# Adipokines: inflammation and the pleiotropic role of white adipose tissue

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# Adipokines: inflammation and the pleiotropic role of white adipose tissue

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**Short title:** Highly cited 2004 *BJN* article

**Key words:** adipokine; adipose tissue; hypoxia; inflammation; leptin; obesity; oxygen; white fat

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I had been working on the endocrine and signalling role of white adipose tissue (WAT) since 1994 following the identification of the *ob* (*Lep*) gene[1], this after some fifteen years investigating the physiological role of brown adipose tissue. The *ob* gene, a mutation in which is responsible for the profound obesity of *ob*/*ob* ($Lep^{ob}/Lep^{ob}$) mice, is expressed primarily in white adipocytes and encodes the pleiotropic hormone leptin. The discovery of this adipocyte hormone had wide ranging implications, including that white fat has multiple functions that far transcend the traditional picture of a simple lipid storage organ. The recognition that white adipocytes secrete a major hormone, and are key endocrine cells, catalysed an increasingly intensive search for other protein signals and factors that might be released from adipose tissue. Given the rapid developments that were then taking place I felt that an overview of the new perspectives on WAT was timely, and especially for a nutritional sciences audience. There was, of course, considerable interest in adipose tissue as a consequence of the escalating levels of obesity and its associated disorders.

I had a particular motivation in submitting the article to the *BJN*; I was at the time the Editor-in-Chief and had introduced a new section - 'Horizons in Nutritional Science' – which I was concerned to see develop. This section was intended to present fresh perspectives in the form of short reviews of rapidly emerging areas in nutritional science. My colleague Stuart Wood and I had written a paper to launch the Horizons series a year earlier - 'Glucose transporters (GLUT and SGLT): expanded families of sugar transport proteins' (this article, with >600 citations, is itself amongst the top twenty most-cited *BJN* papers)[2].

**What did the 2004 paper say?**

Our 2004 article[3] had three elements, each of which may have contributed to its success. The first, and major, is that it provided an overview of the emerging roles of white fat, highlighting the extensive secretory properties of the tissue. These include the secretion of leptin and a further key adipocyte hormone, adiponectin, as well as the then rapidly growing list of other protein signals and factors. The secreted proteins encompass a wide range of physiological functions, including insulin sensitivity, haemostasis, lipid metabolism, blood pressure and energy balance - as summarised in a figure from the 2004 paper (Fig. 2). A number are cytokines and chemokines, such as TNFα, IL-1β, IL-6 and MCP1, and other signals linked to inflammation had also been identified. This, together with reports that macrophages are recruited to WAT in the obese[4,5], underpinned the view that the tissue becomes 'inflamed' as the mass increases, the inflammation leading to the development of obesity-associated disorders such as insulin resistance and the metabolic syndrome.

A second, though minor, element of the article was the attempt to systematise the nomenclature associated with the secretions from white adipocytes and encourage a common terminology. The multiple secreted proteins were being referred to as either 'adipocytokines' or 'adipokines'. We argued that the preferred term was adipokine since adipocytokine can be taken as indicating that these proteins are cytokines, or cytokine-like - and most are not. In practice, adipokine is the name now customarily employed. We also described the totality of protein factors secreted from white adipocytes as the 'adipokinome', which together with the various lipid moieties released constitutes the 'secretome' of these cells.

The third element of the 2004 paper, which is to me the most significant, was the presentation of a novel hypothesis to explain the development of inflammation in WAT in obesity. For several years I had been intrigued as to why inflammation should occur in the tissue as it expands, but there was no clear explanation. We proposed that hypoxia - a relative deprivation of oxygen - occurs in WAT in obesity as a consequence of the enlarging adipocytes becoming more and more distant from the vasculature. We further postulated that the key hypoxia-inducible transcription factor, HIF-1, is recruited leading to increased expression of inflammation-related adipokines. Indeed, extensive cellular and metabolic adaptations in response to hypoxia were envisaged (as recognised in several other contexts, such as in tumours) and this has now been firmly established to be the case (Fig. 3).

At the time, investigation of the molecular and cellular responses to hypoxia was a limited, though growing, area. It is now a major field with the Nobel Prize for Physiology/Medicine being awarded in 2019 to three of the pivotal figures in hypoxia research.

