British Journal of Nutrition (2008), **100**, 236–237
doi:10.1017/S0007114508968239

Invited Commentary

Expanded adipose tissue: 'out of breath' and inflamed

(First published online 3 April 2008)

The study of hypoxia in adipose tissue in relation to obesity is timely, since some very recent studies have put these topics in a physiological context. In this issue of the *British Journal of Nutrition*, Trayhurn *et al.* [1] summarise our current knowledge on hypoxia in adipose tissue and isolated adipocytes. Hypoxia can be observed in both physiological and pathological situations. Each tissue in the human body might be more or less normally characterised by lower O_2 pressure than in arterial blood, as detailed in the paper by Trayhurn *et al.* [1] In fact, compared with O_2 pressure in arterial blood, some organs such as the spleen, thymus and brain seem to be highly hypoxic. As for white adipose tissue, it could be demonstrated that oxygenation is comparable with general tissue oxygenation in lean animals, while obese littermates are characterised by about 60 % lower O_2 pressure in fat[2]. In adipose tissue of mice, hypoxia underlies the increased production of adipokines and the development of obesity and the metabolic syndrome[3]. Furthermore, it could be demonstrated in humans that hypoxia occurs in the obese state[4].

Hypoxia leads to activation of the transcription factor hypoxia inducible factor (HIF)-1α, which is a key player in the adaptive response to low O_2 availability in tissues. HIF-1α stimulates the transcription of various genes that affect cell proliferation, angiogenesis, the vascular tone, glucose metabolism and the extracellular matrix[5]. Hypoxia in isolated adipocytes has been studied to a greater extent than *in vivo*, revealing that hypoxia causes various changes in protein expression and secretion behaviour in this cell type. Isolated adipocytes exposed to hypoxia exhibit the same dysregulation of secretory function as observed in expanded adipose tissue including increased release of IL-6, leptin and vascular endothelial growth factor (VEGF)[6]. In contrast, the release of adiponectin is decreased in hypoxia, possibly through activation of endoplasmic reticulum (ER) stress[3]. In addition to adipokines, hypoxia leads to a prominent induction of GLUT1 and increased glucose uptake while it is unclear if hypoxia affects the translocation of the insulin-sensitive GLUT4[7].

Hypoxia in adipose tissue adds to other mechanisms being involved in the development of obesity and its associated comorbidities, namely inflammation with increased macrophage infiltration into adipose tissue and ER stress. Over the past few years, increasing evidence has supported the concept of chronic low-grade inflammation in expanding fat as a key step to obesity-associated insulin resistance[8]. This process is characterised by macrophages infiltrating adipose tissue[9] and an increase in the release of pro-inflammatory adipokines such as TNF-α, monocyte chemotactic protein (MCP)-1 and IL-8[10]. At present, it is not clear if hypoxia initiates or augments the inflammatory response in adipose tissue. Another upcoming mechanism of adipocyte 'stress' is ER stress. There are several explanations why ER stress occurs particularly in fat in obesity that include increased protein synthesis due to increased energy availability or even glucose deprivation due to insulin resistance in adipose tissue[11]. Hypoxia was also proposed to be a cause of ER stress[3]. Furthermore, hypoxia and ER stress might be closely related since signalling pathways for both forms of stress merge in common pathways, such as activation of mammalian target of rapamycin or c-Jun N-terminal kinase.

Through the secretion of various adipokines, adipocytes may influence other cell types in adipose tissue referred to as the stromavascular fraction. The issue of increased VEGF release by hypoxic adipocytes and macrophages is of special interest[2,6]. This adipokine might stimulate endothelial cells and lead to neovascularisation. Furthermore, adipose tissue-residing macrophages are involved in the process of neovascularisation[12] possibly through MCP-1 signalling from adipocytes, further contributing to the prevention of hypoxia in adipose tissue. This would be an example of macrophages exerting positive effects in adipose tissue, besides inflammation.

