether obese AT is itself insulin resistant. There is currently not a clear answer to this question in humans, as it appears to be the case in some individuals but not in others. This alludes to the increasing acceptance that many sub-types of insulin resistance syndromes exist (Imi et al., 2023). Very little is known about insulin sensitivity of obese AT in horses. A crude measure of insulin signalling components in AT showed no differences between lean horses and those with equine metabolic syndrome (Reynolds et al., 2019); however, insulin signalling is dynamic and relies on altered phosphorylation state, so much more work is required in this area.

The next question is whether dysfunctional obese AT contributes to whole-body insulin dysregulation. The answer is invariably yes in human and rodent models, although there is still debate over the temporal nature of this relationship (Blüher, 2016; Kahn & Flier, 2000; Kahn et al., 2006). In general, it is thought that factors released in greater or lesser quantities from obese AT perturb insulin signalling; whether that is a function of the insulin receptor

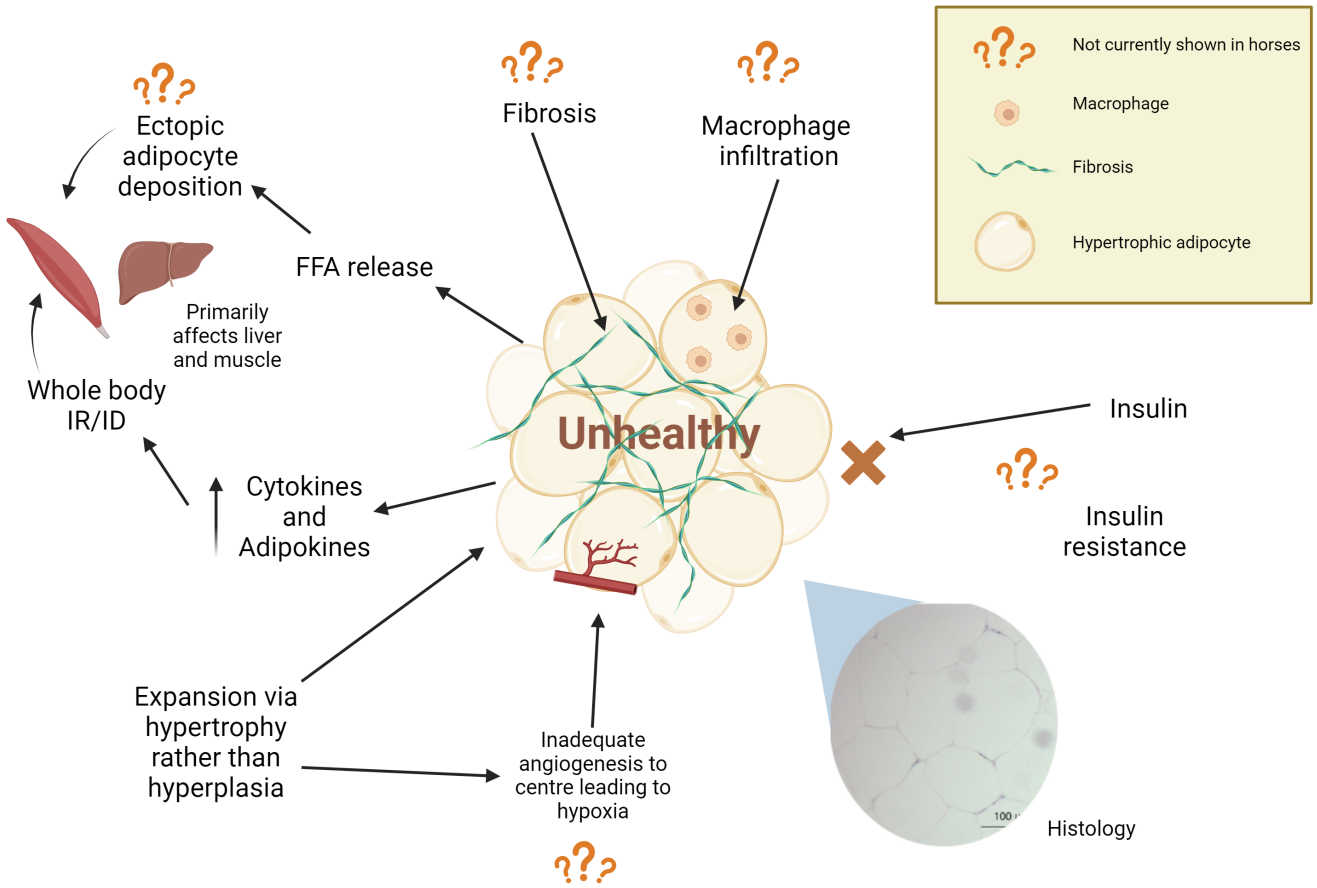

FIGURE 2 Diagram showing some of the known and proposed effects of unhealthy adipose tissue seen in overweight/obese cases. Created with BioRender.com.

itself or the downstream signalling cascade, particularly in liver and muscle but also in AT, is unclear. These downstream factors include adipocytokines (Blüher, 2016), leptin and adiponectin (Yadav et al., 2013). Overloaded adipocytes, especially in VAT, can release free fatty acids into the portal circulation and overwhelm hepatic gluconeogenesis, thus impacting insulin sensitivity (Longo et al., 2019). If adipocytes have reached capacity for safe storage, then lipid will be deposited ectopically in other sites (such as muscle and liver), which is detrimental to insulin sensitivity in those tissues (Longo et al., 2019).

CONCLUSION

The aim of this review was to demonstrate our growing understanding of the complexities of AT and its essential role in the morbidity of equine obesity. It is vital that knowledge gleaned from this work should be translated into practical benefits in terms of equine welfare; helping owners and veterinary surgeons to mitigate the impact of obesity on the domestic equine population. The authors have found that it is useful to include discussion of 'unhealthy' AT when communicating with owners about equine obesity. In doing this, the owner should become aware that the horse is not just fat, but that this fat is producing factors, which negatively impact most other organs in the body. By encouraging the practitioner to consider obesity as a disease in its own right, this review hopes to aid discussions with owners and, therefore, improve compliance.

AUTHOR CONTRIBUTIONS

S. McCullagh is the primary author of this review and was supervised by R. Morgan, who helped with the preparation of the manuscript. J. Keen and M. Dosi reviewed the manuscript and helped finalise it.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest have been declared.

ETHICS STATEMENT

No ethical review or approval is required for this review article.

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