**Subsequent development of my research – what came next?**

How did my research evolve following the appearance of the 2004 article? There were in practise two thrusts to the programme. My Unit in Liverpool continued to search for novel adipokines and several were identified; these included nerve growth factor, IL-18 (a member of the IL-1 cytokine gene family), and the lipolytic agent zinc-$\alpha_2$-glycoprotein[6-8]. Zinc-$\alpha_2$-glycoprotein was particularly intriguing, expression being substantially increased in WAT of mice bearing tumours with the factor being linked to cachexia and to be abundantly produced by white adipocytes[8]. A considerable number of other adipokines have subsequently been identified[9,10].

My second, and major, interest was in examining the effects of hypoxia on the function of white adipocytes, work that was undertaken with my colleagues Stuart Wood and Bohan Wang. Importantly, three years after the publication of the *BJN* article two papers appeared demonstrating reduced $O_2$ tension in WAT depots of both genetic and dietary obese mice,[11,12]

in agreement with the hypoxia hypothesis. However, varying results have been obtained in human studies and it is not yet clear whether hypoxia is a characteristic of WAT in obese humans[9,10].

Our studies on hypoxia centred on human fat cells differentiated in culture from fibroblastic preadipocytes and began with a candidate gene approach in which the expression of selected adipokine genes associated with inflammation were examined together with the release of their encoded proteins[13]. Adipocytes incubated in 1% $O_2$ were compared with those maintained in 20% $O_2$. Increases in the expression and production of leptin, IL-6 and VEGF, for example, were shown to be increased in response to hypoxia, while adiponectin was decreased[13]. PCR arrays, followed by full DNA microarrays, were then used to probe the extent of the effects of hypoxia on adipocyte gene expression[14,15].

The microarray studies demonstrated that the expression of >1,300 genes was modulated in human white adipocytes by hypoxia, approximately half being up-regulated and half down-regulated[15]. Multiple metabolic pathways were found to be altered by low $O_2$ tension, including glucose utilisation, lipid oxidation and cell death[15]. Direct functional studies that we also undertook demonstrated that glucose uptake is substantially increased in human adipocytes under hypoxic conditions, this being facilitated by increased expression and production of the GLUT1 facilitative glucose transporter[16].

Our group was not, of course, alone in examining the effects of hypoxia on adipose tissue function. Important contributions from others included the demonstration of a link between $O_2$ deprivation and the development of tissue fibrosis and cellular dysfunction[17], as well as the rapid induction of insulin resistance in adipocytes[18,19].

Most of my group's studies involved comparing adipocytes incubated in 1% $O_2$ with those under 20% – so-called 'normoxia' - which is the conventional approach to examining the response of cells to hypoxia. However, the $O_2$ tension to which adipocytes (in concert with many other cells) are exposed physiologically is considerably less than the equivalent of 20% and is actually close to 6-8%. In a study in which adipocytes were incubated under various levels of $O_2$ between 20 and 1%, a dose-response was observed in the parameters examined, with the cells titrating small differences in $O_2$ tension including in the expression and secretion of specific adipokines as well as in the uptake and utilisation of glucose[20]. A key observation was that many of the changes occurred between 20 and 10% $O_2$ such that at physiological levels of $O_2$ there is already a marked 'hypoxic' effect. Normoxia, in practise, represents 'hyperoxia' and employing this as the reference point both exaggerates the measured response to hypoxia at 1% $O_2$ and

raises an important question of whether using 20% $O_2$ to culture cells has distorted our view of what is normal cellular metabolism[9,10].

Although the main focus of our work was on adipocytes, we also conducted studies on human preadipocytes – cells which on differentiation become mature fat cells. Marked differences in the response to hypoxia between preadipocytes and adipocytes were observed, and of particular note was the effect on leptin production[21]. Expression of the leptin gene is considered as differentiation-dependent, being absent in preadipocytes. However, in preadipocytes exposed to hypoxia both leptin expression and secretion of the encoded protein were evident. Thus preadipocytes become leptin-secreting endocrine cells under conditions of low $pO_2$. This raises the question of whether at physiological $O_2$ levels *in vivo* preadipocytes do produce leptin and that the endocrine function of these cells has been misrepresented by culturing them in 20% $O_2$ – a potent example of normal cellular function being distorted by employing unphysiological, hyperoxic conditions.

One of the outcomes from my interest in hypoxia is the highlighting of $O_2$ as a cellular nutrient; indeed, cell biologists frequently describe it as such. However, nutritionists do not consider $O_2$ as a nutrient, and nutrition textbooks rarely mention it other than in the context of respiration and energy metabolism. I have recently argued that nutritional science should encompass $O_2$ as a macronutrient – it fulfils the key criteria, but it is only the route of entry (nose/lungs rather than mouth/gastrointestinal tract) that accounts for its omission[22,23].