Hypoxia does not only play a role in pathological states, but occurs also in normal physiology, for example during exercise. Both hypoxia in obesity and hypoxia in exercise activate 5′AMP-activated protein kinase (AMPK). Acute activation of AMPK in exercise leads to increased insulin sensitivity, namely in skeletal muscle and adipose tissue where glucose uptake and fatty acid oxidation increase[13]. Pharmacological activation of AMPK is an interesting drug target for type 2 diabetes. In the obese state, hypoxia in adipose tissue is a chronic effect and may therefore be distinct from acute hypoxia observed in exercise. It may also be speculated that AMPK activation may differ somehow in both situations, explaining why hypoxia may exert such differential effects. So, it must be noticed that hypoxia is not always 'bad' *per se*. However, hypoxia in adipose tissue might also be deleterious in other circumstances than obesity. Namely, one very recent study revealed that obstructive sleep apnoea syndrome patients are characterised by lower adiponectin levels, indicating that repetitive intermittent hypoxia might influence adipocyte secretion and function[14].

In summary, hypoxia occurs in expanding adipose tissue where it contributes together with inflammatory processes and ER stress to the altered secretory function of this tissue. Understanding hypoxic events in adipose tissue might be helpful to better understand the pathophysiology of obesity and to target involved pathways for the treatment of obesity-related diseases.

Henrike Sell and Juergen Eckel
Institute of Clinical Biochemistry and Pathobiochemistry
German Diabetes Center
Auf'm Hennekamp 65
40225 Düsseldorf
Germany
eckel@uni-duesseldorf.de

References

1. Trayhurn P, Wang B & Wood IS (2008) Hypoxia in adipose tissue: a basis for the dysregulation of tissue function in obesity? *Br J Nutr* **100**, 227–235.
2. Ye J, Gao Z, Yin J & He Q (2007) Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. *Am J Physiol Endocrinol Metab* **293**, E1118–E1128.
3. Hosogai N, Fukuhara A, Oshima K, *et al.* (2007) Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes* **56**, 901–911.
4. Cancello R, Henegar C, Viguerie N, *et al.* (2005) Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes* **54**, 2277–2286.
5. Semenza GL (2003) Targeting HIF-1 for cancer therapy. *Nat Rev Cancer* **3**, 721–732.
6. Wang B, Wood IS & Trayhurn P (2007) Dysregulation of the expression and secretion of inflammation-related adipokines by hypoxia in human adipocytes. *Pflugers Arch* **455**, 479–492.
7. Wood IS, Wang B, Lorente-Cebrian S & Trayhurn P (2007) Hypoxia increases expression of selective facilitative glucose transporters (GLUT) and 2-deoxy-D-glucose uptake in human adipocytes. *Biochem Biophys Res Commun* **361**, 468–473.
8. Xu H, Barnes GT, Yang Q, *et al.* (2003) Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* **112**, 1821–1830.
9. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL & Ferrante AW Jr (2003) Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* **112**, 1796–1808.
10. Trayhurn P & Wood IS (2004) Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* **92**, 347–355.
11. Gregor MF & Hotamisligil GS (2007) Thematic review series: adipocyte biology. Adipocyte stress: the endoplasmic reticulum and metabolic disease. *J Lipid Res* **48**, 1905–1914.
12. Khmelewski E, Becker A, Meinertz T & Ito WD (2004) Tissue resident cells play a dominant role in arteriogenesis and concomitant macrophage accumulation. *Circ Res* **95**, E56–E64.
13. Daval M, Foufelle F & Ferre P (2006) Functions of AMP-activated protein kinase in adipose tissue. *J Physiol* **574**, 55–62.
14. Nakagawa Y, Kishida K, Kihara S, *et al.* (2008) Nocturnal reduction in circulating adiponectin concentrations related to hypoxic stress in severe obstructive sleep apnea hypopnea syndrome. *Am J Physiol Endocrinol Metab* **294**, E778–E784.

British Journal of Nutrition