**Coda**

I am delighted that the 2004 paper has been so highly cited (>1,500 citations: Web of Science, September 2021), and is the third most cited article in the 75 years of the *BJN*. I am also pleased, and surprised, that nearly twenty years after its publication it continues to be referenced - despite the number of reviews on WAT that have appeared over the same period. In 2020 alone it received some 66 citations (Web of Science). In 2008 my group published a follow-up review specifically on hypoxia and adipose tissue function, again as a Horizons article in the *BJN*[24], and this has received >300 citations. I was subsequently invited to write articles on hypoxia in WAT in relation to obesity for *Physiological Reviews*[9] and *Annual Reviews of Nutrition*[10], and although they have been well-cited (>400 cites for the *Physiological Reviews* paper) the number of citations do not approach that of the original *BJN* paper, notwithstanding the considerable prestige of these leading journals.

**Acknowledgements**

I am grateful to my colleagues and students at the Obesity Biology Unit, University of Liverpool, for their contributions to the work that led to, and followed, the 2004 paper. I particularly acknowledge the critical contributions of Drs Chen Bing, Bohan Wang and Stuart Wood.

**Conflicts of interest**

The author declares that there are no conflicts of interest pertaining to this article, and that he is not in receipt of any relevant external funding.

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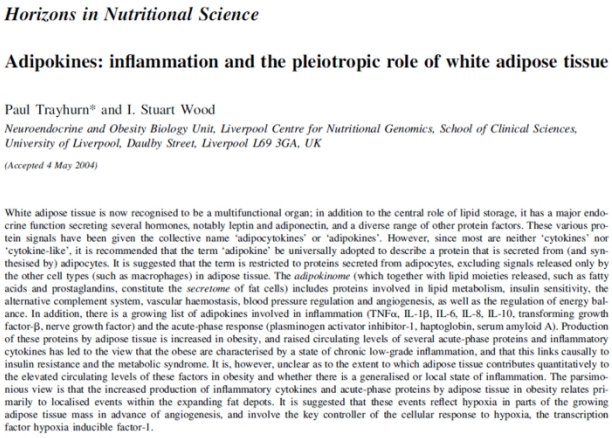
## Legends to Figures

**Fig. 1.** Original abstract from 2004 article[3].

**Fig. 1**. Figure from the original 2004 paper[3] illustrating the key metabolic and physiological processes with which white adipose tissue was – and is - considered to be involved through the secretion of various adipokines.

**Fig. 2.** Schematic representation of some of the central cellular responses to hypoxia (oxygen deficiency) in white adipocytes. The figure illustrates adaptations that are universal to all cell types, particularly the increase in glucose utilisation through anaerobic glycolysis and the reduction in respiration and oxidative phosphorylation (ox phos). Adaptations that are specific to adipocytes are also shown, primarily those relating to lipid utilisation and the production of adipokines as key secretory proteins of these cell types; in some of the examples, such as MT-3 (metallothionein-3), only major changes at the gene expression level have been formally documented. angptl4, angiopoietin-like protein-4; enzy, enzyme; FA, fatty acid; GLUT1, facilitative glucose transporter 1; HIF-1, hypoxia-inducible factor-1; MCT1, monocarboxylate transporter-1; MIF, macrophage migration inhibitory factor; MMPs, matrix metalloproteinases; PAI-1, plasminogen activator inhibitor-1; TF, transcription factors (additional to HIF-1); VEGF, vascular endothelial growth factor. Reproduced from Trayhurn (2019)[23].

Fig. 1



*Horizons in Nutritional Science*

**Adipokines: inflammation and the pleiotropic role of white adipose tissue**

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*(Accepted 4 May 2004)*

White adipose tissue is now recognised to be a multifunctional organ; in addition to the central role of lipid storage, it has a major endocrine function secreting several hormones, notably leptin and adiponectin, and a diverse range of other protein factors. These various protein signals have been given the collective name 'adipocytokines' or 'adipokines'. However, since most are neither 'cytokines' nor 'cytokine-like', it is recommended that the term 'adipokine' be universally adopted to describe a protein that is secreted from (and synthesised by) adipocytes. It is suggested that the term is restricted to proteins secreted from adipocytes, excluding signals released only by the other cell types (such as macrophages) in adipose tissue. The *adipokinome* (which together with lipid moieties released, such as fatty acids and prostaglandins, constitute the *secretome* of fat cells) includes proteins involved in lipid metabolism, insulin sensitivity, the alternative complement system, vascular haemostasis, blood pressure regulation and angiogenesis, as well as the regulation of energy balance. In addition, there is a growing list of adipokines involved in inflammation (TNFα, IL-1β, IL-6, IL-8, IL-10, transforming growth factor-β, nerve growth factor) and the acute-phase response (plasminogen activator inhibitor-1, haptoglobin, serum amyloid A). Production of these proteins by adipose tissue is increased in obesity, and raised circulating levels of several acute-phase proteins and inflammatory cytokines has led to the view that the obese are characterised by a state of chronic low-grade inflammation, and that this links causally to insulin resistance and the metabolic syndrome. It is, however, unclear as to the extent to which adipose tissue contributes quantitatively to the elevated circulating levels of these factors in obesity and whether there is a generalised or local state of inflammation. The parsimonious view is that the increased production of inflammatory cytokines and acute-phase proteins by adipose tissue in obesity relates primarily to localised events within the expanding fat depots. It is suggested that these events reflect hypoxia in parts of the growing adipose tissue mass in advance of angiogenesis, and involve the key controller of the cellular response to hypoxia, the transcription factor hypoxia inducible factor-1.

Original abstract from 2004 article[3].

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Fig. 2

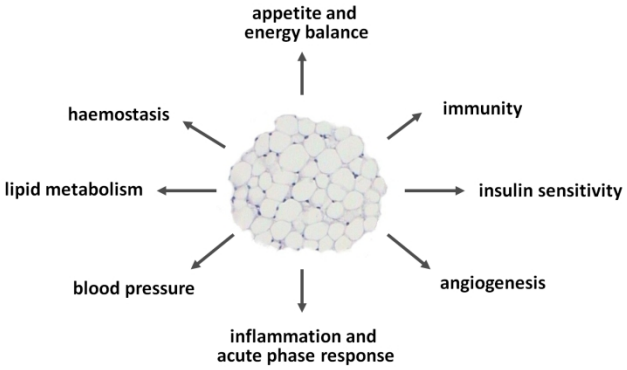


Figure from the original 2004 paper[3] illustrating the key metabolic and physiological processes with which white adipose tissue was – and is - considered to be involved through the secretion of various adipokines.

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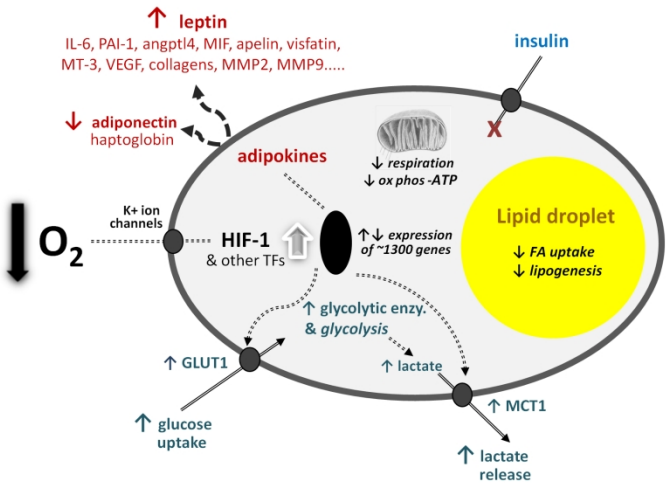
Fig. 3




Schematic representation of some of the central cellular responses to hypoxia (oxygen deficiency) in white adipocytes. The figure illustrates adaptations that are universal to all cell types, particularly the increase in glucose utilisation through anaerobic glycolysis and the reduction in respiration and oxidative phosphorylation (ox phos). Adaptations that are specific to adipocytes are also shown, primarily those relating to lipid utilisation and the production of adipokines as key secretory proteins of these cell types; in some of the examples, such as MT-3 (metallothionein-3), only major changes at the gene expression level have been formally documented. angptl4, angiopoietin-like protein-4; enzy, enzyme; FA, fatty acid; GLUT1, facilitative glucose transporter 1; HIF-1, hypoxia-inducible factor-1; MCT1, monocarboxylate transporter-1; MIF, macrophage migration inhibitory factor; MMPs, matrix metalloproteinases; PAI-1, plasminogen activator inhibitor-1; TF, transcription factors (additional to HIF-1); VEGF, vascular endothelial growth factor. Reproduced from Trayhurn (2019)[23].

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Adipokines: inflammation and the pleiotropic role of white adipose tissue

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